Increased Incidence of Lung Cancer Among Patients With Superficial Transitional Cell Carcinoma: A Potential Risk Cohort for Lung Cancer Screening

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Abstract

Current recommendations for lung cancer (LC) screening do not include transitional cell carcinoma of the bladder (TCC) as a risk factor for determining screening eligibility. On the basis of 91,606 patients with localized TCC, in this study we examined whether patients with bladder cancer have higher LC rates. We found that LC rates are indeed higher in these patients, and therefore, they might benefit from being screened for LC.

Background: Smoking is a major risk factor for lung cancer (LC) and transitional cell carcinoma of the bladder (TCC). Current recommendations for LC screening do not include TCC as a risk factor for determining screening eligibility. In this study we aimed to evaluate whether TCC patients constitute a population who might benefit from LC screening. **Patients and Methods:** The Surveillance, Epidemiology, and End Results 18 database was used to determine the incidence, standardized incidence ratio (SIR), and the average time to diagnosis of LC in patients with localized TCC of the bladder (American Joint Committee on Cancer, sixth edition, stages 0-1). **Results:** On the basis of 91,606 patients with localized TCC, The SIR for LC in men was 1.89 (95% confidence interval [CI], 1.8-1.97), significantly different from the risk for all solid tumors. The SIR for LC in women was 2.43 (95% CI, 2.22-2.65), significantly higher than for men. The 5-year incidence of LC was 3.2%, and the 10-year incidence was 5.94%. The average time to diagnosis of LC was 3.4 years, with >80% of LC cases occurring within 5 years of TCC diagnosis. **Conclusion:** Patients with localized TCC have a higher incidence of LC than the general population. The risk is significantly increased among women compared with men. Considering this increased risk, patients with early stage TCC might stand to benefit from LC screening. Additional differences were noted between male and female TCC patients, which bear further study.

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Introduction

Lung cancer (LC) is the second most common type of cancer in the United States but continues to be the foremost cause of cancer-related mortality in men and women.[1] Although 5-year survival for stage 1 LC is >50%, only 16% of LCs are discovered in this stage.[2] In recent years, several large randomized trials have studied the outcomes of screening for LC using low-dose computed tomography (LDCT). The larger trials showed an initial detection rate of 0.8% to 2.2%, with a total of 2.4% to 4.7% in 34 to 78 months of follow up.[3-5] The largest study, the NLST (National Lung Screening Trial), which compared screening using LDCT with annual chest X-rays, showed a 20% decrease in mortality in the

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screened population.[3] The newer MILD (Multicentric Italian Lung Detection) trial evaluated the benefit of prolonged LDCT screening beyond 5 years and its effect on overall and LC-specific mortality at 10 years, and provides additional evidence that prolonged screening beyond 5 years can enhance the benefit of early detection and achieve a greater overall and LC mortality reduction compared with the NLST trial.[6] Follow-up screening programs for high-risk individuals are now recommended by the European Respiratory Society and have been implemented in the United States under public services since 2015.[7] Current or previous smokers at age 55 to 74 years, with at least 30 pack-years, and who have smoked within the past 15 years, are considered at high risk.[8-10]

Besides being a major risk factor for LC, cigarette smoking is a known major risk factor of transitional cell carcinoma of the bladder (TCC).[11,12] Unlike LC, 85% of TCC is discovered in situ or in stage I, with 5-year survival being as high as 96% for in situ and 70% for stage I.[13] Despite the shared common risk factor, currently there is no large study that has investigated the coincidence of both types of solid cancers (ie, lung and bladder cancers) in the population. Rusthoven et al examined a group of 8300 superficial TCC patients in the years 1983 to 2002 and reported an increased LC incidence, with 340 cases of LC, a 15-year incidence of 8.8%.[14] Del Rey et al examined a group of 231 TCC patients from a single center in the years 1995 to 2003, and reported an increased LC incidence, with 10 cases of LC all of which were in current or former smokers.[15] With all of these data, an important question arises: Do smoking patients in whom early stage TCC is discovered constitute a risk group in which early LC screening can be justified?

In this study we analyzed the incidence of LC compared with the incidence of other cancers in early stage bladder cancer patients, stratified according to sex, LC type, age, county, and smoking data, using the SEER (Surveillances, Epidemiology, and End Results) 18 database. The average time to discovery and cumulative incidence of LC were calculated.

Patients and Methods

The SEER 18 registries database, including >6 million individual records from 18 cancer registries across the United States,[16] was used to extract the data. SEER data are examined for quality and completeness, with the case ascertainment standard being 98%.[17]

Patients included in this study were those with transitional cell carcinomas and papillomas (on the basis of SEER*Stat broad groupings recode, International Classification of Diseases for Oncology [ICD-O-3] morphological codes 8120-8139) of the urinary bladder,[18] diagnosed in Tumor, Node, Metastases stages T0 to T1, N0, M0, equivalent to American Joint Committee on Cancer sixth edition stage 0 to I,[19] in the years 2004 to 2013.

In our study, patients were stratified according to LC type, sex, age (SEER*Stat 5-year age groups were combined into 10-year age groups), and population percentage of ever smokers divided into 3 groups: <25%, 25% to 40%, and >40% smokers.[20-22] Smoking habits were obtained from the SEER small area county data estimates, calculated on the basis of the data from the Behavioral Risk Factor Surveillance System and the National Health Interview Survey, combining the data according to the approach of Raghunathan et al.[22] The most recent smoking data available are from the years 2000 to 2003, and this was used for the entire study period. Per-patient smoking data were not available in the SEER database.

For all patients included in the study, the incidence of a second solid tumor (excluding bladder and lung) and of a lung and bronchus tumor were determined using the multiple primary-standardized incidence ratio (SIR) session. Latency rates were obtained using the SEER*Stat software and used for calculating time to event. Annual incidence rates were obtained and 5- and 10-year incidence rates calculated. Analyses were performed using the SEER*Stat[23] software version 8.3.2. and 8.3.4, using databases and referent rates on the basis of version 8.3.2. In a multiple primary SIR session, incidence rates of second primary tumors in the study group were compared with those of the same cancer in a sample population. The sample population cancer referent rates were on the basis of data from within the SEER database, using the year 2000 US standard population,[21] and are matched to the study population according to sex, age (5-year age groups), calendar year of diagnosis, and race, with the incidence ratio between the groups being the SIR—the relative risk for disease compared with the SEER referent rate. Considering that our primary concern is the screening and discovery of LC in these patients, rather that the temporal order of the tumors, no latency exclusion period was set for the discovery of a second tumor, and person-years at risk and second tumors were counted from the time of diagnosis.

Statistical significance was defined in the SEER*Stat analysis results as $P < .05$. Significance of the difference between SIRs was calculated on the basis of the method of Altman and Bland.[24]

Results

We observed 13,287 second primary solid tumors in 91,606 early stage TCC patients included in this study. Eighteen percent (2346 cases) of those were LC, making LC the most common cause of cancer in TCC patients aside from additional genitourinary cancers. LC represented 17% of solid tumors in men, and 22% in women ($P < .05$).

The SIR for all solid tumors was 1.61 for all patients, 1.67 for men, and 1.31 for women. The SIR for LC was 1.98 for all patients, 1.89 for men, and 2.43 for women. Results were significant with a $P < .05$. Results on the basis of stratification according to age and smoking data are shown in Table 1.

When the SIR for all solid tumors was used as a baseline cancer rate for TCC patients, LC SIR for men and women was significantly higher than the SIR for all solid tumors. The SIR for LC was significantly higher for women than for men, and for counties with >40% ever-smokers. All results were significant with $P < .05$ (Figure 1).

The 5-year cumulative incidence of LC for all patients in the study was 3.2%, and the 10-year rate was 5.94% versus expected rates of 1.6% and 3.21%, respectively (Figure 2).

The 10-year incidence according to age group was 0.96% for men and 0.29% for women for ages 40 to 49 years, 2.98% for men and 4.16% for women for ages 50 to 59 years, 6.31% for men and 6.41% for women for ages 60 to 69 years, 8.5% for men and 6.82% for women for ages 70 to 79 years, and 6.19% for men and 4.58% for women for ages 80 years and older (Figure 3).

The average time from diagnosis of TCC to diagnosis of LC was 3.4 years, with >80% of all cases diagnosed within 5 years of TCC diagnosis. When stratified according to age, average time to diagnosis was 4.3 years for ages 40 to 49 years and 50 to 59 years, 3.6 years for ages 60 to 69 years, 3.4 years for ages 70 to 79 years, and 2.7 years for ages 80 years and older.

Table 1 The SIR for Solid Tumors (Excluding Lung and Bladder) and for Lung Cancer Stratified According to Age Group, County, Smoking Prevalence, and Sex

	Solid Tumors Excluding Lung and Bladder		Lung Cancer	
	Events Observed, n	Observed/Expected: SIR (95% CI)	Events Observed, n	Observed/Expected: SIR (95% CI)
Total	7779	1.61 (1.57-1.64)	2.346	1.98 (1.9-2.06)
Male	6631	1.67 (1.63-1.71)	1.843	1.89 (1.8-1.97)
Female	1148	1.31 (1.23-1.39)	503	2.43 (2.22-2.65)
Stratification According to Age Group and Sex				
		Solid Tumors Excluding Lung and Bladder		Lung Cancer
Age Group (in Years)	Sex	Observed	Observed/Expected: SIR (95% CI)	Observed	Observed/Expected: SIR (95% CI)
0-39	Total	29	4.54 (3.04-6.53)	2	7.58 (0.92-27.38)
	Male	22	6.25 (3.92-9.46)	2	10.71 (13.-38.69)
	Female	7	2.45 (0.98-5.04)	0	0 (0-47.79)
40-49	Total	171	2.43 (2.08-2.83)	16	2.17 (1.24-3.53)
	Male	134	2.72 (2.28-3.23)	14	2.43 (1.33-4.07)
	Female	37	1.76 (1.24-2.42)	2	1.25 (0.15-4.52)
50-59	Total	918	1.86 (1.74-1.99)	167	2.25 (1.92-2.61)
	Male	781	1.97 (1.84-2.12)	128	2.11 (1.76-2.50)
	Female	137	1.41 (1.18-1.67)	39	2.87 (2.04-3.93)
60-69	Total	2363	1.62 (1.55-1.69)	705	2.26 (2.10-2.43)
	Male	2046	1.67 (1.60-1.75)	540	2.10 (1.93-2.29)
	Female	317	1.35 (1.20-1.50)	165	2.98 (2.54-3.47)
70-79	Total	2812	1.57 (1.51-1.63)	969	1.90 (1.78-2.03)
	Male	2426	1.62 (1.56-1.69)	778	1.84 (1.71-1.97)
	Female	386	1.29 (1.16-1.42)	191	2.22 (1.92-2.56)
80-89	Total	1486	1.46 (1.39-1.54)	487	1.73 (1.58-1.89)
	Male	1222	1.53 (1.45-1.62)	381	1.65 (1.49-1.83)
	Female	264	1.20 (1.06-1.35)	106	2.09 (1.71-2.53)
Stratification According to Percentage of Ever-Smokers According to County					
		Solid Tumors Excluding Lung and Bladder		Lung Cancer	
Percentage of Ever-Smokers	Sex	Observed	Observed/Expected: SIR (95% CI)	Observed	Observed/Expected: SIR (95% CI)
13.09%-25.00%	Total	0	0	0	0
	Male	0	0	0	0
	Female	0	0	0	0
25.01%-40.00%	Total	2733	1.58 (1.52-1.64)	697	1.63 (1.51-1.76)
	Male	2332	1.63 (1.57-1.70)	557	1.57 (1.44-1.71)
	Female	401	1.31 (1.19-1.45)	140	1.97 (1.63-2.29)
40.01%-68.20%	Total	5046	1.62 (1.58-1.67)	1649	2.18 (2.07-2.28)
	Male	4299	1.69 (1.64-1.75)	1286	2.07 (1.95-2.18)
	Female	747	1.31 (1.22-1.40)	363	2.69 (2.42-2.98)

Abbreviation: SIR = standardized incidence ratio.

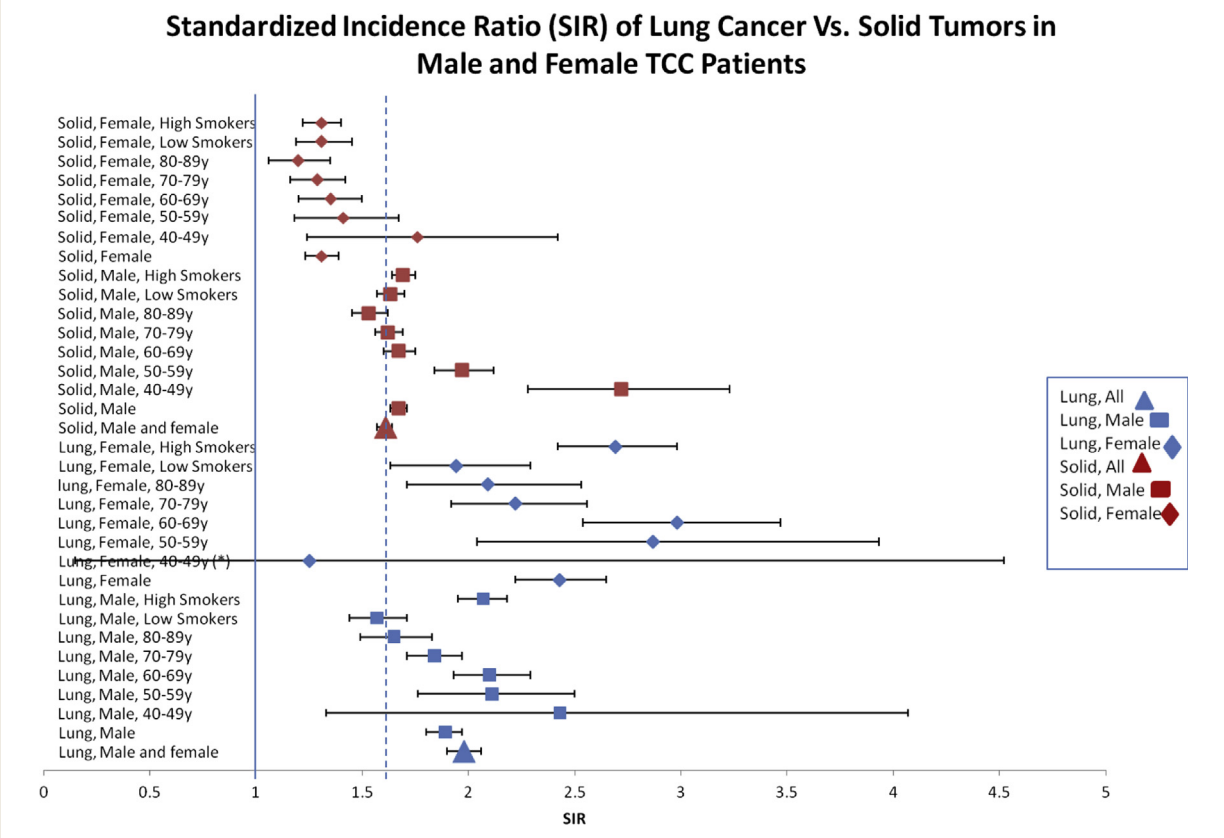
Transitional cell carcinoma of the bladder patients showed a slightly different profile of LC types compared with the general population, with a significantly higher percentage of large-cell, and lower percentage of small-cell carcinomas. Among female TCC patients, there was a significantly higher percentage of squamous cell carcinoma, and among male patients a significantly higher percentage of adenocarcinoma (Figure 4).

Discussion

This study showed a higher incidence of LC versus other solid tumors among early-stage TCC patients. The 10-year incidence of LC among early stage TCC patients increased with age until age 79, with a slight decrease in incidence in the 80 years and older group, probably attributable to death from other causes.

The higher incidence of LC might be explained by the major risk factor these 2 malignancies share—tobacco smoking. Indeed, an

Figure 1 Standardized Incidence Ratio (SIR) of Lung Cancer Versus SIR of Solid Tumors Excluding Lung and Bladder in Early-Stage Bladder Cancer Patients. On the X-Axis, the Solid Vertical Line (1) Is the Risk of All Cancer in the General Population. The Dotted Vertical Line (1.61) Is the SIR of Solid Tumors, Excluding Lung and Bladder in the Study Population. Smokers Is a Percentage of Ever-Smokers According to County. * SIR Not Significant With $P < .05$



increased SIR of LC was observed in TCC patients in counties with >40% active smokers.

The results also show that the SIR of LC was higher in women than men among all age groups older than the age of 50 years. The incidence of LC in women was higher than that of men in the 60 to 69 years age group, and similar to that of men in the 70 to 79 years age group. Additionally, women had a higher percentage of TCC patients with squamous cell carcinoma, which is strongly associated with smoking. These findings might perhaps point to an increased risk of some smoking-related cancers among female smokers. This

Figure 2 Cumulative 10-Year Incidence of Lung Cancer (LC) in Early-Stage Transitional Cell Carcinoma of the Bladder Patients, Versus Expected Rates in Matched Groups

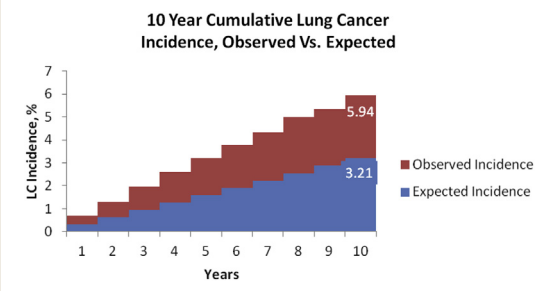


Figure 3 Ten-Year Incidence of Lung Cancer in Early-Stage Transitional Cell Carcinoma of the Bladder Patients According to Age Group and Sex

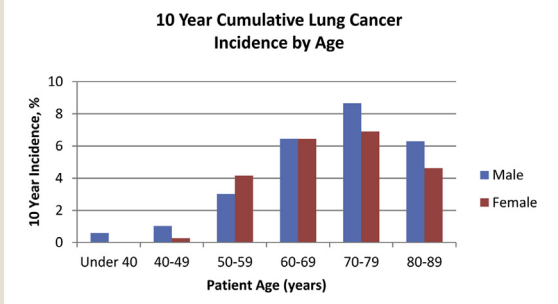
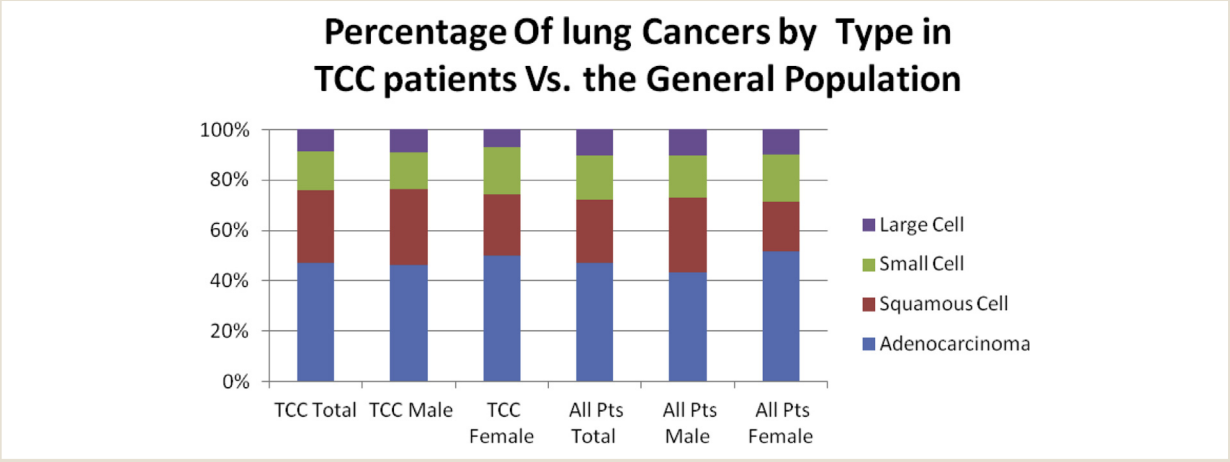


Figure 4 Lung Cancers in Early-Stage Transitional Cell Carcinoma (TCC) Patients (Pts) and in Matched Groups in the General Population, According to Percentage Lung Cancer Subtype



result was unexpected, and further research is recommended to determine the basis for this.

In the NLST, LC was 0.645% per person-year in the spiral computed tomography group, and 0.572% per person-year in the chest radiography group.[3] In our study, results showed 1, 5, and 10-year incidence of 0.7%, 3.2%, and 5.9% per person-year, whereas 1-year incidence in patients older than 70 years was >0.9%, incidence levels that are like those shown in the NLST study. There is no reason to believe that harmful results associated with screening (eg, false positive results and overdiagnosis) would be different in TCC patients than in other populations studied. Furthermore, the lung rads and nodule volumetry methods increase the validity and improve the strategies to quantify the risk of malignancy in "indeterminate nodules."[10,25] Hence, the suitability of a population for screening would be on the basis of the potential benefits of screening, which can be expected to be proportional to the LC risk within that group. Current guidelines of the United States Preventive Services Task Force (USSPTF) additionally recommend screening for patients older than age 54 years with at least 30 pack-years, and other risk factors causing a combined 5-year risk of 5%.

Because of the average time until discovery of LC in early stage TCC patients, it would appear prudent to offer all TCC patients a chest computed tomography scan at the time of diagnosis and staging, and afterward commence screening 1 to 2 years after discovery of early stage TCC among patients older than age 50 years. Considering that >80% of LC cases occurred within 5 years of TCC diagnosis, a limited-time pilot program of screening in early stage TCC patients is likely to yield a relatively high number of cases within a relatively short time, increasing the cost-effectiveness of such a program. Furthermore, screening TCC patients is likely to be cost-effective and relatively simple, because these patients already undergo a diagnostic workup related to their TCC diagnosis. Therefore, the authors are of the opinion that LC screening guidelines should be updated as soon as possible to include TCC patients as a high-risk group, when independent validation of our findings is available.

Advanced stage TCC patients should adhere to the current guidelines regarding staging and routine follow-up. Considering the increased risk for LC in early stage TCC patients, they might benefit from full staging similar to that of advanced TCC.

The primary limitation of this study is that per-patient smoking data were not available in the SEER database, thus limiting our ability to investigate the extent to which TCC is a risk factor for LC in patients without a history of smoking, and to correlate between LC risk and pack-years among smoking TCC patients. Additionally, because of the difference between men and women shown in this study, it is important to know which types of LC are more common among TCC patients. We believe that a large-scale cohort study is highly recommended to provide this information, and to determine the extent to which TCC should be a factor in determining LC screening eligibility.

Conclusion

In this study we examined whether patients with bladder cancer have higher LC rates. We found that LC rates are indeed higher in these patients, and therefore, they might benefit from being screened for LC.

Clinical Practice Points

- Smoking is a major risk factor for LC and TCC. Current recommendations for LC screening do not include TCC as a risk factor for determining screening eligibility.
- The SEER 18 database was used to determine the incidence, SIR, and the average time to diagnosis of LC in patients with localized TCC of the bladder (American Joint Committee on Cancer, sixth edition, stages 0-I). On the basis of 91,606 patients with localized TCC, the SIR for LC in men was 1.89 (95% confidence interval [CI], 1.8-1.97), significantly different from the risk for all solid tumors. The SIR for LC in women was 2.43 (95% CI, 2.22-2.65), significantly higher than for men. The 5-year incidence of LC was 3.2%, and the 10-year incidence was 5.94%. The average time to diagnosis of LC was 3.4 years, with >80% of LC cases occurring within 5 years of TCC diagnosis.

- Patients with localized TCC have a higher incidence of LC than the general population. The risk is significantly increased among women compared with men. Considering this increased risk, patients with early stage TCC might stand to benefit from LC screening. Additional differences were noted between male and female TCC patients, which bear further study.

Disclosure

Nir Peled: advisor and honorarium from AZ, BI, BMS, Lilly, MSD, Novartis, Pfizer, Roche, Takeda, and FMI. The remaining authors have stated that they have no conflicts of interest.

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