US -Death Trends for Neoplasms ICD codes: C00-D48, Ages 15-44

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US - Death Trends for Neoplasms ICD codes: C00-D48, Ages 15-44

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ABSTRACT

In this study we investigate trends in death rates from neoplasms (ICD-10 codes C00-D48) in the USA using crude data from the CDC (Centers for Disease Control and Prevention). We limit our investigation to individuals aged 15 to 44 and for the period of 2010 to 2022. We investigate both trends in neoplasms where these appear on multiple causes (MC) of death, or as the underlying cause (UC), as well as the trends in the ratio of multiple cause to underlying cause death rates. Using different metrics, we compare mortality trends due to neoplasms before the COVID-19 pandemic with the pandemic period.

We show a rise in excess mortality from neoplasms reported as underlying cause of death, which started in 2020 (1.7%) and accelerated substantially in 2021 (5.6%) and 2022 (7.9%). The increase in excess mortality in both 2021 (Z-score of 11.8) and 2022 (Z-score of 16.5) are highly statistically significant (extreme events). When looking at neoplasm death reported as one of multiple cause of death, we observe a similar trend with excess mortality of 3.3% (Z-score of 5.1) in 2020, 7.9% (Z-score of 12.1) in 2021, and 9.8% (Z-score of 15.0) in 2022, which were also highly statistically significant. The results indicate that from 2021 a novel phenomenon leading to increased neoplasm deaths appears to be present in individuals aged 15 to 44 in the US. The greater rise in deaths due to neoplasms in multiple causes compared to underlying cause indicates that some deaths from neoplasms are being brought forward by other causes. The rise in cancer-death rates as underlying cause might be the result of an unexpected rise in the incidence of rapidly growing fatal cancers and/or a reduction in survival in existing cancer cases. Further stratification is underway, for example by age and cancer type to understand these trends and their relationship to pandemic related factors such as access to or utilization of cancer screening and treatment, changes in health-related behaviors such as exercise or smoking, exposure to COVID-19 disease or COVID-19 vaccines.

Keywords: neoplasms, excess mortality, mortality trends

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1 INTRODUCTION

Beginning in early 2020, the world changed due to the emergence of a global pandemic caused by the SARS-CoV-2 virus which, in some individuals, manifested in the form of COVID-19 disease. A short-term increase in mortality rates was anticipated due to the impact of this novel virus. However, excess mortality has continued in many countries despite milder variants of the virus being in circulation, and the introduction of COVID-19 vaccination programmes. For example, CDC's data tracker[1] shows peaks of COVID-19 ascribed deaths in September 2021 and January 2022 with smaller peaks in August 2022, and January and September 2023. Various possible explanations have been proposed for this, including lasting effects of the virus, lockdowns and the resulting impact on healthcare delivery and adverse effects of COVID-19 vaccines, some of which are based on newly-implemented viral vector DNA or mRNA technology. In this context, we have performed several analyses showing excess mortality (all cause) since 2020, from Europe to the USA[2]. We published a methodology report to explain our estimates for excess mortality, which is based on determining excess death rates instead of excess deaths (Alegria, et al., 2024)[1]. By accurately estimating, and then tracking excess mortality trends, we can have a clearer picture of the implications of the different stages of the COVID-19 pandemic, as mentioned above.

After the all-cause mortality trends were understood, our research efforts focused on changes in death rates for particular causes of death, focusing on cancer given the emergence of anecdotal reports of unusually aggressive cancers, particularly in younger individuals. There have been several case reports of rapidly growing malignant neoplasms in humans following COVID-19 vaccine administration. Such examples include cases of haematologic malignancies following administration of the mRNA COVID-19 vaccine produced by Pfizer-BioNTech: A diffuse large B-cell lymphoma and NK/T-cell lymphoma (Zamfir, et al., 2022)[2]; and B-cell (Sekizawa, et al., 2022)[3] (Mizutani, et al., 2022)[4] and T cell (Goldman, et al., 2021)[5] lymphomas.

There is a report of a subcutaneous panniculitis-like T-cell lymphoma following an adenovirus type 26 (Ad26) viral vector–based COVID-19 vaccination produced by Janssen Pharmaceuticals (Kreher, et al., 2022)[6]. Lastly, there is a case report of B-cell lymphoblastic lymphoma occurring after injection of the Pfizer COVID-19 vaccine in one of 14 mice that were part of a study to establish a model of vaccine-induced myocarditis (Eens, et al., 2023)[7].

Evidence of a possible relationship between the novel COVID-19 vaccinations and the development of malignant neoplasms is not available in the form of population-based studies where vaccinated and unvaccinated individuals are compared. However, reports of cancers following the COVID-19 vaccinations made to CDC's VAERS[3] were found to be more numerous than for all previous vaccines combined since 1990 (Section 4.10 in Wiseman et al.)[8].

Additionally, CDC's Disproportionality Signal Analysis using the Proportional Reporting Ratio (PRR) method conducted in July 2022 disclosed under the Freedom of Information Act. shows safety signals for cancers in 11 MedDRA codes (Wiseman, et al., 2023)[8]. As far as we know, an analysis of this signal has not been published by CDC or FDA.

The possibility of an association between excess cancers and the SARS-Cov2 virus itself must also be considered based on work showing that SARS-Cov2 viral RNA can be reverse transcribed with genomic integration (Zhang, et al., 2021)[9] and (Zhang, et al., 2023)[10].

There may also have been adverse consequences of the COVID-19 pandemic on cancer rates due to delays in diagnosis and treatment (Siegel, et al, 2022)[11].

[1] COVID Data Tracker

[2] Phinance Technologies - Humanity Projects - Excess Mortality Project

[3] Vaccine Adverse Events Recording System

These effects may have persisted at least into 2021 (Siegel, et al, 2023)[12].

The COVID-19 pandemic may have resulted in changes in health-related behaviors with consequences on all-cause and cancer mortality, including physical activity and cigarette smoking (Tseng, et al., 2021)[13] (Almeda, et al., 2022)[14] (Gaffney, et al., 2022)[15].

The aggregate effects of the COVID-19 pandemic on mortality rates in general, and cancer deaths rates in particular may not be fully appreciated for several years. (Siegel, et al, 2023)[12].

In a previous study (Alegria, et al., 2024)[1] of 15-44 year olds in England and Wales we observed increases in all-cause mortality in 2020-2022 and cancer-associated mortality in 2021 and 2022. In the present study we investigate if the USA has similar trends. The analysis of US cause of death data provides further clarity in corroborating and understanding the phenomenon of rising cancer deaths. In particular, the US data does not have the same problems of missing datapoints in 2021 and 2022, as we noticed in the UK data. Also, the US data provides the opportunity to analyze trends in cancers both as the underlying cause of death, or as contributing causes of death. Lastly, as the US has a population that is about 6 times larger than the UK, statistically significant signals are easier to identify.

Cancers tend to be slowly-developing diseases with remarkably stable death rates and only small variations over time. This makes any temporal association between a possible explanatory factor (such as COVID-19, the novel COVID-19 vaccines, or other factor) difficult to establish. However, the purpose of this paper is not to explain the mechanisms behind the rise in cancer-related deaths. Rather, our work provides a statistical analysis at a population level, which offers insight for health professionals regarding current trends in population health, and raises questions for further investigation.

2 DATA

2.1 Cause of Death Data

In this study we analyzed the number of deaths that occurred in the USA between 2010 and 2022, by underlying cause code (ICD-10), sex, and 10-year age groups, obtained using the CDC WONDER system (National Center for Health Statistics of the Centers for Disease Control and Prevention - CDC)[4]. The mortality data is final up to 2021 but provisional from 2022 onwards. Additionally, for comparing multiple cause (MC)[5] of death trends from neoplasms with underlying cause (UC)[6] of death trends, we downloaded data from both the multiple cause of death databases and underlying cause of death databases.

Query parameters:

For underlying cause of death data, select variable grouped by: *1. Ten-year-age-groups, 2. Gender, 3. Year, 4. UCD – ICD Chapter*

(Link to the underlying cause of death databases).

For multiple cause of death data, select variable grouped by: *1. Ten-year-age-groups, 2. Gender, 3. Year, 4. MCD – ICD Chapter*

(Link to the multiple cause of death databases)

2.2 Definition of MC of Death and UC of Death

The Centers for Disease Control and Prevention (CDC) classifies deaths based on cause into two primary categories: ”Underlying Cause of Death” and ”Multiple Causes of Death.” The definitions are:

Underlying Cause (UC) of Death: The underlying cause of death is defined as ”the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal

[4] CDC Wonder

[5] CDC Wonder Multiple Cause of Death 1999 - 2020

[6] CDC Wonder Underliyng Cause of Death 1999 - 2020

injury," according to the World Health Organization (WHO).

Multiple Causes (MC) of Death: Multiple causes of death include all causes and conditions reported on the death certificate that contributed to death, not just the underlying cause. This includes the underlying cause, immediate cause, and any other significant conditions contributing to death. Each death certificate contains a single underlying cause of death, and up to twenty additional multiple causes.

2.3 Data Use Restrictions

In this research paper we abide by the CDC's restrictions on data use which are[7]:

"The Public Health Service Act (42 U.S.C. 242m(d)) provides that the data collected by the National Center for Health Statistics (NCHS) may be used only for the purpose for which they were obtained; any effort to determine the identity of any reported cases, or to use the information for any purpose other than for health statistical reporting and analysis, is against the law. Therefore, users will:

- *Use these data for health statistical reporting and analysis only.*
- *Do not present or publish death counts of 9 or fewer or death rates based on counts of nine or fewer (in figures, graphs, maps, tables, etc.).*
- *Make no attempt to learn the identity of any person or establishment included in these data.*
- *Make no disclosure or other use of the identity of any person or establishment discovered inadvertently and advise the NCHS Confidentiality Officer of any such discovery."*

2.4 Population data

Crude death rate (deaths per 100,000) were obtained by selecting the "crude rates" option on the WONDER interface that uses CDC's estimates of population data. We chose to use the CDC population data instead of data from the US Census Bureau for consistency with other researchers' analyses.

2.5 All-cause deaths data

All cause deaths were retrieved from CDC WONDER, by using the following query parameters: *1.Ten-year-age-groups, 2. Gender, 3. Year*

2.6 Data verification and limitations

The CDC WONDER system provides two separate databases from which to query underlying cause of death data and multiple cause of death data. Additionally, each is separated into two datasets comprising of different time periods, so that in order to obtain time series from 2010 to 2022, multiple queries were performed.

Within the multiple cause of death databases, it is also possible to obtain the underlying cause of death data. We downloaded all the available yearly data (for MC of death and UC of death) and compared the different datasets for consistency, whenever the time periods overlapped.

From 2010 to 2021 the MC and UC of death data is final while for 2022 it is provisional. The data for 2023 was not used as apart from being provisional it was also incomplete. Details on provisional CDC deaths data can be found here.[8]

3 METHODOLOGY

In this study, we analyze the trends in death rates for neoplasms (both malignant and benign). We investigate these trends using yearly data and therefore a seasonal adjustment to the data is unnecessary.

In general terms, to estimate trends in these variables we use a methodology of computing excess rates, which is the difference between the actual observed rates and a given baseline (expected rates). Because we want to describe the impact of the COVID-19 pandemic and post-pandemic periods relative to the prior state of the world, our baselines

[7] CDC Wonder - Data Use Restrictions

[8] CDC Wonder Technical Notes for Provisional Mortality

are based upon the estimation of the trend for the period prior to the pandemic.

In this study we will use method 2C, as described in our report on methodologies for measuring excess deaths in the population (Alegria, et al., 2024)[16]. Method 2C is based on computing the trends in death rates (deaths adjusted by the population) instead of deaths, as the baseline for estimating excess mortality. This method significantly reduces the noise of the estimation as it adjusts for population growth or decline, and by also providing different rates for each age category, we adjust for changes in population age distribution. The method also considers the prior trend in death rates, which tends to decline over time as the population grows healthier and risk factors are better managed.

3.1 Method 2C for Estimating Excess Death Rates

$$\begin{bmatrix} Excess \\ Deaths \end{bmatrix}_{t_i}^{AG} = Deaths_{t_i}^{AG} - Baseline_{t_i}^{AG} \quad (1)$$

Equation 1 is a general expression for estimating the excess absence rates relative to a given baseline. We use the superscript AG to indicate a given population age range, as this is the primary focus of the current analysis. Other cohorts which this equation could apply to include a specific region, sex, or underlying cause of death. The subscript t_i refers to time, that is, the corresponding year for which the excess deaths are computed.

For estimating the baseline for "normal or expected" death rates we use a simple linear fit:

$$Baseline(t_i) = \hat{b} + \hat{a}(t_i - t_0) \quad (2)$$

Where $\hat{a}$ and $\hat{b}$ are the estimated coefficients of the death rate trendline from 2010 to 2019. We also compute a Z-score that estimates the normalized deviation from trend:

$$Z = \frac{\Big[Deaths\Big]_{t_i}^{AG} - \Big[Baseline\Big]_{t_i}^{AG}}{\sigma_{2010-2019}} \quad (3)$$

Where σ is the standard deviation of the excess deaths during the pre-pandemic period 2010-2019.

3.2 ICD-10 Code List of Selected Causes of Death for: Neoplasms

For this analysis we selected all the ICD-10 codes from the CDC aggregated chapter lists (Letters C00 to D48), of which C00 to C99 refer to deaths attributed to malignant neoplasms and D00 to D48 refer to benign neoplasms.

4 YEARLY ANALYSIS OF EXCESS DEATH RATES

In this section we analyzed the trend in yearly death rates for individuals aged 15 to 44 in the USA. In this analysis we use the 2010-2019 trend in deaths per 100,000 (death rates) as the baseline estimate for excess death rates. Excess death rates for the 2010-2019 period are in-sample while the rates for 2020, 2021, and 2022 are out of sample computations.

4.1 Deaths from All Causes

The analysis of deaths from all causes allows us to have a context by which we can then compare the death rates from neoplasms. Figure 1 (top) shows the death rate per 100,000 individuals for all deaths in the US from 2010 to 2022, for the 15 to 44 age group. Figure 1 (bottom) shows the actual number of deaths during the period.

We note two differences in these US data compared with those we found from England and Wales[1]. Firstly, the all-cause death rate for this relatively young age group is substantially higher in the US data. The all-cause death rate for the US was about 130 deaths per 100,000 in 2019, while for the England and Wales it was about 67 deaths per 100,000. Secondly, all-cause death rates had been trending higher from 2010 to 2019, compared with the downward trend in the data from England and Wales. While investigating these differences is not

the topic of this paper, we believe they merit further investigation.

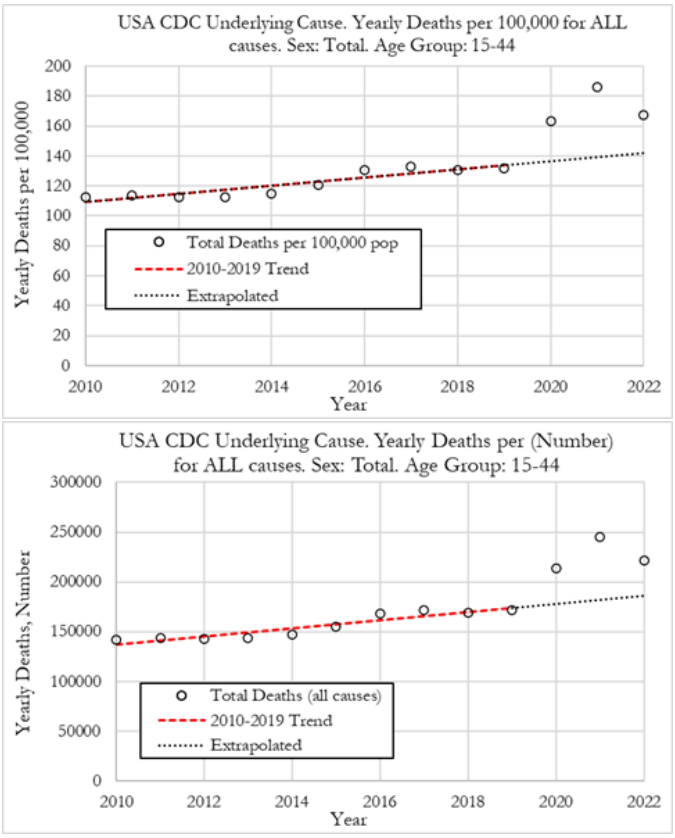

Figure 1. Yearly registered deaths per 100,000 for the US for individuals aged 15 to 44. The red dashed line shows the average from 2010 to 2019. The dotted line shows the extrapolation of the trend from 2020 until 2022. Top: Deaths per 100,000. Bottom: Deaths (Number)

In 2019, the all-cause death rate was about 130 per 100,000 individuals and increased in 2020 to about 162 per 100,000 in 2020 and again in 185 per 100,000 in 2021. In 2022 the death rate dropped slightly to about 170 per 100,000.

4.1.1 Excess all-cause death rates

Figure 2 shows the excess death rate for all-cause deaths in the USA from 2010 to 2022. Figure 2 (top) refers to relative deviations from the 2010-2019 trend, while Figure 2 (bottom) shows the Z-score (signal strength) for the deviations from trend.

Figure 2 shows that excess deaths in 2020 were 19.9%, with a Z-score of 6.5 which is a high level of statistical significance. In 2021 excess deaths jumped to 33.8% with a Z-score above 11.0 indicating very high statistical significance. Excess deaths in 2022 remained abnormally high at 18.2% with a Z-score of 5.9 indicating very high statistical significance.

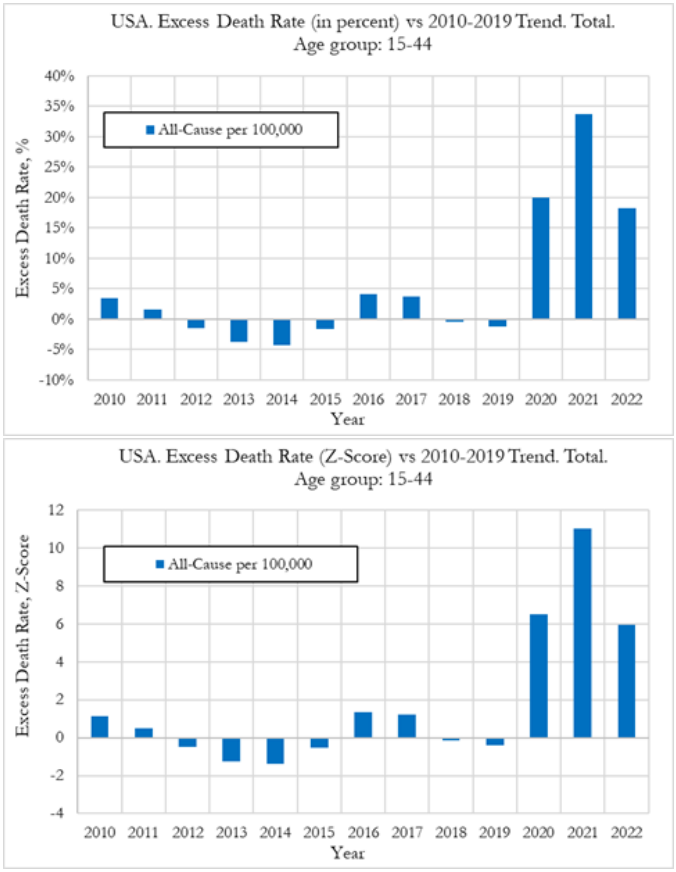

Figure 2. Excess all-cause death rates for both sexes with ages 15 to 44 in the USA. Top: Relative deviation from trend, percent. Bottom: Deviation from trend Z-Score.

4.2 Trends in UC Death Rates for ICD-10 codes C00 to D48 (Neoplasms)

In this section we investigate the trends in death rates from 2010 to 2022 where neoplasms (ICD-10 codes C00 to D48) were classified as the underlying cause of death, for the 15-44 age group of both sexes.

4.2.1 UC Death Rates

Figure 3 (top) shows that the death rate per 100,000 individuals for neoplasm deaths as underlying cause in the US trended significantly downwards with a reduction of 12.1% from 14 per 100,000 in 2010 to around 12.3 per 100,000 in 2019.

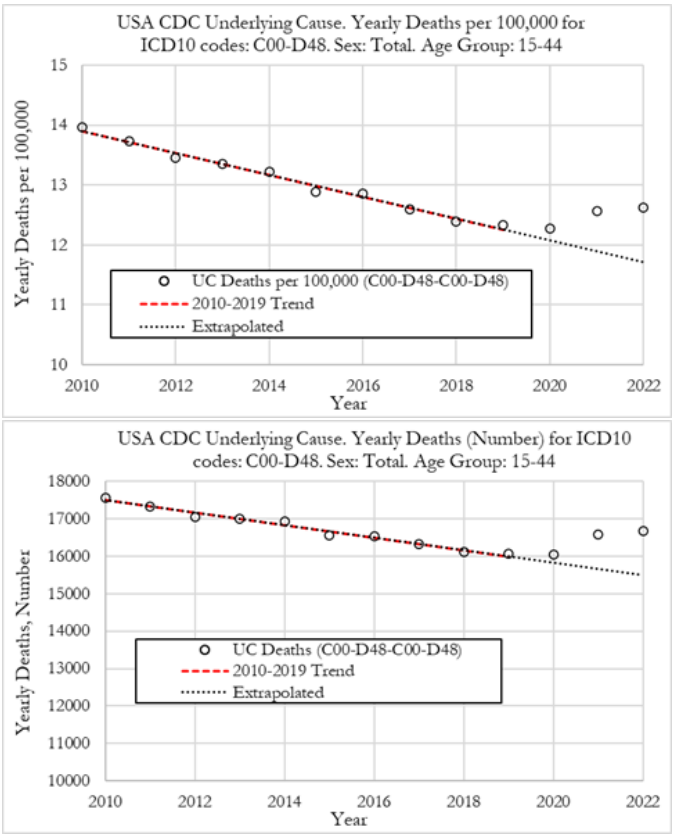

Figure 3. Yearly deaths from neoplasms as underlying cause in the US. The red dashed line shows the average from 2010 to 2019. The dotted line shows the extrapolation of the trend from 2020 until 2022. Top: Deaths per 100,000. Bottom: Deaths (Number).

The death rate dropped slightly in 2020 to about 12.2 per 100,000 and then rose to 12.6 per 100,000 in 2021 and again to about 12.7 per 100,000, similar to that observed in 2017.

The absolute numbers of deaths with neoplasms as underlying cause (Figure 3 bottom), were about 16,000 in both 2019 and 2020 rising to about 16,580 16,670 deaths in 2021 and 2022 respectively.

4.2.2 Excess UC Death Rates

Figure 4 shows the excess death rates for neoplasms as underlying cause in the USA, for the 15 to 44 age group from 2010 to 2022 with the excess all-cause deaths (from Figure 2) for comparison. The upper figure refers to relative deviations from the 2010-2019 trend, while the lower figure shows the Z-score (signal strength) for the deviations from trend.

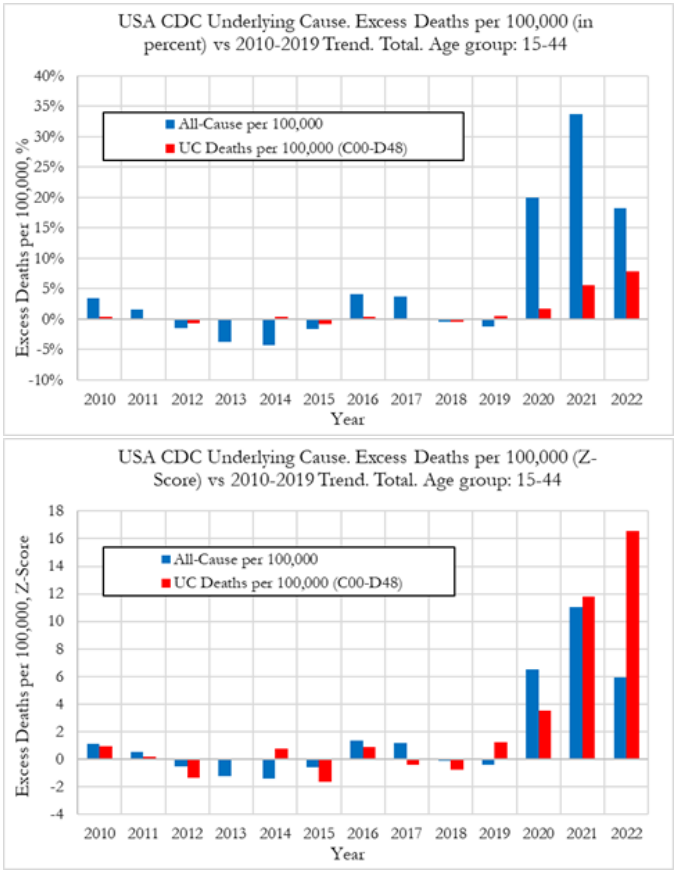

Figure 4. Excess UC death rates from neoplasms from 2010 to 2022 for both sexes of ages 15 to 44 in the USA. Top: Relative deviation from trend, percent. Bottom: Deviation from trend Z-Score. Excess deaths from all causes are shown for comparison.

The excess death rates from neoplasms as the underlying cause were 1.7% in 2020, rose to 5.6% in 2021, and 7.9% in 2022. By comparison, the excess all-cause mortality was 19.9% in 2020, 33.8% in 2021, and 18.2% in 2022. Noteworthy is that the drop in all-cause excess mortality from

2021 to 2022 was not mirrored in a drop in neoplasm deaths. In fact, the opposite occurred, with an increase in excess deaths due to neoplasms as the underlying cause.

In terms of statistical significance of the excess deaths, we observe from Figure 4 (bottom) that the Z-score in 2020 was 6.5, which is a very strong signal. In 2021, the Z-score was 11.0 which is an extreme signal. In 2022 the Z-score dropped to 5.9, which still indicates that the excess deaths are a statistically significant deviation from the 2010-2019 trend.

When looking at excess deaths from neoplasms, while the excess death rate from neoplasms as the underlying cause was only 1.7% in 2020, the Z-score was 3.5 which increased substantially in 2021 and 2022 where we observe Z-scores of 11.8 and 16.5, respectively. These are extreme events that we believe require thorough investigation. The investigation of trends in cancer rates in individuals aged 15 to 44 from the UK (Alegria, et al., 2024)[1], showed much larger deviations from trend in 2021 and 2022, albeit with similar levels of statistical significance as those found in the US data. (The US population is about 6 times larger than the UK population, which provides a much larger sample size. Consequently, a smaller deviation from trend can produce a similar level of statistical significance.) Additionally, the larger increments in death rates from cancers in the UK are more uncertain estimates as they are based upon incomplete datasets where deaths are adjusted using the assumption of proportional deaths for the missing data points. This makes the corroboration of increased death rates from neoplasms in the US data of particular interest.

4.3 Trends in Multiple Cause Death Rates and Excess Deaths for ICD-10 Codes C00 to D48 (Neoplasms)

In this section we investigate the trends in death rates and excess deaths from 2010 to 2022 where neoplasms are reported as one of the multiple causes of death (either underlying or secondary cause of death), for the 15-44 age group of both sexes.

4.3.1 Deaths MC (Multiple Cause) from ICD-10 Codes C00 to D48 (Neoplasms)

In this section we analyze the trends in MC death rates from neoplasms where they were either the underlying cause of death or were recorded as a secondary cause of death. This analysis provides additional information in understanding the phenomenon of increased deaths from cancer during the pandemic years, for this age group.

Figure 5 (top) shows the death rate per 100,000 individuals aged 15 to 44, from neoplasms deaths in the US from 2010 to 2022, where neoplasms are listed as one of multiple causes of death (either underlying or contributing). We can observe that MC deaths per year from neoplasms trended lower from 2010 to 2019, with a significant downward slope. In 2010 the death rate was 14.5 per 100,000 and in 2019 it was around 13.1 per 100,000, a 9.65% drop.

The death rate rose slightly in 2020 to 13.2 per 100,000 and then rose to 13.7 per 100,000 in 2021 where it remained steady in 2022 at a level similar to that observed in 2014.

4.3.2 Excess MC Death Rates

As previously mentioned, MC deaths rates need to be taken with caution as they refer to death rates for a given disease where it is either the underlying cause or a contributing factor towards death. Some diseases, such as respiratory diseases, are mostly attributed as contributing factors for death while other causes are the underlying cause. This means that MC death rates from respiratory diseases could amount to several times the UC death rate. On the other hand, by analyzing both MC death rates and UC death rates, we can have a better understanding of the underlying phenomena that lead to death.

When excess death rates are computed (either MC death rates or UC cause death rates), they adjust

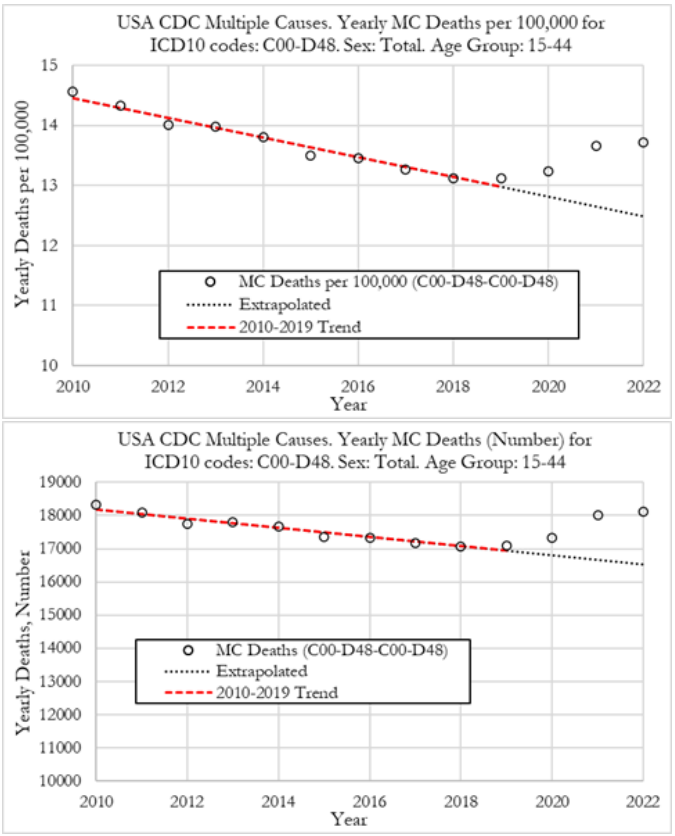

Figure 5. Yearly deaths from neoplasms as one of multiple causes (underlying or contributing factor) in the USA. The red dashed line shows the average from 2010 to 2019. The dotted line shows the extrapolation of the trend from 2020 until 2022. Top: Deaths per 100,000. Bottom: Deaths (Number).

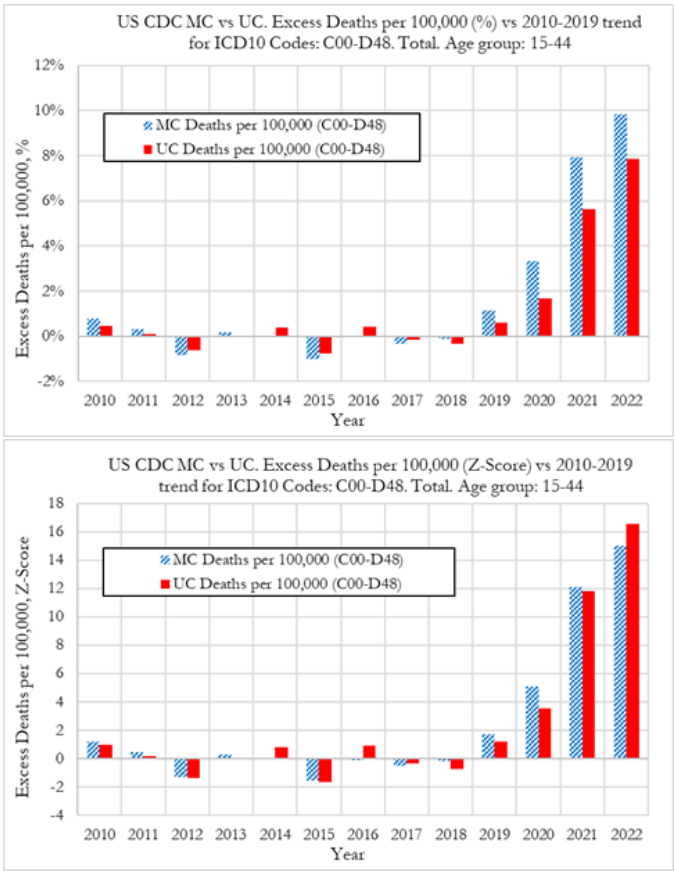

Figure 6. Excess MC death rates from neoplasms from 2010 to 2022 for both sexes of ages 15 to 44 in the USA. Top: Relative deviation from trend, percent. Bottom: Deviation from trend Z-Score. Excess UC death rates are shown for comparison.

for prior trends in death rates which are also scale-adjusted when relative deviation from trends are computed. Excess death rates are also adjusted by the volatility in deviations from trend (dispersion around the trend), which allows for a direct comparison of excess MC death rates with excess UC death rates.

Figure 6 compares the excess MC and UC death rates from neoplasms from 2010 to 2022 showing the relative deviations (top) and the Z-score (signal strength) for the deviations (bottom) from the 2010-2019 trend.

In Figure 6 (top) we observe that the excess MC death rates from neoplasms were 3.3% in 2020, then rose to 7.9% in 2021, and 9.8% in 2022. By comparison, the excess UC death rates were 1.7% in 2020, 5.6% in 2021, and 7.9% in 2022. Of note is that the excess mortality for MC deaths from cancer was greater than for UC deaths in all three pandemic years, particularly in 2020.

The Z-score for excess deaths with neoplasm as a multiple cause in 2020 was 5.1, indicating a very strong signal. A trend emerged with substantial increases in Z-scores of 12.1 and 15.0 for 2021 and 2022, respectively. These are extreme events, akin to those observed for UC cancer deaths.

4.4 Comparison of MC and UC Death Rates for ICD-10 Codes C00 to D48 (Neoplasms)

In this section we compare the trends in death rates from MC and UC deaths from neoplasms,

attempting to determine whether the increase in neoplasm MC deaths in 2020 represents an increase in cancers per se, or a consequence of the pandemic on mortality for people with existing cancers.

Figure 7 (top) plots together the UC and MC death rates from neoplasms in the US, from 2010 to 2022 previously plotted in Figures 3 and 5, respectively. Figure 7 (bottom) shows the ratio of MC/UC death rates and illustrates that the fraction of cancer deaths recorded as a secondary cause was relatively stable, at 4% to 5% of the number of deaths with cancer as the underlying cause, from 2010 to 2016.

However, a departure from this existing trend emerged in 2017 when this fraction trended upwards reaching 1.08 in 2020, indicating that for an increasing proportion of decedents for whom cancer was listed as a multiple cause, the underlying cause of death was attributed to another cause. In 2020, this could be explained by deaths from COVID-19 or other health effects of the pandemic lockdowns on individuals suffering from cancer. In 2021 the fraction of MC to UC cancer deaths rose to close to 1.09 and remained at a similar level in 2022.

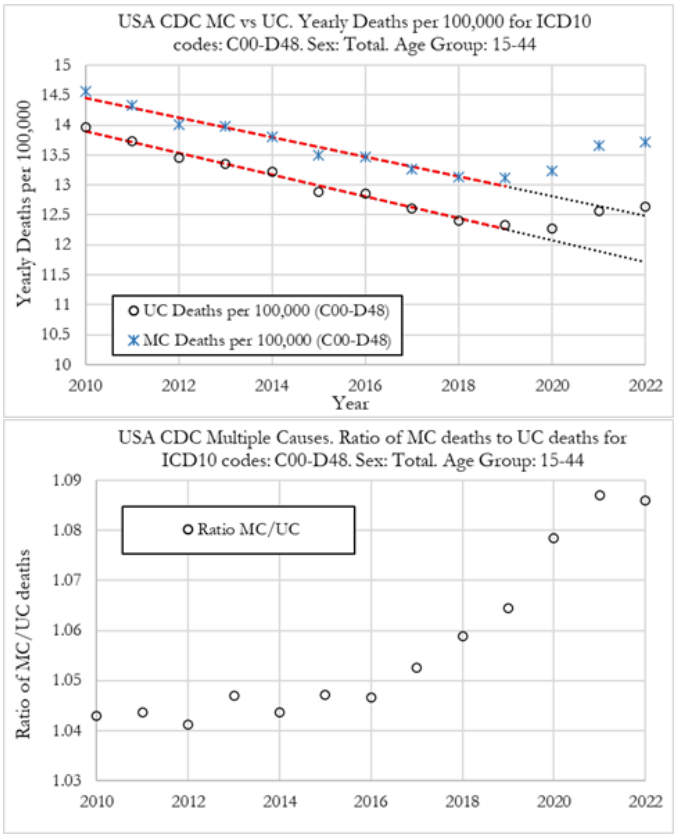

Figure 7. Yearly deaths from neoplasms as multiple cause (underlying or contributing factor) in the USA. The red dashed line shows the average from 2010 to 2019. The dotted line shows the extrapolation of the trend from 2020 until 2022. Top: Deaths per 100,000. Bottom: Deaths (Number).

4.5 Trends in UC Death Rates for Males and Females.

In this section we analyze the trends in UC death rates from neoplasms in males and females.

4.5.1 UC Death Rates for Males and Females from ICD-10 Codes C00 to D48 (Neoplasms)

Figure 8 shows the death rates per 100,000 individuals for males and females, where neoplasms were the underlying cause of death. We can observe that UC death rates have been trending lower from 2010 to 2019, with significant downward slopes, for both males and females in the 15-44 age group.

For females, in 2010 the death rate was 14.9 per 100,000 and in 2019 it was 13.2 per 100,000, an 11.4% drop. The death rate dropped slightly in 2020 to 13 per 100,000 and then rose to 13.4 per 100,000 in 2021, remaining at this level in 2022.

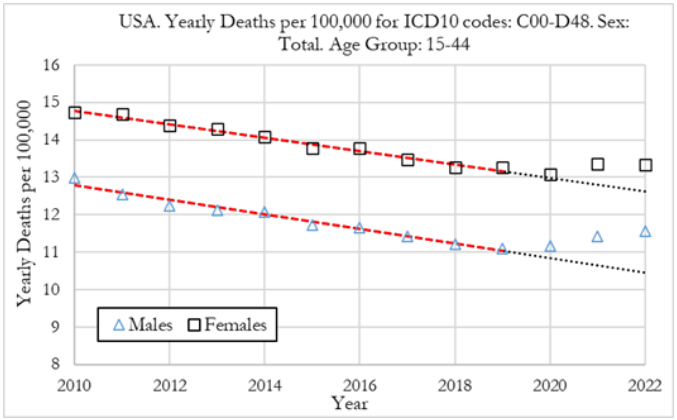

Figure 8. Yearly UC death rates from neoplasms in the USA for males and females of ages 15-44. The red dashed line shows the average from 2010 to 2019. The dotted line shows the extrapolation of the trend from 2020 until 2022.

For males, in 2010 the death rate was 13 per 100,000 and in 2019 it was 11 per 100,000, a 15.4% drop. The death rate rose slightly in 2020 to 11.1 per 100,000 and then rose to 11.4 per 100,000 in 2021 and 11.5 per 100,000 in 2022.

4.5.2 Excess UC Death Rates for Males and Females

When comparing excess UC death rates attributed to neoplasms for males and females (Figure 9) we observe that in 2020, while females had no significant excess mortality, males experienced about 3% excess mortality, with a Z-score of about 3.5 indicating a statistically significant deviation from trend.

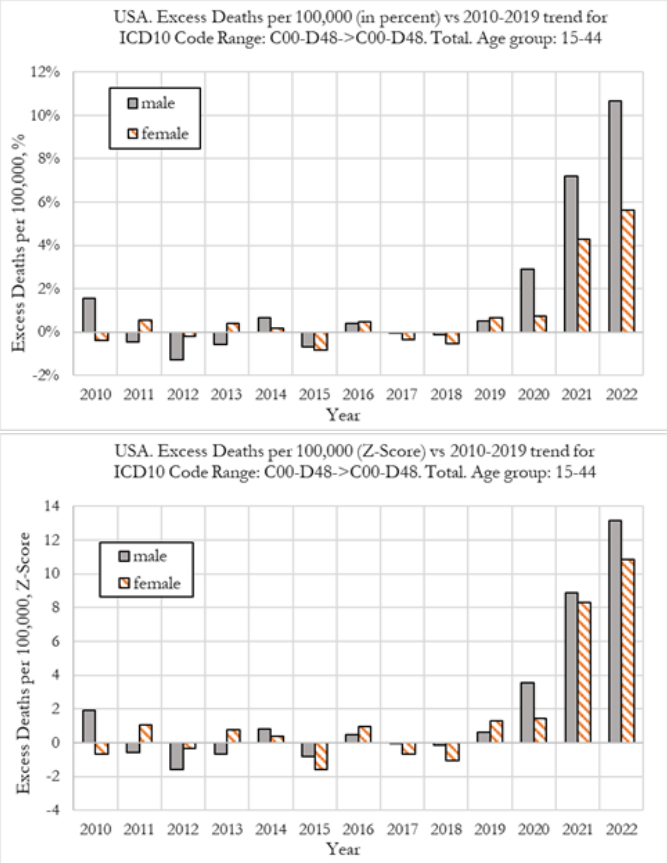

Figure 9. Excess deaths rates by neoplasms for males and females, in the US. Top: Relative deviation from trend, percent. Bottom: Deviation from trend Z-Score.

In 2021 excess UC death rates from neoplasms for males was 7.2% while only 4.2% for females, both having Z-scores close to 8, indicating very high statistical significance (Figure 9 bottom). Males experienced about a 70% higher excess mortality from neoplasms compared with females in 2021.

In 2022 the excess UC death rate from neoplasms for males was about 10.7%, almost double that for 5.8% for females, both having Z-scores above 10, indicating extreme occurrences.

5 SUMMARY OF FINDINGS AND COMMENTARY

In our study we analyze trends in death rates from neoplasms in individuals aged 15-44 in the USA. We compare excess death rates for neoplasms where they are classified as the underlying cause of death (UC) or with cancers as MC of death (either underlying cause or contributing cause).

UC deaths from neoplasms

When analyzing UC death rates from neoplasms, our computations show that the excess death rates from neoplasms for the 15-44 age group were 1.7% in 2020, 5.6% in 2021, and 7.9% in 2022 (Figure 4). Even though the deviation from trend was small, the excess death rate in 2020 was statistically significant with a Z-score of 3.5. The excess UC death rates in 2021 and 2022 can be considered extreme events with respective Z-scores of 11.8 and 16.5.

For comparison, excess mortality for all-cause deaths was 19.9% in 2020, 33.8% in 2021, and 18.2% in 2022. It should be noted that as excess mortality for all-cause deaths dropped from 2021 to 2022, this was not associated with a drop in excess UC death rates from neoplasms; rather, the reverse occurred.

When comparing UC death rates for males and females we observe that while death rates for females did not show a significance increase in 2020, males experienced a statistically significant 3% excess mortality from neoplasms. In 2021 excess UC death rates from neoplasms for males was 7.2% while only 4.2% for females, both having Z-scores

close to 8, indicating very high statistical significance (Figure 9 bottom). In 2022 excess UC death rates from neoplasms for males was about 10.7% while about 5.8% for females, both having Z-scores above 10, indicating extreme occurrences.

Males experienced an approximately 70% increase in excess deaths from neoplasms compared with females in 2021, doubling in 2022. These results are corroborated by the findings of our previous work (Alegria, et al., 2024)[1] on cancer rates in individuals aged 15 to 44 from the UK.

MC deaths from neoplasms

When analyzing MC death rates we found that the excess death rate from neoplasms was 3.3% in 2020, then rose to 7.9% in 2021, and 9.8% in 2022 (Figure 6). The excess death rate in 2020 was highly statistically significant with a Z-score of 5.1. The excess MC death rates in 2021 and 2022 can be considered extreme events with respective Z-scores of 12.1 and 15.0.

The rise in MC cancer deaths in 2020 may be due at least in part to other causes such as COVID-19 or the effect of the lockdowns, which may have limited access to diagnosis or treatment. In 2021 and 2022 we observe larger rises in deviations from trend in MC death rates from neoplasms, compared to deviations from trend in UC death rates. In 2021 the ratio of MC to UC cancer deaths rose to 1.09 and remained at that level in 2022.

Comments

Our observations are consistent with those (all ages) published by the American Cancer Society (ACS) in their two most recent summaries of cancer statistics. Their 2023 report (Siegel, et al., 2023)[12] noted "Despite the pandemic, and in contrast with other leading causes of death, the cancer death rate continued to decline from 2019 to 2020" Although their 2024 paper (Siegel, et al., 2024)[17] reported that cancer mortality (all age) continued to decline through 2021, they noted that cancer-related mortality (i.e., cancer as an underlying or contributing cause) increased from 2019 to 2020 and again in 2021. Citing Fedeli, et al.(2024)[18] the ACS contrasted these increases with the two decades of decline in mortality rates, speculating that this was a "secondary consequence of the COVID-19 pandemic." Fedeli et al. [18] drew particular attention to increases in mortality related to prostate and hematologic cancers.

To explain the observed trends in rising cancer-related death rates from 2020, we propose two general hypotheses:

a) Individuals aged 15-44 with existing cancers died at higher rates, from multiple underlying causes, during 2020, 2021, and 2022. This hypothesis implies that a certain number of individuals would have died at a later date, of the neoplasm itself or other incidental illnesses, but that COVID-19 infection or other pandemic impacts "brought forward" their deaths. Causes unrelated to COVID-19 have also contributed to the pre-pandemic rise in the MC/UC ratio that began in 2017. (Fedeli, et al., 2024)[18]

b) Cancer rates and/or the severity of cancers within the 15-44 age group rose significantly during 2020, 2021 and 2022, leading to rises in cancers as the underlying cause of death and also rates of death with cancers as secondary causes.

And finally, we have a situation where a combination of the above hypotheses occurred simultaneously.

c) Combinations of both previous hypotheses. Increased cancer rates and/or severity in the 15-44 age group, combined with earlier deaths from cancer and/or other illnesses (bring-forward effect), resulted in higher neoplasm deaths from 2020.

Hypothesis a) is supported by the fact that death involving cancer as a multiple cause started rising in 2020, when death rates from cancers as the underlying cause did not rise significantly. COVID-19 or other causes of death, associated with lockdowns and reduced medical care (Burus, et al., 2024)[19] during the pandemic, are factors that were not

present before 2020 and could have contributed towards increased MC deaths from cancer in 2022.

On the other hand, the bring-forward effect usually implies that after a period of higher excess deaths, there would be an equivalent period of negative excess deaths that compensates for the bring-forward effect i.e. deaths that were precipitated by the COVID-19 pandemic would then be absent from counts of deaths in subsequent time periods. The opposite has so far occurred, with both MC and UC cancer death rates accelerating in 2021 and 2022. No period of negative excess neoplasm deaths has materialized so far for this age group.

Although COVID-19 disease became milder (less lethal) in 2021 and 2022 with the emergence of the Omicron variant, the virus became more transmissible leading to a surge in the overall number of deaths attributed to COVID-19 ”bringing forward” neoplasm MC deaths.

Hypothesis b) is supported mainly by the rising trend in both MC and UC cancer excess death rates. Higher than expected cancer death rates could originate from higher incidence of cancers, an acceleration of existing cancer cases, and/or more rapidly-progressing cancers.

If the initial rise in cancer-related deaths in 2020 is explained by the bring-forward effect, it was not followed by an expected compensatory period of negative excess deaths, but by a continued rise in neoplasm death rates in 2021 and 2022. Thus, a different phenomenon may be occurring, overlapping in timescale, of increased incidence or severity of cancers, supporting the combination hypothesis c). Some insight into these observations might be gained from cancer incidence rates. However, ACS (Siegel at al, 2024) note difficulty in analyzing diagnoses data from 2020 because of the large anomalous drop in apparent incidence due to COVID-19 health care disruptions. Delays in diagnosis were not uniformly distributed across cancer types, age, or severity of cancer, adding to the complexity of the problem.

Indeed, in the present study, a reduction in cancer screening and diagnostics during the pandemic years leading to higher deaths could be a confounding factor. However, the younger age group of 15 to 44 are not likely to be affected significantly by this factor, as the majority of cancer screening is carried out in age groups over 45. This is supported by the observation by the ACS (Siegel et al 2024) that the drop in incidence rates in 2020 was lower for childhood (4%) and adolescent (6.5%) cancers.

Limitations of the study

The main limitation from our analysis is that the 2022 data from the CDC for the different causes of death is provisional, at the date of the data download (2023-12-20) which means that it might be subject to change, particularly in the classification of underlying cause or when adding secondary causes of disease. This might lead to some discrepancies when the final data are released.

Our analysis does not allow us to look in detail at whether cancer incidence has increased since 2020, and when this may have occurred. As noted by (Siegel, et al., 2024)[17], incidence and mortality data may not become publicly available for 2-4 years.

We have reported here trends based on crude rates, and recognize that a variety of adjustments may be made, for example for age, and reference to an index year and using analytical tools such as Joinpoint and DevCan[9]. However, as ACS notes (Siegel, et al., 2024)[17] these tools may be limited as they were not designed to accommodate the sorts of data anomalies occurring between 2019 and 2020 due to COVID-19 related disruptions in health care. The very strong signals detected in our analysis based on crude rates are sufficient justification for further exploration.

Other limitations are implied by the following discussion on Future Work.

[9] National Cancer Institute - Methods & Tools for Population-based Cancer Statistics

Future work

We concur with Fedeli, et al. (2024)[18] that further research is needed to determine the relative contributions of what are likely to be multiple factors affecting the rise in cancer-related death rates during or after the COVID-19 pandemic.

In particular, cancer trends need to be further stratified by age, gender and cancer type. Health disparities during the COVID-19 pandemic related to race and ethnicity may be particular sources of confounding. The relationship between cancer deaths as a multiple cause for other underlying causes must be dissected. Additionally, changes in incidence and survival statistics during the COVID-19 pandemic must be examined, when reliable data are available.

The possible effect of the modRNA COVID-19 vaccines, which were rolled out from 2021 and prioritized for vulnerable groups such as those with cancer should be studied. This imperative is based on a growing body of evidence supporting plausibility including the case reports and CDC's cancer signals derived from VAERS described in our introduction. Accordingly, future work should compare cancer rates in vaccinated and unvaccinated individuals.

CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REFERENCES

[1] Alegria C, Nunes Y. Uk - death and disability trends for malignant neoplasms, ages 15-44 (2024). doi:10.13140/RG.2.2.34374.45123. (link).

[2] Zamfir MA, Moraru L, Dobrea C, Scheau AE, Iacob S, Moldovan C, et al. Hematologic malignancies diagnosed in the context of the mrna covid-19 vaccination campaign: A report of two cases. *Medicina* **58** (2022) 874. doi:10.3390/medicina58070874. (link).

[3] Sekizawa A, Hashimoto K, Kobayashi S, Kozono S, Kobayashi T, Kawamura Y, et al. Rapid progression of marginal zone b-cell lymphoma after covid-19 vaccination (bnt162b2): A case report. *Frontiers in Medicine* **9** (2022). doi:10.3389/fmed.2022.963393. (link).

[4] Mizutani M, Mitsui H, Amano T, Ogawa Y, Deguchi N, Shimada S, et al. Two cases of axillary lymphadenopathy diagnosed as diffuse large b-cell lymphoma developed shortly after bnt162b2 covid-19 vaccination. *Journal of the European Academy of Dermatology and Venereology* **36** (2022) e613–e615. doi:10.1111/jdv.18136. (link).

[5] Goldman S, Bron D, Tousseyn T, Vierasu I, Dewispelaere L, Heimann P, et al. Rapid progression of angioimmunoblastic t cell lymphoma following bnt162b2 mrna vaccine booster shot: A case report. *Frontiers in Medicine* **8** (2021). doi:10.3389/fmed.2021.798095. (link).

[6] Kreher M, Ahn J, Werbel T, Motaparthi K. Subcutaneous panniculitis-like t-cell lymphoma after covid-19 vaccination. *Journal of the American Academy of Dermatology, Case Reports* **28** (2022) 18–20. doi:10.1016/j.jdcr.2022.08.006. (link).

[7] Eens S, Van Hecke M, Favere K, Tousseyn T, Guns PJ, Roskams T, et al. B-cell lymphoblastic lymphoma following intravenous bnt162b2 mrna booster in a balb/c mouse: A case report. *Frontiers in Oncology* (2023) 1–7. doi:10.3389/fonc.2023.1158124. (link).

[8] Wiseman DM, Guetzkow J, Pantazatos S, Rose J. National academies committee on review of relevant literature regarding adverse events associated with vaccines march 30 2023: Written material accompanying oral remarks. *ResearchGate* (2023). doi:10.13140/RG.2.2.27009.74089. (link).

[9] Zhang L, Richards A, Barra M, Jaenisch R. Reverse-transcribed sars-cov-2 rna can integrate into the genome of cultured human cells and can be expressed in patient-derived tissues. *Proceedings of the National Academy of Sciences* **118** (2021) e2105968118. doi:10.1073/pnas.2105968118. (link).

[10] Zhang L, Bisht P, Flamier A, Barrasa MI, Friesen M, Richards A, et al. Line1-mediated reverse transcription and genomic integration of sars-cov-2 mrna detected in virus-infected but not in viral mrna-transfected cells. *Viruses* **15** (2023). doi:10.3390/v15030629. (link).

[11] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *A Cancer Journal for Clinicians* **72** (2022) 1–93. doi:10.3322/caac.21708. (link).

[12] Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *A Cancer Journal for Clinicians* **73** (2023) 1–112. doi:10.3322/caac.21763. (link).

[13] Tseng TS, Li M, Kao YH, Chen LS, Lin HY. The impact of covid-19 on risky behaviors and health changes in african-american smokers who are eligible for ldct screening. *Frontiers in Public Health* **9** (2021). doi:10.3389/fpubh.2021.745925. (link).

[14] Almeda N, Gómez-Gómez I. The impact of the covid-19 pandemic on smoking consumption: A systematic review of longitudinal studies. *Frontiers in Psychiatry* **13** (2022). doi:10.3389/fpsyt.2022.941575. (link).

[15] Gaffney A, Himmelstein DU, Woolhandler S. Smoking prevalence during the covid-19 pandemic in the united states. *Annals of the American Thoracic Society* **19** (2022) 873–1080. doi:10.1513/AnnalsATS.202110-1184RL. (link).

[16] Alegria C, Nunes Y. On measuring excess mortality. *ResearchGate* (2024). doi:10.13140/RG.2.2.16889.44646. (link).

[17] Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *A Cancer Journal for Clinicians* **74** (2024) 12–49. doi:10.3322/caac.21820. (link).

[18] Fedeli U, Amidei CB, Han X, Jemal A. Changes in cancer-related mortality during the covid-19 pandemic in the united states. *Journal of the National Cancer Institute* **116** (2024) 167–169. doi:10.1093/jnci/djad191. (link).

[19] Burus T, Lei F, Huang B, Christian WJ, Hull PC, Ellis AR, et al. Undiagnosed cancer cases in the us during the first 10 months of the covid-19 pandemic. *JAMA Oncology* (2024). doi:10.1001/jamaoncol.2023.6969. (link).