

# Amount of tobacco consumption is associated with superficial bladder cancer progression

Associação entre o consumo de tabaco e a progressão do câncer superficial da bexiga

Fernando Korkes<sup>1</sup>, César Augusto Braz Juliano<sup>2</sup>, Maria Alice Peluso Bunduky<sup>3</sup>, Ana Carolina Duarte Martins Costa<sup>4</sup>, Marília Germanos de Castro<sup>5</sup>

## ABSTRACT

**Objective:** To evaluate the association between smoking habits and outcome of patients with superficial bladder cancer. **Methods:** A retrospective study was performed evaluating 99 patients (67.0 ± 13.2 years, ranging from 31.4-93.4 years, 72.7% males and 27.3% females) treated at our institution with non muscle-invasive bladder cancer, between 1994 and 2000, with a mean follow-up of 49.3 months (range 4.0-177.9 months). Patients were divided according to smoking status, and the main measured outcome was progression to invasive disease. Additional cohort analysis was performed dividing patients according to previous tobacco exposure: smokers and non-smokers. Smokers were stratified into former smokers, early-quitters, late quitters and continued smokers. **Results:** Smoking habit was significantly more common in males ( $p = 0.03$ ). Cancer also occurred at an earlier age among smokers (70.8 *versus* 64.8 years,  $p = 0.030$ ). Tobacco consumption was present in 62.7% of the patients with bladder cancer. There was a significant higher progression rate to muscle-invasive disease in patients that had more than 60 pack-years of exposure (52.9 *versus* 26.2%,  $p = 0.037$ ). These patients had a mean progression time of 59.3 months, whereas patients who had smoked less than 60 pack-years progressed after a mean time of 131.8 months. **Conclusions:** A direct association between the amount of tobacco consumed and disease progression is observed in patients with bladder cancer, as suggested by the present study. Tobacco consumption has a direct association with progression of superficial bladder cancer to invasive disease and also shortens the period of time for muscle invasion. Larger and prospective studies are still necessary to bring further definitive conclusions about reproducibility of our data and to better understand how smoking cessation affects progression of superficial bladder cancer.

**Keywords:** Urinary bladder; Carcinoma, transitional cell; Survival analysis; Smoking; Smoking cessation; Neoplasm recurrence, local

## RESUMO

**Objetivo:** Avaliar a relação entre os hábitos tabágicos e a evolução de pacientes com carcinoma urotelial de bexiga superficial. **Métodos:** Foi realizado um estudo retrospectivo com 99 pacientes (67,0 ± 13,2 anos, variando de 31,4-93,4 anos, 72,7% homens e 27,3% mulheres) tratados de carcinoma urotelial de bexiga não-invasivo entre 1994 e 2000, com seguimento médio de 49,3 meses (4,0-177,9 meses). Os pacientes foram divididos em tabagistas e não-tabagistas, e os tabagistas foram substratificados entre ex-tabagistas, interruptores precoces, interruptores tardios e tabagistas persistentes. O principal desfecho avaliado foi a progressão para doença invasiva. **Resultados:** O tabagismo foi mais comum entre os homens ( $p = 0,03$ ), sendo que 62,6% do total de pacientes avaliados eram tabagistas. O diagnóstico do câncer ocorreu em uma idade mais precoce entre os tabagistas (70,8 *versus* 64,8 anos,  $p = 0,03$ ). Observou-se uma progressão significativamente maior para doença invasiva entre os pacientes com carga tabágica acima de 60 maços/ano (52,9 *versus* 26,2%,  $p = 0,037$ ). Estes pacientes tiveram um tempo de progressão de 59,3 *versus* 131,8 meses para aqueles com menor carga tabágica. **Conclusões:** Há associação direta entre a carga tabágica e progressão do carcinoma urotelial de bexiga para doença músculo-invasiva em um curto intervalo de tempo. Estudos prospectivos e com maior número de pacientes são necessários para entender como a interrupção do tabagismo afeta a progressão do carcinoma superficial de bexiga.

**Descritores:** Bexiga urinária; Carcinoma de células de transição; Análise de sobrevivência; Tabagismo; Abandono do hábito de fumar; Recidiva local de neoplasia

Study carried out at Urology Discipline and Pathology Division of Faculdade de Ciências Médicas da Santa Casa de São Paulo – FCMSCSP, São Paulo (SP), Brazil.

<sup>1</sup> Assistant physician at Department of Urology of Faculdade de Medicina do ABC – FMABC, Santo André (SP), Brazil.

<sup>2</sup> MD; Resident in Urology at Faculdade de Medicina do ABC – FMABC, Santo André (SP), Brazil.

<sup>3</sup> MD; Resident in Gynecology and Obstetrics at Santa Casa de SP, São Paulo (SP), Brazil.

<sup>4</sup> MD; Preceptor of Otorhinolaryngology of Faculdade de Medicina da Universidade de São Paulo – USP, São Paulo (SP), Brazil.

<sup>5</sup> Adjunct professor of the Department of Pathology of Santa Casa de SP, São Paulo (SP), Brazil.

Corresponding author: Fernando Korkes – Rua Pirapora, 167 – Ibirapuera – CEP 04008-060 – São Paulo (SP), Brazil – Tel.: 11 3884-2233 – e-mail: fkorkes@terra.com.br

Received on Jan 05, 2010 – Accepted on Oct 11, 2010

## INTRODUCTION

Urothelial carcinoma is the ninth most common malignancy in the world, most often diagnosed as a superficial disease<sup>(1)</sup>. However, superficial bladder cancer has a high tendency to recur and to progress in a significant subset of patients<sup>(1)</sup>. Some well-known prognostic factors are related to disease progression and cancer-specific survival. Several risk factors are involved, being tobacco use the most important<sup>(2-5)</sup>. Smoking cessation after diagnosis of bladder cancer is a widely accepted recommendation. However, a systematic review demonstrated that little is known about whether it reduces the risk of recurrence or progression<sup>(6)</sup>. Few studies evaluated this issue and did not achieve conclusive results, even though smoking cessation seems to be related to better outcomes<sup>(6-11)</sup>.

## OBJECTIVE

To evaluate the association between smoking habits and the outcome of patients with superficial bladder cancer.

## METHODS

A retrospective case-control study was performed evaluating 99 patients ( $67.0 \pm 13.2$  years, range of 31.4-93.4 years) treated at our institution with non muscle-invasive bladder cancer between 1994 and 2000, with a mean follow-up of 49.3 months (range 4.0-177.9 months). All patients with incomplete registers were excluded from the study. Other reported bladder conditions included recurrent urinary tract infection (20%) and chronic indwelling bladder catheter (6%).

Oncologic follow-up was performed according to an institutional protocol for superficial bladder cancer: after transurethral resection of the tumor, re-resection was performed one month later for high-grade tumors; cystoscopy, cytology, chest X-ray and abdominal ultrasound were performed every three months for the first year, every six months for the first three years, and yearly thereafter in case of no recurrence.

Additional adjuvant treatments were performed when indicated: intravesical BCG (80 mcg/week for six weeks for induction and after this period of time 80 mcg/ week for three weeks every six months as maintenance treatment). Intravesical mitomycin C was applied after the first recurrence following a BCG course, or when BCG was contraindicated.

Patients were divided according to disease progression (progression *versus* non-progression to muscle invasive disease), and smoking status. Additional cohort analysis was performed dividing patients according to previous tobacco exposure: smokers and non-smokers. Smokers were stratified into former smokers, early-quitters, late quitters and continued smokers. Former smokers were considered all patients who had quit smoking at least one year prior to cancer diagnosis. Early quitters were patients who quit smoking in the first year after diagnosis of cancer, and late quitters were those who had quit more than a year after the initial diagnosis. Measured outcomes included recurrence free survival, progression to muscle-invasive disease and cancer specific-mortality.

Statistical analyses were performed using the Statistical Package for Social Sciences software (SPSS for Mac OS X, SPSS, Inc., Chicago, Illinois). Groups were compared by Pearson's  $\chi^2$  test and Student's *t* test. Disease-specific survival and progression to muscle-invasive disease plots were made using the Kaplan-Meier method. Survival rates were analyzed for significance using the log rank test. Statistical significance was determined at  $p < 0.05$ .

## RESULTS

Of 99 patients, 72.7% were males and 27.3% were females. Tobacco use was reported by 62.7% of patients with bladder cancer. Smoking was significantly more common among males than females ( $p = 0.03$ , Table 1). Cancer also occurred at an earlier age for smokers (70.8 *versus* 64.8 years,  $p = 0.03$ , Table 1). Mean smoking history was of  $37.5 \pm 13.3$  years (Table 2). Of the 62 smokers, 16 were classified as former smokers, 19 as early-quitters, 7 as late-quitters and 20 as continued-smokers. When patients were divided according to muscle progression, there was no statistical difference between smokers and non-smokers or between subgroups of smokers. Of the 20 continued-smoking patients, 40.0% had progressed to muscle-invasive disease, as compared to 28.6% of the former smokers and early quitters ( $p = 0.160$ , Figure 1). If distributed according to tobacco exposure, there was a significant higher rate of progression to muscle-invasive disease in patients that had more than 60 pack-years of exposure (52.9 *versus* 26.2%,  $p = 0.037$ , Table 3). These patients had a mean progression time of  $59.3 \pm 16.4$  months, whereas patients who smoked less than 60 pack-years progressed after a mean time of  $131.8 \pm 14.2$  months ( $p = 0.041$ , Figure 2).

**Table 1.** Patients' demographic data and comparison between non-smokers and smokers at initial diagnosis of cancer

Patient's demographic data	Non-smokers (n = 37)	Smokers (n = 62)	p value
	Mean ± SD	Mean ± SD	
Age (years)	70.8 ± 14.5	64.8 ± 12.2	0.030*
Follow-up	43.3 ± 14.2	52.1 ± 48.1	0.473
Tumor size (cm)	1.8 ± 1.8	2.6 ± 1.5	0.622
Number of tumors	1.6 ± 1.0	1.6 ± 1.1	0.817
Male/female	48.6%/51.4%	90.3%/9.7%	0.001*
	<b>% (n)</b>	<b>% (n)</b>	
High-grade	54.1 (20)	56.5 (35)	0.184
Lamina propria invasion	24.3 (9)	38.7 (24)	0.061
Muscularis mucosa invasion	18.9 (7)	32.3 (20)	0.068
Adjuvant treatment	29.7 (11)	41.9 (26)	0.083

\*p < 0.05.

**Table 2.** Smoking history

Smoking history	Mean ± SD	Range
Smoking time (years)	37.5 ± 13.3	(10 – 61)
Pack/day	1.0 ± 0.5	(0.1 – 3.0)
Pack/year	39.7 ± 25.5	(4.0 – 100.0)

**Table 3.** Distribution of patients according to their past tobacco exposure

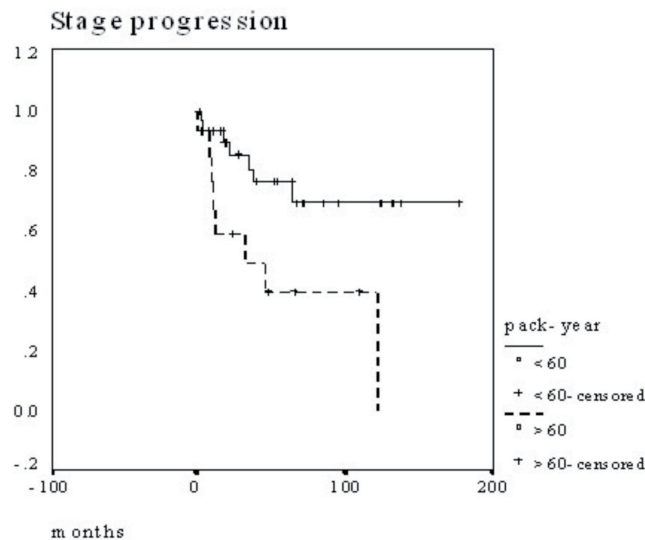
Data	<60 pack/year	>60 pack/year	p value
	% (n)	% (n)	
Number of patients	(42)	(17)	
Muscle invasion	26.2 (11)	52.9 (9)	0.037*
Cystectomy	23.8 (10)	41.2 (7)	0.103
Cancer-related death	9.5 (4)	17.6 (3)	0.223

\*p < 0.05.

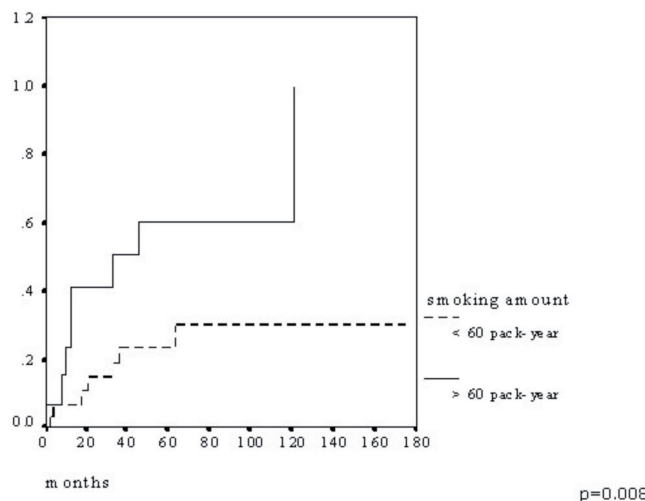
**DISCUSSION**

Tobacco use is the main risk factor for bladder cancer, and different aspects of smoking habit have been analytically characterized<sup>(9,11)</sup>. After bladder cancer is diagnosed, it seems logical that smoking interruption might bring benefits. However, to the present date, there are no conclusive studies evaluating this issue<sup>(6)</sup>. This study has some important findings.

**Prognostic factors upon diagnosis:** a recent study observed worse prognostic factors upon initial diagnosis of bladder cancer among smokers, though similar recurrence patterns were found when compared to non-smokers<sup>(12)</sup>. This finding is different from our observations. In the present study, there were similar prognostic factors after initial transurethral resection when comparing smokers to non-smokers, as observed by other authors<sup>(7)</sup>. Maybe the relatively small sample can explain our results, as we could not reproduce these findings. However, after a mean time of 37.5 ± 13.3 years of smoking, our patients had cancer diagnosed at an earlier age (70.8 versus 64.8 years, p = 0.03). As early diagnosis of bladder cancer has



**Figure 1.** Kaplan-Meier plot according to smoking amount related to progression to muscle invasion



**Figure 2.** Kaplan-Meier plot according to smoking amount related to progression to muscle invasion

become more frequent with routine check-ups, if these patients had a later diagnosis, they would possibly have worse prognostic factors. Additionally, cystectomy was progressively more required for continued smokers than for quitters or non-smokers.

**Smoking status:** the role of smoking status over prognosis after the initial diagnosis of bladder cancer is not well understood yet. A recent study suggested that smoking interruption seems to be an independent risk factor for disease progression<sup>(7)</sup>. Other studies failed to prove such relation<sup>(12)</sup>. In a systematic review, Aveyard et al. found only one high quality study evaluating this issue, and concluded that the evidence is weak since most studies were not statistically significant<sup>(6)</sup>. Although we observed a trend towards higher progression rates among continued-smokers, our study also failed to

demonstrate a statistically significant difference in recurrence patterns when comparing former smokers, quitters and continued-smokers. What we observed was an earlier age of cancer onset when comparing smokers to non-smokers, a data similar to what was previously reported<sup>(10)</sup>. It is worth mentioning that our relatively small sample becomes even smaller when these subgroups of patients are stratified. But the amount of tobacco consumption was associated with higher and earlier progression rates. Previous studies already reinforced the association between the amount of tobacco use and cancer diagnosis<sup>(13)</sup>. Although these studies have demonstrated a direct association between the amount of tobacco smoking and higher risk of developing bladder cancer<sup>(9)</sup>, the risk of disease progression has not been demonstrated.

A significant higher progression rate was observed in patients who were exposed to more than 60 pack-years. This group of patients had also a faster progression to muscle-invasive disease.

We believe that our study can bring very useful information for both patients and clinicians who treat bladder cancer patients. It might be stimulating for patients with diagnosis of a highly recurrent cancer to know that there is something they can do to reduce the risk of disease progression. Patients should be encouraged to reduce and/or quit smoking. Additional measures that could reduce exposure of bladder urothelium to carcinogens might also be encouraged. In a study involving almost 8,000 men, researchers found that men who drank higher amounts of water had a significantly reduced incidence of bladder cancer. Men who drank more than five cups of coffee daily had also an increased risk of bladder cancer<sup>(14)</sup>. As suggested by the authors, bladder cancer might partly be caused by contact with carcinogens excreted in urine. Therefore, patients with a prior diagnosis of bladder cancer should be stimulated not only to quit smoking but also to quit drinking coffee and to drink large amounts of water. A close follow-up of these patients is also essential to allow early diagnosis and to avoid cancer metastasis. The present study has several limitations. Other factors seem to be associated with tobacco-related bladder cancer, such as the type of tobacco consumed<sup>(11)</sup> or concomitant coffee ingestion<sup>(15)</sup>, and these factors were not evaluated in the present study. Our sample size is also relatively small, limiting the power of statistical analysis. However, the present study brings several relevant insights for both clinicians and patients.

## CONCLUSIONS

This study suggested a direct association between the amount of tobacco consumed and disease progression

is observed in patients with bladder cancer. Tobacco consumption has direct association with progression of superficial bladder cancer to invasive disease and also shortens the period of time for muscle invasion. This information might help clinicians to convince their patients with bladder cancer that by quitting smoking they will improve their prognosis. Larger and prospective studies remain necessary to bring further definitive conclusions about the reproduction of our data and to better understand how smoking cessation affects the progression of superficial bladder cancer.

## REFERENCES

1. O'Donnell MA. Advances in the management of superficial bladder cancer. *Semin Oncol*. 2007;34(2):85-97.
2. Murta-Nascimento C, Schmitz-Drager BJ, Zeegers MP, Steineck G, Kogevinas M, Real FX, et al. Epidemiology of urinary bladder cancer: from tumor development to patients death. *World J Urol*. 2007;25(3):285-95.
3. Altwein JE. [Primary prevention of bladder cancer. What's new?]. *Urologe A*. 2007;46(6):616-21.
4. Korkes F, Silveira TS, Castro MG, Cuck G, Fernandes RC, Perez MD. Carcinoma of the renal pelvis and ureter. *Int Braz J Urol*. 2006;32(6):648-53; discussion 653-5.
5. Takashi M, Wakai K, Hattori T, Furuhashi K, Ono Y, Ohshima S, et al. Multivariate evaluation of factors affecting recurrence, progression, and survival in patients with superficial bladder cancer treated with intravesical bacillus Calmette-Guerin (Tokyo 172 strain) therapy: significance of concomitant carcinoma in situ. *Int Urol Nephrol*. 2002;33(1):41-7.
6. Aveyard P, Adab P, Cheng KK, Wallace DM, Hey K, Murphy MF. Does smoking status influence the prognosis of bladder cancer? A systematic review. *BJU Int*. 2002;90(3):228-39.
7. Chen CH, Shun CT, Huang KH, Huang CY, Tsai YC, Yu HJ, et al. Stopping smoking might reduce tumour recurrence in nonmuscle-invasive bladder cancer. *BJU Int*. 2007;100(2):281-6; discussion 286.
8. Kontani K, Kawakami M, Nakajima T, Katsuyama T. Tobacco use and occupational exposure to carcinogens, but not N-acetyltransferase 2 genotypes are major risk factors for bladder cancer in the Japanese. *Urol Res*. 2001;29(3):199-204.
9. Brennan P, Bogillot O, Cordier S, Greiser E, Schill W, et al. Cigarette smoking and bladder cancer in men: a pooled analysis of 11 case-control studies. *Int J Cancer*. 2000;86(2):289-94.
10. Fleshner N, Garland J, Moadel A, Herr H, Ostroff J, Trambert R, et al. Influence of smoking status on the disease-related outcomes of patients with tobacco-associated superficial transitional cell carcinoma of the bladder. *Cancer*. 1999;86(11):2337-45.
11. Vineis P, Esteve J, Hartge P, Hoover R, Silverman DT, Terracini B. Effects of timing and type of tobacco in cigarette-induced bladder cancer. *Cancer Res*. 1988;48(13):3849-52.
12. Garcia Mediero JM, Angulo Cuesta J, Lujan Galan M, Rodriguez Garcia N, Berenguer Sanchez A. [Smoking habit and superficial bladder tumours natural history]. *Actas Urol Esp*. 2007;31(4):349-54.
13. Caicoya M, Miron JA. [Lung cancer and smoking in Asturias, Spain. A case-control study]. *Gac Sanit*. 2003;17(3):226-30.
14. Villanueva CM, Cantor KP, King WD, Jaakkola JJ, Cordier S, Lynch CF, et al. Total and specific fluid consumption as determinants of bladder cancer risk. *Int J Cancer*. 2006;118(8):2040-7.
15. Lopez-Abente G, Escolar A. Tobacco consumption and bladder cancer in non-coffee drinkers. *J Epidemiol Community Health*. 2001;55(1):68-70.