Age-dependent responses of organs to tuberculosis and cancer

Peter Richmond\(^1\) and Bertrand M. Roehner\(^2\)

Abstract
Both tuberculosis (TB) and cancer (C) can affect many organs, e.g. brain, bones, skin. We consider the age-specific response of each organ \(j\), particularly how fast lesions develop and how serious they become. A convenient identification of the response of organ \(j\) to TB is provided by the following age-dependent death ratio:

\[ T_j(t) = \frac{\text{death by type } j \text{ TB}}{\text{all TB deaths}} \]

A similar function will describe the deaths due to cancer lesions:

\[ C_j(t) = \frac{\text{death by type } j \text{ cancer}}{\text{all cancer deaths}} \]

We compare the organs’ responses in all cases for which death data are available. We will see that these ratios provide signatures that are much more readable than their numerators and denominators. Although such responses are highly organ-dependent, it appears that for the same organ at age \(t\):

\[ T_j(t) \sim C_j(t) \]

In other words, the idiosyncrasies of each organ are more important than the functional differences induced by TB or cancer.

For instance, with regard to brain lesions, both TB and cancer mortalities peak around the age of 10. Such parallel features may bring to light vulnerabilities due to (temporary) faults or deficiencies of the immune system.

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Key-words: age-specific death rate, death ratio, tuberculosis, cancer

1: School of Physics, Trinity College Dublin, Ireland. Email: peter_richmond@ymail.com
2: Institute for Theoretical and High Energy Physics (LPTHE), University Pierre and Marie Curie, Paris, France. Email: roehner@lpthe.jussieu.fr
Introduction

This paper is written by two physicists. Historically, the very spirit of physics has been to find mechanisms which can apply to a broad range of situations. For instance, the mechanism of gravitational attraction explains many phenomena, from the fall of an apple, to the “fall” of the Moon toward the Earth, to the formation of black holes, to the rotation of spiral galaxies. It should not come as a surprise, therefore, that when they turn to the fields of biology and medicine, physicists adopt a comparative perspective with the purpose of finding parallels and common rules for phenomena which, so far, had been considered unrelated. It is hoped that such a macro-biological perspective may prove of value in complement to the highly detailed descriptions permitted by the techniques of modern molecular biology and genetic sequencing.

At first sight, tuberculosis (TB) and cancer appear as very different diseases. Whereas TB is due to the proliferation of a bacteria, *Mycobacterium tuberculosis* (MTB), cancer results from the boundless reproduction of body cells which, for some reason, have freed themselves from the controls generated by their neighbors. TB starts with a foreign pathogen whereas in cancer it is a body cell which spins out of control.

However, if we look at it more closely, the mechanisms are not too different for indeed through a kind of reprogramming process the pathogen is able to twist the behavior of host cells (in the case of viruses) or macrophages (in the case of bacteria) which try to eliminate it. For instance, once a bacterium has been “imprisoned” into a vesicle of a macrophage, a common trick (used for instance by MTB or *Legionella pneumophila*) is to prevent the injection into the vesicle of enzymes which would kill the pathogen. In short, by manipulating their host successful pathogens are able to kill it and then to proliferate.

There are also similarities in subsequent stages.

- One knows that the formation of a tumor is a multistep process; so is also the development of TB as illustrated by the following features. (i) In only 10% of infected persons will TB manifest itself. The other 90% will remain asymptomatic. (ii) In those cases where TB develops, one sees the formation of granulomas. Not unlike tumors, these are nodules of a diameter of about 3mm in which pathogens and macrophages are clustered together.

- Primary cancer tumors can develop in many organs. Although pulmonary TB

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1This epistemological approach was emphasized particularly by Pierre Duhem (1906, p. 140) as attested by the following excerpt: “The history of physics shows that the search of analogies between different categories of phenomena may have been the most productive of approaches tried by theoretical physics”. Among recent examples, one can mention (i) “Quantum Chromodynamics” which was built on the model of “Quantum Electrodynamics” and (ii) Yang-Mills gauge theories which started from gauge invariance in electromagnetism (Yang et al. 1954).

2The diameter of a human macrophage is about 20 micrometers which is 10 times more than the length of a MTB or *Legionella* bacterium.
is the most frequent, TB can also develop in several parts of the body: bones, skin, intestines, meningitis, genito-urinary organs. On the other hand there are some locations (e.g. skeletal muscles) where the development of both cancer and TB is uncommon.

- Although fairly rare, TB of the breast (tuberculosis mastitis) does occur and it is far more frequent (about 20 times) in women than in men (Wilson et al. 1990); it is particularly likely in reproductive age. As a matter of fact, being irregular and hard, TB breast lesions may be indistinguishable from breast carcinoma (Baharoon 2008).

- One of the most important properties of cancer cells is their ability to spread to other organs where they may form secondary tumors. There is a parallel in TB in the sense that the granulomas can migrate to other organs such as the liver or the kidneys. Such cases which are called miliary TB represent 20% of the extra-pulmonary cases.

Although too short and schematic, the previous description suggests that it is not completely absurd to think that there may be connections between the development of TB and cancer.

**Purpose and method**

**Purpose**

The objective of this paper is very simple. If, as argued above, there is indeed a connection between the growth of TB and cancer in various organs, can it be that these links manifest themselves by similar responses of various organs? How can one design an operational procedure that will unravel such possible links?

It turns out that among the set of persons who will develop a cancer during their lifetime the probability $C_b(t)$ that this cancer will affect the brain is highest around the age of 10 years: $C_b(10) = 23\%$ (Fig. 1). At older ages this probability falls off sharply. At the age of 25 it is down to 5%, and at the age of 50 to 1%. Do we currently have a clear understanding of why $C_b(t)$ is highest in childhood? To our best knowledge, it does not seem so. Now, as can be seen in Fig. 1, the probability $T_b(t)$ for developing TB affecting the brain is also maximum at the age of 10 and falls off in older ages even more sharply than $C_b(t)$. Subsequently, for the sake of brevity, a curve such as $C_b(t)$ will be called the *age-profile* of brain cancer.

It could well be that the similarity in the age-profiles $C_b(t)$ and $T_b(t)$ is merely a coincidence. However, if for a number of other organs the same similarity is observed, it may suggest that some organ-specific factors are at work which account for similar responses for the two diseases.
What can be the practical interest of these observations? Taken alone, they will not give us a full fledged explanation of why such brain diseases appear at that specific age. However, they suggest that the idiosyncrasies of the organ under consideration plays a more important role than the nature of the disease itself. For instance, as far as brain diseases are concerned, the screening defects of the blood-brain barrier may be the key. In other words, in this shield versus sword issue, our observation will tend to focus attention on the macrobiological properties of the shield.

**Method**

In the previous subsection we defined our objective and we broadly delineated how the observation will be organized. Presently, we will explain how in practice it can be implemented.

The main difficulty is the following. As we wish to explore the affinity a disease ($\alpha$) has for a specified organ ($S$) we would need incidence data rather than mortality data. As a matter of fact, mortality data mix two very different effects (i) the prevalence of $\alpha$ in $S$ (ii) how effectively this specific disease can be cured. As an extreme case, for a disease whose cure rate is 100% or which simply is not a deadly disease (as for instance is the case of most forms of herpes) it is altogether impossible to get any information about incidence from mortality data.

Because nowadays in all developed countries TB is cured in very effective ways, it is impossible to use present-time data for our investigation. On the other hand, if we consider US data from the early 20th century there will also be two difficulties. (i) The international classification of diseases will be very different from the present-day classification and it will be much less detailed. Thus for TB there will be only 5 types and they will include labels such as “Pott’s disease” (TB of the spine) or “White swellings” (TB of the joints) with which we are no longer familiar. (ii) In 1910, only 58% of the US population was included in the federal death registration area. This would reduce the number of deaths by a factor of two. Starting from 1933, the death registration area included 100% of the population. This led us to the methodological choice of using data from the period 1934-1945.

In 1934 there were substantial numbers of deaths in almost all types of TB or cancer except for a few. We have been using averages over a number of successive years in order to reduce the statistical fluctuations. Naturally, the fluctuations are conditioned by the number of deaths. As an illustration, one can mention the case of skin TB.

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3 Some of the “holes” of this barrier are described in Kim (2010 p.33-34) and Sorge et al. (2012). For instance, the barrier can be penetrated by using so-called “Trojan horse” mechanisms.

4 In 2015 in the US the total number of TB deaths was 470 which is 152 times less than in 1934. In 1910 there were even 2.4 times more TB deaths than in 1934. For cancer it is a different situation in the sense that there were 140,771 deaths in 1934 and 612,207 in 2015.
for which there were less than 10 deaths in almost all age groups except in the oldest ones. In this case the smoothing process required to take averages over 10 successive years that is to say from 1934 to 1943.

## Results

If one can assume that the death records have been filed correctly, all disease locations documented in US mortality data are for primary lesions. The comparison between the profiles of TB types and cancer types is shown in Fig. 1a,b.

![Graph showing comparison between TB and cancer profiles](image)

Fig. 1a (continued in Fig. 1b). Comparison between the conditional probabilities represented by the ratios: (deaths by TB type)/(all TB deaths) (blue line with round dots) and (deaths by cancer type)/(all cancer deaths) (red line with squares), USA 1934-1943. The left-hand scale refers to TB whereas the right-hand scale refers to cancer. Sources: Bureau of the Census: Mortality Statistics 1934-1936, and Bureau of the Census: Vital Statistics of the United States, Part 1, 1937-1943.

As a matter of curiosity, one may wish to know to what extent the cancer profiles of 1934 differed from those of 2015. Of the 7 profiles, only two were markedly different, namely (i) cancer of the respiratory system and (ii) skin cancer. For (i) in
Fig. 1b (continued from Fig. 1a). Comparison between the conditional probabilities represented by the ratios: (deaths by TB type)/(all TB deaths) (blue line with round dots) and (deaths by cancer type)/(all cancer deaths) (red line with squares), USA 1934-1943. The left-hand scale refers to TB whereas the right-hand scale refers to cancer. The TB ratios represent the conditional probability of dying at a given age from a specified type of TB within the set of all people dying from TB. There is a similar definition for cancer. The 7 cases shown in Fig. 1a, b do not result from a selection; they represent all cases for which data are available. The correlations, confidence intervals (for a probability level of 0.95) and ICD codes are given below in the following form: cor, CI, TB/C. (1) cor = 0.55 (0.17, 0.79), 23/47; (2) cor = 0.67 (0.35, 0.85), 24/subclass of 53; (3) cor = −0.560 (−0.81, −0.24), 25/subclass of 46; (4) cor = 0.46 (0.046, 0.74), 26/27a,b/subclass of 53; (5) cor = 0.91 (0.79, 0.96), 28/52; (6) cor = 0.01 (−0.41, 0.43), 29/72b; (7) cor = 0.56 (0.18, 0.79), 30/46+51. All correlations are significant except (3) and (6). Moreover under an age shift of 10 years the two curves of (6) become correlated too. Sources: Bureau of the Census: Mortality Statistics 1934-1936, and Bureau of the Census: Vital Statistics of the United States, Part 1, 1937-1943.

2015 there was only one peak near the age of 65. The narrow peak centered on the age of 20 does no longer exist. For (ii) it is so to say the opposite in the sense that in 2015 in addition to the ratio which surges up beyond the age of 75 there is also around the age of 25 a major peak which reaches the level of 4%.

The TB-cancer correlations are given in the caption of Fig. 1. They show that in 5 of
the 7 cases (i.e. 71%) there is a significant correlation. For these 5 cases the average correlation is: \( r = 0.61 \pm 0.11 \).

In addition two points should be observed.

- Even for the “intestines” and “lymphatic” cases for which there is no correlation the profiles share some common features. Thus, for “intestines” after the age of 25 the two ratios do not fall to zero (as is the case for “brain” or “bones”) but increase more or less steadily (applying a smoothing moving average would almost eliminate the ups and downs of the cancer profile). Moreover, an age shift of only 10 years would bring the peaks of the two curves of the lymphatic case together.

- It must be realized that the profiles are of very different shapes which makes similarities arising merely by chance fairly unlikely.

### Conclusion and perspectives

#### Death rates versus death profiles

What is the present-day situation regarding TB and cancer? As shown in Fig. 2, roughly speaking in terms of order of magnitude TB and cancer death rates differ by a factor 100 at all ages. However, contrary to their levels, the age-profiles of death rates are not very different. The parameters of the two laws differ by 20% on average (23% for the exponent \( \gamma \) and 18% for the doubling time \( T \)).

![Fig. 2 Comparison between the death rates of TB and cancer, USA 1999-2015. Left: age from 1 day to 10 years, right: age over 10 years. Whereas the death levels are very different, the shapes of the age-specific death rates are fairly similar. For all causes of death, in the 0-10 year age range the death rate is an hyperbolic function of age of the form: \( \mu_b \sim 1/t^\gamma \) (Berrut et al. 2016). For TB: \( \gamma = 0.33 \pm 0.3 \), for cancer: \( \gamma = 0.43 \pm 0.2 \). In the range 10-100 year, it is the Gompertz law which applies, that is to say an exponential increase: \( \mu \sim \exp(t/\tau) \). The doubling times \( T = \tau \log(2) \) expressed in years are as follows. TB: \( T = 9.7 \pm 0.8 \), cancer: \( T = 7.9 \pm 0.7 \). Source: CDC Wonder database 1999-2015 (underlying causes of death). As of April 2017 the relevant web-address was: https://wonder.cdc.gov](https://wonder.cdc.gov)
**Birth defects versus wear-out**

The curves of Fig. 1 suggest that there is a connection in the way TB and cancer lesions develop in different organs. A rough distinction can be made between the lesions (e.g. 2,4,6) which develop mostly in young age (and are likely due to birth defects) and the lesions (e.g. 1,3,5,7) which develop mostly in old age (and are likely due to a wear-out process).

Such conclusions would have been impossible to reach by using death rates instead of death ratios. Indeed, as shown in Fig. 2, age-specific death rate curves in the adult age-range are increasing exponential functions, a feature that would preclude any shape comparison. On the contrary, the age-profiles of the death ratios have very contrasted shapes that can be compared significantly. The aim of this article was to convey our belief that the age-profiles offer useful “signatures” of the corresponding diseases.

**Extension of the present study**

For the purpose of this paper we had by necessity to use data from the first half of the 20th century because our main requirement was to have enough death cases to keep the statistical fluctuations under control. How can we extend this analysis to a greater number of lesions?

If, instead of using death rates we could use incidence rates the number of cases would be multiplied by a large factor. This factor depends of course upon how lethal a lesion is; for instance lesions of the thyroid can be cured with high probability which means that the incidence rate may be 20 or 30 times higher than the death rate. This will allow an interesting extension.

TB and cancer are not the only diseases which can target different organs; syphilis or diabetes are other examples. This will provide a second extension. It will be interesting to see if there are meaningful connections between such families of diseases.

Finally, it can be observed that the present article is another application of the concept of age spectrometry which was introduced in Berrut et al. (2017). As a matter of fact, it is the age-specific profile which provided the signature of each type of lesions.

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