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The genetic patterns of bladder cancer. Where do we stand now?

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Bladder cancer (BCa) remains a commonly occurring disease [1]. Multiple risk factors of BCa have been identified, the most important of which are cigarette smoking and various occupational exposures. As a matter of fact, a thorough understanding of the epidemiology of bladder cancer can assist in the prevention and early detection of the disease. Approximately 75–80% of bladder tumors present as non-muscle invasive (NMI) disease and the remainder present as muscle-invasive disease (MI). Proper staging, grading, and risk stratification are critical for determining the most appropriate management strategies for NMI based on risk of recurrence and progression. Although the family predisposition to BCa is uncertain, the possibility of an inherited subtype of bladder cancer could not be excluded. Importantly, the issue of genetic alterations in BCa has recently been raised several times by Banaszkiwicz et al. [2, 3].

The manuscript by Edyta Wieczorek et al. [4] represents the second study on the same group of Polish patients diagnosed with BCa recently published by the same author [5]. The article brings up an issue of the association between genetic polymorphism in the promoter region of the matrix metalloproteinases (*MMP7* and *MMP8*) and the overall risk of BCa. As underlined by the authors, the described proteinases present different activities: *MMP7* is a negative prognostic factor of various malignances, while *MMP8* exhibits an inhibitory effect on tumorigenesis and metastasis.

What can we learn from this study? The authors analysed a very heterogeneous group of 241 patients with BCa demonstrating different clinical stages (T1–T4) and grades (G1–G3). Most of the patients (70%) had NMI disease and in over 12% of cases the pathology was not specified. The control group consisted of 199 healthy individuals. The authors concluded that the genetic variations in two genes encoding members of the *MMP7* and *MMP8* were not associated with the risk of BCa in the Caucasian population.

The article, despite presenting interesting data, has some major flaws. First of all, the study control group is not well characterized. The authors stated the control consisted of 199 healthy individuals that were collected at the First Department of Urology (Łódź). Considering the blood was taken from urological patients, how do the authors know they were healthy? Most of those patients, despite not having been diagnosed with BCa, must have been affected with other illnesses. What other reason might there have been for admitting almost 200 healthy patients to the Department of Urology?

Why were the tumor stage and grade not specified in as many as 31 and 26 cases, respectively? What was the reason to include as many as 57 patients (23%) without a well-known pathology? Shouldn't the transurethral resection of bladder tumor (TURBT) and the pathology be repeated in the above cases? Was there any case of Ta tumor or CIS in the study? It is very difficult to recognize if all of the reported NMI tumors were T1 only. Can we then rely on the quality of resection and the pathology reports in the present study? What impact might this have on the statistics and study outcomes? In my opinion, considering the methodological shortcomings, the results of the study by that Wieczorek et al. might be different from that described by Srivastava et al. [6].

It is a pity Wieczorek et al., concentrated their study on the group of NMIBC (70%). I think the results of the study would have been much more clinically relevant and maybe different from those described, if the authors had compared controls with the group of patients affected with the muscle invasive disease. Did the authors lack clinical and pathological work-up or might the methodology have been affected by the wrong concept that: "about 20% of NMIBC occur as recurrences of MIBC and are related with an increased risk of metastases and short survival"? With the current status of knowledge, only a small percentage of NMI tumors (20%) progress and most

of the invasive BCa are identified as *de novo* lesions without a previous history of NMI disease.

Unfortunately, in the study by Wieczorek et al., the clinical information about tumor size, number, intravesical therapy and dates of recurrence (if any), chemotherapy, radical cystectomy and pathological findings at cystectomy is missing. Perhaps the authors considered the data as irrelevant for study purposes. Furthermore, the manner of stratifying smokers (especially ex-smokers as those individuals, who were abstinent for at least one year before the interview), from the clinical point of view, seems far from the ideal. Does only one year of smoking abstinence have any impact on health status? The authors also observed the higher prevalence of MMP7 GG genotypes among BCa patients than in the controls (OR, 1.54; 95% CI, 0.93–2.55; $p = 0.093$). Does it have any particular meaning knowing it is not statistically significant?

In conclusion, Wieczorek and colleagues, in an interesting study, evaluated the association of MMPs polymorphisms and BCa risk [4]. Due to some drawbacks in methodology (most probably related to insufficient advice received by the researchers from their clinical counterparts), the study appears much more relevant for scientists than urologists.

What is important, the authors underline that “the search for new biomarkers of cancer is still required and more extensive research on genetic polymorphisms of *MMP* in BCa should be undertaken in the future”. Perhaps, the recently accepted (by the British Journal of Urology) manuscript “Genetic polymorphisms in matrix metalloproteinases (MMPs) and tissue inhibitors of MPs (TIMPs), and bladder cancer susceptibility” by Wieczorek et al. will bring more answers to the intriguing issue of *MMP* polymorphisms in BCa [5].

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