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The impact of smoking exposure on genomic alterations in muscle-invasive bladder cancer

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Background

- Smoking exposure: Most important risk factor for developing muscle-invasive bladder cancer (MIBC)
- Incidence of MIBC and lung cancer correlates to
  - smoking status (current versus never smoker)
  - duration (years) of smoking exposure
  - the number of cigarettes smoked per day.
- Carcinogenic toxins similar to cigarette smoke administered to rodents to model the effects of smoking on the development of MIBC

Aim:

- To investigate genomic alterations in MIBC and the patient smoking status
- To compare these findings with lung adenocarcinoma (LAC) and
- To compare with the biological characteristics of chemically induced MIBC in rodents

Material & Methods

Datasets from the public domain (MIBC and LAC):
- TCGA and MSK-IMPACT from cbioportal.org

TCGA dataset

Genomic data:
- Genomic DNA sequencing data
- mutation count in Signature 5*
- Total mutational burden
- RNA sequencing

Clinical data:
- Follow-up and survival
- Number of pack years
- Smoking history (current/former/never)

MSK-IMPACT dataset

Genomic data:
- Genomic DNA sequencing data
- Total mutational burden

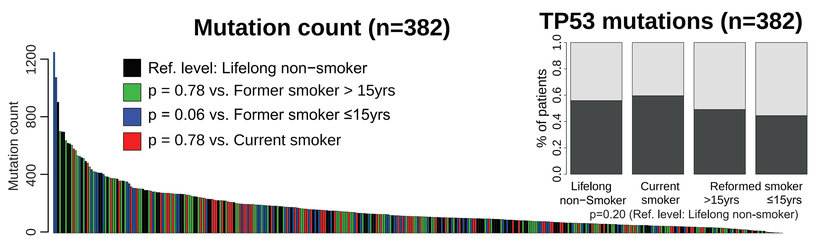
Clinical data:
- Number of pack years
- Smoking history (current/former/never)

Outcome measurements

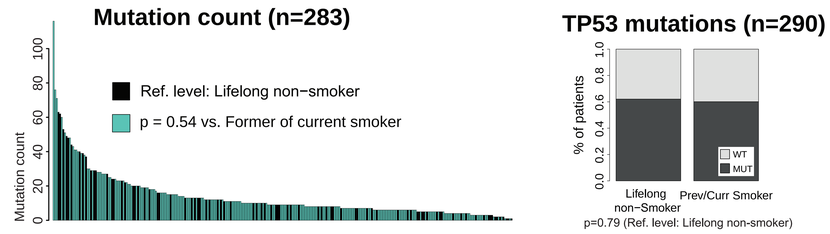
Effects on of smoking exposure on:
- Patient outcomes
- Mutational burden
- Signature 5*
- Molecular subtypes

Results

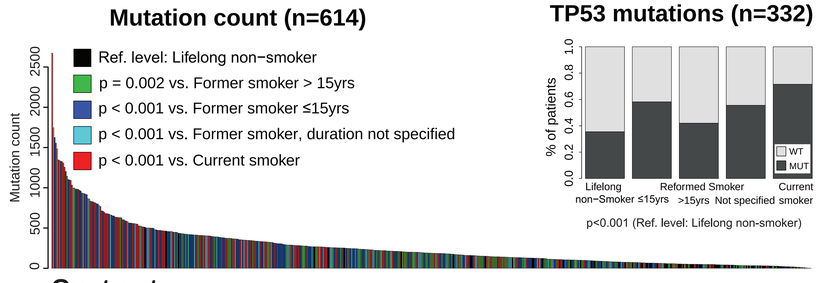
Bladder Cancer TCGA



Bladder Urothelial Carcinoma from MSK-IMPACT



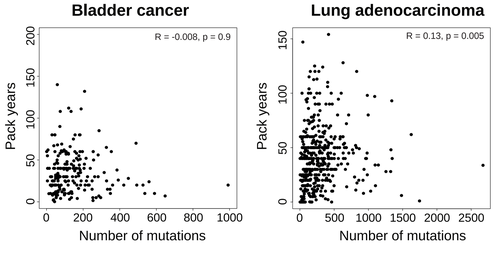
Lung adenocarcinoma from Pan Lung Cancer TCGA



Contrast:

No association with smoking and mutational burden in bladder cancer but in Lung adenocarcinoma

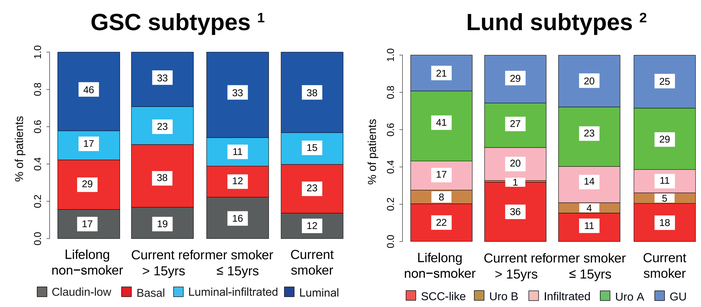
Mutation counts vs. pack years



Contrast:

Positive correlation in lung adenocarcinoma but not in bladder cancer

Smoking status and molecular subtype

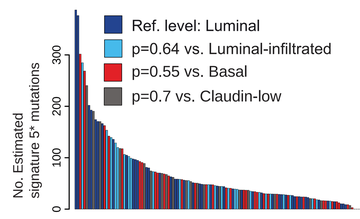


No association with smoking and molecular subtypes

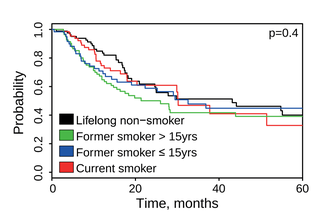
Contrast:

Chemically induced bladder cancers in rodents show a Basal-like[3] or Urobasal B [4] phenotype

Signature 5*



Disease-free survival



Signature 5* is associated with smoking [5]. We found no association of Signature 5* and molecular subtypes.

Conclusions

- **Impact of smoking exposure on genomic alterations in MIBC not obvious**
- **In contrast to LAC: Higher mutational burden and enrichment of mutations in known oncogenes (e.g. TP53) in smokers**
- **Cigarette smoke contains over 4000 compounds, which may prevent a direct comparison to rodent models that are induced by a single toxin.**

References

1. Seiler, Eur Urol 2017; 2. Sjödahl, Clin Cancer Res, 2012; 3. Kim, PloS one 2011;
4. Bivalacqua, J Urol 2017; 5. Kim, Nature Genetics 2016