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Cancer-specific incidence rates of tuberculosis

A 5-year nationwide population-based study in a country with an intermediate tuberculosis burden

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Abstract

Population-based studies of the incidence of tuberculosis in cancer patients according to the type of cancer are limited. We investigated the cancer-specific incidence of tuberculosis in a nationwide population-based cohort in a country with an intermediate burden of tuberculosis.

We used mandatory National Health Insurance claims data to construct a cancer cohort of adults (aged 20–99 years) with newly diagnosed malignancies other than lung cancer, from January 2008 to December 2012. Patients who developed tuberculosis in this period were identified in the cancer cohort and the general population. Standardized incidence ratios (SIRs) of tuberculosis in the cancer cohort according to type of cancer and time after cancer diagnosis were calculated by comparing the observed incidence rates with those inferred from the age- and gender-specific incidence rates in the general population.

A total of 855,382 cancer patients and 1589,876 person-years (py) were observed. A total of 5745 patients developed tuberculosis; the mean incidence rate was 361.3 per 100,000 py, and the SIR was 2.22 (95% confidence interval [CI], 2.17–2.27). The incidence rate was highest for hematologic malignancy and lowest for thyroid cancer. It was also highest as 650.1 per 100,000 py, with SIR of 3.70 (CI, 3.57–3.83) for the first 6 months after diagnosis of malignancy and then declined. However, it still remained higher than that of the general population after 24 months (SIR = 1.43, CI, 1.36–1.51).

The incidence of tuberculosis increases after diagnosis in patients with malignancies. The risk of tuberculosis differs according to the type of cancer and remains elevated even 24 months after cancer diagnosis. Tuberculosis should be considered an important comorbidity in patients with malignancies.

Abbreviations: CI = confidence interval, HIRA = Health Insurance Review and Assessment Service, ICD-10 = International Classification of Disease, Tenth edition, IQR = interquartile range, NHI = National Health Insurance, NTM = nontuberculous mycobacteria, py = person-years, SIR = standardized incidence ratio.

Keywords: cancer, incidence, intermediate burden, malignancy, population-based, tuberculosis

1. Introduction

The incidence of cancer has increased with time, and the average length of survival of cancer patients has also been prolonged due to advances in treatment.[1,2] Thus, the size of the population suffering from malignancies is expanding, and the management of complications in this population is growing in importance. Infection remains a major cause of morbidity and mortality in patients with cancer.[3] Tuberculosis, a widespread infectious disease, remains a major public health problem and is not uncommon in patients with cancer. However, studies of tuberculosis in cancer patients are rare and tend to be neglected except for lung cancer. The incidence of tuberculosis has been reported to increase in patients with malignancies.[4,5] Immunologic deterioration due to the cancer itself or to the treatments for the cancer and accompanying malnutrition are thought to play an important role in the reactivation of tuberculosis.

In Korea, the incidence of tuberculosis is decreasing but is still as high as 78.5 per 100,000 person-years (py).[6,7] The proportion of the elderly among new tuberculosis cases is increasing, and malignancy is becoming a common comorbidity.[8] As identification of high-risk groups can help in the early detection of active tuberculosis cases, it is important to establish whether cancer increases the risk of tuberculosis, and, if so, under what circumstances. One hospital-based study reported an increased incidence of tuberculosis in patients with malignancies in Korea.[9] However, no large population-based study has been conducted on this issue. Data on cancer-specific incidence rates of

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tuberculosis are limited. We have investigated the incidence of tuberculosis in patients with malignancies according to the type of cancer in a nationwide population-based study.

2. Methods

2.1. Data sources

We used Health Insurance Review and Assessment Service (HIRA) insurance benefits reimbursement claims. In Korea, the National Health Insurance (NHI) system is a mandatory health insurance program which offers universal medical care for all citizens. All medical institutions are covered by the NHI, and they submit insurance claims to the HIRA, which then reimburses them after review of the claims. The claims data include age, gender, medication, and primary discharge diagnosis. Diagnoses were classified using the International Classification of Disease, Tenth edition (ICD-10).

2.2. Study populations

We performed a retrospective cohort study from January 1, 2008 to December 31, 2012. We constructed a cancer cohort of patients, aged 20 to 99 years, who were newly diagnosed with malignancies during the period. We included those patients who were admitted to a hospital whose discharge diagnosis was cancer according to the ICD-10 code. Patients with a diagnosis of lung cancer were excluded because they tended to be prescribed antituberculosis medication even when the diagnosis was uncertain. The date of the first day of admission was recorded as the date of cancer diagnosis. To include only patients whose malignancy was newly detected, patients with a record of 1 or more in-hospital treatment or 4 episodes of ambulatory care with a diagnosis of cancer during the previous year were excluded.

Patients who developed tuberculosis during the study period were identified among the general population using the same nationwide database of HIRA, and those who were included in the cancer cohort were identified. Patients who were given any 3 of the antituberculosis drugs—isoniazid, rifampin, ethambutol, pyrazinamide, cycloserine, prothionamide, and *para*-aminosalicylic acid—were assumed to have developed active tuberculosis. To exclude patients who were already under antituberculosis treatment at the beginning of our study, we checked the prescription data for 1 year before the study period, and patients who had a record of antituberculosis medication before the diagnosis of cancer were excluded. The date of the first prescription of antituberculosis medication was recorded as the date of diagnosis of tuberculosis. Patients in the cancer cohort were followed up until tuberculosis was diagnosed, or until the day of their last hospital visit, or December 31, 2012.

2.3. Standardized incidence ratio of tuberculosis

The age- and gender-specific reference incidences of tuberculosis in the general population were calculated. Ages were divided into 5-year intervals. The expected incidence of tuberculosis was obtained by applying these reference incidences of tuberculosis to the population with the given cancer type. The standardized incidence ratio (SIR) of tuberculosis was calculated by comparing the calculated expected incidence with the observed incidence. The SIRs of tuberculosis according to the specific cancer types were identified. The incidence rates and SIRs of tuberculosis according to the time after diagnosis of cancer were also calculated.

2.4. Statistical analysis

We assumed that the development of tuberculosis followed a Poisson distribution, and the SIRs were calculated using the Poisson distribution. R statistics (version 2.15.3/R package; http://www.r-project.org) was used for the statistical analysis.

2.5. Ethical review

This study was exempt from review by the ethical committee of the Seoul National University Bundang Hospital (no. X-1509-316-905).

3. Results

3.1. Tuberculosis incidence rate and the standardized incidence ratio in patients with cancer

A total of 855,382 patients with cancer were enrolled. Of these patients, 47.4% were male. Median age was 59.0 years, and interquartile range (IQR) was from 48 to 70 years. Follow-up was for a median 1.6 years (IQR 0.6–3.0), and 1589,876 py were observed. During the study period, 5745 patients developed tuberculosis, and the incidence rate was 361.3 per 100,000 py among the patients with cancer.

In the same study period, 230,247 patients developed tuberculosis in the general population between ages 20 and 99 years. Their median age was 53.0 years (IQR 38.0–70.0), and 57.4% were male. The average incidence rate of tuberculosis in the general population was 125.3 per 100,000 py, and the expected incidence rate in the population with newly diagnosed malignancies was 163.0 per 100,000 py. Because the observed incidence rate of tuberculosis was 361.3 per 100,000 py, the SIR of this population was 2.22 (95% confidence interval [CI], 2.17–2.27, $P < 0.001$).

3.2. Incidence rates and SIRs for specific cancer types

Among the 855,382 enrolled patients, 170,597 (19.9%) had thyroid cancer and 153,158 (17.9%) had gastric cancer; 83,512 (9.8%), hepatocellular carcinoma; 77,903 (9.1%), colon cancer; 75,801 (8.9%), breast cancer; 32,026 (3.7%), hematologic malignancy; 22,822 (2.7%), pancreas cancer; 20,452 (2.4%), biliary tract cancer; and 219,111 (25.6%), other cancers. The incidence rate of patients with a given cancer was highest at 1068.6 per 100,000 py for hematologic malignancy and lowest at 139.9 per 100,000 py for thyroid cancer. The corresponding SIRs were 6.67 (95% CI, 6.19–7.17; $P < 0.001$) for hematologic malignancy and 1.52 (95% CI, 1.41–1.63; $P < 0.001$) for the thyroid cancer. Incidence rates and SIRs for specific cancers are shown in Table 1.

3.3. Incidence rates and SIRs for specific periods after diagnosis of cancer

The incidence rates of tuberculosis after the diagnosis of malignancy differed depending on the time after diagnosis. The incidence rate was 650.1 per 100,000 py for the 6 months following diagnosis, 364.3 per 100,000 py for 6 to 11 months, 281.6 per 100,000 py for 12 to 23 months, and 220.2 per 100,000 py for more than 24 months after diagnosis. The SIRs were 3.70 (95% CI, 3.57–3.83; $P < 0.001$), 2.19 (95% CI, 2.08–2.30; $P < 0.001$), 1.75 (95% CI, 1.67–1.84; $P < 0.001$), and 1.43 (95% CI, 1.36–1.51; $P < 0.001$), respectively (Fig. 1). For

Table 1

The incidence rate and the SIR of tuberculosis according to the cancer type.

	Number of patients with cancer	Number of patients with cancer who developed tuberculosis	Incidence rate* of tuberculosis	SIR (95% CI)
Total	855,382	5745	361.3 (163.0)	2.22 (2.17–2.27)
Thyroid cancer	170,597	526	139.9 (92.0)	1.52 (1.41–1.63)
Gastric cancer	153,158	1484	513.1 (204.4)	2.51 (2.40–2.62)
Hepatocellular carcinoma	83,512	460	451.2 (193.6)	2.33 (2.15–2.52)
Colon cancer	77,903	586	405.5 (211.1)	1.92 (1.79–2.06)
Breast cancer	75,801	322	188.9 (86.7)	2.18 (1.98–2.39)
Hematologic malignancy	32,026	508	1068.6 (160.3)	6.67 (6.19–7.17)
Pancreas cancer	22,822	112	669.3 (211.4)	3.17 (2.69–3.70)
Biliary tract cancer	20,452	72	305.8 (227.4)	1.34 (1.09–1.64)
Other cancers	219,111	1675	399.0 (200.0)	2.00 (1.92–2.08)

CI = confidence interval, SIR = standardized incidence ratio.

* Age–gender-matched expected incidence rate of tuberculosis per 100,000 person-years.

patients with thyroid cancer and biliary tract cancer, the SIRs of tuberculosis did not differ significantly 6 months after the diagnosis of cancer. In contrast, the SIRs for hematologic malignancy, pancreatic cancer, gastric cancer, and hepatocellular carcinoma remained above 1.5, even 24 months after the diagnosis of cancer. The detailed data on the incidence rates and SIRs according to time and type of cancer are shown in Table 2.

4. Discussion

We demonstrated that the risk of tuberculosis in patients with cancer is higher than general population and the risk differs according to the type of cancer and remains elevated even 24 months after cancer diagnosis in a country of intermediate burden of tuberculosis. We identified patients with newly diagnosed cancer and checked whether they developed tuberculosis. We used our own definitions to identify the patients with malignancies and tuberculosis using the HIRA database. We calculated the SIR of tuberculosis as 2.22 in patients with cancer compared to the general population. Among the specific cancers, the SIR was the highest in patients with hematologic malignancy, followed by the patients with pancreatic cancer, gastric cancer, hepatocellular carcinoma, and breast cancer.

In relation to immunologic deterioration due to the cancer itself and its treatment, the cancer stage at the time of diagnosis and treatment could be an important influence on the development of tuberculosis. Because we did not collect detailed information about cancer stage and chemotherapy regimen, it is not easy to determine why the SIR depends on the type of cancer. We could only examine the effect of cancer stage at diagnosis indirectly using other data. Among the solid organ cancers, the pancreatic cancer had the highest SIR (3.17). We carefully presume that this high SIR is associated, at least in part, with the fact that patients with pancreatic cancer had the highest rate of advanced or metastatic disease among the solid tumors. According to the data in the National Cancer Registry, 45.4% of those patients had advanced disease at the time of diagnosis of cancer.[2] In addition, the low SIR (1.52) of thyroid cancer is thought to reflect the fact that most of them (99.2%) are early-stage cancers and that the recurrence rate is very low.[10]

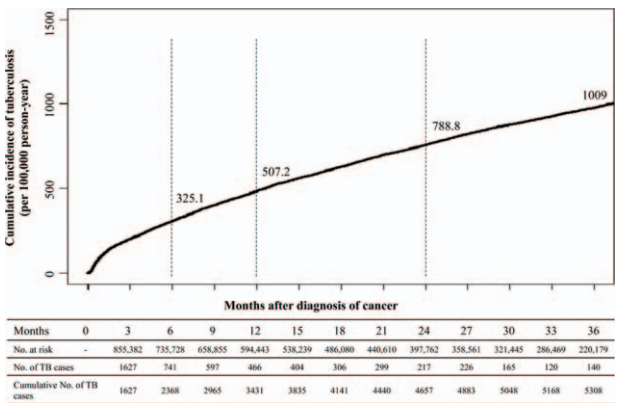

Figure 1. Cumulative incidence of tuberculosis after the diagnosis of malignancy.

When the SIRs were calculated according to the specific period after diagnosis of cancer, they were highest immediately after the diagnosis of cancer. Patients with cancer usually receive the most medical attention and undergo the most frequent examinations soon after diagnosis, and this may lead to the highest tuberculosis incidence (650.1 per 100,000 py immediately after diagnosis of cancer). It is also probable that the early treatments of cancer, such as surgery and chemotherapy, impair immunity, leading to increased infection or reactivation of tuberculosis. The incidence gradually decreased toward that of the general population, but still remained higher for more than 24 months after the diagnosis of cancer. The SIR also remained significantly above 1. We therefore suggest that a history of cancer treatment within the previous 2 years should be considered a risk factor of tuberculosis along with other medical conditions, such as diabetes and chronic kidney disease.[11,12] The period-specific SIRs of thyroid cancer formed an unusual pattern. The SIR increased to 3.33 immediately after the diagnosis and gradually decreased to around 1 over 6 months. This probably also reflects the low severity of illness and low recurrence rate of thyroid cancer and the fact that it is overdiagnosed in some way.[13]

The strength of our study is its large population size. Previously 1 hospital-based report suggested a higher incidence of tuberculosis in patients with cancer in Korea.[9] However, our large population-based study allowed a comparison with the incidence of tuberculosis in the general population. Although we applied our own definitions to the specific database, we confirmed them using the result of national registry data on cancer and the tuberculosis.

Table 2

The incidence rate and the SIR of tuberculosis according to the time after diagnosis of cancer.

Time after cancer diagnosis	0–5 mo		6–11 mo		12–23 mo		More than 24 mo	
Type of cancer	IR*	SIR (95% CI)	IR*	SIR (95% CI)	IR*	SIR (95% CI)	IR*	SIR (95% CI)
Total	650.1	3.70 (3.57–3.83)	364.3	2.19 (2.08–2.30)	281.6	1.75 (1.67–1.84)	220.2	1.43 (1.36–1.51)
Thyroid cancer	309.7	3.33 (2.99–3.70)	97.8	1.06 (0.85–1.30)	99.5	1.08 (0.92–1.27)	91.1	1.00 (0.85–1.17)
Gastric cancer	774.2	3.58 (3.33–3.86)	504.6	2.44 (2.20–2.70)	447.8	2.21 (2.02–2.42)	390.1	1.99 (1.82–2.17)
Hepatocellular carcinoma	645.8	3.12 (2.76–3.52)	454.2	2.31 (1.93–2.75)	349.6	1.85 (1.54–2.20)	326.4	1.81 (1.50–2.18)
Colon cancer	794.1	3.57 (3.22–3.96)	339.2	1.58 (1.32–1.88)	314.1	1.50 (1.29–1.74)	239.6	1.18 (1.00–1.39)
Breast cancer	357.3	4.03 (3.45–4.68)	195.6	2.24 (1.78–2.78)	154.9	1.79 (1.46–2.17)	113.3	1.33 (1.07–1.63)
Hematologic malignancy	2122.7	12.01 (10.81–13.30)	1215.4	7.44 (6.31–8.71)	650.8	4.17 (3.44–5.01)	396.4	2.70 (2.12–3.39)
Pancreas cancer	1048.0	4.59 (3.77–5.54)	397.1	1.94 (1.17–3.03)	336.6	1.71 (0.96–2.84)	367.2	1.94 (1.01–3.39)
Biliary tract cancer	392.4	1.59 (1.14–2.17)	257.7	1.12 (0.65–1.81)	274.9	1.24 (0.78–1.89)	267.3	1.29 (0.80–1.99)
Other cancers	699	3.30 (3.09–3.52)	457.4	2.24 (2.05–2.45)	318.2	1.61 (1.47–1.75)	221.8	1.17 (1.06–1.29)

CI = confidence interval, IR = incidence rate, SIR = standardized incidence ratio.
* Age–gender-matched expected incidence rate of tuberculosis per 100,000 person-years.

We defined patients with newly diagnosed cancer based on the primary discharge diagnosis and admission data, and the population statistics inferred by this method agreed grossly with the National Central Cancer Registry data. For example, according to the National Central Cancer Registry, 6231 men and 29,790 women developed new thyroid cancer in 2010,[2] and using our method, we identified 5936 men and 29,231 women with newly diagnosed thyroid cancer in 2010. The statistics on gastric cancer, colorectal cancer, and breast cancer agreed in a similar way.

Tuberculosis is a nationally notifiable communicable disease in Korea. The Korean Centers for Disease Control and Prevention publishes annual reports on notified tuberculosis.[14] They reported that 22,371 men and 17,186 women newly developed tuberculosis de novo in 2011, and 20,547 men and 15,298 women in 2009. Our method identified 26,545 men and 19,856 women who started antituberculosis medication in 2011, and 28,785 men and 21,354 women in 2009. It thus identified a roughly 20% larger population than the registry data. We think that this difference was due to the relapsed patients who had been treated for tuberculosis several years before the diagnosis of cancer, as we only excluded patients who were under antituberculosis treatment within 1 year before the diagnosis of cancer. We thought it was preferable to include these patients because they represent reactivated tuberculosis.

Our study has several limitations. First, we could not identify comorbid conditions that might have affected the development of tuberculosis; poorly controlled diabetes, corticosteroid or immunosuppressant treatment, and malnutrition are known risk factors for reactivation of tuberculosis and could have confounded our results.[4] Second, we may have missed patients whose initial antituberculosis medication included quinolones or injectable drugs. In addition, conversely some patients in our study could have had infections caused by nontuberculous mycobacteria (NTM), such as *Mycobacterium kansasii*, which is treated with antituberculosis medications. However, considering the low prevalence of NTM disease—4.38 per 100,000 py—we think that this effect should be only minimal.[15] Third, our method could not provide a reliable estimate of the incidence of tuberculosis in patients with lung cancer. The calculated that incidence in patients with lung cancer was even higher than the incidence in patients with hematologic malignancy (data not shown). Although several reports suggest that lung cancer is closely related to tuberculosis,[16] we regard our finding as invalid because tuberculosis is considered a possible differential diagnosis during the initial evaluation of lung cancer in this country with an intermediate tuberculosis burden. Thus, patients without tuberculosis also tend to be prescribed with antituberculosis medication and erroneously included in the analysis. We excluded the patients with lung cancer from the analysis. Finally, when calculating the incidence rate of tuberculosis in the general population, cases of tuberculosis in patients with malignancy were also included as tuberculosis cases. To identify the increased risk related with the malignancy and its treatment, incidence of tuberculosis in the patients with malignancy needs to be compared with that in healthy control. However, it was almost impossible to get healthy control population from the HIRA database because it was a medical reimbursement database and thus included various kinds of patients who had different potential to develop tuberculosis. We considered that it would be more meaningful to compare the tuberculosis incidence between the patients with malignancy and the total general population. Even more, the proportion of tuberculosis in the patients with malignancy is low, 2.49% (5745/230,247), among the general population and thus would not change the incidence rate greatly.

In summary, our population-based study shows that the incidence of tuberculosis increases after diagnosis in patients with malignancies. Among the specific types of cancer, patients with the hematologic malignancy, gastric cancer, hepatocellular carcinoma, and colon cancer had increased the incidence of tuberculosis. The incidence was highest immediately after the diagnosis of cancer and then gradually decreased. However, it still remained higher than that of the general population even 24 months after the diagnosis. Tuberculosis should be considered an important comorbidity in patients with malignancies.

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