The risk of bladder cancer in patients diagnosed with other primary neoplasms: Analysis of the SEER database

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Abstract

Objective: We evaluated patients with history of previous malignancy to determine risk of an ensuing bladder cancer.

Materials and methods: The National Cancer Institute’s Surveillance, Epidemiology, and End Results 9 registry database from 1973 to 1999 (SEER) was reviewed for patients with initial primary cancers in oral cavity and pharynx, colon and rectum, respiratory system, breast, prostate, testis, or penis. This group of patients was then examined to identify subsequent separate primary malignancies in the bladder. Comparison was made to the incidence of bladder cancer in the general population to determine a standardized incidence ratio (SIR). Additional analysis was performed based on age at diagnosis, stage, gender, race, and use of external beam radiation for treatment of initial cancer.

Results: A total of 7,289 (0.5%) of patients had a bladder cancer following their initial malignancy. Patients with prostate cancer had the largest increase in risk of bladder cancer with a SIR of 8.24, and all initial cancer groups had an elevated risk of bladder cancer relative to the general population. External beam radiation and non-White gender were associated with an increased risk of bladder cancer. Older age at diagnosis of the initial cancer correlated with a lower risk of subsequent bladder cancer.

Conclusions: This study suggests an increased risk of bladder cancer following a separate initial cancer. Lower threshold for working up those patients for bladder cancer may be warranted. © 2013 Elsevier Inc. All rights reserved.

Keywords: Bladder; Cancer; Neoplasm

1. Introduction

It is well known that patients diagnosed and treated for muscle invasive bladder cancer have a high chance of recurrence after cystectomy due to micrometastasis. Thus, early detection of bladder cancer may allow for better outcomes through treating the cancer at an earlier stage. Mass population surveillance is not feasible, but the identification of patients who are at increased risk of having such cancer for early detection may be the way to go to keep the costs down and achieve higher survival rates [1,2].

It is becoming apparent, with the great advances in cancer epidemiology, that many cancers share the same risk factors and thus may occur synchronously or metachronously in the elderly population. In this study, we evaluate the history of a previous malignancy to determine its association with subsequent development of bladder cancer. If the history of a previous malignancy does increase bladder cancer incidence, a lower threshold for evaluating patients for bladder cancer may be indicated despite the low yield of bladder cancer screening in the general population.

2. Materials and methods

The National Cancer Institute’s Surveillance, Epidemiology, and End Results 9 registry database 1973–1999 (SEER) [3] was used as the source of patient information for this study to allow for enough follow up time. Data from the 1,345,169 patients with 1 of 7 initial malignancies were included in this analysis. Malignancies were chosen based on their shared exposures, radiation, and smoking, with bladder cancer. These initial malignancies, as defined by the SEER database, were oral cavity and pharynx (n = 60,943),...
colon and rectum \((n = 286,618)\), respiratory system \((n = 339,366)\), breast \((n = 354,989)\), prostate \((n = 286,131)\), testis \((n = 14,144)\), and penis \((n = 2,978)\). In the SEER database, the initial malignancy is a patient’s first known cancer, and subsequent and separate primary malignancies are included as they are diagnosed.

For this study, patient data were included even if there were additional malignancies diagnosed between the initial malignancy and the diagnosis of bladder cancer. All histologic subtypes were included in each malignancy group. Patients with bladder cancer found simultaneous to their initial malignancy were excluded. Patients with age < 20 years were excluded.

Data analysis was done using SAS statistical package (SAS Institute Inc., Cary, NC). Incidence of bladder cancer in the general population was extracted from the SEER database. The standardized incidence ratio (SIR) was calculated by dividing the incidence of bladder cancer in the respective initial malignancy groups by incidence of bladder cancer in the general population (this incidence was age or gender adjusted for those respective subgroup analysis). Additional subgroups of each initial cancer were formed. These subgroups were broken down by age at diagnosis, stage, gender, race, and use of external beam radiation for treatment of initial cancer. SIR was calculated for each subgroup as well.

### 3. Results

Patient and malignancy characteristics are shown in Table 1. Bladder cancer was diagnosed as an ensuing primary neoplasm in 7,289 (0.5%) of the patients in this study (Table 2). Among patients with an oral cavity and pharynx neoplasm, bladder cancer was identified subsequently in 0.6%; among those with colorectal cancer, 0.6%; with a respiratory system cancer, 0.3%; with breast cancer, 0.3%; and with prostate cancer, 1.1%. Of note, prostate cancer had the highest SIR of 8.24 and breast and testis cancer had the lowest SIR of 1.36.

Race and gender were analyzed to determine any effect on subsequent bladder cancer development. Gender was pertinent only for oral cavity and pharynx, colon and rectum, and respiratory system malignancies. In these groups, the differences in gender were small but did show a slight male predominance, even after the increased incidence of bladder cancer in males was factored into the SIR. For oral cavity and pharynx male SIR = 5.30 and female SIR = 4.64,
colon and rectum male SIR = 6.47 and female SIR = 5.13, and respiratory system male SIR = 6.51 and female SIR = 6.28. Analysis by race showed a tendency towards increased risk in non-White racial groups across all cancer groups. Most notable here were the SIR in the oral cavity and pharynx group (Asian SIR = 6.1, Black SIR = 6.4, White SIR = 4.1), colon and rectum (Asian SIR = 6.8, Black SIR = 6.2, White SIR = 4.0), respiratory (Asian SIR = 9.0, Black SIR = 6.8, White SIR = 5.0), and prostate (Asian SIR = 13.3, Black SIR = 11.7, White SIR = 7.9).

As patients with more than 2 malignancies were not excluded from this study, the place of bladder cancer in a patient’s sequence of malignancies was determined. Bladder cancer was the second malignancy in 89% of patients, the third malignancy in 10% of patients, and the fourth or greater in only 1% of patients.

Age at diagnosis of initial cancer appeared to play an important role in elevated risk of bladder cancer. As shown in Fig. 1, there was a prominent decrease in SIR as age at diagnosis of first cancer increased.

Finally, the effects of radiation to the pelvis during treatment of the initial cancer and stage of the initial cancer were evaluated. The stage of the initial cancer did not play an important role in the SIR of a subsequent bladder cancer. Also, we did not find a discernable trend to a higher SIR with more advanced initial malignancy stage. Radiation to the abdomen and pelvis did, on the other hand, have a correlation with increasing risk of subsequent bladder cancer. For colon and rectum cancer, the SIR for patients not receiving radiation treatment \( n = 254,224 \) was 4.25 vs. 5.72 for patients receiving external beam radiation \( n = 26,418 \). For prostate cancer the SIR were 7.59 for patients without radiation \( n = 198,474 \) vs. 10.10 for patients previously treated with external beam \( n = 75,317 \).

### 4. Discussion

As treatment of malignant neoplasms has improved survival and common epidemiologic grounds are shared between different cancers, the question of whether one malignancy is associated with increased risk of a second separate primary malignancy has become a more important one and, with it, the obvious corollary of whether this association is strong enough to warrant intensifying efforts for early detection. While there is no overall increase in second malignancies in general following a primary neoplasm [4], there are multiple examples of increased risk of second primary malignancies following specific urologic tumors. Salinen et al. followed 10,014 patients with bladder cancer and found a significantly increased risk of lung cancer with an SIR of 1.31 [5].

Once the link between select initial malignancies and subsequent primary tumors was established, much speculation occurred as to the etiology of this observation. Possible explanations include a common genetic basis leading directly to malignancy or at least to an increased propensity to form neoplasms after an environmental exposure. The type or extent of environmental exposure could also play a role. These exposures could be encountered in everyday life or as part of treatment for the initial cancer (e.g., radiation treatment), and could have an effect of more than 1 cancer system [8].

Our study shows increased incidence of bladder cancer after other malignancies known to be associated with tobacco consumption. In an analysis of 279,745 patients from the Finnish Cancer Registry, Teppo et al. found significantly elevated SIR for bladder cancer following both larynx and lung cancer (SIR 1.83), but not for colon or prostate cancer [4]. In an epidemiologic review, Begg et al. utilized the SEER database from the early 1990s to determine risk of second primary malignancy. Elevated SIR ranging from 1.5 to 3.7 were found for bladder cancer following both head/neck and lung cancer. These elevated SIR remained significant when subgroups were analyzed by gender and time from initial primary to second primary [9]. Unfortunately, smoking history is not included in the SEER database and it was not possible to determine if a specific level of tobacco usage was necessary to increase the risk of subsequent bladder cancer.

There are previous studies that suggested therapeutic radiation for pelvic malignancies as a risk factor for developing subsequent bladder cancer [10]. Our results confirm such an association. One caveat here is that SIR continued to be elevated in a subset analysis that included non-radiation-treated colon, rectum, and prostate cancer patients; a common exposure or shared genetic bases may help explain that it is also
important to realize that radiation delivery systems have evolved over the years to be more organ targeted, which decreases radiation effect on the surrounding organs and may thus decrease the risk of secondary malignancies. The nature of the SEER database and the time frame of the study limit our ability to further investigate this assumption.

In addition to radiation, age at diagnosis of the first cancer played an even more prominent role in the risk of subsequent bladder cancer. As seen in Fig. 1, younger age was not only associated with higher risks of bladder cancer, but it had the largest impact of any of the factors investigated in this study. This effect was also found by Teppo et al. who noted that younger patients had noticeably higher relative risks of subsequent cancers [4]. This might be explained by a more intense exposure to risk factors, like smoking, leading to an early incidence of the primary malignancies as well as bladder cancer.

In this study, the initial primary cancer with the highest SIR was prostate cancer. Teppo et al. who identified no increased risk of bladder cancer following prostate cancer, [4] Wegner found a relative risk of 2.3 [11] and Liskow et al. had a relative risk of 5.1 [12] for bladder cancer following prostate cancer. Kim and Ignatoff found a higher than expected number of simultaneously diagnosed bladder and prostate cancers [13].

The strengths of this study are the large number of patients included and the 26-year period over which data was collected. Weaknesses include the retrospective nature of the data collection and the possible bias towards identifying bladder cancer in patients already diagnosed with another urologic malignancy. Another limitation was that we did not look at pelvic gynecologic malignancies, which represent another group of patients who may be at increased risk of developing bladder cancer due to shared risk factors and exposures with the cancer under study in this paper. Also, Patients diagnosed with primary malignancies may have had elevated SIR for bladder cancer due to more intense health care and follow up. The SIR were, however, high and may not completely explained by such assumption. Finally, other recent studies have looked at the same subject [14], but our study includes more cancers and is applicable to a larger proportion of the population seen in the daily urology clinic.

5. Conclusion

Patients with an initial malignancy are at increased risk of a subsequent bladder cancer. This risk is most prominent in young patients with prostate cancer, but does persist in the younger age groups of the other cancers analyzed. Such association indicates that attention to the signs of bladder cancer and having lower threshold for work-up is warranted in this group of patients. It remains that a prospective study is necessary to prove that such a modification in management would prevent morbidity and/or mortality from bladder cancer.

References