

DNA Repair Capacity in Metastatic Castration-Resistant Prostate Cancer Patients using lymphocytes as surrogate markers

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13th Annual Puerto Rico Oncology Symposium
February 2-3, 2024

Background

- Prostate cancer (PCa) is the leading type of cancer diagnosed in men worldwide.
- PCa is the second leading cause of cancer-related mortality in men in the US and the first in Puerto Rican men.
- Metastatic castration-resistant prostate cancer (mCRPC) results when localized disease becomes unresponsive to androgen deprivation therapy (ADT) and migrates outside of the prostate.
- mCRPC is incurable and the prognosis of these patients is quite poor with a median survival ranging from 9–13 months.
- Additional tools to track disease progression to mCRPC are needed.

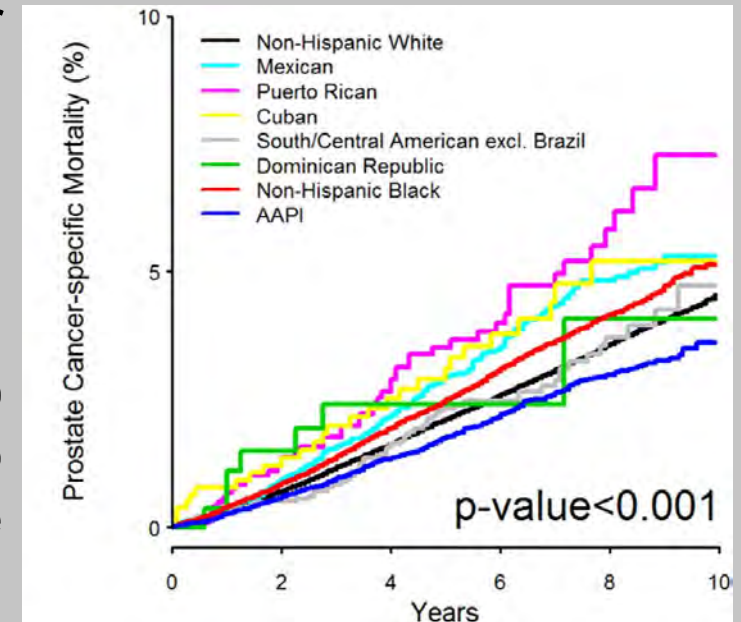


Figure 1. Cumulative incidence of prostate cancer-specific mortality in years divided by race and/or ethnicity. Source: China *et al.* 2017.

Background

- Dysregulation of at least three DNA repair pathways, nucleotide excision repair (NER), homologous recombination repair (HRR), mismatch repair (MMR) has been associated with the carcinogenesis process in PCa.
- DNA repair capacity (DRC) is an important factor contributing to the inter-individual variability in response to carcinogens and cancer susceptibility in the general population.
- Epidemiological studies using functional repair assays in lymphocytes have demonstrated that DRC (measured through the NER) varies greatly among individuals and that having a low DRC level is a risk factor for the development of several types of cancers.
- Ortiz-Sanchez et al (2022) shows that DRC is significantly reduced in patients with PCa when compared to controls without the disease.



Objectives

- The aim of this study was to evaluate for the DRC levels in Puerto Rican men with metastatic castrate-resistant prostate cancer (mCRPC) using lymphocytes as surrogate markers of the overall DRC.

Hypothesis

- Variations in mean DRC values are expected to be detected among the three study groups including: controls, non-mCRPC, and mCRPC.

Methods

Men without PCa (controls):

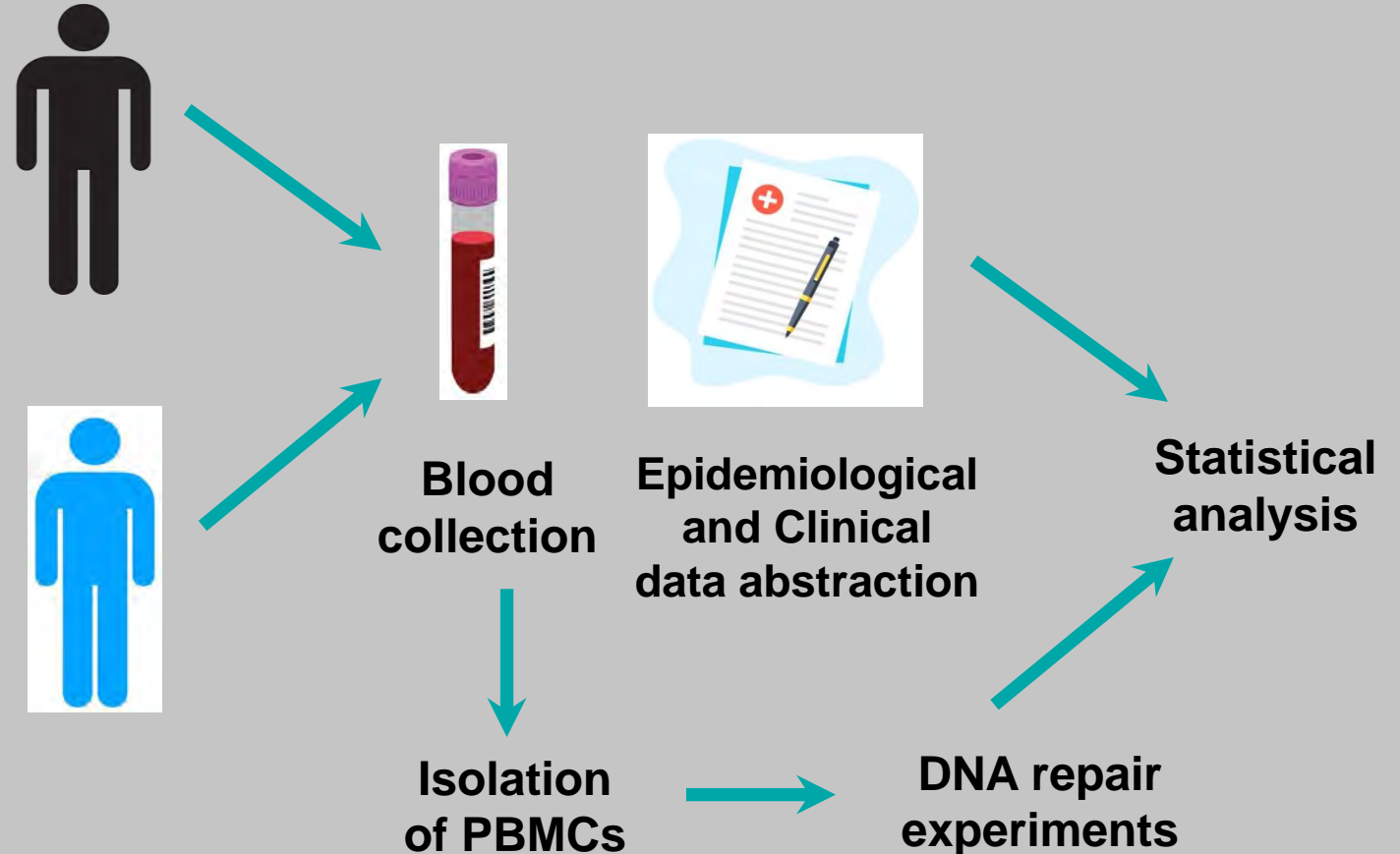
- Age ≥ 50 years old
- Normal Digital Rectal Examination
- Normal Prostate Specific Antigen (<4 ng/mL)

Men with PCa (cases):

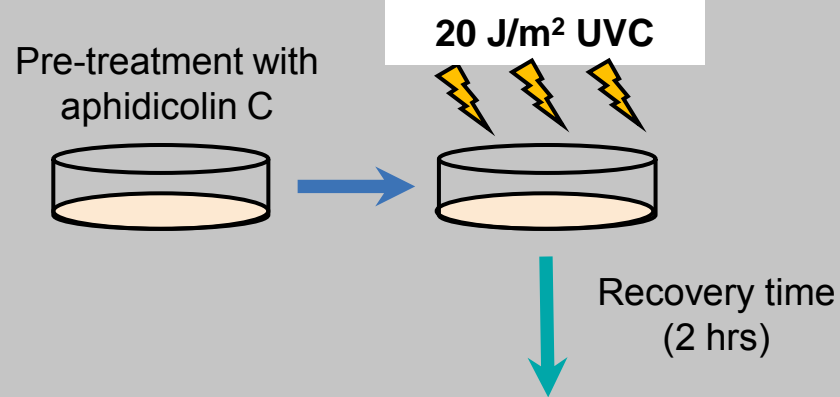
- Age ≥ 50 years old
- Pre-operative cases
- Pathologically confirmed primary PCa
- Treatment naïve (chemotherapy and radiation)

Men with mCRPC:

- Age ≥ 50 years old
- mCRPC diagnosis



Experimental setup for the DNA repair measurements: NER pathway

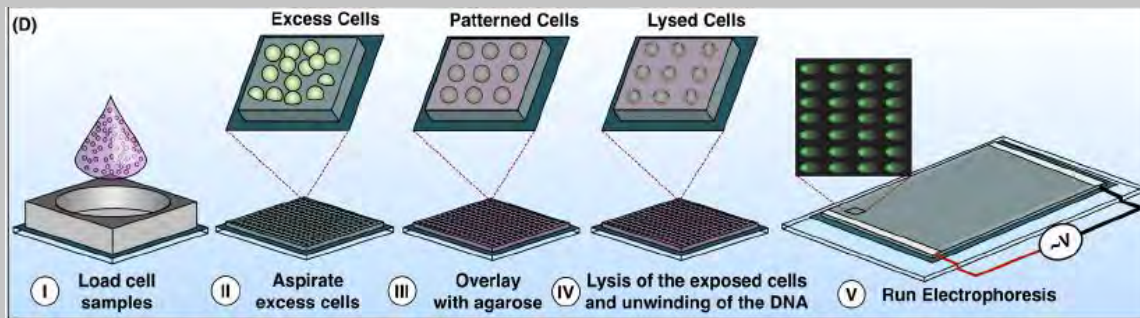


Aphidicolin C: DNA polymerase inhibitor

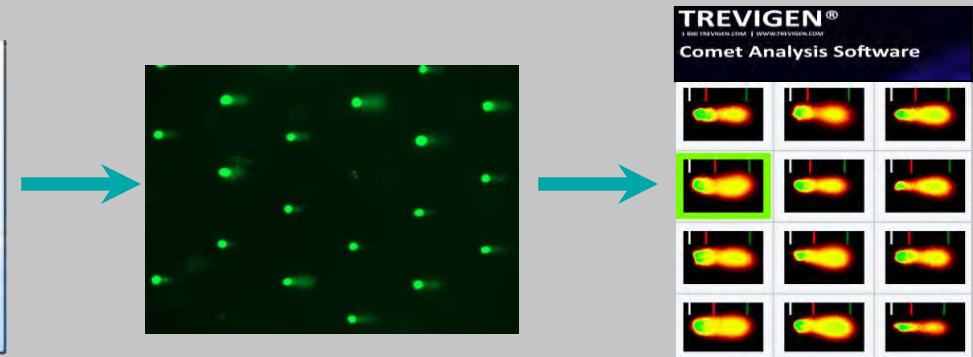
- **Function:** leads to the accumulation of repair incisions in lymphocytes treated with the corresponding inducer for the DNA repair

Inducer of DNA repair:

- **UVC** for NER



Watson *et al.* (2014)



Calculations for the DRC levels were performed using the data obtained on the percent of DNA in the tail of the samples with the different treatments and the equation presented in the work of Vande Loock *et al.* (2010).

$$\text{DRC} = \%TD (\text{APC} + \text{UVC}) - \%TD (\text{UVC}) - \%TD (\text{APC}), \text{ where TD is tail density.}$$

Results

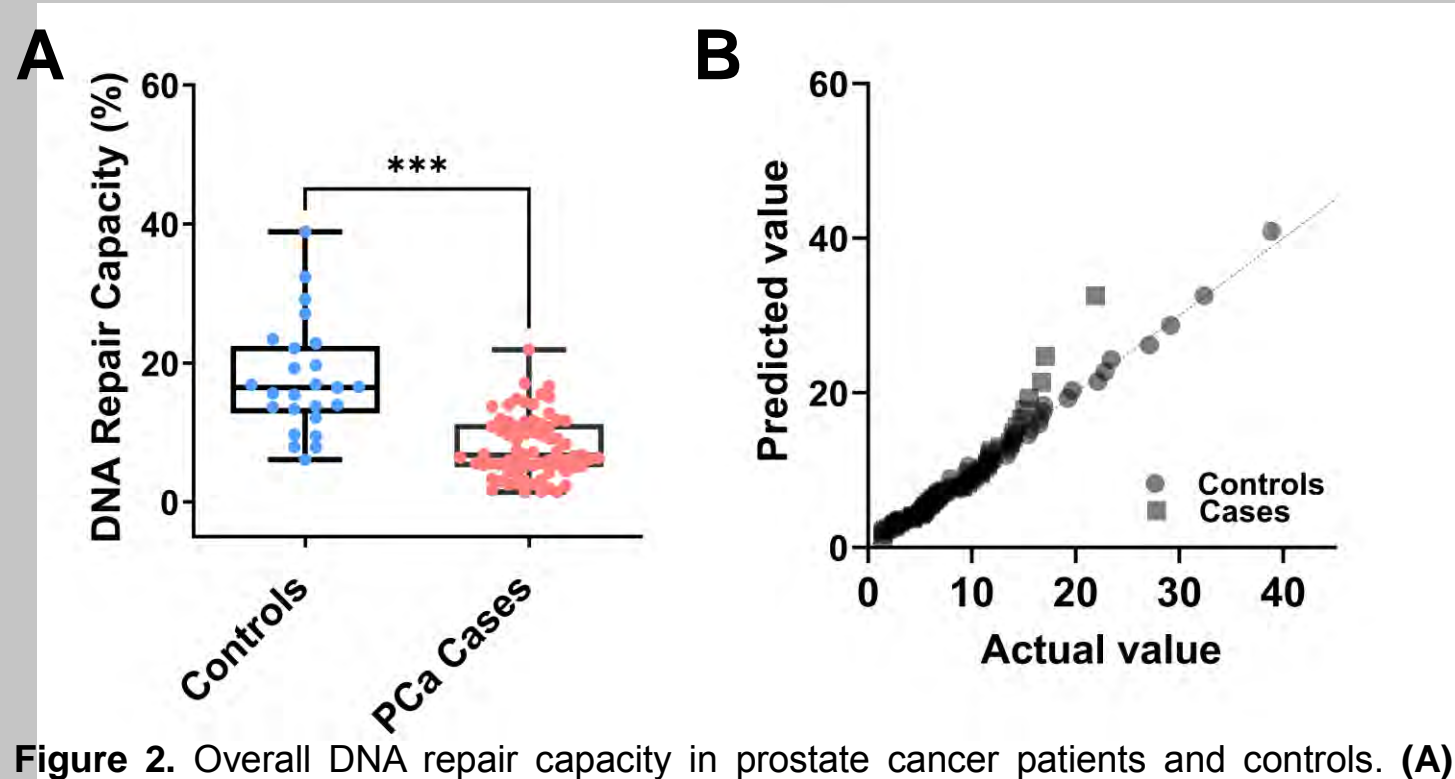


Figure 2. Overall DNA repair capacity in prostate cancer patients and controls. **(A)** Sample distribution including controls (n=25) and PCa cases (n=71). Blue dots represent the DRC values of the control group and values from the case group are represented by guava colors. **(B)** Linearity test: the DRC values were transformed based on a log-normal distribution model. All the DRC values obtained from the study cohort were included in this analysis.

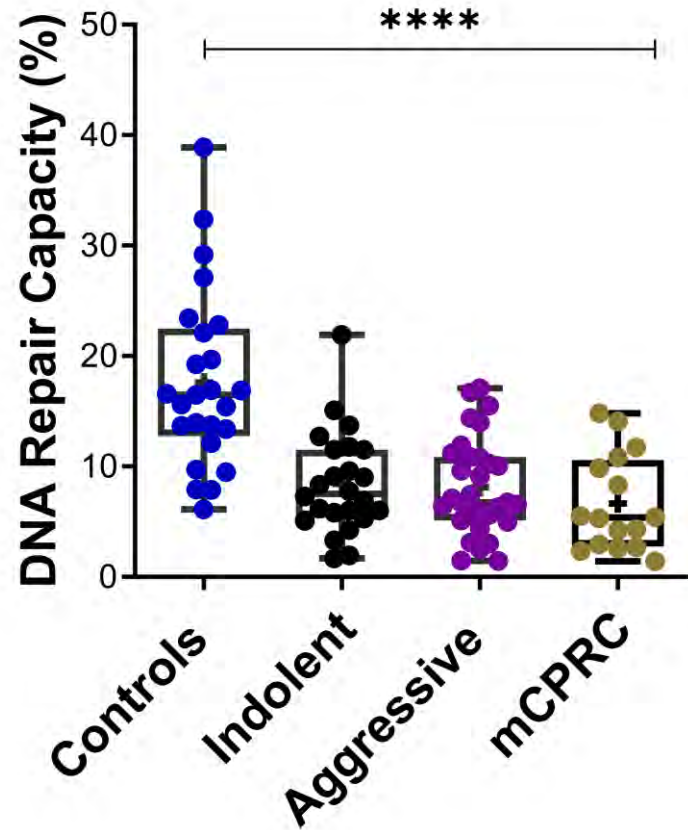


Figure 3. Based on their Gleason scores, the tumors from PCa cases were stratified into indolent (n = 24) and aggressive (n = 31). Symbols represent individual DRC values. Mean DRC value for each group is represented with a plus (+) sign. Asterisk (****) denotes statistical significance ($p < 0.001$, Kruskal–Wallis test).

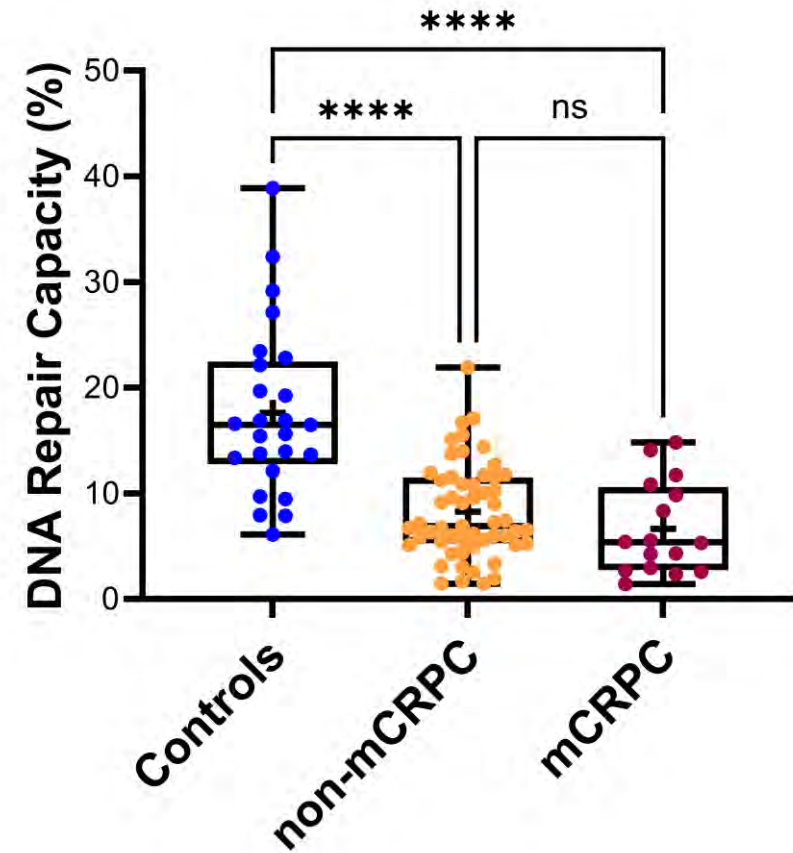


Figure 4. Overall DNA repair capacity in controls and prostate cancer patients stratified by disease type. Sample distribution among study groups including: controls (n=25) and prostate cancer cases diagnosed with mCRPC (n=16) and non-mCRPC (n=55). The mean value for the control group was 17.63%. In terms of the PCa groups the mean was 8.27% for the non-mCRPC and as for mCRPC was 6.60%. Mean DRC value for each group is represented with a plus (+) sign. Asterisk (****) denotes statistical significance ($p < 0.0001$, Kruskal–Wallis test).

Conclusions

- Our results show that DRC, measured through the NER pathway, is significantly reduced in PR men with PCa when compared to controls.
- In terms of disease aggressiveness, no significant differences were detected. Although, mCRPC cases showed the lowest mean DRC value.
- When comparing mCRPC, non-mCRPC, and controls significant differences were observed between the controls and each of the cancer groups. The mean DNA repair value for the mCRPC group was 6.65% while for the non-mCRPC group it was 8.27%.
- Our results represent an innovative step in developing a blood-based screening test for PCa based on DRC levels.
- Our efforts have the potential to significantly advance research in the biology of lethal PCa and reduce the burden of lethal PCa health disparities in Puerto Rican men.

Future directions

- Increase the sample size of the study groups.
- Modeling the effects of treatment status and additional clinical variables in function of the DRC.
- Evaluate the functionality of the homologous recombination repair pathway to gain additional insights regarding the DRC of the individuals.

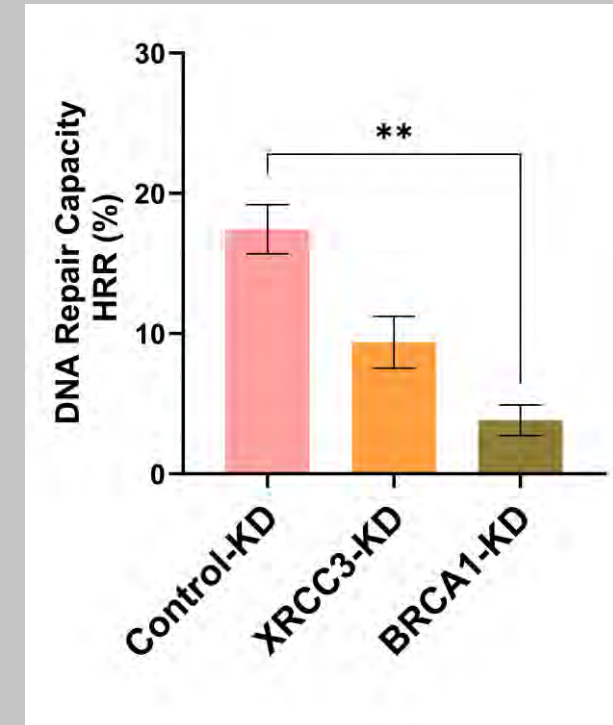


Figure 5. Assessment of the DNA repair capacity of human glioma cell lines using the CometChip with deficiencies in the homologous recombination repair pathway. Each bar represents the mean \pm SD of three independent experiments. Asterisks denote statistical significance: (**) $p < 0.01$ and (***) $p < 0.001$.

Acknowledgements

- Dr. Gilberto Ruiz-Deyá's clinical practice staff
- UroCentro del Sur: Dr. Claudio Bernaschina, Dr. Javier Castillo, and Dr. Adrian Santana along with their staff
- Puerto Rico Biobank at PHSU/PRI
- Special thanks go to Dr. Marie Ramirez, Mrs. Sonia Abac, and Dr. Wilzaida Perez for their valuable help regarding patient recruitment.

Funding:

- Department of Defense/US Army Award #W81XWH-21-1-0241
- U54 PHSU-MCC Partnership Grants #U54CA163071 and #U54CA163068
- Ponce Research Institute
- Puerto Rico Science and Technology Trust agreement #2017-00003



QUESTIONS

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