

Cancer Risk in Tuberculosis Patients in A High Endemic Area

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Abstract

Objective

To evaluate the risk of cancer after tuberculosis (TB), we performed a case-control study of the prevalence rate of TB in a high endemic area.

Methods

From January 2016 to December 2018, a total of 45,455 patients were consecutively enrolled and divided into a malignant tumor group (n=32,539) and a benign tumor group (n=12,916). Patients with active and inactive TB before the diagnosis of cancer were retrospectively identified in the two groups.

Results

A significantly higher prevalence rate of TB was found in the malignant tumor group (n=1776, 5.46%) than in the control (benign tumor) group (n=175, 1.35%) ($p<0.0001$). The highest and lowest prevalence rates of TB in the malignant group were in patients with non-Hodgkin's lymphoma (16.74%) and thyroid cancer (0.77%), respectively. In multivariate analysis adjusting for age, sex, and ethnicity, TB remained an independent risk factor for all cancers (odds ratio (OR) 1.68; 95% confidence interval (CI) 1.43-1.97). Furthermore, TB was associated with a significantly higher risk of non-Hodgkin's lymphoma, cervical cancer, esophageal cancer, "other" cancers, ovarian cancer, and breast cancer. Moreover, females with TB were more likely to develop cancer than males ($p<0.0001$), except for esophageal cancer and lymphoma.

Conclusion

TB patients have an elevated cancer risk. A screening strategy for TB should be taken into consideration before treatment in patients with some cancer types that are associated with a high prevalence rate of TB.

Introduction

Tuberculosis (TB) may induce a chronic inflammatory state and impair T-cell-mediated immunity, contributing to the development of cancer.[1-3] Understanding the risk of the development of cancer after TB in a high endemic area has some practical clinical significance, such as improving the prevention and diagnosis of cancer.

Western China is a high endemic area for TB.[4, 5] The patient diagnosis rate of pulmonary TB was 0.34 (95% confidence interval (CI) 0.25-0.44) in the 2010-2011 Xinjiang survey.[4] In addition, the burden of multidrug-resistant and extensively drug-resistant TB cases was also found to be substantial in the Xinjiang area.[5] A number of epidemiologic studies have shown that the risk of cancer is the greatest in the first two years after the diagnosis of TB diagnosis [2, 3, 6-8] but remains elevated for long periods.[7, 9-13] However, limited data are available from western China to support the link between cancer and TB. Data from such areas might add valuable insights into the relationship between TB and malignant cancer. Therefore, we performed a retrospective case-control study to compare the prevalence rate of TB in malignant tumor patients and benign tumor patients.

Patients And Methods

Patient selection method

From January 2016 to December 2018, a total of 46,371 inpatients were treated at Xinjiang Cancer Hospital, a tertiary cancer center in Xinjiang. This cohort was then divided into two groups, namely, the malignant tumor group (n=32,539) and the control (benign tumor) group (n=12,916) (Table 1), based on the definitive pathological diagnosis confirmed by at least 2 experienced pathologists. Patients who were diagnosed with TB after being diagnosed with cancer (n=272) and those lacking definitive pathological reports (n=644) were excluded from this study. This study was performed in accordance with the principles of the Declaration of Helsinki.

Identification of tuberculosis patients

A retrospective TB survey was performed in the two groups. Patients with active and inactive TB before the diagnosis of cancer (benign or malignant) were identified from the Department of TB Registry in Xinjiang Cancer Hospital. Among the TB patients, 1,673 had pulmonary TB, and 103 had extrapulmonary TB in the malignant tumor group, while 153 and 22 patients had pulmonary and extrapulmonary TB in the control group, respectively. In the malignant tumor group, most patients with TB disease had inactive pulmonary TB, according to clinical and radiological indicators such as old pulmonary TB (n=1690). Active pulmonary TB was found in 78 patients in the malignant tumor group who were positive for smear or culture results (n=12) or had radiographic abnormalities consistent with active pulmonary TB (n=66). In the control group, 167 patients had inactive pulmonary TB, and only 2 patients had radiographic abnormalities consistent with active pulmonary TB. Only 8 and 6 patients in the malignant tumor and control groups, respectively, had a past medical history of pulmonary TB diagnosed by their doctors.

In both groups, when patients were hospitalized multiple times, only the first hospitalization was included in this study. "Other cancer" refers to any cancer defined by type or site accounting for less than 5‰, including cancer originating in the testis, vulva, penis, vagina, labia majora, labia minora, perineum, scrotum, hydatidiform mole, chorion, notochord, adrenal cortex, neuroendocrine system, mediastinum, sweat glands, mesothelium, thymus, or umbilical tube.

Statistical analysis

Data were analyzed using SPSS (version 25.0; SPSS, Chicago, IL). To identify the risk of cancer associated with TB, age, sex, and ethnicity were adjusted for in the statistical analysis. Logistic regression was used to estimate the adjusted odds ratio (OR) and 95% confidence interval (CI). A 2-tailed P value < 0.05 was considered statistically significant.

Results

High prevalence rate of TB in malignant cancer patients

To assess the relationship between TB and tumors, we assigned the inpatients to two groups: the control group (benign tumor group, n=12,916) and the study group (malignant tumor group, n=32,539). The identified prevalence rates of TB in the control and malignant groups are presented in Table 1. In total, 175 patients (1.35%) in the control group and 1,776 patients (5.46%) in the study group had had TB prior to the diagnosis of cancer ($p < 0.0001$). In univariate analysis, TB was a risk factor for malignant cancer, in addition to traditional risk factors, such as age and sex ($p < 0.0001$). However, no significant difference in the prevalence rate of TB was found between patients of Han and non-Han ethnicities.

TB may be associated with an increased risk of specific cancer types

The prevalence rate of TB may vary among patients with different cancer sites or types. The prevalence rates of TB in patients with different cancer sites/types and the multivariate logistic regression analysis results stratified by cancer site/type and sex are shown in Table 2. The highest prevalence rate of TB was found in patients with hematologic

malignancies (15.66%), followed by those with unknown primary cancer (8.84%), “other” cancers (7.76%), digestive tract cancer (7.35%), genitourinary cancer (6.81%), head and neck cancer (6.63%), skin cancer (6.52%), central nervous system (CNS) cancer (3.83%), breast cancer (3.14%), and bone and soft tissue sarcoma (2.92%). In contrast, the lowest prevalence rate of TB was found in patients with thyroid cancer (0.77%). The fold change in the prevalence rate of TB for different cancer sites in the study group compared with the control (benign tumor) group is also shown in Figure 1.

In the multivariate logistic regression analysis, TB remained an independent risk factor for all cancers (OR 1.68, 95% CI 1.43-1.97), including lung cancer (OR 1.44, 95% CI 1.06-1.95) and extrapulmonary cancer (OR 1.72, 95% CI 1.46-2.02) after adjusting for sex and age. Analysis stratified by specific types of cancer revealed high risks of non-Hodgkin's lymphoma, cervical cancer, esophageal cancer, “other” cancer, ovarian cancer, head and neck cancer, and breast cancer, and reduced risks of thyroid and liver cancer after TB. No statistically significant elevations in the risk of cancers originating from the gastric-esophageal junction, stomach, colon, rectum, anus, or skin were observed. With the exception of esophageal cancer and non-Hodgkin's lymphoma, the relative cancer risk after TB was significantly elevated in females but not in males in the study group.

Discussion

The current case-control study was performed in Xinjiang Province in China, where the prevalence of pulmonary TB is high.[4] In this study, we found a higher prevalence rate of TB in patients with malignant cancers than in those with benign tumor. One interesting finding was that prior TB might increase the risks of some extrapulmonary cancers, including hematologic malignancies, esophageal cancer, genitourinary cancers, head and neck cancer, breast cancer, and “other” cancers. Furthermore, females seem to have a higher risk of developing cancer than males after TB, although esophageal cancer and non-Hodgkin's lymphoma were exceptions. Therefore, TB may contribute to the site- and sex-specific development of malignant cancer.

In accord with several prior studies[2, 6, 8, 10, 14], our results indicate an association between TB and certain cancer types (Table 3). Notably, prior TB has been consistently found to be associated with a subsequent high risk of hematological malignancies, including non-Hodgkin's lymphoma, Hodgkin's lymphoma, multiple myeloma, and leukemia. In addition, more than one published study has shown that patients with TB are relatively more susceptible to cancer in the digestive tract, genitourinary tract, and head and neck. Consistent with these findings, we showed that TB patients have elevated risks of esophageal cancer, cervical cancer, head and neck cancer, and ovarian cancer. Furthermore, we showed that TB patients had an elevated risk of breast cancer. However, our data did not show that there was an elevated risk of skin cancer risk after TB. In contrast to the increased risk of hepatobiliary cancers shown by Su *et al.*[10], we found that TB has a protective effect against liver cancers. The differences in the risk of specific types of cancer risk in TB patients might be due to both differences in the study populations and differences in the research design.

This study was performed in a high endemic area for TB with a large sample size. However, the current study was limited by estimating the real incidence of cancer after TB. In our study, we adjusted for age, sex, and ethnicity but lacked data to examine the role of tobacco smoking and other confounding factors associated with both TB and cancer. Furthermore, the misclassification of TB was also possible, although we included both active and inactive TB cases.

In clinical practice, clinicians should be alert to the association between cancer and TB. Some cohort studies have shown that the incidence of cancers in TB patients ranged from 7.2% to 11.6% (Table 3). The present study indicated that approximately 5% of cancer patients had prior TB in a high endemic area in China. Indeed, some scientists reported that the reactivation of latent TB infection had detrimental effects on outcomes in cancer patients during treatment with

immune checkpoint inhibitors[15] and intensive chemotherapy[15-18]. Thus, we recommend screening for latent or active TB before initiating immunotherapy and intensive chemotherapy in most cancer patients. However, we were unable to calculate the benefits of this screening strategy in cancer patients. A future prospective study assessing the relationship of TB with the prognosis in cancer patients is warranted.

Abbreviations

TB: tuberculosis; OR: odds ratio; CI: confidence interval; CNS: central nervous system.

Declarations

Ethics approval and consent to participate

This study was reviewed and approved by the Xinjiang Medical University Institutional Review Board.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Authors' contributions

S. Yang and D.M. Ji contributed equally in the initial conception, design and coordination of this study. All authors provided input and guidance in the revision and development of the study. Statistical support in preparing the study was provided by G.L. Chen and L. Guo. The manuscript was drafted by G.L. Chen and D.M. Ji. All authors have read and approved the final manuscript

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Competing interests

The authors have declared that no competing interests exist.

References

1. Cao S, Li J, Lu J, Zhong R, Zhong H: Mycobacterium tuberculosis antigens repress Th1 immune response suppression and promotes lung cancer metastasis through PD-1/PDI-1 signaling pathway. *Cell Death Dis* 2019, 10(2):44.
2. Simonsen DF, Farkas DK, Sogaard M, Horsburgh CR, Sorensen HT, Thomsen RW: Tuberculosis and risk of cancer: a Danish nationwide cohort study. *Int J Tuberc Lung Dis* 2014, 18(10):1211-1219.

3. Shu CC, Liao KM, Chen YC, Wang JJ, Ho CH: The burdens of tuberculosis on patients with malignancy: incidence, mortality and relapse. *Sci Rep* 2019, 9(1):11901.
4. Mijiti P, Yuehua L, Feng X, Milligan PJ, Merle C, Gang W, Nianqiang L, Upur H: Prevalence of pulmonary tuberculosis in western China in 2010-11: a population-based, cross-sectional survey. *Lancet Glob Health* 2016, 4(7):e485-494.
5. Qi YC, Ma MJ, Li DJ, Chen MJ, Lu QB, Li XJ, Li JL, Liu W, Cao WC: Multidrug-resistant and extensively drug-resistant tuberculosis in multi-ethnic region, Xinjiang Uygur Autonomous Region, China. *PLoS One* 2012, 7(2):e32103.
6. Kuo SC, Hu YW, Liu CJ, Lee YT, Chen YT, Chen TL, Chen TJ, Fung CP: Association between tuberculosis infections and non-pulmonary malignancies: a nationwide population-based study. *Br J Cancer* 2013, 109(1):229-234.
7. Yu YH, Liao CC, Hsu WH, Chen HJ, Liao WC, Muo CH, Sung FC, Chen CY: Increased lung cancer risk among patients with pulmonary tuberculosis: a population cohort study. *J Thorac Oncol* 2011, 6(1):32-37.
8. Everatt R, Kuzmickiene I, Davidaviciene E, Cicenias S: Non-pulmonary cancer risk following tuberculosis: a nationwide retrospective cohort study in Lithuania. *Infect Agent Cancer* 2017, 12:33.
9. Everatt R, Kuzmickiene I, Davidaviciene E, Cicenias S: Incidence of lung cancer among patients with tuberculosis: a nationwide cohort study in Lithuania. *Int J Tuberc Lung Dis* 2016, 20(6):757-763.
10. Su VY, Yen YF, Pan SW, Chuang PH, Feng JY, Chou KT, Chen YM, Chen TJ, Su WJ: Latent Tuberculosis Infection and the Risk of Subsequent Cancer. *Medicine (Baltimore)* 2016, 95(4):e2352.
11. Kamboj M, Sepkowitz KA: The risk of tuberculosis in patients with cancer. *Clin Infect Dis* 2006, 42(11):1592-1595.
12. Brenner DR, McLaughlin JR, Hung RJ: Previous lung diseases and lung cancer risk: a systematic review and meta-analysis. *PLoS One* 2011, 6(3):e17479.
13. Jia Z, Cheng S, Ma Y, Zhang T, Bai L, Xu W, He X, Zhang P, Zhao J, Christiani DC: Tuberculosis burden in China: a high prevalence of pulmonary tuberculosis in household contacts with and without symptoms. *BMC Infect Dis* 2014, 14:64.
14. Omoti CE, Olu-Eddo AN, Nwannadi AI: Co-existence of TB and adult haematological cancers in Benin City, Nigeria. *Trop Doct* 2009, 39(4):205-207.
15. Anastasopoulou A, Ziogas DC, Samarkos M, Kirkwood JM, Gogas H: Reactivation of tuberculosis in cancer patients following administration of immune checkpoint inhibitors: current evidence and clinical practice recommendations. *J Immunother Cancer* 2019, 7(1):239.
16. . In: *Latent tuberculosis infection: updated and consolidated guidelines for programmatic management*. edn. Geneva; 2018.
17. Force USPST, Bibbins-Domingo K, Grossman DC, Curry SJ, Bauman L, Davidson KW, Epling JW, Jr., Garcia FA, Herzstein J, Kemper AR *et al*: Screening for Latent Tuberculosis Infection in Adults: US Preventive Services Task Force Recommendation Statement. *JAMA* 2016, 316(9):962-969.
18. Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America. (IDSA), September 1999, and the sections of this statement. *Am J Respir Crit Care Med* 2000, 161(4 Pt 2):S221-247.

Tables

Table 1. Cancer risk in patients with tuberculosis (TB) stratified by patient characteristics

Characteristics	Malignant tumor group (N=32,539)		Benign tumor group (N=12,916)		P
	No	%	No	%	
Sex					<0.0001
Male	12,420	38.17	791	6.12	
Female	20,119	61.83	12,125	93.88	
Age, years					<0.0001
Median	55.0	-	41.4	-	
Range	2-99	-	5-91	-	
Ethnicity					0.2155
Han	21,845	67.13	8,734	67.62	
Non-Han	10,694	32.87	4,182	32.38	
Tuberculosis					<0.0001
TB	1,776	5.46	175	1.35	
Non-TB	30,763	94.54	12,741	98.65	

Notes: OR, odds ratio; 95% CI, 95% confidence interval.

* The OR was adjusted by sex and age (as a continuous variable).

Table 2. Prevalence rate of tuberculosis (TB) and cancer risk in patients stratified by tumor site

Cancer type (N.)	Total			Male			Female		
	N. of TB	%	Adjusted OR* (95% CI)	N. of TB	%	Adjusted OR# (95% CI)	N. of TB	%	Adjusted OR# (95% CI)
Benign tumor (n=12,916)	175	1.35	Reference	26	3.27	Reference	149	1.23	Reference
Malignant cancers (n=32,539)	1,776	5.46	1.68 (1.43-1.97)	861	6.93	1.12 (0.79-1.60)	915	4.55	1.83 (1.53-2.19)
Lung cancer (n=3968)	223	5.62	1.44 (1.06-1.95)	165	6.48	1.27 (0.83-1.94)	58	4.08	1.57 (1.04-2.37)
Adenocarcinoma (n=2046)	91	4.45	2.05 (1.43-2.95)	59	5.58	1.72 (1.06-2.81)	32	3.34	2.09 (1.28-3.41)
Squamous cell carcinoma (n=763)	57	7.47	1.35 (0.82-2.22)	50	7.37	1.53 (0.90-2.62)	7	8.24	NA
Small cell (n=497)	25	5.03	NA	22	5.66	NA	3	2.78	NA
Other (n=662)	50	7.55	1.38 (0.87-2.18)	34	8.04	1.44 (0.81-2.57)	16	6.69	NA
Extrapulmonary tumor (n=28,571)	1,553	5.44	1.72 (1.46-2.02)	696	7.05	1.17 (0.82-1.68)	857	4.59	1.88 (1.57-2.24)
CNS (n=287)	11	3.83	NA	6	3.33	NA	5	4.67	NA
Thyroid (n=4,784)	37	0.77	0.30 (.021-0.44)	6	0.57	NA	31	0.83	0.42 (0.28-0.62)
Head and neck (n=799)	53	6.63	1.52 (1.01-2.30)	35	6.52	1.09 (0.66-1.81)	18	6.87	NA
Digestive (n=8,722)	641	7.35	1.33 (1.05-1.68)	476	8.10	1.17 (0.80-1.70)	165	5.80	1.41 (1.05-1.88)
Esophagus (n=1,611)	241	14.96	2.23 (1.65-3.02)	185	16.53	2.49 (1.64-3.79)	56	11.38	1.91 (1.24-2.95)
Gastric-esophageal junction (n=522)	46	8.81	0.80 (0.48-1.33)	38	8.70	0.69 (0.39-1.22)	8	9.41	NA
Stomach (n=2,055)									
Colon, rectum and anus (n=2,424)	141	6.86	1.12 (0.80-1.56)	111	7.58	1.04 (0.68-1.60)	30	5.08	1.20 (0.76-1.90)
Liver (n=1,316)									
Biliary tract (n=369)	124	5.12	0.74 (0.53-1.03)	83	5.79	0.69 (0.44-1.08)	41	4.14	0.85 (0.55-1.29)
Pancreas (n=425)									

	53	4.03	0.50 (0.32- 0.79)	41	4.05	0.53 (0.32- 0.87)	12	3.96	NA
	19	5.15	NA	8	5.44	NA	11	4.95	NA
	17	4.00	NA	10	3.82	NA	7	4.29	NA
Hematologic malignancies (n=894)	140	15.66	4.88 (3.66- 6.51)	88	18.14	4.07 (2.66- 6.21)	52	12.71	4.87 (3.39- 7.01)
Non-Hodgkin's lymphoma (n=675)	113	16.74	4.57 (3.35- 6.24)	71	19.72	4.27 (2.74- 6.66)	42	13.33	4.21 (2.80- 6.33)
Hodgkin's lymphoma (n=122)	20	16.39	NA	12	18.46	NA	8	14.04	NA
Multiple myeloma (n=87)	6	6.90	NA	4	7.41	NA	2	6.06	NA
Leukemia (n=10)	1	10.00	NA	1	16.67	NA	0	0.00	NA
Genitourinary (n=5,711)	389	6.81	2.22 (1.82- 2.70)	NA	NA	NA	NA	NA	NA
Cervix (n=2,839)	261	9.19	3.49 (2.79- 4.38)	NA	NA	NA	NA	NA	NA
Uterus (n=780)									
Ovary (n=1,045)	22	2.82	NA	NA	NA	NA	NA	NA	NA
Prostate (n=277)	56	5.36	1.88 (1.33- 2.64)	NA	NA	NA	NA	NA	NA
Bladder (n=314)									
Kidney (n=456)	16	5.78	NA	NA	NA	NA	NA	NA	NA
	17	5.41	NA	14	6.06	NA	3	3.61	NA
	17	3.73	NA	13	4.59	NA	4	2.31	NA
Skin cancer (n=491)	32	6.52	0.84 (0.51- 1.37)	15	6.05	NA	17	7.00	NA
Melanoma (n=174)	12	6.90	NA	6	7.06	NA	6	6.74	NA
Nonmelanoma (n=317)	20	6.31	NA	9	5.52	NA	11	7.14	NA
Bone and soft tissue (n=718)	21	2.92	NA	9	2.59	NA	13	3.50	NA
Breast (n=5,443)	171	3.14	1.29 (1.02- 1.62)	0	0.00	NA	171	3.16	1.36 (1.08- 1.73)
Unknown primary (n=181)	16	8.84	NA	8	8.16	NA	8	9.64	NA
Other* (n=541)	42	7.76	1.93 (1.28- 2.90)	10	4.46	NA	32	10.09	2.41 (1.53- 3.80)

Notes: NA, not applicable; N., number

*, this category included cancers originating from the testis, vulva, penis, vagina, labia majora, labia minora, perineum, scrotum, hydatidiform mole, chorion, notochord, adrenal cortex, neuroendocrine system, mediastinum, sweat glands, mesothelium, thymus, umbilical tube and so on.

OR, odds ratio; 95% CI, 95% confidence interval; CNS, central nervous system;

*The OR was adjusted by sex and age (as a continuous variable).

The OR was adjusted by age (as a continuous variable).

Table 3. A summary of studies of the risk of cancer in tuberculosis (TB) patients compared with the general population

	Type of TB infection	Type of study	Sample Size	Incidence of cancer in TB patients	Hazard ratio or relative risk	Extrapulmonary cancer type	PMID
Kuo et al. 2013	Latent	Retrospective population-based study	530	7.91%	All cancers: 2.07, 95% CI, 1.90–2.26 Nonpulmonary cancer: 1.71, 95% CI: 1.54-1.90	Head and neck, Digestive tract, Skin, Bladder, Hematological malignancies	23652313
Simonsen et al. 2014	Active	Cohort study	15,024	11.6%	All cancers: 1.52, 95% CI 1.45-1.59; Extrapulmonary cancer: 1.29, 95% CI: 1.22-1.36	Malignant pleural mesothelioma, Hodgkin's lymphoma, ovarian, non-Hodgkin's malignant lymphoma	25216835
Su et al. 2016	Latent	Retrospective population-based study	11,522	8.46%	All cancers: 2.29, 95% CI: 1.26-4.17 Nonpulmonary cancer: NA	Multiple myeloma, kidney, bladder, hepatobiliary, gastrointestinal	26825880
Everatt et al. 2017	Active	Retrospective cohort study	21,986	7.2%	All cancers: 1.76, 95% CI: 1.67-1.85; Nonpulmonary cancer: 1.41, 95% CI: 1.33–1.50	Mouth and pharynx, esophagus, stomach, larynx, cervix uteri, leukemia, hematological cancers, "other" cancers	28572839
Chen et al, 2020	Mixed	Case-control study	32,539 cases and 12,916 controls	NA	All cancers: 1.68, 95% CI: 1.43-1.97; Nonpulmonary cancer: 1.72, 95% CI: 1.46-2.02	Non-Hodgkin's lymphoma, cervical cancer, esophageal cancer, "other" cancer, ovarian cancer, head and neck cancer, breast cancer	This study

NA, not available

Figures

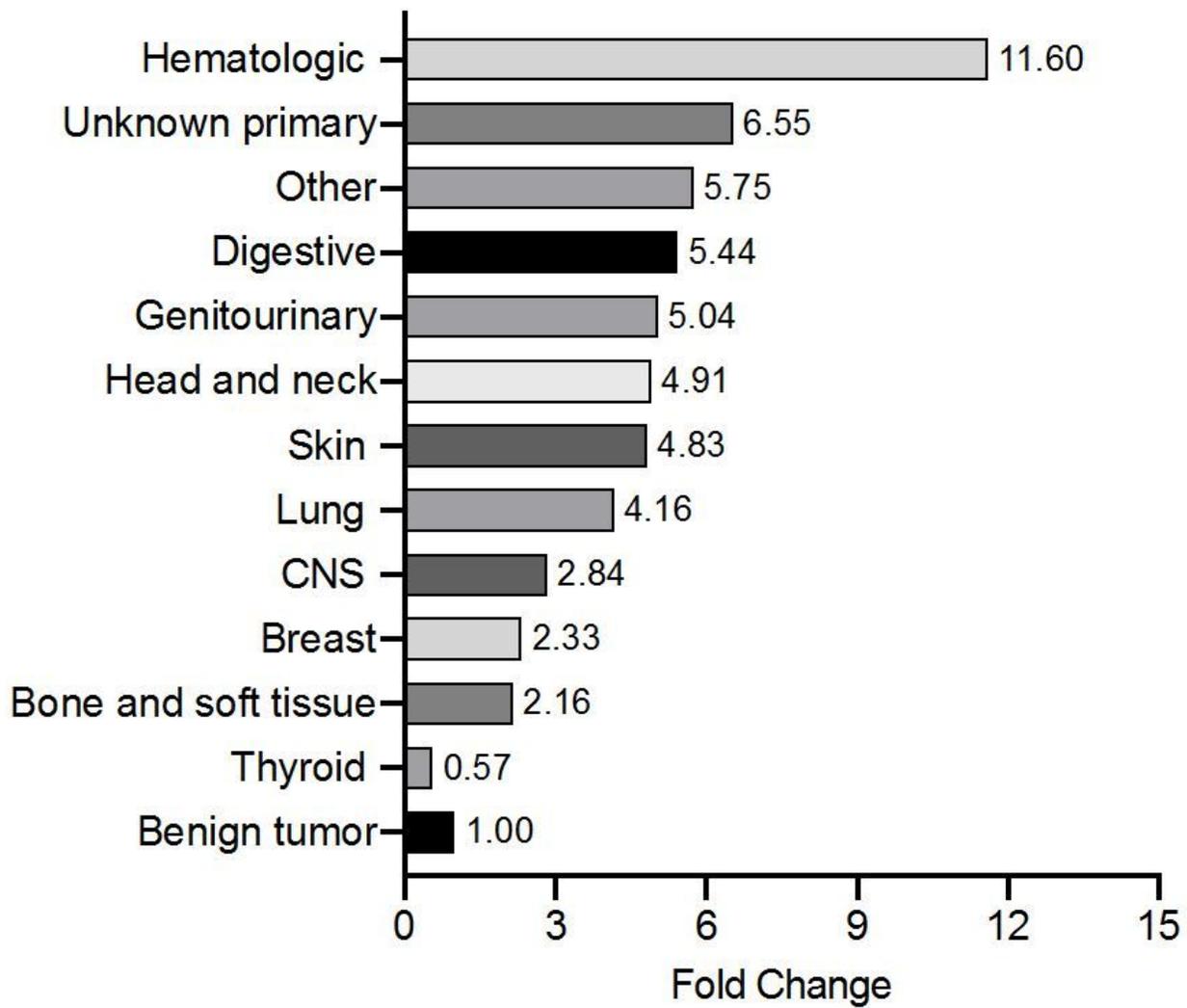


Figure 1

The fold change in the prevalence rate of tuberculosis in patients with different cancer sites in the malignant group compared with the benign tumor group. Note, CNS, central nervous system