

# Tuberculosis Chemotherapy and Risk of Bladder Cancer

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In a population-based study of 2982 bladder cancer patients and 5782 population controls from 10 geographical areas of the US, no excess risk was associated with medications used for tuberculosis treatment or prophylaxis (relative risk (RR) = 0.95). The findings agree with other epidemiological studies that have not confirmed earlier reports linking isoniazid (INH) exposure to bladder cancer.

Isoniazid (INH) has been widely used since 1952 as the drug of choice in tuberculosis treatment and prophylaxis. In 1974, an increased risk of bladder cancer was reported in association with INH use<sup>1</sup> and confirmed in a second study among females but not males.<sup>2</sup> An elevated bladder cancer risk was also reported in a cohort study of 878 patients treated with INH.<sup>3</sup> The possibility that altered tryptophan metabolism which can be induced with INH<sup>4</sup> may be related to bladder cancer susceptibility<sup>5,6</sup> has raised further concern about the safety of this drug.

On the other hand, follow-up studies of several thousand individuals given INH in the US, Canada and Puerto Rico have shown no elevation in bladder cancer incidence.<sup>7–10</sup> Similarly, no relationship was seen in a case-control study of 142 bladder cancer patients.<sup>11</sup>

To determine if an association exists between tuberculosis chemotherapy and bladder cancer, we analysed data collected in a national case-control study of 2982 patients with bladder cancer and 5782 controls, which was conducted to evaluate the role of artificial sweeteners and other suspected risk factors for bladder cancer.

## METHODS

Through the Surveillance, Epidemiology and End Results (SEER) Program and the New Jersey Cancer Registry, we identified residents of metropolitan Atlanta, Detroit, New Orleans, San Francisco, Seattle and the states of Connecticut, Iowa, New Mexico,

Utah, and New Jersey, aged 21–84, who were newly diagnosed with histologically proven carcinoma of the urinary bladder during a one-year period beginning in December 1977. Details of the study and methods are presented elsewhere.<sup>12,13</sup> During the study period, 4045 eligible cases were identified and contacted for interview within 90 days of diagnosis; 3673 cases were alive at time of contact and 2982 agreed to be interviewed.

Controls comprised an age- and sex-stratified random sample of the general population in the 10 geographical areas, using a 2:1 frequency-matching ratio of controls to cases. Controls aged 21–64 were chosen from a census of individuals obtained through a random-digit dialling procedure, in which telephone numbers were randomly selected from all residential telephones in each area (98% of cases also had telephones). Controls aged 65–84 were randomly selected from the enumeration of US citizens over age 65 obtained by the Health Care Financing Administration. Eighty-three per cent of the controls thus selected agreed to participate (5782 controls).

Structured questionnaires were administered through personal interviews conducted by trained interviewers in homes of respondents. They were asked whether medication was ever taken for tuberculosis or because a tuberculosis patch test was positive.

The measure of association used is the maximum likelihood estimate of the relative risk (RR). Potentially confounding variables were controlled through multiple contingency table analysis,<sup>14</sup> and through multiple logistic regression analysis with bladder cancer as the outcome variable.<sup>15</sup> Confidence intervals (CI) for individual risk estimates obtained through multiple

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contingency table analysis were calculated according to Gart.<sup>14</sup>

## RESULTS

A history of medication for tuberculosis was reported by 2% of study participants (51 cases, 111 controls), and was not associated with an increased risk of bladder cancer (overall RR = 0.95, adjusted for age, sex and smoking; 95% CI 0.66–1.37). Adjustment for potential confounding through contingency table and multivariate analyses for alcohol intake, education or race gave similar estimates.

Relative risk estimates were also examined according to the usual adult pattern of cigarette use (Table 1), since a history of tuberculosis chemotherapy was associated with cigarette smoking. The risk of bladder cancer associated with tuberculosis chemotherapy was not consistently elevated by pattern of cigarette use.

Due to the common prescription of INH for tuberculosis treatment and prophylaxis since 1952, it is likely that most younger respondents reporting tuberculosis medication had used this drug. Among individuals under age 35, the risk of bladder cancer associated with tuberculosis chemotherapy was 2.8 but was based on one case and was not statistically significant. No elevation or trend in risk was seen for people aged 35–44, 45–64, or 65 and older (RR = 1.0, 0.6 and 1.1, respectively).

TABLE 1 *Relative risks of bladder cancer associated with history of tuberculosis chemotherapy, by pattern of cigarette use\*; 10 geographical areas of the United States, 1978.*

Pattern of cigarette use	Males	Females	Total**
Never smoked	1.0 (5,19) <sup>†</sup> [0.3–3.0]	1.7 (9,17) [0.7–4.2]	1.4 [0.7–2.7]
Smokers:***			
<20 cigarettes/day	1.3 (8,14) [0.5–3.4]	0.8 (3,6) [0.2–3.9]	1.1 [0.5–2.6]
20–39 cigarettes/day	1.2 (19,23) [0.6–2.3]	— (0,4)	1.0 [0.5–1.9]
40+ cigarettes/day	0.3 (4,18) [0.1–1.1]	— (0,0)	0.3 [0.1–1.1]

\* Maximum likelihood estimate of relative risk adjusted for race and age.

\*\* Additionally adjusted for sex.

\*\*\* Smoker refers to current or ex-smoker. Number of cigarettes per day refers to usual adult pattern of use.

<sup>†</sup> Number of exposed cases and controls in parentheses; 95% CI in brackets.

## DISCUSSION

This population-based study of nearly 3000 patients with bladder cancer does not support an association with prior exposure to tuberculosis chemotherapy. It should be noted, however, that information was not available on the years during which this medication was used. Since a long latency period appears involved in bladder carcinogenesis,<sup>16</sup> it is possible that an insufficient period of time may have elapsed to detect an increased risk associated with INH. In addition, a few of the respondents who reported taking medication for tuberculosis therapy or prophylaxis may not have received INH. The proportion of such individuals would be small, however, since other drugs such as streptomycin were used only a short period of time before INH became available in 1952, and INH has since become the drug of choice for tuberculosis treatment and prophylaxis. Furthermore, the percentage of controls in our study who took tuberculosis medication is similar to that for INH use in two positive studies.<sup>1,2</sup>

In 1974 and 1978, case-control studies of bladder cancer in urology clinic outpatients by the same investigators suggested a two- to three-fold increased risk of bladder cancer associated with INH use.<sup>1,2</sup> However, the results did not reach statistical significance, and one study<sup>2</sup> found the association only among females. An excess risk of bladder cancer was also suggested in a cohort study (RR = 2.5),<sup>3</sup> but all subsequent investigations have shown no relationship between INH experience and bladder cancer.<sup>7,11</sup> Nor did our study, with sufficient statistical power to detect a significant risk of 1.5, support an association. Although our data could not delineate the effects of single drugs, dosage or latency, the results provide further evidence that the usual course of medication for tuberculosis treatment or prophylaxis does not increase the risk of bladder cancer.

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