

CONSIDERATIONS REGARDING THE IMPLICATIONS OF RISK FACTORS ON BLADDER TUMORS

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Abstract: *Like all the human neoplasia, the causes of the bladder tumors are still an enigma. Regardless, bladder tumors represent the sole case where etiological factors such as carcinogenic substances can be recognised. It can be stated that bladder tumors are the mostly related to exposure to chemical substances, most of the carcinogenic factors being aromatic amines. The most important risk factors for developing bladder cancer is smoking and professional exposure. This article is about our experience regarding the implication of risk factors on bladder cancer.*

Key words: *bladder tumors, risk factors, smoking.*

1. Introduction

Bladder cancer situates itself on the ninth place regarding incidence amongst all oncological diseases. In men it represents the fourth neoplasia as global incidence, following prostate cancer, lung cancer and rectal cancer, and in women it stands in the ninth place [5, 7, 11]. According to the National Cancer Institute in USA in the year 2000, 53200 new cases appeared and 12200 deaths were documented and in the year 2008, 68810 new cases and 14100 deaths have been recorded and caused by

bladder cancer. It is also known that during the years 1985 and 2005 the number of patients diagnosed with bladder tumors has risen with about 50% [11, 15].

The incidence of bladder tumours grows with age (average age is 69 years for male patients and 71 for women). Bladder tumours are 2-3 times more frequent in men (statistic variation 2.7/1 and 4/1) [4, 6, 11, 15].

Global incidence of bladder tumors varies significantly, with a maximum incidents in western countries such as Egypt and North America, and a minimum

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in Asian countries and South America. In Europe, a high incidence has been recorded in countries such as Denmark, England, Belgium, Italy. In Romania, according to data obtained from the National Statistics Comitee, in the year 1996, bladder cancer occupied the 6th place between all types of cancers, for the male population. In the general population, bladder cancer was the 11th cause of death among the neoplastic diseases, occupying the 11th place in the male population and the 16th place in the female population [13].

As to the environment of incidence, bladder cancer has a higher rate of incidence in the urban environment in comparison to the rural one, scaling proportional with the socio-economical status [2, 5, 7, 11].

Like all the human neoplasia, the causes of the bladder cancer are still an enigma. Regardless, bladder tumors represent the sole case where etiological factors such as carcinogenic substances can be recognised. It can be stated that bladder tumors are the mostly related to exposure to chemical substances, most of the carcinogenic factors being aromatic amines. Studies concur that over 80% of bladder tumors are associated with occupational exposure [6, 11, 12, 13, 14, 15].

Smoking – cigarette smoke is the most important factor in the apparition of bladder tumors, being responsible for no less than 50% of the bladder cancers in men and 35% in women [16]. It is stated that smokers have a 2-4 higher risk of developing this neoplasia in comparison with non-smokers regardless of the sex. The risk rises with the number of cigarettes smoked/day and the degree of smoke inhalation. Cigarette smoke contains various carcinogenic substances that stand as a pillar in the development of bladder cancer: α -naftilamine, β -naftilamine,

nitrozamine, metabolites of triptophane, 4-aminobiphenil. The metabolites of these carcinogens can be identified in the urine of smokers, a fact that only strengthens the ipoheses. Cacinogenes induce mutations in the urothelial DNA, and the nicotinic acid and derivates of the nicotinic acid reduce the protection of the urothelium [3, 4, 5, 6, 15].

Professional exposure – the implication of various professions in which labourers are exposed to some carcinogenic substances is proven: chemical colorant industry, painters, rubber industry, leatherworkers, plastic and textile industry, dental technicians. In all these situations, labourers come in contact with aromatic amines, that are responsible for at least 5-20% of all bladder cancers. Anyway, the relative risk of professional factors is different from country to country [4, 5, 8, 9, 11, 12].

Coffee – initially some authors have incriminated coffee consumption as a factor in the development of some neoplasia, but recent studies suggest that there is not a clear association. The major problem which appears in the independent evaluation of coffee consumption is its association with smoking [4, 5, 10, 11, 13, 14, 16].

Artificial sweetener consumption – ciclamates and saccharin are potential agents of carcinogenesis, fact that associates a concern for the use of these products by people. Some authors have combated this hypothesis, stating that biochemical mechanism of carcinogenesis is different in humans from animals [5, 11, 13, 14, 15].

Analgesic drug consumption – high consumption of analgesic drugs such as fenacetin, seems so be correlated with the increase in incidence of bladder cancer, which banned this substance from use. Acetaminophen is today a high usage

substance, used for treating pain. Metabolites of this substance are compounds which possess a chemical structure similar to some compounds contained by anilinic dyes [13].

Diet – alimentary excesses of fat, heavy metal salts, high nitrate, nitrite and chlorine excessive water consumption can be incriminated in the development of bladder tumors. Low consumption of fluids seems to be one of the leading factors in carcinogenesis. The bladder is an urine depositing organ, which determines a long term action of carcinogenic factors on the urothelium [11, 14, 15].

Infection and chronic inflammation have been implicated in the etiology of bladder tumors especially because of the urinary nitrates resulted due to the chronic infections. It seems that patients that have recurrent cystitis, infections or inflammation of the bladder resulted after instrumentary exploration of the urinary tract, of bladder lithiasis, urethro-vesical catheters or vesical residue, have a high risk of developing bladder cancer. Cystitis from infections with *Schistosoma haematobium* (frequently in Egypt, Africa) stands as a pillar in the development of squamous bladder carcinoma [5, 11, 13, 14, 15].

Chemotherapy – according to many studies, patients treated with cyclophosphamide for diverse neoplasia gain a 9 times higher risk of developing bladder cancer [7, 11, 13, 15].

Pelvic irradiation – women that undergo radiotherapy for cervix cancer have a 2-4 times higher risk of developing a bladder tumor, usually with a high degree

of anaplasia. The mutagen effect of radiation is well known [5, 11, 13].

Heredity – familial bladder cancer is very rare, comparatively with other types of tumors [1, 5].

2. Purpose

The purpose of this study is to evaluate the importance and probability of risk factor implication in the development of bladder cancer and based on the experience of the Clinic of Urology Brasov.

3. Material and Method

During the years 2006-2010, the Urology Clinic whitening the Emergency Clinical County Hospital Brasov, 244 patients were diagnosed and treated by endoscopy (TURv) for non-invasive bladder tumors. Among these 244, 182 have been histopathologically diagnosed as T1. The study group consists of 106 patients with T1 bladder tumors. The patients age was between 42 and 74 years if age with the higher frequency in the 7th decade.

4. Results

Age distribution shows that the most frequent incidence was in patients with ages above 50 years of age, especially in the 7th decade of life, which confirms data from literature.

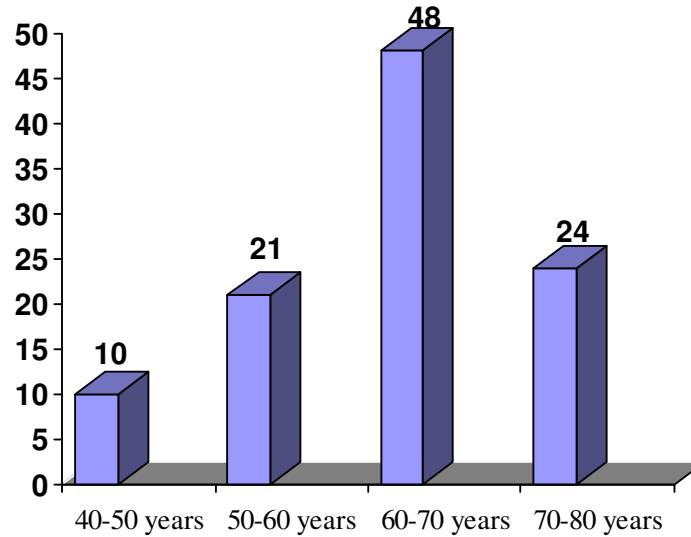


Fig. 1. *Distribution based on age*

Sex distribution shows a higher incidence in male patients in a ratio of 2.7/1 and 4/1 with a medium ratio of 3/1. Global statistics mention a variation between 2.7/1 and 4/1 with a medium ratio of 3/1. Global 2.2/1 (71 male and 32 female).

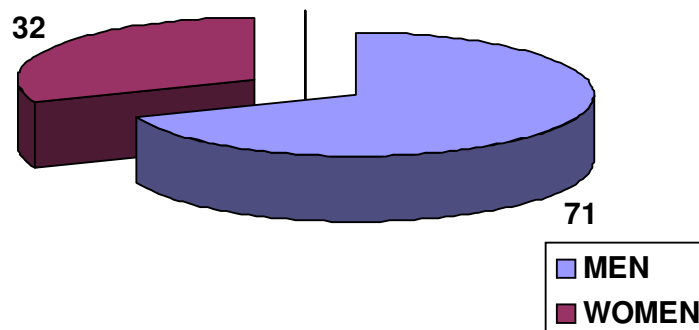


Fig. 2. *Distribution based on sex*

As to the environmental factors, we have revealed a higher preponderance of patients from the urban environment (74 patients), explained firstly by the greater accessibility and the early discovery of these tumors due to the possibility of imagistic investigations. Higher preponderance in the urban environment can also be connected to bias factors in much larger numbers.

DISTRIBUTION BASED ON ENVIRONMENTAL FACTORS

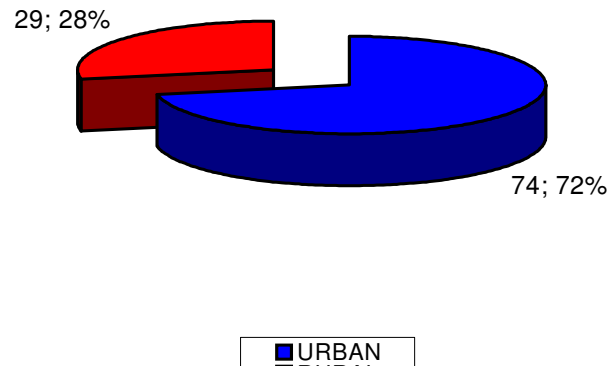


Fig. 3

During the history interview, data referring to the possible risk factors have been collected. In order to statistically analyze the data obtained another group of 47 patients has served as a control group.

Speciality literature stated that urban environment represents a risk factor in the development of bladder tumors. In order to check this hypothesis we have calculated the relative risk (Odds ratio) and the risk ratio (Risk Ratio) for these patients, consequently obtaining two alternatives:

1. Nule hypothesis: between the developments of bladder tumors and the urban environments there is no connection;
2. The alternative hypothesis: the urban environment is a risk factor in the development of bladder tumors.

Data analysis has discovered $p=0.1659201528$, larger than 0.05, therefore there is not a significant statistic difference between the two variables. Also the value of $OR=1.4460$ with IC 95%

(0.6942; 3.0118) indicates the fact that urban environment is a risk factor for the development of bladder tumors. In conclusion, it can be said that although not statistically different, the data analysis shows an increase of risk for patients in the urban environment. OR value of 1.4460 means that there is a 1.44 higher chance that a person in the urban environment is going to develop bladder cancer.

The most important risk factor in the development of bladder tumors is smoking. In the study group, 52 patients have declared that they are or have been active smokers. In order to verify this hypothesis we have calculated the Odds Ratio and the Risk Ratio and we have come up with two alternatives:

1. Nule hypothesis: between the development of bladder tumors and smoking there is no connection;
2. Alternative hypothesis: smoking is a risk factor in the development of bladder tumors.

Data analysis has shown p value = 0.0016246275, lower than 0.05, therefore there is a significant statistic difference between the two variable. Also, OR value 0 2.9299 with IC 95% (1.4249; 6.0246), indicates the fact that smoking is a risk factor in the development of bladder tumors. In conclusion, data analysis from the study group shows an increase of risk for smoking patients. OR value of 2.9299 means that there are 2.9299 more chances for a smoking person to develop bladder cancer. In conformity with global studies, continuing smoking is an element of negative prognosis, being responsible for an increase of recurrences.

Another risk factor for the development of bladder tumors is patients' occupation. Labourers in the painting chemical colorants, rubber industry, leatherworkers, plastic material, textile industry, come in contact with aromatic amines and theoretically are more predisposed to develop bladder tumors. In order for us to verify the hypothesis we have calculated the Odds Ratio and the Risk Ratio for the patients in the study group and came up with two alternatives:

1. Nule hypothesis: between the development of bladder tumors and occupation there is no connection;
2. Alternative hypothesis: the occupation is a risk factor for the development of bladder tumor.

We have decided that risk professions which theoretically predispose to the development of bladder tumors and have been correctly stated from the patients' history interview.

Data analysis has stated p value of 0.3861209658, larger than 0.05, therefore there is no significant statistical difference between the two variables. Also OR value of 1.1261 with IC 95% (0.5238; 2.4208) indicates that profession is a risk factor for

the development of bladder tumors. In conclusion, even if it is not significant statistically conclusive, data analysis from the study lot shows an increase of risk in persons that worked in risk occupational places. OR value of 1.1261 means that there is 1.1261 more chance that a person with this risk factor will develop bladder cancer.

Although statistically insignificant and with a lower value in comparison with other data from the global literature, the risk is somewhat larger for patients what have worked in the high risk places. Upon this subject there are numerous contradictory data, different from a country to another, fact accountable by the distribution of occupations around the globe. In Brasov and its surroundings there was a high development of the chemical colorants, textile and typography industry and can explain the shown data.

Concluding from the history interview data and other possible risk factors for the development of bladder tumors, but we have not tried to prove the statistic signification of the risk factors, the number of patients being very small in numbers: analgesic drug use - 4 patients, alcohol use - 6 patients, large consumption of coffee - 14 patients, pelvic irradiation - 1 patient.

5. Conclusions

Due to the chronic and multiple recurrent characters of the bladder tumors, these raise great issued financially in the entire world. The Agency for Health Care Policy and Research of the US Public Health Service states that annually in the USA 2.2 billions dollars are spent for the diagnosis and treatment of the bladder tumors, at least double by comparison with the necessary funds for the treatment of prostate cancer. The rate of relapse for the

bladder tumors is fairly high, some studies show that 80% of the patients have at least 1 relapse [9].

Even though there are some bladder tumor cases diagnosed in the early years of life, these are far more frequent in patients with ages over 50 and especially in the 7th decade of life, our study shows that 40.60% of the patients are ages 60-70 years old.

Bladder tumors are more frequently encountered in male patients (2.2/1 in our study, and especially in the urban environment (74.72%).

Although there is no knowledge of why the cells start to divide and form a tumor, bladder tumors represent one of the few cases of neoplasia where etiological factors can be recognized.

Smoking is the main implicated factor, numerous studies showing this. Our study demonstrated that smoking is associated with the development of bladder tumors, and smokers and ex-smokers have a 2.92 more chance to develop this kind of neoplasia.

From the moment of quitting smoking, patient risk drops with over 30% in the first 4 years and with over 60% after 25 years of quitting. With all this, the risk of neoplasia development in an ex smoking patient will never be as low as a non-smoker.

Urban environment is another risk factor associated with the increase of incidence to develop bladder tumors. Therefore, the study results are contradictory, some other risk factors could be implicated (the most important being the patient access to clinical and paraclinical investigations). Anyway, our study does not state a statistically significant bond between the urban environment and the development of bladder cancer, but showing a 1.44 higher

chance of urban people developing bladder neoplasia.

Another risk factor we have analysed is the patients occupation. It is estimated that 5-10% of the bladder tumors in european men are caused by occupational factors. The most exposed people are the ones in contact with aromatic amines: chemical paint industry, painting shops, leatherworking, rubber and plastic material industry, textile industry and dental technicians. Our study does not show a statistic significant relation between patient occupation and development of bladder tumors, but show a 1.12 higher chance of developing a bladder tumor for the labourers in the risk segments. Even the global literature studies contain many contradictory data on this subject, ranging from insignificant data to studies that implicate some substances in the development of neoplasia. It must not be forgotten that truck drivers can be affected in some measure from the exposure to aromatic amines and polihidrocarbonites mostly encountered in volatile goudrons resulted from exhaust fumes.

Implication of other risk factor in the development of bladder tumors is still in trial, data must be verified in much longer periods. Data available momentarily clearly show a much larger implication of occupational and environmental risk factor in the development of bladder tumors, comparative to other types of neoplasia.

Although bladder tumors where hereditary factors can be recognised are much less common, currently genetic aspects are being studied, these studies wanting to explain why some patients, even strongly exposed to some risk factors, quickly metabolize carcinogenic substances and do not develop this kind of neoplasia.

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