Editorial Commentary

Understanding bladder cancer by genome-wide association studies

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Recently, Koutros *et al.* (1) pooled data from 32 genome-wide association studies (GWAS) to identify new genetic risk factors for bladder cancer. Some of these GWAS were initiated as early as 1970s and many of them are still ongoing. For example, The Health-Professionals Follow-Up Study was established in 1986 to identify healthy lifestyle factors for men. Their complement investigation, Nurses' Health Study began in 1976 and it only included women. The EPICURO study was initiated in 1997 in Spain, and it focused on identifying risk factors of bladder cancer.

Combined, the 32 studies provided genome-wide data on 13,790 bladder cancer cases and 343,502 controls for Koutros *et al.* (1) analysis. The authors focused their investigation on individuals of European ancestry and filtered them out of the pooled data using principal component classification. In short, the study found five novel chromosomal regions linked to bladder cancer: 6p22.3, 7q36.3, 9q31.1, 10q22.1, and 19q13.33. They also confirmed two previously suspected regions as genetic markers: 6p22.3, and 8q21.13. All previously identified regions were confirmed as markers in the new analysis except for one: 3q26.2.

Koutros *et al.* (1) stratified data based on smoking status and gender to identify genes that are only associated with bladder cancer in the presence of other factors. A sixth novel genome-wide significant region was identified after stratification by smoking status: 9p21.3. Single nucleotide polymorphism (SNP) in this region was associated with bladder cancer risk only in current and ever smokers. Interestingly, the newly identified region 8q21.1 was shown to pose higher risk of bladder cancer among non-smokers.

Gender stratification of their data did not reveal any new significant regions but the previously identified region 4p16.3 posed a stronger risk for women. The 4p16.3 region codes two important proteins: fibroblast growth factor receptor 3 (FGFR3) and transforming acidic coiled-coil-containing protein (TACC3). A mutated fusion version of the two proteins is commonly encountered in bladder cancers (2). Koutros *et al.* (1) found higher frequency of FGFR3 somatic mutation in women with non-muscle invasive bladder cancer (NMIBC) than in men. Fortunately, in their stratified analysis, they considered the confounding effect of smoking status on gender.

Clinical implications of the study findings

Using their 24 genetic markers and combining it with gender and smoking status, Koutros *et al.* (1) developed a polygenic risk score (PRS) and externally validated it with

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data from two studies, showing hazard ratios of 1.51, and 1.32. Advances in clinical screening tools for those at high risk of bladder cancer are needed to test the utility of well-calibrated risk models before a clinician may accommodate this PRS in practice to assess a healthy individual for lifelong risk of developing bladder cancer. Koutros *et al.* (1) claim that "*the 24-marker PRS explains 14.8% of the familial risk of bladder cancer for individuals of European ancestry*".

Unfortunately, environmental factors were not included in the calculation of this PRS, limiting its predictive value in clinical decision-making. According to a 2018 systematic review, bladder cancer is generally not considered a hereditary cancer, and both occupational and environmental exposures to carcinogens attribute largely to the risk of its development (3).

A closer look at newly identified regions

The novel chromosomal regions associated with bladder cancer may provide new insights into molecular etiology of this disease. A 6p22.3 mutation may cause abnormal production of cancer susceptibility candidate 15 (*CASC15*). This gene codes a long noncoding RNA (lncRNA) with possible role in cancer proliferation (4).

The chromosomal region 7q36.3 is an uncharacterized location in human genome.

An SNP in 9q31.1 may cause abnormal production of structural maintenance of chromosomes protein 2 (SMC2). This protein plays critical role in chromosome condensation and organization during mitosis (5).

The 10q22.1 mutation may disturb collagen type XIII alpha 1 chain (COL13A1) production. This collagen is found mostly in connective tissue; its complete absence has manifestation in neuromuscular synapses (6).

The 19q13.33 is related to two genes, *SULT2B1* and *FAM83*. The former produces a sulfotransferase that participates in cholesterol sulfation and production of sex hormones (7). Family with sequence similarity 83 (*FAM83*) genes are upregulated in many tumors and FAM83E expression level is shown to have prognostic value in some cancers (8).

Limitation of the study

The results are achieved by pooling massive amounts of data from different studies; results from various laboratories with varying protocols/arrays, and by pooling many heterogenous individuals together.

While filtering for individuals with European ancestry helps to address the issue of heterogeneity, future larger, diverse GWAS are warranted for cross-ancestry studies, to provide the bladder cancer understanding among other ancestries beyond European.

Stratified analysis by gender and tobacco exposure was also advantageous in dealing with heterogeneity. The 32 studies included in their analysis used nine different array kits. In their supplementary material, Koutros *et al.* (1) stratified the results by the array, elucidating disagreement among arrays. Fortunately, genome-wide studies are based on DNA, a molecule that is designed to last the entire lifespan of an individual. The resilient nature of DNA makes it less susceptible to variations in laboratory protocols or environmental factors.

As a final touch to their analysis, Koutros *et al.* (1) performed a "functional analysis" by matching their findings with The Cancer Genome Atlas (TCGA) and UROMOL expression data. Contrary to DNA, RNA is designed to be a transient molecule; it is highly unstable when extracted and its expression is influenced by many elements such as medications (all types of steroids), hormones, temperature, and even the circadian cycle (9). Subsequently, we find the functional analysis by Koutros *et al.* less reliable than the rest of the study. Also, clinical data related to disease progression or treatment response were not available.

Conclusions

Koutros *et al.* (1) performed a robust meta-analysis of all the available data on bladder cancer GWAS. Their study identified new chromosomal regions that could assist in understanding the etiology of bladder cancer. Their PRS, if combined with environmental factors, can provide a reliable tool in the detection of at-risk individuals in the future.

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