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# *Mycobacterium tuberculosis*, Tuberculosis and Cancer

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## Abstract

Tuberculosis (TB) is an infectious disease caused by mycobacteria, principally *Mycobacterium tuberculosis*. This disease can affect all organs but mainly the lungs, remains a major public health challenge, particularly in low and middle-income countries. TB disease can occur after infection and can cause death. There is evidence of an increased risk of cancer, particularly of the lung, in people with a history of TB or with an active form of the disease. The BCG vaccine, derived from a weakened strain of *Mycobacterium bovis,* offers protection against severe forms of tuberculosis in children and is also employed in the treatment of bladder cancer. The objective of this article is to examine the associations between *Mycobacterium tuberculosis,* tuberculosis and cancer.

***Keywords:*** *Mycobactium tuberculosis, Tuberculosis, Risk factors, Lung cancer*

## Introduction.

Tuberculosis is an infectious disease caused by a mycobacterium of the tuberculosis group, mainly *Mycobacterium tuberculosis*, whose usual reservoir is man, more rarely *Mycobacterium bovis* or *africanum*. The incidence of tuberculosis remains high in countries with low or middle economic income, and this potentially fatal infectious disease remains a global public health issue. The infection initially remains latent, linked to airborne transmission of bacilli and can progress to tuberculosis disease, mainly in the lungs, with the possibility of poly-visceral extension, particularly via the haematogenous route, in immunodeficient patients. It can also cause sequelae and encourage the development of cancer, particularly lung cancer. However, this mycobacterium can play a role in the treatment of other cancers, and represents an area of research in this field.

## Epidemiology

The causative agent of tuberculosis is *Mycobacterium tuberculosis.* In 2023, tuberculosis (TB) remains a major public health issue worldwide, although it is no longer one of the top ten causes of death on a global scale. However, it is the leading cause of death from infectious agents, ahead of HIV infection, having caused 1.3 million deaths. Of the new cases diagnosed, 70% were of the pulmonary variety. The eight countries accounting for more than two-thirds of global TB cases are India (26%), Indonesia (10%), China (6.8%), Philippines (6.8%), Pakistan (6.3%), Nigeria (4.4%), Bangladesh (3.6%) and Democratic Republic of Congo (2.9%). More than 400,000 people have developed a form of TB resistant to rifampicin, almost 80% of these have developed a multi-drug resistant form [1].

More than 80% of TB cases and 90% of induced deaths occur in low- and middle-income countries. The mortality rate due to tuberculosis is falling by around 3% a year, and an overall decline of 42% was observed over the period 2000-2017 [2]. It is estimated that more than 1.5 billion people (23% of the world's population) are infected with the tubercle bacillus, and are thus at risk of developing TB [2].

## The Tubercle Bacillus

### Bacteriological Aspects

*Mycobacterium tuberculosis* (MBT) is a strict aerobic bacillus. This pathogenic agent has an outer lipid membrane bilayer ; it divides very slowly (16 to 20 hours) and is either very weakly 'Gram-positive' or does not retain its colour due to the high lipid and mycolic acid content of its wall. In nature, the bacterium can only develop inside the cells of a host organism. This acid-fast bacillus can be identified under the microscope. The most common staining method is the Ziehl-Nielsen stain, which highlights MBT in bright red. Auramine staining and luminescence microscopy can also highlight it [1-3].

The *Mycobacterium tuberculosis complex* (MBTC) includes four other mycobacteria responsible for tuberculosis: *M. bovis*, *M. africanum*, *M. canetti* and *M. microti* [3]. *M. africanum* is not very widespread, but it is a major cause of tuberculosis in Africa. *M. bovis* used to be a common cause of tuberculosis, but the pasteurisation of milk has virtually eliminated its responsibility in developed countries. *M. Canetti* is mainly responsible for tuberculosis in the Horn of Africa, while *M. Microti* can be implicated in immunocompromised individuals [3].

The other known pathogenic mycobacteria are *M. leprae* (Hansen's bacillus), which causes leprosy, and *M. avium* and *M. kansasii*, classified as 'non-tuberculous mycobacteria' (NTM), which can cause pulmonary infections similar to tuberculosis. [4,5].

Calmette and Guérin bacillus developed from an attenuated strain

of *Mycobacterium bovis*, is the basis of the tuberculosis vaccine. It is used to protect (80% efficacy for more 5 years) young children against serious forms of tuberculosis, such as tuberculous meningitis and miliary tuberculosis [2]. It is much less effective against other forms of TB, particularly pulmonary. It stimulates the immune system so that it can identify and fight the mycobacteria responsible for tuberculosis in the event of exposure. In countries where the incidence of TB is low (United States of America, Canada, Western Europe, Australia) the vaccine is less widely used or reserved for high-risk population groups. On the other hand, it is given to newborns in countries with a high incidence of tuberculosis, and to children living in environments where active cases of tuberculosis may be present. Health professionals or those working in high-risk environments (laboratories, etc.) may also be vaccinated. A single dose by intradermal injection is recommended in the first few weeks of life ; in older children, the absence of tuberculosis infection should be verified by a tuberculin or IGRA test prior to vaccination. This vaccine has a high rate of tolerance, with minor ulceration at the injection site being the only common side effect. Complications are rare, and include local abscesses and adenopathy in the drainage area. In exceptional cases, disseminated infections may occur in immunocompromised individuals [6].

## Transmission of Infection

The risk of transmission of the infection from one person to another depends on several factors: the number of small (0.5 and 5 µm) contagious droplets (Flügge droplets) which can remain suspended in the air for up to 9 hours after they are emitted. The transmission of the same clone of bacteria from one patient to another has been proven by genotyping studies of mycobacteria [6].

People who are in frequent, close contact with people suffering from pulmonary, laryngeal or tracheobronchial tuberculosis, especially in a small, poorly ventilated space, are particularly exposed to the risk of infection when patients emit MBT during verbal exchanges, episodes of coughing, spitting or sneezing. It is estimated that a person with active tuberculosis can infect at least 10 to 20 people. People suffering from tuberculosis must therefore be isolated while their sputum is sterilised, and wear a protective mask, as must their carers [6] and any infection should be detected in people contacts.

## Natural History of Tuberculosis Infection

### *Transmission of Infection*

Defence mechanism against MBT. Once inhaled, the tubercle bacilli are deposited in the distal alveolar spaces, mainly in the upper parts of the lungs. They are phagocytosed by alveolar macrophages (AMs), accompanied by a local cell-mediated inflammatory response involving CD4 T lymphocytes (Th1), which activate AMs and stimulate the production of cytotoxic CD8 lymphocytes, thereby facilitating the response against intracellular MBT. Numerous cytokines are released, including interferon gamma (INFγ), interleukin 2 (IL2), tumour necrosis factor (TNFα) and the recruitment of circulating mononuclear cells, all of which play a part in the defence mechanism against this infection. Phagocytic dendritic cells carrying antigenic peptides reach the lymph node relays and present these antigens to CD4 T lymphocytes, which return to the lung to organize the formation of an inflammatory granuloma with a satellite lymph node reaction, leading to the formation of a lymph node-lung complex [6,7].

Latent tuberculosis infection (LTI) is characterised by a delayed hypersensitivity reaction to MBT, leading to positive tuberculin and IGRA tests (Interferon Gamma Release Assays), whether Quantiferon-TB Gold Plus or T-SPOT.TB. In 90% of cases, the body's immune response prevents MBT proliferation and controls the infection in less than 10 weeks, resulting in latent tuberculosis infection. This is generally clinically asymptomatic and poses no risk of contagion. However, MBTs may persist in a quiescent state in macrophages for a long time [6,7].

In the context of tuberculosis (TB), it is important to note that 70% of cases progress to tuberculosis disease within two years of initial infection. Following this, the risk gradually decreases, though it appears to be lifelong. TB disease can occur as a result of a decline in cellular immunity or reinfection with MBT. This risk is increased at the extremes of life, particularly in children under the age of five who have not been vaccinated with the Mycobacterium bacille Calmette-Guérin (BCG) vaccine, and in people over the age of 65. People at particular risk may also develop TB disease, the main clinical symptoms of which are asthenia, weight loss, fever and coughing in the case of respiratory infection. Radiologically, the lesions predominantly affect the upper lungs and can take a variety of forms, including infiltrates, excavations, nodules, disseminated forms, mediastinal lymph node involvement and pleurisy. Extra-thoracic sites may or may not be associated (e.g. laryngeal, peripheral lymph nodes, bone, genitourinary, digestive) An inflammatory biological picture with anaemia is most often identified. Diagnosis is made by detecting MBT in sputum, or by bronchial aspiration using bronchoalveolar lavage. Culture on liquid or solid medium (Löwenstein-Jensen) is used to identify the type of MBT and its resistance to anti-tuberculosis drugs. Once treatment has been initiated, and provided the patient complies and the MBT are not drug-resistant, sputum and cultures can be sterilised in less than 2 months [6,7].

### *Risk Factors for TB Infection and TB Disease*

The development of tuberculosis is influenced by various internal or external risk factors that increase the likelihood of infection or progression from latent infection to disease.

**Internal Risk Factors:** The innate deficiency of defences against MBT, with deficient production of INFγ or IL4, IL10, IL12, must be taken into account before vaccination with BCG vaccine [8].

Diabetes, which doubles the risk of LTI and quadruples the risk of TB disease, often with severe presentations (pulmonary excavations, disseminated forms, recurrences or resistance to anti-tuberculosis drugs). The explosion in the number of cases of diabetes worldwide could worsen the epidemiological situation for TB [8].

**External Risk Factors:** The poor socio-economic conditions and social insecurity in which people live, including precarious housing, detention, malnutrition, migration and difficulty in accessing healthcare, favour the development of TB [8-10].

Exposure to outdoor or indoor air pollution involving various pollutants (e.g. CO, CO2, SO2, O3, PM2.5 microparticles, PAHs) are risk factors for MBT infection [8].

Exposure to active or passive smoking causes dysfunction of the mucociliary escalator, which promotes the persistence of germs in the respiratory tract, and impairment of the mechanisms of anti-infectious immunity (reduced function of AMs, reduced release of TNF-α, imbalance in the CD4/CD8 ratio and reduced production of IFN-γ). Tobacco smoke could stimulate grow and/or the virulence of tuberculosis bacilli. In smokers suffering from TM, a reduction in IFN-γ response was noted, which may affect the performance of IGRA tests. In active smokers, the risk of pulmonary tuberculosis was assessed (OR= 2.6; 95% CI: 2.1 - 3.4). This risk is dose-dependent (CR = 4.4 for 10 cigarettes smoked daily; CR = 5 for 10 years of smoking). Smoking increases the risk of death from TB (RR =2.15 ; 95% CI: 1.38-3.3), of recurrence of TB and of anti-tuberculosis drug-resistant forms (OR = 1.70; 95% CI: 1.3-2.23) [11].

Alcohol abuse, often associated with socio-economic disadvantage, is a risk factor for MBT infection and TB disease. Alcohol alters the immune response and phagocytic function of macrophages. The risk is dose-dependent ; four drinks a day quadruples the risk of developing TB [12].

HIV infection is a major driver of the TB epidemic, particularly in Africa, where almost 10% of TB patients are thought to be living with HIV. Widespread use of screening and antiretroviral treatment (ART) has led to a significant reduction in TB mortality in HIV-infected patients [8,13].

The use of corticosteroids to treat chronic inflammatory diseases is associated with an excess risk of developing TB; this risk is dose-dependent: prednisolone ≤ 15 mg per day (OR=2.8; 95%CI: 1.0-7.9), dose ≥ 15 mg per day (OR=7.7; 95% CI: 2.8-21.4), and increases with prolonged treatment [8]

Immunomodulatory drugs (anti-TNF) used to treat chronic inflammatory diseases may favour the development of TB; screening for LTI and prophylactic treatment are essential prior to their use [8]. Immunosuppressive drugs used during visceral transplantation may also favour the development of TB [8].

Renal failure, with or without dialysis, increases the risk of TB [8].

Finally, there is good evidence that people exposed to silica crystals or suffering from silicosis have a higher risk of TB [14].

## Tuberculosis and Cancer

Studies show an association between tuberculosis and cancers. Patients with a history of pulmonary tuberculosis have a higher relative risk of cancer than the general population. Increased rates of lung cancer have been reported in regions where TB is endemic [15,16]. However, the association between TB and cancer is often multifactorial and depends on many factors (environment, comorbidities, smoking, immune status of the patient). In many cases, the co-occurrence of TB and cancer makes it impossible to determine the nature of the association between these two types of disease [15,16].

### Tuberculosis is a Risk Factor for Cancer

Tuberculosis can promote the development of certain cancers, the mechanisms involved are complex and multifactorial.

#### *General Mechanisms*

Tuberculosis causes chronic inflammation in tissues, especially the lungs. This inflammation can damage the DNA of cells, promoting carcinogenesis. Tuberculosis granulomas cause fibrosis and tissue remodelling, creating a microenvironment conducive to cancer development. AM and immune cells produce reactive oxygen species (ROS) to fight infection, but these damage DNA and increase the risk of carcinogenesis [16-18].

Cofactors may be involved in carcinogenesis. People living with HIV, who are more susceptible to tuberculosis, have a weakened immune system, which can increase the risk of lung cancer, as well as Kaposi's sarcoma, lymphoma and anogenital cancers. Exposure to substances such as silica, asbestos and polycyclic aromatic hydrocarbons all promote carcinogenesis. Smoking, which is common among TB patients, is a major risk factor for cancer, especially lung cancer [19,20].

### Different Types of Cancer

#### *Lung Cancer*

*Mycobacterium tuberculosis* infection may increase the risk of lung cancer, which may be twice as common after TB as in the general population. In particular, squamous cell carcinoma, although other types such as adenocarcinoma and large cell carcinoma have also been reported. The prolonged chronic inflammation, oxidative stress with excessive production of pro-inflammatory cytokines (TNF-α, IL-6) and free radicals observed in TB cause DNA damage that is a factor in carcinogenesis. After TB disease, fibrotic lesions often form in the damaged areas, which are conducive to the growth of cancer cells ('scar cancer'). By evading the immune system, *Mycobacterium tuberculosis* can cause local immunosuppression ; the imbalance in the immune response can create a microenvironment favourable to the growth of cancer cells. Finally, certain metabolites or molecules released by MBT may facilitate cell transformation by interfering with normal cell regulation mechanisms [20-23].

#### *Extrapulmonary Cancers*

Cancers can develop in the viscera affected by TB (e.g. lymph nodes, bones, peritoneum) by the mechanisms described above. In Denmark, a cohort study of 15,024 patients with tuberculosis (median follow-up 8.5 years) showed the occurrence of 1747 cancers. The risk of cancer 3 months after tuberculosis was 1.83%, reflecting a high standardised incidence ratio (SIR=11.09 ; 95% CI: 9.82-12.48), particularly for malignant pleural mesothelioma (368.4), lung cancer (40.9), but also Hodgkin's lymphoma (30.6), ovarian cancer (26.4) and malignant non-Hodgkin's lymphoma (23.8) [24]. Other studies suggest an association between urogenital TB and an increased risk of bladder cancer, although this association is less well documented [16].

## Practical Attitudes

### *Differential Diagnosis of Cancer and Tuberculosis*

Patients with active or past tuberculosis must be carefully monitored, especially if they are smokers or have been exposed to carcinogens, to differentiate recurrent tuberculosis from lung cancer. Symptoms of lung cancer may mimic those of tuberculosis and require a thorough diagnostic work-up. In some cases, the two conditions may occur simultaneously [25-28].

### *Effects of Anti-tuberculosis or Cancer Chemotherapy*

Anti-tuberculosis treatments are effective and cancer chemotherapies have made considerable progress. Both can be a source of immunosuppression or adverse events that interfere with the simultaneous treatment of cancer and TB [29,30]. TB can occur during cancer treatment [31].

### *Prevention and Patient Follow-up*

Primary prevention. It is essential to ensure early diagnosis and treatment of TB, to monitor adherence to treatment and to follow the course of the disease to reduce the incidence of chronic infection and pulmonary sequelae. BCG vaccination in regions where tuberculosis is endemic. Socio-economic conditions and access to health care need to be improved [2,32].

Secondary prevention. Regular monitoring of patients allows early detection of signs of cancer. Chest CT scans are used to monitor scarring, and pulmonary function tests are used to detect dysfunction, especially in persistent smokers who should be helped to quit. Screening and management of diabetes is essential [33-35].

## Mycobacteria in Cancer Treatment

The approach is to use the immunostimulatory properties of mycobacteria to activate the body's immune defences against cancer cells. MBT are not used because of their pathogenicity, but attenuated strains such as the BCG vaccine are used for their anti-tumour effects [36,37].

### BCG and Bladder Cancer

#### *Mechanism of Action*

Mycobacteria strongly activate macrophages, which secrete pro-inflammatory cytokines (such as TNF-α and IFN-γ), recruit other immune cells and activate T lymphocytes, which are essential for the anti-tumour response. Stimulation of the immune system in the vicinity of the tumour can induce a generalised immune response against cancer cells (bystander effect) [37,38].

#### *Methods of Use*

BCG is injected directly into the bladder (intravesical instillation). It causes local inflammation that attracts immune cells (macrophages, T lymphocytes) to the bladder. These immune cells then attack the cancer cells, reducing the risk of recurrence or progression.

#### *Main Indications*

Non-invasive bladder cancer (urothelial carcinoma) or following transurethral resection of the bladder. BCG significantly reduces the risk of recurrence and progression to an invasive form of this cancer [38].

### Limitations

This treatment is well tolerated, although it can cause adverse effects such as cystitis and haematuria. Local or disseminated infection with BCG is rare [37,39]. Its efficacy is essentially limited to bladder cancer, but its value in other cancers is being investigated [40].

### Therapeutic Prospects

Research is underway into genetically modifying mycobacterial strains to enhance their immunotherapeutic potential, while reducing their infectious risks. Genetically modified strains of MBT or *M. smegmatis* are being studied as experimental therapeutic agents. Components of mycobacteria could improve the efficacy of anti-cancer vaccines. Mycobacteria could be combined with immune checkpoint inhibitors (anti-PD-1 or anti-CTLA-4) to enhance their anti-tumour effect. Finally, the use of certain components, such as the lipids in the cell wall of mycobacteria, could make it possible to develop nanomedicines or targeted delivery systems [41-43].

## Conclusion

*Mycobacterium tuberculosis* is the main cause of tuberculosis, which remains a major public health issue. The International Agency for Research on Cancer (IARC) has classified it as a carcinogen. There is evidence of an increased risk of lung cancer in patients with a history or active form of tuberculosis. The chronic inflammation, immunological disorders and genomic abnormalities induced by MBT infection underline the fact that it is a precursor to carcinogenesis [44]. One hundred years ago, the BCG vaccine against tuberculosis was developed from an attenuated strain of *Mycobacterium bovis,* and subsequently proved effective in treating bladder cancer. Research is needed to clarify the relationship between *Mycobacterium tuberculosis*, tuberculosis and cancer in order to improve our knowledge of oncogenesis and cancer prevention and treatment.

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