DNA repair gene polymorphisms, tumor control, and treatment toxicity in prostate cancer patients treated with permanent prostate brachytherapy

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Abstract

Background: Radiotherapy and brachytherapy are common treatments for localized prostate cancer (PCa). However, very few studies evaluated the association of variations in DNA damage response genes and treatment outcomes and toxicity in brachytherapy-treated patients.

Purpose: To evaluate the association of inherited germline variations in DNA repair-associated genes with tumor control and treatment toxicity in patients treated with low-dose-rate prostate brachytherapy (LDRB).

Material and Methods: The cohort consists of 475 I-125 LDRB patients with a median follow-up of 51 months after seed implantation. Patients were genotyped for 215 haplotype tagging single nucleotide variations (htSNPs) in 29 candidate genes of DNA damage response and repair pathways. Their association with biochemical recurrence (BCR) was assessed using Cox regression models and Kaplan-Meier survival curves. Linear regressions and analysis of covariance (ANCOVA) between early and late International Prostate Symptom Score (IPSS) with htSNPs were used to evaluate the association with urinary toxicity.

Results: After adjustment for the established risk factors, six htSNPs in five genes were found to be significantly associated with an altered risk of BCR, with adjusted hazard ratios (HRadj) ranging between 3.6 and 11.1 (P < .05). Compared to carriers of the ERCC3 rs4150499C allele, patients homozygous for the T allele (n = 22) had a significantly higher risk of BCR with a HR of 11.13 (IC95 = 3.9–32.0; P < .0001; q < 0.001). The Kaplan-Meier survival curve revealed a mean BCR-free survival time reduced from 213 ± 7 to 99 ± 12 months (log-rank P < .0001) for homozygous T carriers compared to noncarriers. For late IPSS (>6 months after treatment), htSNP rs6544990 from MSH2 showed a statistically significant b-coefficient of 1.85 ± 0.52 (P < .001; q < 0.1). Homozygous carriers of the MSH2
1 | INTRODUCTION

Prostate cancer (PCa) is the most common among North American men representing approximately 20% of all new cancers in this population. While some patients might be observed under active surveillance programs, treatments are required for intermediate and high-risk PCa patients. Many can be cured with standard treatments, but 27 to 53% of patients will have BCR of their disease.

With surgery, radiotherapy (RT) is one of the common available treatments for PCa. Notably, low-dose-rate (LDR) brachytherapy with 125 permanent seed implants is indicated for low- to intermediate-risk localized PCa patients. Current established prognostic factors for PCa rely on tumor stage, Gleason score, and serum concentration of prostate-specific antigen (PSA). In the context of personalized treatments, these markers are imperfect since they do not account for the heterogeneity of the disease. The lack of molecular markers associated with treatment outcomes impairs our ability to offer patients an effective and fully personalized therapeutic plan. Notably, genetic variations from patient to patient have been suggested to influence their risk of cancer recurrence. Since radiation therapy induces DNA damage in targeted cancer cells, previous genetic associations studies have suggested that genetic variations among genes implicated in the DNA-damage response (DDR) might affect treatment outcome and/or toxicity. Indeed, after RT for PCa, variants of LIG4, ERCC2, MDC1, XRCC1, and XRCC3 were associated with altered risk of treatment toxicities. Moreover, a XRCC1 variant was also associated with lower survival probability. A more recent study by Zanusso et al reported the significant association of polymorphisms in ERCC2 and EXO1 with altered risk of BCR after RT. They also showed that a MSH6 rare variant was associated with better overall survival (OS). Except for one investigation, these studies were mainly conducted on patients treated with external-beam RT (EBRT). Since in LDR brachytherapy, the prescribed dose is delivered continuously over about 6 months, the DNA repair mechanisms at play might differ from those observed during EBRT. It is therefore plausible that other genetic variants in DDR genes could be linked to LDR treatment outcome or toxicity in this specific patient population.

In this study, we investigated in a cohort of 478 patients, the association of inherited germline variations in candidate genes implicated in DDR pathways and assessed their association with BCR and treatment toxicity after LDR brachytherapy treatment.

2 | MATERIALS AND METHODS

2.1 | Clinical data

Between February of 1995 and December of 2015, 475 patients with low-risk PCAs were treated at our institution by 125 LDR brachytherapy with a median follow-up of 51 months after seed implantation. All patients signed a consent form for genomic research by sampling of blood. The project was approved by the Comité d’Éthique de la Recherche of the CHU de Québec-Université Laval and given number A12-08-955.

2.2 | DNA isolation and genetic analysis

DNA was extracted from peripheral blood mononuclear cells obtained at the time of patient enrollment and stored at −80°C until genetic analysis. The selection of genes was based on the rationale that response to RT is related to the capacity of cells to repair their DNA damage. Two hundred fifteen haplotype tagging single nucleotide variations (htSNPs) were analyzed among 29 selected candidate genes related to gene regulation and repair of DNA damage: ACVRL1, ERCC1-6 and 8, LIG1,3 and 4, MGMT, MLH1, MSH2,3 and 6, RAD9A, RAD50, RAD51A, D, TP53BP1 and XRCC1-6. For each gene, a region covering all exons, introns, and 5 kb of each 5′ - and 3′-flanking region were screened to maximize coverage and to explain most of the haplotype diversity in the HapMap population of European ancestry. The htSNPs were genotyped as described previously. Among them, 215 htSNPs were successfully assayed (listed in Table S1).

2.3 | Statistical analysis

The association of treatment-related genitourinary toxicity with htSNP was evaluated by linear regression using early and late International Prostate Symptoms Score (IPSS) as dependent continuous variables. The regression models included pretreatment IPSS, age, hormone-therapy status, Gleason score, PSA level, prostate volume, and htSNP as potential predictors of posttreatment IPSS. Because the vast majority of our patients were treated before 2014, further validation is required before translational clinical advances.

rs6544990C allele (n = 62) had a mean late IPSS 3.6 points higher than patients homozygous for the A allele (n = 132). This difference was significant when tested by ANCOVA using pretreatment IPSS as a covariate (P < .01).
when evidence found that dose delivered to the bladder neck was associated to urinary toxicity, this dosimetry parameter could not be included in our toxicity analysis. The posttreatment IPSS values were compared for every level of significant htSNP at a constant IPSS pretreatment value by analysis of covariance (ANCOVA). The association of SNPs with BCR was first analyzed using a genomic model based on three categories: major-allele homozygotes, heterozygotes, and minor-allele homozygotes. For rare homozygotes with a frequency of less than 2%, minor-allele homozygotes were combined with the heterozygotes. SNP that significantly differed from Hardy–Weinberg distribution were excluded from the analysis. Multivariate Cox proportional hazard regression was performed on each SNP using the following clinicopathological covariates: age, pretreatment PSA level, Gleason score, hormonal therapy usage, and dose delivered to 90% of the prostate gland (D90). The time to event variable was BCR. Since multiple SNPs were tested, false-discovery rates (q-values) were calculated, using the q value R-package. Only the htSNPs with q < 0.1 were considered significant. After analyses with the genomic model, a secondary model was developed (recessive or dominant) for each statistically significant SNP. Cox regression and Kaplan–Meier biochemical failure-free survival (BCRFS) curves with log-rank tests analyses were computed for each SNP in the secondary model. In recessive models, minor allele homozygotes are compared to major allele homozygotes and heterozygotes combined. All other statistical analyses were performed using IBM© SPSS© Statistics Version 25.

3 | RESULTS

Table 1 presents the clinical characteristics of the studied cohort. Overall, 475 men treated with LDR brachytherapy at our institution were retrospectively enrolled in this study. Their mean age was 62.3 (8.4) years with a median follow-up of 51 months. The great majority had low (71.2%) or intermediate risk (27.2%) localized PCa, according to D’Amico’s risk classification. Of the studied patients, 81% never received androgen-deprivation therapy (ADT). Among the cohort, 31 patients presented a biochemical failure (BCR) after treatment.

The association of treatment-related genitourinary toxicity with htSNP was evaluated by linear regression using early and late IPSS as endpoints. For early IPSS (1 to 6 months after treatment), no htSNP were found to have a prognostic value. For late IPSS (more than 6 months after treatment), htSNP rs6544990 from MSH2 showed a statistically significant b-coefficient of 1.85 ± 0.52 (Table 2, P = .0003; q = 0.087). As depicted in Figure 1, homozygous carriers of the MSH2 rs6544990C allele (n = 62) had a mean late IPSS 3.6 points higher than patients homozygous for the rs6544990A allele (n = 132). This difference was significant when tested by ANCOVA using pretreatment IPSS as a covariate (P = .001).

The multivariate Cox proportional hazard regression found six htSNPs in the ERCC1, 3 and 5, TP53BP1, and XRCC6 genes significantly associated with BCR after LDR brachytherapy (Table 3). All these SNPs were linked to an increased risk of BCR. Relative frequencies of SNPs in cancer patients, genetic linkage, and their corresponding hazard ratios (hazard ratios [HRs]; 95% confidence interval [CI]) along with P and q-values are presented in Table 2. Only the ERCC3 rs4150499 rare homozygote variant (4.9%) had a q-value of .00096 under the false-discovery threshold. Therefore, further analysis related to BCR was only performed with this marker. Table 4 presents the univariate and multivariate Cox regression models assessing the association between the tested variables and BCR. Higher pretreatment PSA levels, older age, ADT usage, and rs4150499 homozygosity were all significantly associated with an increased risk of BCR in both univariate and multivariate analysis. In multivariate analysis, HR ratios ranged between 1.16 for PSA as a continuous variable to

### Table 1 Patients clinical and pathological characteristics

| Patient characteristics | n = 475 |
|-------------------------|--------|
| Age                     | 62.3 (8.4) |
| Follow-up Mean (SD)     | 50 (0-243) |
| Stage                   |         |
| T1A-T2A                 | 472 (99.4%) |
| T2B-T2C                 | 3 (0.6%)  |
| PSA Pre-Tx              |         |
| <5 ng/mL                | 249 (52.4%) |
| 5-10 ng/mL              | 203 (42.7%) |
| >10 ng/mL               | 23 (4.8%)  |
| Gleason score           |         |
| <7                      | 380 (80.0%) |
| 7                       | 93 (19.6%)  |
| >8                      | 2 (0.4%)   |
| D’Amico risk            |         |
| Low                     | 338 (71.2%) |
| Intermediate            | 129 (27.2%) |
| High                    | 8 (1.7%)   |
| ADT use                 | 91 (19.2%)  |
| No ADT                  | 384 (80.8%) |
| BCR                     | 31 (6.5%)   |

**Abbreviations:** ADT, androgen-deprivation therapy; BCR, biochemical relapse; PSA, prostate-specific antigen; SD, standard deviation.

### Table 2 Explanatory variables for late IPSS found by linear regression

| Explanatory variable | Unstandardized B-coefficient (SE) | Standardized B-coefficient | P-value |
|----------------------|-----------------------------------|-----------------------------|---------|
| Constant             | 8.29 (0.68)                       | ...                         | <.00001 |
| Pre-Tx IPSS          | 0.354 (0.06)                      | 0.29                        | <.00001 |
| MSH2 rs6544990       | 1.87 (0.51)                       | 0.18                        | .0003   |

**Adjusted R² = 0.112**

**Abbreviation:** IPSS, International Prostate Symptoms Score.
11.13 for rs4150499T rare homozygote carriers. The P-values for these HR were from below .00001 (rs4150499T homozygotes) to .01 (age >60 years).

Since patients carrying rare genotypes were at an increased risk of BCR, a secondary model which combined the common homozygotes and heterozygotes in a single group was also developed. The results of the multivariate Cox regression analysis of the secondary model are presented in Table 5. Similar to the above results, the HR for rs4150499T homozygotes was also highly significant with a HR of 8.87 (P = .000007).

The 10-year Kaplan–Meier BCRFS curves for the primary and secondary models are depicted in Figure 2A,B. In the primary model, the BCR-free survival is not significantly different between rs4150499 common homozygotes and heterozygotes with BCR-free survival of 94.7 and 90.0% (P = .169) at 120 months, respectively. The rare homozygotes have a 120-month BCR-free survival significantly different than the common homozygotes (32.0 vs 94.7%, P = 9.62e-8) and heterozygotes (32.0 vs 90.0%, P = .00021). The survival difference between the rare homozygotes and the two other groups combined in the secondary model is also highly significant (32.0% vs 92.7%, P = 4.37e-7).

Next, the GTex portal was consulted to verify whether both SNPs had a known biological impact on gene expression in prostatic tissue. In the case of ERCC3, the database contained 221 prostate samples in which expression of quantitative trait loci (eQTL) were assayed for rs4150499. The plot generated by the portal for the normalized expression of ERCC3 messenger RNA (mRNA) is depicted in Figure S1. The plot shows a stepwise reduction in the expression of ERCC3 in the presence of the htSNP (P = 8.86e-16). In the case of MSH2, no association with gene expression was observed in the prostate.

### DISCUSSION

In this study, we analyzed the associations of common genetic variation in pathways of DNA repair in relation to clinical and toxicity outcomes of RT-treated PCa patients. To our knowledge, very few studies addressed the impact of genetic variations in these pathways...

### TABLE 3 Significant HRs after Cox multivariate analysis between SNPs and BCR in patients with prostate cancer treated with LDR brachytherapy

| Gene/SNP   | Genotype (n) | HR   | 95% CI          | P-value | q-value |
|------------|--------------|------|-----------------|---------|---------|
| ERCC3 rs4150499 |              |      |                 |         |         |
|            | CC (241)     | 1    |                 |         |         |
|            | TC (183)     | 2.034| 0.888-4.658     | .093    |         |
|            | TT (22)      | 12.394| 4.221-36.394   | .000005 | 0.00955 |
| ERCC1 rs3212980 |              |      |                 |         |         |
|            | TT (239)     | 1    |                 |         |         |
|            | TG (187)     | 0.995| 0.449-2.204     | .99     |         |
|            | GG (20)      | 4.733| 1.649-13.585    | .004    | 0.191   |
| ERCC1 rs4803823 |              |      |                 |         |         |
|            | CC (274)     | 1    |                 |         |         |
|            | CT (138)     | 1.398| 0.609-3.208     | .429    |         |
|            | TT (20)      | 4.543| 1.552-13.296    | .006    | 0.229   |
| ERCC5 rs873601 |              |      |                 |         |         |
|            | GG (230)     | 1    |                 |         |         |
|            | GA (179)     | 1.434| 0.641-3.208     | .38     |         |
|            | AA (27)      | 3.715| 1.272-10.848    | .016    | 0.437   |
| XRCC6 rs11703638 |           |      |                 |         |         |
|            | GG (233)     | 1    |                 |         |         |
|            | GA (168)     | 0.900| 0.403-2.007     | .796    |         |
|            | AA (37)      | 4.047| 1.255-13.051    | .019    | 0.454   |
| TP53BP1 rs2242069 |          |      |                 |         |         |
|            | AA (296)     | 1    |                 |         |         |
|            | AC (115)     | 1.641| 0.726-3.711     | .234    |         |
|            | CC (22)      | 3.586| 1.158-11.103    | .027    | 0.573   |

Abbreviations: BCR, biochemical relapse; CI, confidence interval; HR, hazard ratio; LDR, low dose rate; SNP, single-nucleotide polymorphism.
and outcomes after LDR brachytherapy. After correction for multiple testing, two hSNPs were found to be significantly associated with increased risk of BCR and late genitourinary toxicity: ERCC3 rs4150499T and MSH2 rs6544990C, respectively. ERCC3 is responsible for the production of the XPB protein, which is involved in nucleotide excision repair.22 MSH2 encodes for the MSH2 protein that plays a role in DNA mismatch repair.23 To our knowledge, this study is the first to report an association of the ERCC3 hSNP rs4150499 with RT outcomes. Although the number of rare rs4150499 homozygotes (n = 22) remains limited in our study, the results obtained were highly significant (q = 0.00096). Indeed, more than 90% of common homozygotes and heterozygotes are free of BCR 10 years after treatment compared to only 32% of homozygotes for rs4150499T homozygotes (Figure 2 and Table 5).

Both SNPs found to be associated with either disease progression or toxicity after LDR brachytherapy are intronic variants located in ERCC3 and MSH2. It is well known that introns can contain functional polymorphisms that might affect the transcriptional activity or the splicing efficiency of their carrier genes.24‐26 In the case of ERCC3, results from expression analysis (GTex) revealed a significant gene dosage reduction in mRNA expression for carriers of the rs4150499T variant, supporting a functional role for this variant or a linked variation. Thus, it is possible that rs4150499 is associated with an altered expression of ERCC3 in prostate cells. This might be potentially explained by the fact that rs4150499 putatively colocalizes with an AP-2gamma transcription factor binding-site (Figure S2). It is important to note however that the reduced expression of the ERCC3 rs4150499T variant found in GTex applies only to normal cells and not cancer cells. Further research is thus necessary to (a) evaluate if this variant affect ERCC3 gene expression in the cancer compartment and (b) additional molecular studies are required to characterize this relationship with radiation resistance. ERCC3 encodes for the XPB protein that is a subunit of the transcription factor IIH (TFIIH). TFIIH is an essential component of the nucleotide-excision repair (NER) pathway, which is mainly known to remove UV-induced DNA lesions,22 but is also essential for the repair of ionizing radiation-induced 8,5′-cyclo-2′-deoxyguanosine DNA lesions.27,28 Further studies on the biological impact of positive variants identified herein will be necessary and is beyond the scope of this study.

Some of the assessed hSNPs in the present work were also previously studied in relation with RT-treated PCa. As observed herein, one study did not find any association of XRCC2 rs3218536

| Table 4 | Univariate and multivariate Cox regression analysis for predictors of BCR |
|-----------------|-----------------|-----------------|-----------------|
| Predictor       | Univariate HR   | 95% CI          | P-value         | Multivariate HR | 95% CI          | P-value         |
| PreTx-PSA       | 1.21            | 1.12-1.32       | <.0001          | 1.16            | 1.06-1.27       | .001            |
| Prostate D90    | 1.004           | 0.990-1.017     | .592            |                 |                 |                 |
| ADT             |                  |                 |                 | 1.36            | 1.20-1.55       | .0001           |
| Yes             | 3.06            | 1.49-6.28       | .002            | 2.90            | 1.31-6.39       | .008            |
| No              | 1               |                 |                 | 1               |                 |                 |
| Age             |                  |                 |                 | 1.36            | 1.18-1.59       | .0001           |
| ≤60             | 2.58            | 1.18-5.66       | .018            | 2.99            | 1.29-6.90       | .01             |
| >60             | 2.14            | 0.81-5.65       | .144            | 2.18            | 0.81-5.65       | .144            |
| ERCC3 rs4150499 |                  |                 |                 |                 |                 |                 |
| CC/CT           |                  |                 |                 |                 |                 |                 |
| CC              | 1               |                 |                 | 1               |                 |                 |
| CT              | 1.48            | 0.65-3.38       | .345            | 1.59            | 0.68-3.69       | .282            |
| TT              | 8.63            | 3.13-23.81      | <.0001          | 11.13           | 3.87-32.03      | <.00001         |
| Abbreviations: ADT, androgen-deprivation therapy; BCR, biochemical relapse; CI, confidence interval; HR, hazard ratio; PSA, prostate-specific antigen.

| Table 5 | Multivariate Cox regression analysis for predictors of BCR in the rs4150499 secondary model |
|-----------------|-----------------|-----------------|-----------------|
| Predictor       | HR   | 95% CI          | P-value         |
| PreTx-PSA       | 1.17 | 1.07-1.28       | 0.0046          |
| ADT             |      |                 |                 |
| No              | 1    |                 |                 |
| Yes             | 2.75 | 1.25-6.04       | 0.0118          |
| Age             |      |                 |                 |
| ≤60             | 1    |                 |                 |
| >60             | 2.79 | 1.23-6.35       | 0.0146          |
| ERCC3 rs4150499 |      |                 |                 |
| CC/CT           |      |                 |                 |
| CC              | 1    |                 |                 |
| CT              | 1.48 | 0.65-3.38       | .345            |
| TT              | 8.63 | 3.13-23.81      | <.00001         |
| Abbreviations: ADT, androgen-deprivation therapy; BCR, biochemical relapse; CI, confidence interval; HR, hazard ratio; PSA, prostate-specific antigen.
with late toxicity in patients treated with conformal RT for PCa.\textsuperscript{10} Another study also did not report any association of $\text{MLH1}\ rs1799977$ with GU or GI toxicity in patients treated with 3D-CRT.\textsuperscript{13} Langsenlehner et al\textsuperscript{12} found a protective role for $\text{XRCC1}\ rs25489$ heterozygosity against late grade 2 or higher toxicity in 3D-CRT-treated patients. However, this SNP was not linked to any significant effect in two earlier PCa studies\textsuperscript{10,11} and in the present study. One recent study by Zanusso et al\textsuperscript{16} previously evaluated the impact of DNA repair gene polymorphisms on BCR and OS after EBRT-treated PCa. It was found that carriers of at least one allele of $\text{ERCC2}\ rs1799793A$ were at a lower risk of BCR compared to $\text{rs1799793G}$ homozygotes. The opposite was found for $\text{EXO1}\ rs4149963T$ variant, which was associated with higher odds of BCR. Moreover, $\text{MSH6}\ rs3136228$ carriers were found to have an increased probability of OS at 5 and 10 years after treatment compared to carrier of the wild-type allele. These particular $\text{ERCC2}$ and $\text{MSH6}$ SNPs were not specifically assessed in our study, but those tested were not associated with BCR or treatment toxicity. These differences in findings might be in part related to the type of radiation delivery in both studies (EBRT vs LDR brachytherapy). It is noteworthy that Zanusso et al also found an SNP ($\text{ERCC2}\ rs1799793$) from the NER pathway to be associated with BCR and encoding for the XPD protein that is a catalytic partner of XPB in TFIIH.\textsuperscript{22}
There are limitations to the work reported here which remains exploratory in a population of LDR brachytherapy-treated PCa patients. Limitations include its retrospective nature and a possible selection bias that cannot be excluded, and the absence of a separate LDR brachytherapy validation cohort for replication of positive findings. Strengths of the study include an adequate sample size, a well-characterized cohort of patients with significant follow-up time, data on toxicities and clinical outcomes, and correction for multiple testing. Moreover, to the best of our knowledge, only one other study has appraised the impact of genetic polymorphism of the DDR pathways and DNA repair on outcomes and toxicities in LDR-treated patients.

5 | CONCLUSION

This study suggests an association of the ERCC3 rs4150499T and MSH2 rs6544990C intronic variants with elevated risk of BCR and late urinary toxicity, respectively, after LDR brachytherapy treatment for PCa. An independent validation is required to confirm these results, whereas the underlying biological mechanisms remain to be assessed. If validated in larger studies, rs4150499T homozygosity could support the use of alternative treatment in carriers of these variants. It would also be of interest to evaluate the association of these gene variants on HDR brachytherapy and EBRT treatments outcome for PCa patients and in other RT-treated cancers.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Study concept, design, and supervision: CG, EL, and EV. Data analysis: DC, TL, and PD. Drafting of the manuscript: DC, TL, and EL. Critical revision of the manuscript for intellectual content: CG, EL, and EV. Patient recruitment and clinical data: SM, AGM, PD, WF, and EV. Obtaining funding: EV, EL, and CG. Other: biobank management and genotyping: CG, EL, LV, and SD.

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REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69(1):7-34. https://doi.org/10.3322/caac.21551
2. Artibani W, Porcaro AB, De Marco V, Cerruto MA, Siracusano S. Management of biochemical recurrence after primary curative treatment for prostate cancer: A review. Urol Int. 2018;100(3):251-262. https://doi.org/10.1159/000481438
3. Walsh PC, DeWeese TL, Eisenberger MA. Clinical practice. Localized prostate cancer. N Engl J Med. 2007;357(26):2696-2705. https://doi.org/10.1056/NEJMc0706784
4. Fraser M, Sabelnykova VY, Yamaguchi TN, et al. Genomic hallmarks of localized, non-indolent prostate cancer. Nature. 2017;541(7637):359-364. https://doi.org/10.1038/nature20788
5. Lalonde E, Ishkanian AS, Sykes J, et al. Tumour genomic and micro-environmental heterogeneity for integrated prediction of 5-year biochemical recurrence of prostate cancer: A retrospective cohort study. Lancet Oncol. 2014;15(13):1521-1532. https://doi.org/10.1016/S1470-2241(14)71021-6
6. Mateo J, Boysen G, Barbieri CE, et al. DNA repair in prostate cancer: Biology and clinical implications. Eur Urol. 2017;71(3):417-425. https://doi.org/10.1016/j.euro.2016.08.037
7. Audet-Walsh E, Bellemare J, Lacombe L, et al. The impact of germline genetic variations in hydroxysteroid (17-beta) dehydrogenases on prostate cancer outcomes after prostatectomy. Eur Urol. 2012;62(1):88-96. https://doi.org/10.1016/j.eururo.2011.12.021
8. Shui IM, Lindström S, Kibé AS, et al. Prostate cancer (PCa) risk variants and risk of fatal PCa in the national cancer institute breast and prostate cancer cohort consortium. Eur Urol. 2014;65(6):1069-1075. https://doi.org/10.1016/j.eururo.2013.12.058
9. Helfand BT, Roehl KA, Cooper PR, et al. Associations of prostate cancer risk variants with disease aggressiveness: results of the NCI-SPORE Genetics Working Group analysis of 18,543 cases. Hum Genet. 2015;134(4):439-450. https://doi.org/10.1007/s00439-015-1534-9
10. Damaraju S. Association of DNA repair and steroid metabolism gene polymorphisms with clinical late toxicity in patients treated with conformal radiotherapy for prostate cancer. Clin Cancer Res. 2006;12(8):2545-2554. https://doi.org/10.1158/1078-0432.CCR-05-2703
11. Burri RJ, Stock RG, Cesaretti JA, et al. Association of single nucleotide polymorphisms in SOD2, XRCC1 and XRCC3 with susceptibility for the development of adverse effects resulting from radiotherapy for prostate cancer. Radiat Res. 2008;170(1):49-59. https://doi.org/10.1667/rr1219.1
12. Langsenlehner T, Renner W, Gerger A, et al. Association between single nucleotide polymorphisms in the gene for XRCC1 and radiation-induced late toxicity in prostate cancer patients. Radiother Oncol. 2011;98(3):387-393. https://doi.org/10.1016/j.radonc.2011.01.021
13. Fachal L, Gómez-Caamaño A, Peleteiro P, et al. Association of a XRCC3 polymorphism and rectum mean dose with the risk of acute radio-induced gastrointestinal toxicity in prostate cancer patients. Radiat Oncol. 2012;105(3):321-328. https://doi.org/10.1016/j.radonc.2012.09.013
14. Gao R, Price DK, Dahut WL, Reed E, Figg WD. Genetic polymorphisms in XRCC1 associated with radiation therapy in prostate cancer. Cancer Biol Ther. 2010;10(1):13-18. https://doi.org/10.4161/cbt.10.1.12172
15. Pugh TJ, Keyes M, Barclay L, et al. Sequence variant discovery in DNA repair genes from radiosensitive and radiotolerant prostate brachytherapy patients. Clin Cancer Res. 2009;15(15):5008-5016. https://doi.org/10.1158/1078-0432.CCR-08-3357
16. Zanusso C, Bortolus R, Dreussi E, et al. Impact of DNA repair gene polymorphisms on the risk of biochemical recurrence after radiotherapy and overall survival in prostate cancer. Oncotarget. 2017;8(14):22863-22875. https://doi.org/10.18632/oncotarget.15282
17. Labriet A, De Mattia E, Cecchin E, et al. Improved progression-free survival in irinotecan-treated metastatic colorectal cancer patients carrying the HNF1A coding variant p.I27L. Front Pharmacol. 2017;8:712. https://doi.org/10.3389/fphar.2017.00712
18. Steggerda MJ, Witteveen T, Van Den Boom F, Moonen LMF. Is there a relation between the radiation dose to the different sub-segments
of the lower urinary tract and urinary morbidity after brachytherapy of the prostate with I-125 seeds? Radiother Oncol. 2013;109:251-255. https://doi.org/10.1016/j.radonc.2013.07.019

19. Ghadjar P, Zelefsky MJ, Spratt DE, et al. Impact of dose to the bladder trigone on long-term urinary function after high-dose intensity modulated radiation therapy for localized prostate cancer. Int J Radiat Oncol Biol Phys. 2014;88:339-344. https://doi.org/10.1016/j.ijrobp.2013.10.042

20. Hathout L, Folkert MR, Kollmeier MA, Yamada Y, Cohen GN, Zelefsky MJ. Dose to the bladder neck is the most important predictor for acute and late toxicity after low-dose-rate prostate brachytherapy: Implications for establishing new dose constraints for treatment planning. Int J Radiat Oncol Biol Phys. 2014;90(2):312-319. https://doi.org/10.1016/j.ijrobp.2014.06.031

21. Storey JD, Bass AJ, Dabney A, Robinson D qvalue: Q-value estimation for false discovery rate control. 2015. https://doi.org/10.18129/B9.bioc.qvalue

22. Marteijn JA, Lans H, Vermeulen W, Hoeijmakers JHJ. Understanding nucleotide excision repair and its roles in cancer and ageing. Nucleic Acids Res. 2014;15(7):465-481. https://doi.org/10.1038/nrm3822

23. Li GM. Mechanisms and functions of DNA mismatch repair. Cell Res. 2008;18(1):85-98. https://doi.org/10.1038/cr.2007.115

24. Cooper DN. Functional intronic polymorphisms: Buried treasure awaiting discovery within our genes. Hum Genomics. 2010;4(5):284. https://doi.org/10.1186/1479-7364-4-5-284

25. Chiang HL, Wu JY, Chen YT. Identification of functional single nucleotide polymorphisms in the branchpoint site. Hum Genomics. 2017;11(1):27. https://doi.org/10.1186/s40246-017-0122-6

26. Hong MJ, Yoo SS, Choi JE, et al. Functional intronic variant of SLC5A10 affects DRG2 expression and survival outcomes of early-stage non-small-cell lung cancer. Cancer Sci. 2018;109(12):3902-3909. https://doi.org/10.1111/cas.1381

27. Dizdaroglu M, Dirksen ML, Jiang HX, Robbins JH. Ionizing-radiation-induced damage in the DNA of cultured human cells. Identification of 8,5-cyclo-2-deoxyguanosine. Biochem J. 1987;241(3):929-932. https://doi.org/10.1042/bj2410929

28. Huang H, Das RS, Basu AK, Stone MP. Structure of (5’S)-8,5-cyclo-2-deoxyguanosine in DNA. J Am Chem Soc. 2011;133(50):20357-20368. https://doi.org/10.1021/ja207407h

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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