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Prevalence of DNA repair gene mutations in localized prostate cancer according to clinical and pathologic features: Association of Gleason score and tumor stage

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Abstract

Background: DNA repair gene mutations are present in 8–10% of localized prostate cancers. It is unknown if this is influenced by clinicopathologic factors.

Methods: We interrogated localized prostate adenocarcinomas with tumor DNA sequencing from the TCGA validated (n=333) and Nature Genetics (n=377) datasets. Homologous recombination repair genes included: *ATM, BRCA1/2, CDK12, CHEK1/2, FANCA, FANCD2, FANCL*, *GEN1, NBN, PALB2, RAD51* and *RAD51C*. Proportions of cases with pathogenic DNA repair mutations (and in *ATM/BRCA1/2* specifically) were reported by Gleason grade group, clinical T stage, pathological T and pathological N stage. Odds ratios and Fisher's exact tests were used to compare proportions between categories.

Results: Those with Gleason Grade Groups 3 and higher were 2.2 times more likely to harbor any DNA repair mutation (95% CI 1.2–4.2; 10.3% versus 5.0%) and 2.7 times more likely to have *BRCA1/2* or *ATM* mutations (95% CI 1.3–6.6; 7.0% versus 2.7%) as those in Gleason Grade Groups 1–2. Patients with pathologic stage pT3/pT4 were 2.6 times more likely to have any DNA repair mutation (95% CI 1.3–6.6; 13.0% versus 5.5%) and 3.2 times more likely to have *BRCA1/2* or *ATM* mutations (95% CI 1.2–11.3; 9.5% versus 3.1%) compared to those with pT2 disease. There was no difference by clinical tumor or nodal stage. Among men with Gleason Grade Group ≥3 *and* clinical stage ≥cT3, 21.3% (1 in 5) had a DNA repair mutation in any gene and 11.7% (1 in 9) had a mutation in *ATM*/*BRCA1*/*2*.

Conclusions: The prevalence of pathogenic DNA repair gene alterations is enriched in men with advanced tumor stages and higher Gleason Grade groups, with maximal enrichment observed in

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those with Gleason Grade group ≥3 *and* clinical stage ≥cT3 disease. This information can be used to guide eligibility criteria for genomically-targeted clinical trials in the neoadjuvant/adjuvant settings.

Keywords

DNA repair mutations; prostate cancer; neoadjuvant; adjuvant; clinical trials

Introduction

Approximately 160,000 patients will be diagnosed with prostate cancer annually.[1] While most of these men will be cured with surgery or radiation targeting the prostate alone, many will go on to develop disease recurrence. The natural history of prostate cancer can be quite variable and there have been many attempts to identify biomarkers and clinical features of the disease to accurately predict recurrence risk after local therapy with curative intent. The most widely accepted clinical features used to risk stratify patients are tumor staging, nodal staging, and Gleason score.[2–4]

With the development and incorporation of somatic next-generation DNA sequencing into clinical practice, there have been further attempts to use genomics to risk-stratify patients and to select patients for targeted therapies. Within prostate cancer, genes in the DNA repair pathway have been found to be pathologically mutated in approximately 8–12% of localized prostate cancers[5,6] and about 20–25% of advanced metastatic castration-resistant prostate cancers.[7] *BRCA1* and *BRCA2* mutations, for example, have been associated with more aggressive forms of prostate cancer and with higher recurrence and mortality rates.[8–11] Furthermore, poly-ADP ribose polymerase (PARP) inhibitors have emerged as a potential therapeutic option for men harboring these mutations in the advanced prostate cancer setting.[12,13] Identifying men harboring these mutations early could be helpful to guide therapies and clinical trial design, for example when selecting patients for PARP inhibitor trials.

PARP inhibitors are currently being explored in multiple clinical trials in men with mutations in DNA repair pathway genes, particularly genes regulating the homologous recombination repair pathway (NCT03040791, NCT03442556, NCT03012321, NCT02952534, NCT02975934, NCT02854436). Given the lower prevalence of these mutations in localized prostate cancer compared to advanced disease, neoadjuvant and adjuvant trials targeting men with these mutations would be challenging to conduct if enrolling patients indiscriminately or if screening all patients for germline and somatic mutations (*i.e.* the number needed to screen (NNS) to find one patient with a homologous repair gene mutation would be very large). Histological variants, such as intraductal or ductal morphologies, and the presence of lymphovascular invasion, have both been shown to enrich for the presence of a germline DNA repair gene mutation.[14] It is currently unknown if somatic mutations in DNA repair genes vary according to clinical or pathologic factors.

Therefore, we sought to determine if clinical factors used for risk-stratifying patients – *i.e.* Gleason score, tumor stage and nodal status – could also identify those men with prostate cancers more likely to harbor a DNA repair gene mutation, specifically a homologous repair

mutation that may be used as inclusion for participation in a PARP inhibitor clinical trial. We hypothesized that such mutations would be more common in cases with higher Gleason score, higher tumor stage, and positive nodal status. We also sought to determine the best combination of clinicopathologic factors that would maximally enrich for presence of DNA repair gene mutations, aiding in the selection of eligibility criteria for neoadjuvant/adjuvant clinical trials.

Methods

Study Design

Genomic data was obtained from primary localized prostate adenocarcinoma cases from prostatectomies with somatic DNA sequencing data in The Cancer Genome Atlas (TCGA) repository validated dataset[6,15,16] and the Nature Genetics dataset[17] that are publically available on cBioPortal (http://www.cbioportal.org/). Gleason scores were available in both datasets, analyzed by Gleason sum, and also classified into their corresponding Gleason Grade Groups (1–5) to use a contemporary classification.[18]

Clinical and pathologic tumor stage and pathologic nodal stage were available in the TCGA dataset only. Clinical tumor (cT) stage, pathologic tumor (pT) stage, and pathologic nodal (pN) stage were analyzed when available and were correlated with DNA repair gene mutation status. Clinical N stage and prostate specific antigen (PSA), were excluded due to multiple missing data elements. Tumor stages T1 and T2 were combined as organ-confined disease and T3 and T4 were combined to represent locally-invasive disease outside of the prostate, consistent with staging from the American Joint Committee on Cancer (AJCC).[19]

DNA repair gene mutations were defined as pathogenic alterations in the following genes: *ATM, BRCA1/2, CDK12, CHEK1/2, FANCA, FANCD2, FANCL, GEN1, NBN, PALB2, RAD51* and *RAD51C*. These genes were selected based on the fact that they are involved in the homologous recombination repair pathway, and would thus be expected to enrich for sensitivity to PARP inhibitor therapy. A separate analysis was also conducted restricting the gene list to only *BRCA1/2* and *ATM* specifically (since these 3 genes are anticipated to be most closely linked with PARP inhibitor response). For all genes, mutations were counted as pathogenic if they were homozygous gene deletions, protein-truncating DNA sequence alterations (frameshift mutations, nonsense mutations, missense mutations), or splice site mutations affecting the conserved splice acceptor or donor sites. Missense and silent mutations were not included as pathogenic for the purposes of this analysis. From cBioPortal, it was not possible to distinguish mono-allelic from bi-allelic sequence alterations using this publicly-available data, so both types of alterations were included.

Statistical analysis

The proportions of DNA repair gene mutations were reported as a whole and according to Gleason grade group, clinical T stage, pathological T stage and pathological N stage. Odds ratios were calculated and the Fisher's exact test was used to compare proportions between different groups. To ensure feasibility and interpretability we calculate sensitivity, specificity, population positive-predictive value, and population negative-predictive value for

different cutoffs of clinical factors and different combinations of clinical factors. The population positive-predictive value and population negative-predicative value were calculated based on an estimate of a 10% prevalence of any DNA repair gene mutations and a 6% prevalence of *BRCA1/2* and *ATM* mutations specifically.[20] The combination with the highest positive-predictive value was chosen as the optimal enrichment threshold. Analyses were performed using *R* version 3.4.4.[21]

Results

Overall prevalence of DNA repair gene mutations

Within the entire population, 8.0% of individuals (57 of 710) had any somatic DNA repair gene mutation, and 5.4% had *ATM* or *BRCA1/2* mutations specifically. The five most commonly mutated genes were *ATM* (2.7%), *BRCA2* (2.0%), *CDK12* (1.5%), *BRCA1* (0.7%), and *PALB2* (0.7%) (Figure 1). Mutation breakdown by dataset and clinical and pathologic factors are presented in the supplementary tables.

Gleason grade group and DNA repair mutations

There were a total of 657 evaluable patients (from both datasets) with Gleason score information. The prevalence of any DNA repair mutation was 4.5% in Gleason Grade Group 1, 5.2% in Gleason Grade Group 2, 10.5% in Gleason Grade Group 3, 8.5% in Gleason Grade Group 4, and 11.0% in Gleason Grade Group 5 (Table 1, Figure 2). Combined, those in Gleason Grade Groups 3 and higher had a prevalence of 10.3% (number needed to screen (NNS) = 20) and were 2.2 times more likely (95% CI 1.2–4.2) to harbor a mutation compared to those in Gleason Grade Groups 1 and 2 (prevalence 5.0%, (number needed to screen (NNS) = 10); p-value for difference 0.01). Considering those who specifically had mutations in *ATM* or *BRCA1/2*, those with Gleason Grade Groups 3 and higher had a prevalence of 7.0% (NNS=37) and were 2.7 times more likely (95% CI 1.3–6.6) to have a mutation than those in Gleason Grade Groups 1 and 2 (prevalence 2.7%, NNS=15, p-value for difference 0.01) (Table 1, Figure 2).

Tumor Stage and DNA repair mutations

There were 258 evaluable patients for clinical T stage. The prevalence of any DNA repair mutation was 4.7% for cT1 stage, 10.7% for cT2 disease, 15.8% for cT3 and there were no mutated cases among those with cT4 disease. Of those patients with organ-confined disease by clinical exam (cT1 or cT2), 7.8% were found to be mutation-positive (NNS=13) compared to 15.0% (NNS=7) being mutation-positive if clinical stage was cT3 or cT4 (*P*=0.14) (Table 2). When only considering *ATM* or *BRCA1*/*2* mutations, 4.7% of those with cT1 disease, 7.1% of those with cT2 disease, 10.5% with cT3 disease and no patients with cT4 disease were found to have pathogenic mutations in these genes (only 2 men with cT4 disease in sample). There was no statistically significant difference between prevalence of these mutations based on extent of organ involvement (6% in cT1/T2 and 10% in cT3/cT4; *P*=0.31)(Table 2).

There were 327 evaluable patients for pathologic T staging. Those who had pT2 disease had a 5.5% prevalence of any DNA repair mutation, those with pT3 had a 12.9% prevalence, and

those with pT4 disease had a 16.7% prevalence of any DNA repair mutation. Combined, those with pT3 or pT4 disease were more likely to have a DNA repair mutation (OR 2.6, 95% CI 1.1–6.6) and did have significantly higher prevalence (13.0%; NNS=8) compared to those with pT2 disease (5.5%; *P*=0.03; NNS=19). Considering only *ATM* or *BRCA1*/2, those with pT3/pT4 disease were 3.2 times as likely to have a DNA repair mutation (95% CI 1.2–11.3) and had a significantly higher proportion of men harboring mutations in those genes (9.5%; NNS=11) compared to cases with pT2 disease (3.1%; *P*=0.04; NNS=33) (Table 2).

Nodal Stage and DNA repair mutations

There were 285 evaluable patients for pathologic N staging. Of those with no evidence of nodal disease (pN0), 10.7% had a mutation of any DNA repair gene (NNS=10), which was not statistically significantly different from those with nodal disease (pN1) of whom 11.5% had a mutation in a DNA repair gene (*P*=0.81; NNS=9). There was also no difference between prevalence of mutations in *ATM* or *BRCA1*/*2* specifically by nodal status (7.3% versus 7.7%; *P*=1.0; NNS = 14 versus 13) (Table 2).

Combination Strategies

Next, we sought to determine the best combination of clinical factors that would predict the highest prevalence of DNA repair gene mutations. Among men with Gleason Grade Group 3 and higher *and* clinical stage cT3 or cT4, 21.3% had any DNA repair gene mutation and 11.7% had a mutation in *ATM* or *BRCA1*/*2*. Using these criteria, this translates into having to screen 5 men to find one with any homologous repair mutation, or screening 9 men to find one with an *ATM* or *BRCA1/2* mutation. Among men with Gleason Grade Group 3 and higher *and* pathologic stage pT3 or pT4, 14.2% had any DNA repair mutation and 9.7% had a mutation in *ATM* or *BRCA1*/*2*. Using these criteria, this translates into having to screen 7 men to find one with any homologous repair mutation, or screening 11 men to find one with an *ATM* or *BRCA1/2* mutation. Among men who had Gleason Grade Group 3 and higher *or* clinical stage cT3/cT4, 13.1% had at least one mutation in a DNA repair gene and 8.2% had a mutation in *ATM* or *BRCA1*/*2* specifically. Using these criteria, this translates into having to screen 8 men to find one with any homologous repair mutation, or screening 13 men to find one with an *ATM* or *BRCA1/2* mutation. Finally, among those who had Gleason Grade Group 3 and higher *or* pathologic stage pT3/pT4, 11.9% had at least one mutation in a DNA repair gene and 7.4% had a mutation in *ATM* or *BRCA1*/*2* (Table 3). Using these criteria, this translates into having to screen 9 men to find one with any homologous repair mutation, or screening 14 men to find one with an *ATM* or *BRCA1/2* mutation.

Discussion

To our knowledge, this is the largest study to examine the prevalence of somatic alterations in DNA repair pathway genes (specifically, homologous recombination genes) in localized prostate cancer to help identify those who should be targeted for genomic screening. We report that mutations in DNA repair genes, and in *ATM/BRCA1/2* specifically, are enriched in localized prostate cancers with more advanced Gleason scores (Gleason grade group ≥3, *i.e.* primary pattern 4 and higher). Additionally we found that tumor extension outside of the

prostate by pathologic stage was associated with a higher prevalence of DNA repair mutations. This is similar to what was observed in other studies of men harboring *BRCA1* and *BRCA2* germline mutations.[8–11,22] In contrast to previous research, we did not find an association between the prevalence of DNA repair gene mutations and pathological lymph node involvement. Lymph node metastases have been reported to be more common in men with germline *BRCA* mutations.[9] However, our research suggests this does not apply when considering somatic mutations in *BRCA* as well as other DNA repair gene mutations. This may be because there is a smaller difference and insufficient power to detect in our study, misclassification within the populations used, or confounded by other associations.

Currently, there is no consensus on which men with localized prostate cancer should undergo tumor mutational testing.[23,24] Our primary motivation for conducting the present study was to inform clinical trial designs in the neoadjuvant and adjuvant spaces, particularly in the context of PARP inhibitor use. Taken together, the totality of our data suggest that the maximal enrichment for the presence of a somatic homologous recombination mutation occurs if patients are selected using a combination of Gleason grade ≥3 histology (*i.e.* primary Gleason pattern 4 and above) *and* clinical stage cT3 or T4 disease. Under these circumstances, 5 men would need to be screened to find one with any homologous repair mutation, and 9 men would need to be screened to find one with an *ATM* or *BRCA1/2* mutation. Therefore, if for example one was designing a clinical trial testing a PARP inhibitor in the adjuvant setting in 50 patients with a homologous repair gene mutation, 235 such patients would need to be screened to find 50 eligible men. If the same trial targeted men with *ATM/BRCA1/2* mutations more specifically, then 425 such patients would need to be screened to find 50 eligible subjects. This type of rational selection of patients based on particular Gleason grades and tumor stages would limit unnecessary screening of men who had a very low likelihood of harboring a DNA repair gene mutation and would greatly decrease the cost and timeframe of such a study. If considering the general population of men with localized prostate cancer, 13 men would need to be screened to identify one with any DNA repair mutation and 20 would need to be screened to get one *ATM/BRCA1/2* mutation based on a prevalence of 8.0% and 4.9% respectively. Therefore, the enrichment by clinical features reduces this by more than half. Additional enrichment could perhaps be achieved by targeting variant histologies, such as ductal or intraductal morphologies,[14] although the association between somatic DNA repair defects and ductal/intraductal histology remains to be confirmed. Furthermore, there is emerging evidence that men harboring DNA repair mutations may respond differently to other therapies used in prostate cancer, such as abiraterone, enzalutamide and platinum-based chemotherapies.[25,26] Therefore, these data may be useful for other types of clinical trials as well.

There are several limitations of this study. First, this was a retrospective analysis and we did not have tumor or nodal staging on all men. Second, prostate-specific antigen (PSA) levels, another widely used component of nearly all risk-stratification methods, was not available in our dataset. This prevented further risk classification based on National Comprehensive Cancer Network categories, for example. The Gleason score was based on radical prostatectomy samples and therefor may not be the same as Gleason score from biopsies. Furthermore, we did not have information on histologic variants and we were not able to combine this dataset with other larger DNA sequencing datasets of localized prostate cancer.

Another shortcoming is that these databases report only somatic alterations, and thus germline mutations may have been missed, potentially resulting in an underestimate of the true prevalence of homologous repair deficiency mutations in this study. We were not able to distinguish mono-allelic from bi-allelic sequence alterations. While those with bi-allelic inactivation are theorized to be the most sensitive, current clinical trial paradigms do not consider this as criteria for enrollment. Finally, we were not able to study mismatch repair gene mutations (which could also affect treatment decisions[27]) due to an overall very low prevalence.

Conclusion

In conclusion, DNA repair gene mutations in localized prostate cancer are more prevalent in men with higher Gleason grades (Group 3 and higher) and more advanced clinical and pathologic stages (T3/T4 disease). When designing neoadjuvant/adjuvant clinical trials aimed at capturing homologous repair-deficient patients, these clinicopathologic characteristics can be used to determine eligibility criteria. Maximum enrichment for these PARP inhibitor-sensitivity mutations will occur in men with both Gleason Grade group ≥3 *and* clinical stage ≥cT3, where only 5 men would need to be screened to identify one with a homologous repair gene mutation (in any gene) and 9 men would need to be screened to find one with a *ATM/BRCA1/2* mutation specifically. These findings may inform clinical trial design.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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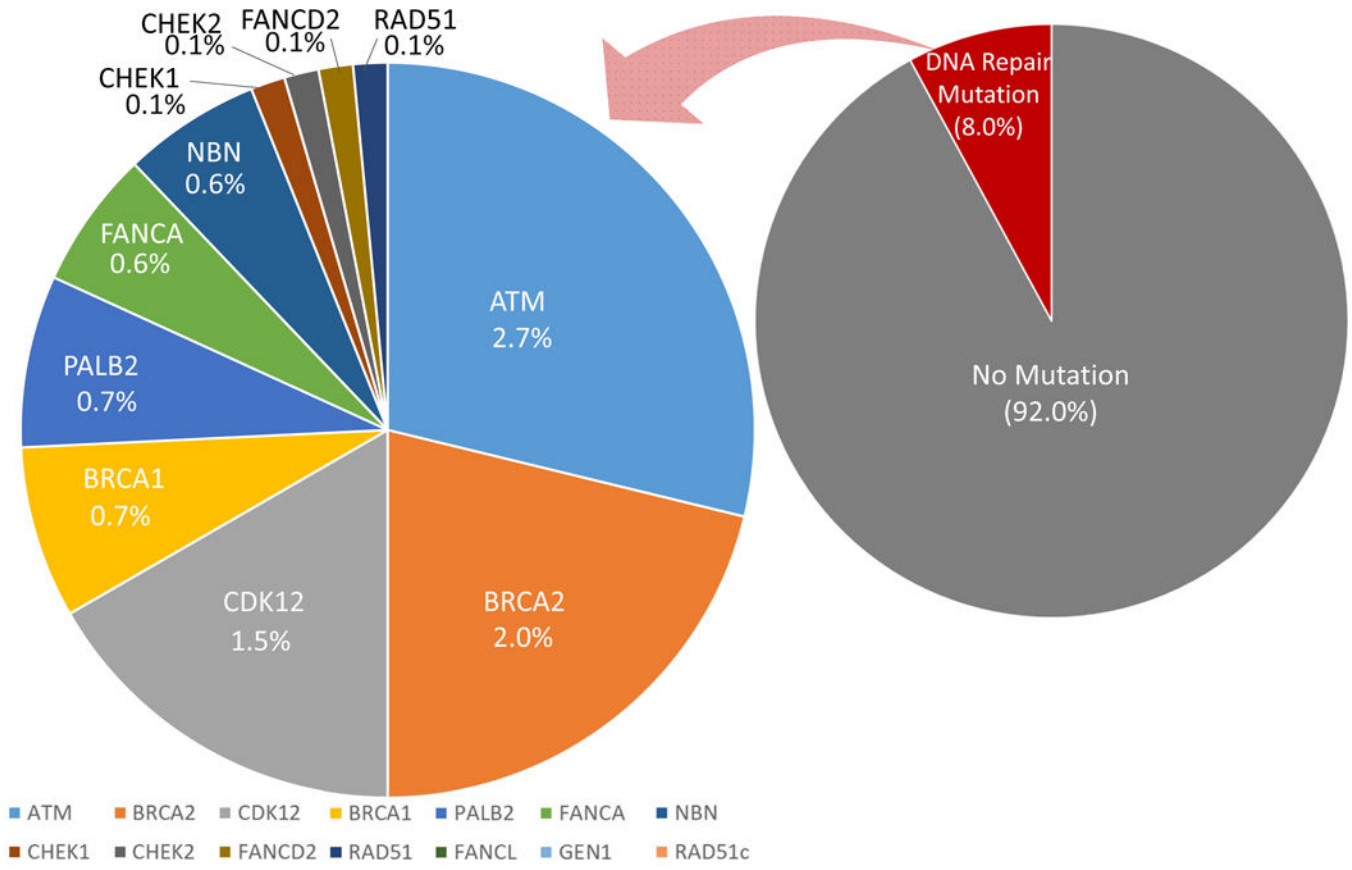

Figure 1.
Percentage of patients with DNA repair gene mutations, overall and according to each individual gene

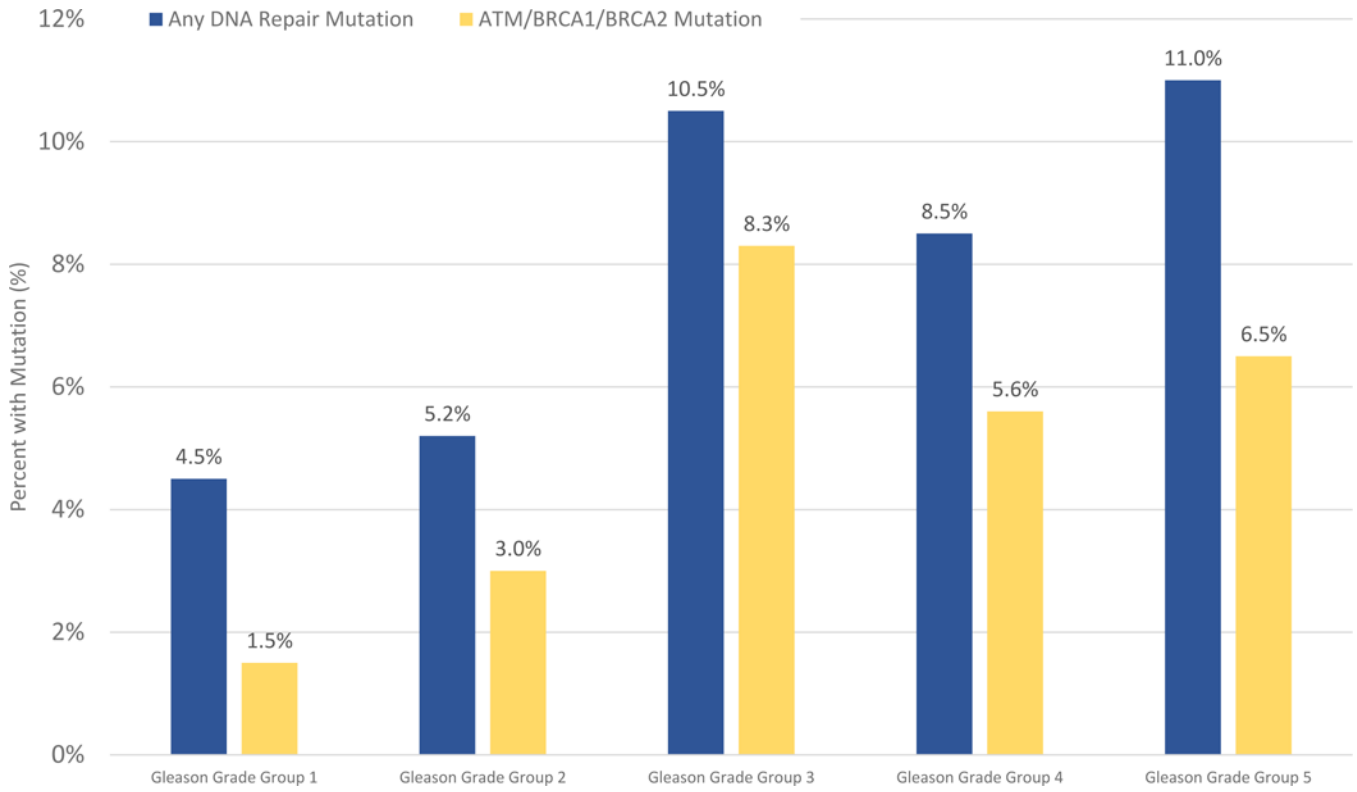

Figure 2.
Prevalence of DNA repair mutation by Gleason Grade Group

Table 1.

Prevalence of DNA repair gene mutations according to Gleason grade group.

Gleason Grade Group	Any DNA Repair Mutation					*ATM/BRCA1/2* mutations				
	Prevalence	95% CI	N/Total		NNS	Prevalence	95% CI	N/Total		NNS
1	4.5%	0.9–12.7	3/66	5.0%	20	1.5%	0–8.2	1/66	2.7%	37
2	5.2%	2.7–8.8	12/233			3.0%	1.2–6.1	7/233		
3	10.5%	5.9–17.0	14/133	10.3%	10	8.3%	4.2–14.3	11/133	7.0%	15
4	8.5%	3.2–17.5	6/71			5.6%	1.6–13.8	4/71		
5	11.0%	6.6–17.1	17/154			6.5%	3.2–11.6	10/154		
	p-value=0.14					p-value =0.11				

(NNS = Number needed to screen)

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Table 2.

Prevalence of DNA repair gene mutations according to tumor stage and nodal status.

	Any DNA repair mutation					*ATM/BRCA1/2* mutations				
Stage	**Prevalence**	**95% CI**	**N/Total**	**Prevalence**	**NNS**	**Prevalence**	**95% CI**	**N/Total**	**Prevalence**	**NNS**
cT1	4.7%	1.5–10.7	5/106	7.8%	13	4.7%	1.5–10.7	5/106	6.0%	17
cT2	10.7%	5.7–18.0	12/112			7.1%	3.1–13.6	8/112		
cT3	15.8%	6.0–31.3	6/38	15.0%	7	10.5%	2.9–24.8	4/38	10%	10
cT4	0.0%	0–84.2	0/2			0.0%	0–84.2	0/2		
	p-value=0.14					p-value=0.08				
pT2	5.5%	2.2–11.0	7/127	5.5%	19	3.1%	0.9–7.9	4/127	3.1%	33
pT3	12.9%	8.5–18.4	25/194	13.0%	8	9.3%	5.6–14.3	18/194	9.5%	11
pT4	16.7%	0.4–64.1	1/6			16.7%	0.4–64.1	1/6		
	p-value=0.05					p-value=0.46				
pN0	10.7%	7.1–15.4	25/233	10.7%	10	7.3%	4.3–11.4	17/233	7.3%	14
pN1	11.5%	4.4–23.4	6/52	11.5%	9	7.7%	2.1–18.5	4/52	7.7%	13
	p-value=0.81					p-value=1.00				

(NNS = Number needed to screen)

Table 3.

Combined analysis of prevalence of at least one DNA repair gene mutation and at least one *ATM/BRCA1/2* mutation, combining Gleason grade group and tumor stage.

	Any DNA repair mutation		***ATM/BRCA1/2* mutation**	
	Prevalence	**NNS**	**Prevalence**	**NNS**
Gleason Group ≥3 AND clinical stage ≥cT3	21.3%	5	11.7%	9
Gleason Group ≥3 AND pathologic stage ≥pT3	14.2%	8	9.7%	11
Gleason Group ≥3 OR clinical stage ≥cT3	13.1%	8	8.2%	13
Gleason Group ≥3 OR pathologic stage ≥pT3	11.9%	9	7.4%	14

(NNS = Number needed to screen)