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**This is a pre print version of the following article:**

*Original Citation:*

*Availability:*

This version is available <http://hdl.handle.net/2318/1679188> since 2018-10-29T12:34:34Z

*Published version:*

DOI:10.1158/1538-7445.AM2016-778

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(Article begins on next page)

## **DNA repair capacity, chromosomal damage, methylation and gene expression levels in bladder cancer: an integrated analysis**

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Bladder cancer (BC) is the sixth most commonly diagnosed tumor worldwide. DNA repair capacity (DRC) is a system of defenses designed to protect the integrity of the genome and DNA damage pathways have been implicated in BC risk. It has been observed that individuals with low DRC tend to accumulate more damage than those with a more efficient DRC. This inter-individual variability is modulated by the genetic background, as well as differential epigenetic and gene expression regulation.

We aimed at studying the relationship between DRC and DNA damage (evaluated by H2AX phosphorylation and micronucleus assays) and BC risk and clinical outcome, integrating with gene expression and epigenetic profile data.

Phenotypic assays to evaluate DRC were performed on cryopreserved lymphocytes from 159 cases and 159 controls matched by age and smoking habits, enrolled in the Turin Bladder Cancer Study (TBCS).

Whole genome expression and methylation levels were measured on RNA and DNA of cryopreserved lymphocytes from a subset of BC cases and controls selected for DNA repair assays.

We investigated  $\gamma$ -H2AX levels in peripheral blood mononuclear cells before and after their exposure to ionizing radiation. We did not find any significant difference among cases and controls. However, we observed a significant association between  $\gamma$ -H2AX basal levels and risk of disease recurrence/ progression. In particular, both BC patients as a whole and the subgroup of non-muscle invasive BC (NMIBC) with high basal H2AX phosphorylation levels had a significantly decreased risk of recurrence/progression (for all BC HR 0.70, 95% CI 0.52-0.94,  $p=0.02$ ; for NMIBC HR 0.68, 95% CI 0.50-0.92,  $p=0.01$ ), suggesting a protective effect of basal DSB signalling in terms of preventing BC recurrence or progression.

Micronuclei and nuclear buds frequencies analyses on 148 healthy controls and 152 BC cases showed significant differences, with higher number of these damages in cases compared to controls ( $p=0.0002$  and  $p=0.002$  respectively).

Preliminary analyses on methylation levels and gene expression did not show any significant difference between cases and controls. Further analyses are ongoing to investigate interaction among DRC, epigenetic changes and expression levels.