Excess Cancer Mortality after mRNA-Lipid Nanoparticle SARS-CoV-2 Vaccination in Japan: Observation until 2023

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Conflict of Interest

The authors declare no potential conflicts of interest.

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Abstract

Excess mortality during the COVID-19 pandemic is a serious global health issue. This remains a significant concern in Japan, with its rapidly aging population. In Japan, cancer is the leading cause of death. Therefore, this study aims to assess how the age-adjusted mortality rates (AMRs) for various types of cancer in Japan changed during the COVID-19 pandemic, from 2020 to 2023. Official statistics from Japan were used to compare the observed annual and monthly AMRs from 2020 to 2023 with the rates predicted by data from 2010 to 2019, before the pandemic, using logistic regression analysis. There was no significant excess mortality during the first year of the pandemic in 2020. However, the AMRs for all cancers and some specific types of cancer, including ovarian cancer, leukemia, lip/oral/pharyngeal cancer, prostatic cancer, and pancreatic cancer, were observed to deviate from the predicted rates in the direction of excess with statistical significance from 2021 to 2023, when the large-scale mRNA-lipid nanoparticle vaccination was carried out in Japan. For each of the four most common cancers (lung, colorectal, stomach, and liver), there was a decreasing trend in AMR from the pre-pandemic period onwards and no statistically significant deviation from the predicted rates was found during the pandemic. The causal relationship between excess cancer deaths and large-scale vaccination cannot be analyzed in this study, but the coincidence of timing might require further research. Possible explanations for this excess cancer mortality were discussed.

Introduction

The COVID-19 pandemic began in December 2019 in Wuhan, China, and was first identified in Japan in January 2020. In response, a range of healthcare and socio-economic restrictions were implemented to curb the spread of the disease. Since February 2021, the mRNA-lipid nanoparticle (mRNA-LNP) SARS-CoV-2 vaccine has been available for emergency use, and it has been recommended for all individuals aged 6 months and older, especially those at high risk. As of the end of 2023, 80% of the population had received their first and second doses, and 67%, 46%, 30%, 20%, and 13% had received their third, fourth, fifth, sixth, and seventh doses [1]. Despite these national measures, 46.8 million people had been newly infected and 106,000 deaths had been attributed to COVID-19 in Japan by the end of 2023 [2,3]. Additionally, there have been reports of excess deaths from causes other than COVID-19 in various countries [4-10], including cancers [11-14], and Japan is no exception [15, 16]. Cancer is the leading cause of death in Japan, accounting for one-quarter of all deaths. Therefore, it is essential to understand how the cancer mortality rates were affected by the pandemic from 2020 to 2023. Age adjustment is necessary for accurate evaluation, especially in diseases that tend to occur in the elderly, such as cancer. Japan has several conditions that make it appropriate for analyzing the impact of the pandemic on cancer mortality rates, including its large population of 123 million, official statistics, and the accuracy of death certificates, which have been evaluated as 80% correct according to autopsy studies [17].

Materials & methods

Statistical data

The data used in this analysis are all publicly available national data. The numbers of deaths were taken from the Vital Statistics [18], which include monthly and annual deaths by cause, sex, and age (5-year age groups). As causes of death, following WHO recommendations, the attending physician should enter the direct causes in part I and any other significant condition contributing to the fatal outcome in part II of the cause of death section of the death certificate, and then the administrative officer identifies an underlying cause of death from the entries to compile the demographic statistics [19]. Cancers are divided into 20 subclassifications. The target samples were limited to Japanese individuals living in Japan. Population estimates by age group required for the age-adjusted analysis were also taken from the national data [20]. The number of confirmed COVID-19-infected persons was obtained from the Ministry of Health, Labour and Welfare (MHLW) and Moderna websites [2, 3]. The vaccination rates by age group were obtained from the websites of the Prime Minister’s Office and MHLW [21].

Age-specific mortality rates (ASMRs)

The annual crude number of deaths was observed in 10-year age groups for those aged 0–39, who had fewer deaths, and in 5-year age groups for those aged 40 and older, who had more deaths (with one exception: those aged 90 and older were combined into one group because of small population size).

ASMRs (per 100,000 people)

= age-specific number of deaths/population in that age group *100,000

Age adjustment by direct standardization

Because ASMRs are too detailed to provide an overview of mortality from all types of cancer, we used the age-adjusted mortality rate (AMR) from direct standardization as a summarized indicator. For comparisons of mortality rates over time, as in our study, all samples are the Japanese population as a whole, with almost the same large number and age composition of people. The specific death rates per age group are known, so direct standardization is appropriate [22]. MHLW in Japan reportedly uses direct standardization with smoothed standard population data from 2015 (125.32 million) [23], and the same approach was used in this study. The formulas for the calculations are as follows:

・ Age-adjusted number of deaths = $\sum_{i=1} \frac{d_i}{p_i} \times ps_i$

・ Age-adjusted mortality rate (AMR/100,000 people) = $\frac{\sum_{i=1} \frac{d_i}{p_i} \times ps_i}{\sum_{i=1} ps_i} \times 100{,}000$

where i=age group, d_{i}=number of deaths in that age group, $\mathrm{p_i}$=number in that age group in the observed population, ps_{i}=number in that age group in the standard population.

Age adjustment for sex-specific cancers was performed using the “sex-specific smoothed standard population dataset 1” [24].

In leap years, the deaths had occurred in 366 days, so the number of deaths and AMR were multiplied by 365/366 to correct them.

Excess mortality during the COVID-19 pandemic

Excess mortality in this study was defined as follows:

・ Excess number of deaths = observed number of deaths − predicted number of deaths in a corresponding year or month.

・Excess mortality (%) = $\frac{\text{observed rate - predicted rate}}{\text{predicted rate}} \times 100(\%)$

(The rates were ASMR or AMR in a corresponding year or month.)

The predicted rates based on the period 2010–2019 preceding the COVID-19 pandemic were calculated using logistic regression analysis [7]. The predicted AMRs for each month were also calculated using the data from a corresponding month in 2010–2019. R version 4.3.1 was used for statistical software.

The confidence intervals (CIs) and prediction intervals (PIs) around the predicted numbers and rates were calculated by the logit-transformed values using the following formulas and then transformed inversely. Annual or monthly age-adjusted mortality rates were considered to be statistically significant when they were above or below the 95% prediction interval.

residual variance (*Ve*) = $\frac{\sum_{t=1} \left(\text{observed value}_t - \text{predicted value}_t\right)^2}{\mathrm{n - p - 1}}$

standard error (SE) for confidence interval (CI) = $\sqrt{\left(\frac{1}{n} + \frac{\left(x_o - \bar{x}\right)^2}{\sum_{i=1} \left(x_t - \bar{x}\right)^2}\right) \times \mathrm{Ve}}$

standard error (SE) for prediction interval (PI) = $\sqrt{\left(1+\frac{1}{n}+\frac{\left(x_o-\bar{x}\right)^2}{\sum_{i=1}\left(x_i-\bar{x}\right)^2}\right)\times \mathrm{Ve}}$

CI or PI = predicted value$_0$ ± t_{n-p-1}(probability) * SE
value $_i$: logit-transformed ASMR or AMR
n: the number of observations (here, it is 10, from 2010 to 2019)
p: the number of explanatory variables (here, it is 1)
x_o: current year (here, one of 2010, 2011, … , 2022, 2023)

$\bar{x}$: $\Sigma_{i=1}\ x_i$/n

t_{n-p-1} (probability): t value at the degree of freedom (n-p-1), and the probability of interest

Results

Mortality for all causes and cancers

Table 1 shows the number of crude, age-adjusted, and excess deaths for all causes, all cancers, and each cancer type, as well as the excess mortality rates, during each year of the pandemic from 2020 to 2023. Types of cancer are listed in decreasing order of the crude number of deaths in 2023.
For all causes, the annual numbers of age-adjusted deaths in 2020, 2021, 2022, and 2023 were 1,206,126 (962.4), 1,244,976 (993.4), 1,320,768 (1053.9), and 1,303,207 (1039.9), respectively. AMRs for all causes showed a gradual downward trend before the pandemic. In 2020, the first year of the pandemic, there was a statistically significant decrease in mortality (<99% lower PI). However, in 2021, a significant excess mortality of 2.1% emerged, escalated to 9.6% in 2022, and continued to 9.5% in 2023 (all >99% upper PI) for all causes. The number of excess deaths amounted to 25,453 (95%CI: 16,841, 34,006) in 2021, 115,799 (106,018, 125,501) in 2022, and 112,620 (101,668, 123,473) in 2023.
For all cancers, the annual numbers of age-adjusted deaths in 2020, 2021, 2022, and 2023 were 345,248 (275.5), 345,625 (275.8), 344,114 (274.6), and 336,944 (268.9). AMRs for all cancers also showed a gradual downward trend before the pandemic until 2020, the first year of the pandemic. However, in 2021, an excess mortality of 1.1% (>95% upper PI) emerged, continued to 2.1% in 2022 (>99% upper PI) and 1.4% in 2023 (>95% upper PI). The number of excess deaths was 3,870 (95%CI: 1,739, 5,989) in 2021, 7,162 (4,786, 9,522) in 2022, and 4,729 (2,110, 7,327) in 2023 for all cancers (Table 1, Figure 1). The right side of Figure 1 shows the monthly excess/deficit in mortality rates (%) during the pandemic. The rate exceeded the 99% upper PI for the first time in August 2021, coinciding with the peak of the first and second mass vaccinations, and rose again from May 2022, two months after the peak of the third mass vaccination, again exceeding the 99% upper PIs for four months until December. The months with excess deaths were also observed in 2023.
The ranking of the number of deaths for each cancer type was almost the same from 2020 to 2023 (Table 1).

Cause of death and ICD-10 codes		Crude number of deaths				Age-adjusted number of deaths				Excess number of deaths (age-adjusted)				Excess mortality (age-adjusted)			
		2020	2021	2022	2023	2020	2021	2022	2023	2020	2021	2022	2023	2020	2021	2022	2023
All-cause of deaths		1,372,648	1,439,809	1,568,961	1,575,936	1,206,126	1,244,976	1,320,768	1,303,207	-28,126	25,453	115,799	112,620	-2.3%‡	2.1%⁑	9.6%⁑	9.5%⁑
Malignant neoplasms C00-C97		378,356	381,497	385,787	382,492	345,248	345,625	344,114	336,944	-1,379	3,870	7,162	4,729	-0.4%	1.1%*	2.1%⁑	1.4%*
Subclassification	Malignant neoplasm of trachea, bronchus and lung C33–C34	75,581	76,212	76,664	75,762	68,721	68,832	68,292	66,649	-352	672	1,033	279	-0.5%	1.0%	1.5%	0.4%
	Malignant neoplasm of colon, sigmoid, and rectum C18–C20	51,784	52,416	53,088	53,130	47,303	47,498	47,338	46,880	-859	-380	-259	-438	-1.8%	-0.8%	-0.5%	-0.9%
	Malignant neoplasm of pancreas C25	37,674	38,578	39,468	40,174	34,590	35,249	35,593	35,781	296	651	688	565	0.9%*	1.9%⁑	2.0%⁑	1.6%⁑
	Malignant neoplasm of stomach C16	42,318	41,624	40,711	38,767	38,388	37,458	35,940	33,764	-199	366	286	-509	-0.5%	1.0%	0.8%	-1.5%
	Other remaining malignant neoplasm in C00–C97	28,592	28,934	29,646	29,654	26,024	26,065	26,273	26,014	-115	149	579	539	-0.4%	0.6%	2.3%	2.1%
	Malignant neoplasm of liver and intrahepatic bile ducts C22	24,839	24,102	23,621	22,908	22,561	21,708	20,960	20,015	-42	161	421	437	-0.2%	0.7%	2.0%	2.2%
	Malignant neoplasm of gallbladder and other parts of biliary tract C23–C24	17,772	18,172	17,758	17,239	15,810	15,990	15,303	14,597	-255	333	43	-275	-1.6%	2.1%	0.3%	-1.9%
	Malignant neoplasm of breast C50	14,650	14,803	15,911	15,628	14,089	14,185	15,109	14,738	-558	-631	122	-421	-3.8%†	-4.3%†	0.8%	-2.8%
	Malignant lymphoma C81–C86	13,995	13,997	14,230	14,428	12,591	12,507	12,437	12,404	239	64	-98	-224	1.9%	0.5%	-0.8%	-1.8%
	Malignant neoplasm of prostate C61	12,758	13,216	13,440	13,429	10,775	10,981	10,835	10,568	131	547	604	539	1.2%	5.3%*	5.9%*	5.4%*
	Malignant neoplasm of esophagus C15	10,978	10,958	10,918	10,750	10,298	10,248	10,105	9,812	-381	-226	-170	-267	-3.6%	-2.2%	-1.7%	-2.6%
	Leukemia C91–C95	8,983	9,120	9,758	9,869	8,280	8,397	8,868	8,843	-16	143	656	673	-0.2%	1.7%	8.0%*	8.2%*
	Malignant neoplasm of bladder C67	9,166	9,443	9,597	9,590	8,060	8,196	8,114	7,991	-181	-68	-171	-317	-2.2%	-0.8%	-2.1%	-3.8%
	Malignant neoplasm of lip, oral cavity and pharynx C00–C14	7,826	8,000	8,429	8,586	7,257	7,364	7,636	7,724	-46	92	395	514	-0.6%	1.3%	5.5%*	7.1%*
	Malignant neoplasm of uterus C53–C55	6,806	6,818	7,156	7,137	6,568	6,589	6,877	6,824	-73	-86	168	82	-1.1%	-1.3%	2.5%	1.2%
	Malignant neoplasm of ovary C56	4,875	5,081	5,182	5,154	4,732	4,928	4,989	4,966	114	347	442	455	2.5%	7.6%⁑	9.7%⁑	10.1%⁑
	Other malignant neoplasms of lymphoid, hematopoietic,etc. C88–C90, C96	4,295	4,351	4,391	4,323	3,857	3,888	3,850	3,696	-136	-45	-22	-118	-3.4%	-1.1%	-0.6%	-3.1%
	Malignant neoplasm of central nervous system C70–C72, C75.1–C75.3	2,847	3,054	3,106	3,178	2,729	2,944	2,966	3,022	-165	-46	-120	-165	-5.7%	-1.5%	-3.9%	-5.2%
	Malignancy of skin C43–C44	1,707	1,718	1,806	1,861	1,532	1,512	1,546	1,567	8	1	47	81	0.6%	0.1%	3.2%	5.4%
	Malignant neoplasm of larynx C32	781	795	798	791	714	721	707	702	-62	-27	-15	6	-8.0%	-3.6%	-2.1%	0.9%

Table 1. Number of observed crude, age-adjusted, and excess deaths for all causes, all cancers, and each cancer type with the excess mortality rates during the pandemic, from 2020 to 2023

Each cancer type is listed in decreasing order of the crude number of deaths in 2023.

Excess mortality = (observed AMR − predicted AMR)/predicted AMR * 100 (%). (Predicted AMRs based on the period 2010–2019 preceding the pandemic were calculated using logistic regression.)

⁑ >99% upper prediction interval (PI) highlighted in pink; * >95% upper PI, in yellow; ‡ <99% lower PI, in blue; † <95% lower PI, in green.

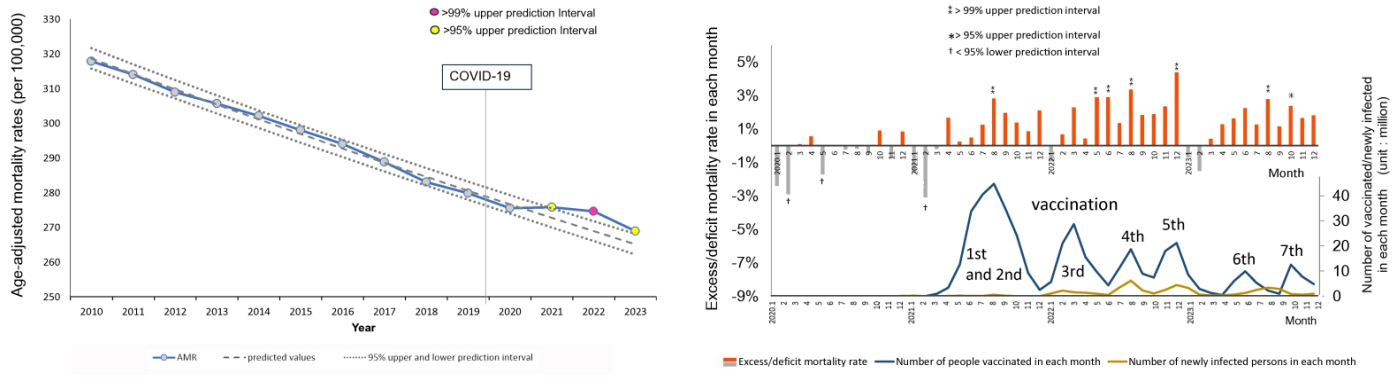

Figure 1. Age-adjusted mortality rates (AMRs) over time and excess/deficit in mortality in each month: all cancers

(Left side) Observed age-adjusted mortality rates (AMRs) (per 100,000 population) are represented by a blue line with circles, while the predicted trend by logistic regression analysis is shown as a dashed line, and the 95% prediction intervals (PIs) are shown as dotted lines. Yellow circles represent years exceeding 95% upper PIs and red circles show years exceeding 99% upper PIs. The onset time of COVID-19 in Japan is shown by the vertical line. There was a decreasing trend in AMR until 2020, but the decline stopped in 2021, exceeding the 95% upper PI in 2021 and the 99% upper PI (not shown in the figure) in 2022. In 2023, AMR also exceeded the 95% upper PI.

(Right side) The horizontal axis indicates each month during the pandemic from 2020 to 2023, while the vertical axis on the left side indicates the excess mortality (%) (observed AMR − predicted AMR in a corresponding month)/predicted AMR in a corresponding month*100. The predicted AMRs based on the period 2010–2019 preceding the COVID-19 pandemic were estimated by logistic regression analysis. The vertical axis on the right side indicates the number of domestic vaccinations and the number of people newly infected with COVID-19. The ⁑ symbol means > 99% upper PI, * means < 95% upper PI, † means < 95% lower PI.

The monthly excess mortality exceeded the 99% upper PI for the first time in August 2021, coinciding with the peak of the first and second mass vaccinations, and exceeded the 99% upper PIs again for four months from May 2022, two months after the peak of the third mass vaccination. The months with excess deaths were also observed in 2023.

Age-specific mortality for all cancers

Prior to the pandemic, all age groups except those aged 90 and above showed a decreasing trend in the crude age-specific mortality rates for all types of cancer from 2010 to 2019 (data not shown). In 2020, there was a deficit in mortality in most age groups except those aged 75–79. Excess mortality was 3.9% in 2020 and 7.9% in 2021 for 75–79 year olds; 9.5% for 75–79 and 2.9% for 80–84 year olds in 2022; and 6.3% for 50–54, 8.9% for 75–79, and 2.8% for 80–84 year olds in 2023, each exceeding the 95% or 99% upper PI.

No statistically significant deviation from predicted mortality was detected in the younger age groups, which had a lower number of deaths. The chart below shows that the number of all cancer deaths peaked in the 80–84 age group (Figure 2). Figure 3 shows 92% of those over 65 received the third vaccination dose, while only 64% of 12–64 year olds did so [1,21]. MHLW reported that more than 99.9% of formulations administered were mRNA-LNPs, with BNT162b2 accounting for 78.1% and mRNA-1273 accounting for 21.8% [21]. All doses up to the third dose were monovalent vaccine.

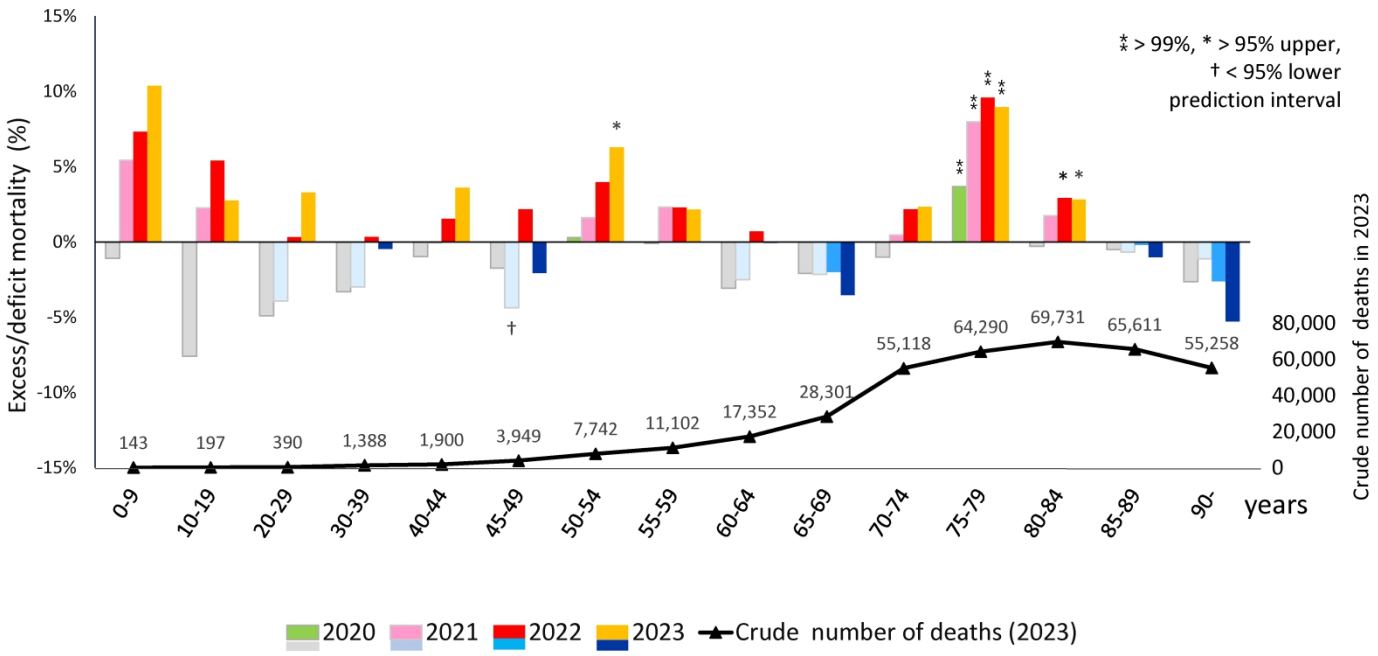

Figure 2. Excess mortality during the pandemic in 2020, 2021, 2022, and 2023 (above) and the crude numbers of all cancer deaths in 2023 (below) in each age group

The excess age-specific mortality = (observed ASMR − predicted ASMR)/predicted ASMR * 100 (%). Predicted ASMRs based on the period 2010–2019 preceding the COVID-19 pandemic were calculated using logistic regression analysis. ‡ >99% upper PI, * >95% upper PI, † <95% lower PI.

In 2020, there was a deficit in mortality in most age groups except those aged 75–79. Excess mortality was 3.9% in 2020 and 7.9% in 2021 for 75–79 year olds; 9.5% for 75–79 and 2.9% for 80–84 year olds in 2022; and 6.3% for 50–54, 8.9% for 75–79, and 2.8% for 80–84 year olds in 2023, each exceeding the 95% or 99% upper PIs. The chart below shows that the number of all cancer deaths peaked in the 80–84 age group.

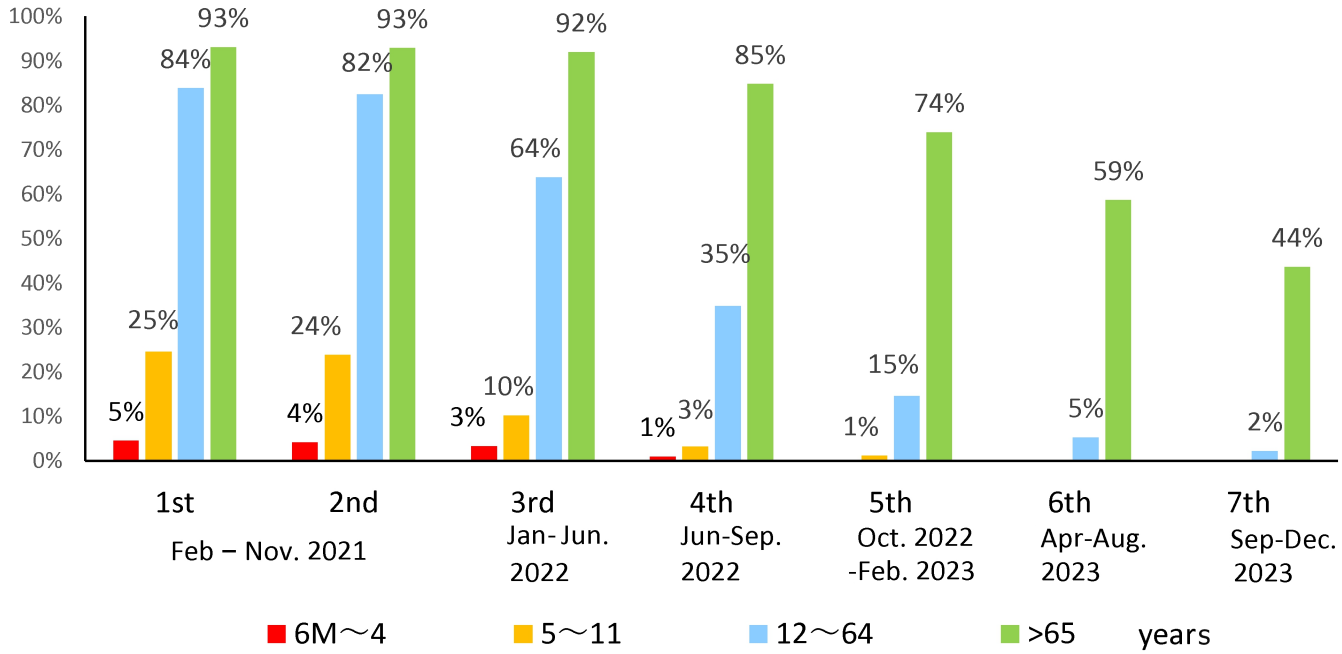

Figure 3: Vaccination rates by age group

92% of those over 65 received the third vaccination dose and 85% the fourth dose, whereas 64% and 35% of 12–64 year olds received the third and fourth doses, respectively. The vaccination rate for elderly people gradually declined later.

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Mortality by each cancer type

Figure 4 shows the excess mortality rates for each type of cancer during the pandemic years. In 2020, only pancreatic cancer slightly exceeded the 95% upper PI for AMR. However, in 2021, 3 out of 20 types of cancer, and in 2022 and 2023, 5 out of 20 types of cancer showed statistically significant excess mortality. These were, in order of highest excess mortality rate in 2023, ovarian cancer, leukemia, lip/oral/pharyngeal cancer, prostatic cancer, and pancreatic cancer. AMRs for ovarian cancer exceeded the predicted rates by 7.6% (95% CI: 5.6, 9.5) in 2021, 9.7% (7.5, 12.0) in 2022, and 10.1% (7.8, 12.3) in 2023, while the excess mortality for leukemia was 1.7% (−2.1, 5.7), 8.0% (3.4, 12.8), and 8.2% (3.3, 13.0); lip/oral/pharyngeal cancer was 1.3% (−1.4, 4.1), 5.5% (2.3, 8.7), and 7.1% (3.6, 10.5); prostatic cancer was 5.3% (2.7, 7.9), 5.9% (3.0, 8.9), and 5.4% (2.2, 8.5); and pancreatic cancer was 1.9% (0.4, 3.4), 2.0% (0.3, 3.7), and 1.6% (1.0, 2.2) in 2021, 2022, and 2023, respectively.

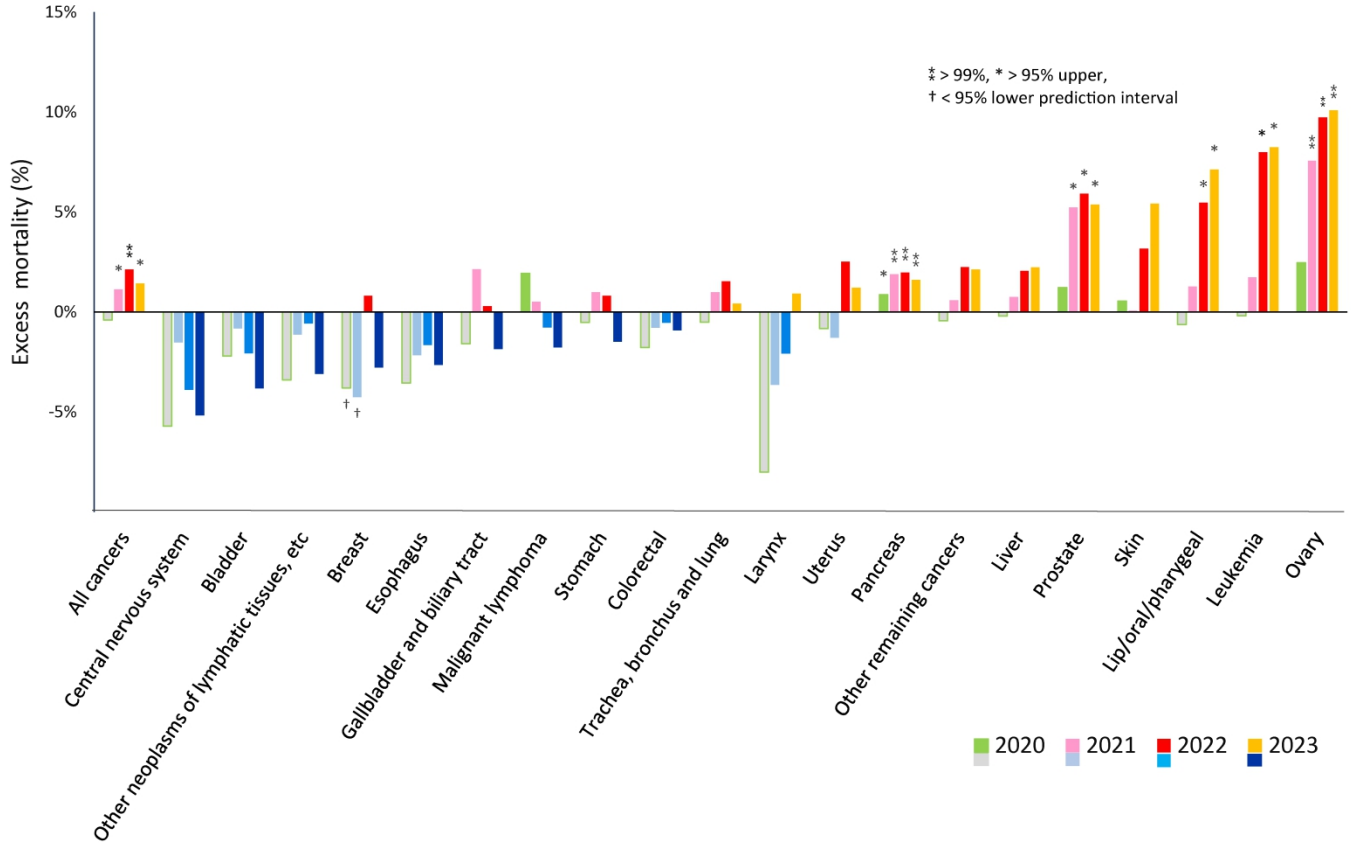


Figure 4. Excess mortality for each cancer type during the pandemic in 2020, 2021, 2022, and 2023

Excess mortality = (observed AMR − predicted AMR)/predicted AMR * 100 (%).

Predicted AMRs based on the period 2010–2019 preceding the pandemic were calculated using logistic regression. ‡ >99% upper PI, * >95% upper PI, † <95% lower PI.

On the far left, all cancer mortality showed excesses in 2021, 2022, and 2023 over 95%, 99%, and 95% upper PI, respectively. Of the 20 types of cancers, 5 showed significant excess mortality. These were ovarian cancer, leukemia, lip/oral/pharyngeal, prostatic, and pancreatic cancers, in decreasing order of excess mortality in 2023. Breast cancer showed a significant deficit in mortality in 2020 and 2021.

Among the 20 subclassifications, the five most common cancers (lung, colorectal, stomach, pancreatic, and liver cancer) accounted for 61% of all cancer deaths (Table 1). The AMRs for the four most common cancers (lung, colorectal, stomach, and liver cancer) stayed within the 95% PIs during the pandemic period from 2020 to 2023 (Figure 5).

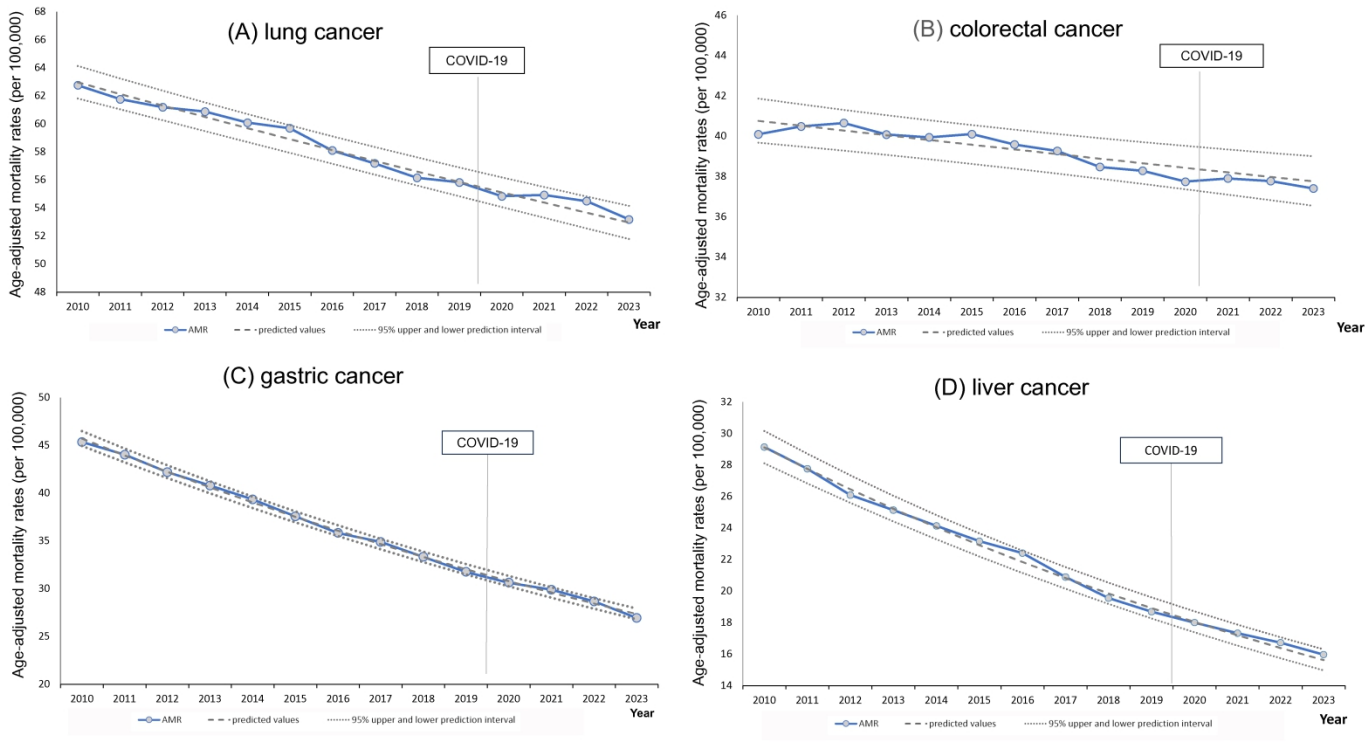


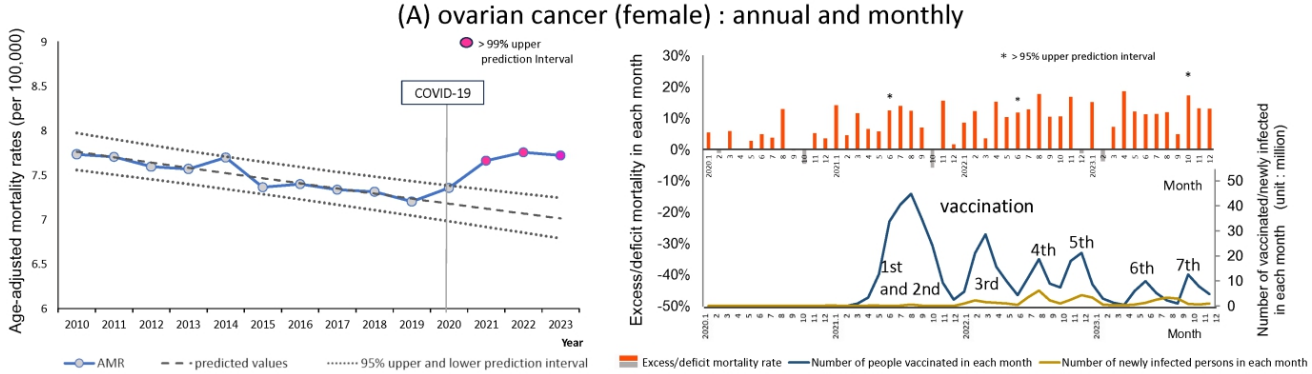
Figure 5. Trends in age-adjusted mortality rates over time for leading cancers (lung, colorectal, stomach, and liver)

Age-adjusted mortality rates (AMRs) for lung, colorectal, stomach, and liver cancers showed similar decreasing trends, with the AMRs staying within the 95% PIs during the pandemic period from 2020 to 2023. The data for pancreatic cancer, another of the leading causes of death, are described in Figure 6.

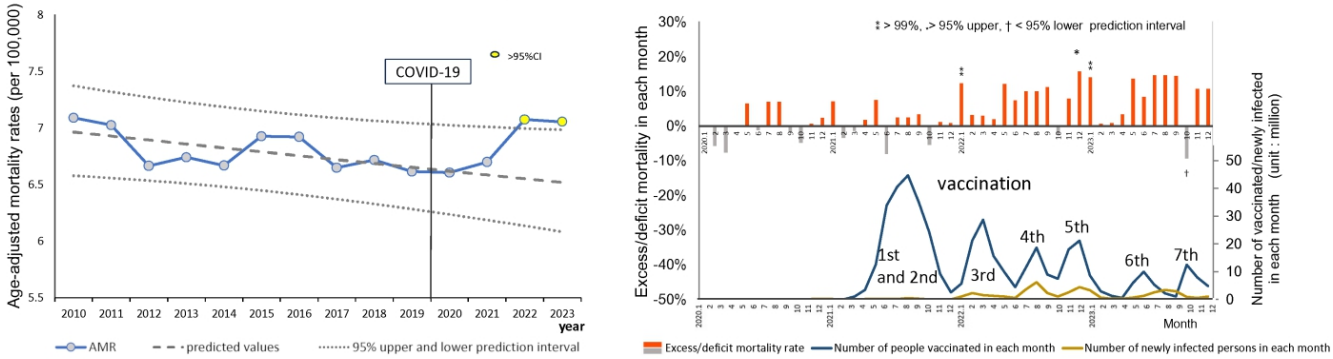
Trends in AMRs for cancer types with excess mortality in 2021, 2022, and 2023

The AMRs for five types of cancer, namely ovarian cancer, leukemia, lip/oral/pharyngeal, prostatic, and pancreatic cancer, exceeded the predicted values in these years. Only these five types of cancer caused excess annual deaths between 2021 and 2023, and no other cancer type showed statistically significant excess mortality. Figure 6 illustrates the trends by year and by month for these types of cancer. Before the pandemic, four of them showed a gradual decline, while pancreatic cancer displayed an increasing trend over time. All five types of cancer showed an increase in 2021 compared with 2020, with ovarian, prostatic, and pancreatic cancers exceeding 95% upper PIs in 2021, and all five cancer types exceeded 95% upper PIs in 2022 and 2023. Monthly excess mortality gradually rose for these cancers from 2021 to 2023, compared with 2020.

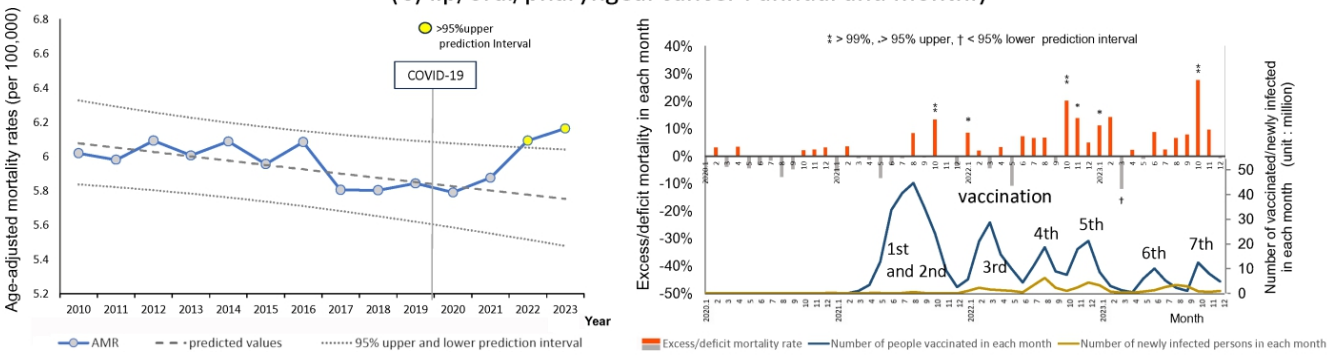
(A) ovarian cancer (female) : annual and monthly



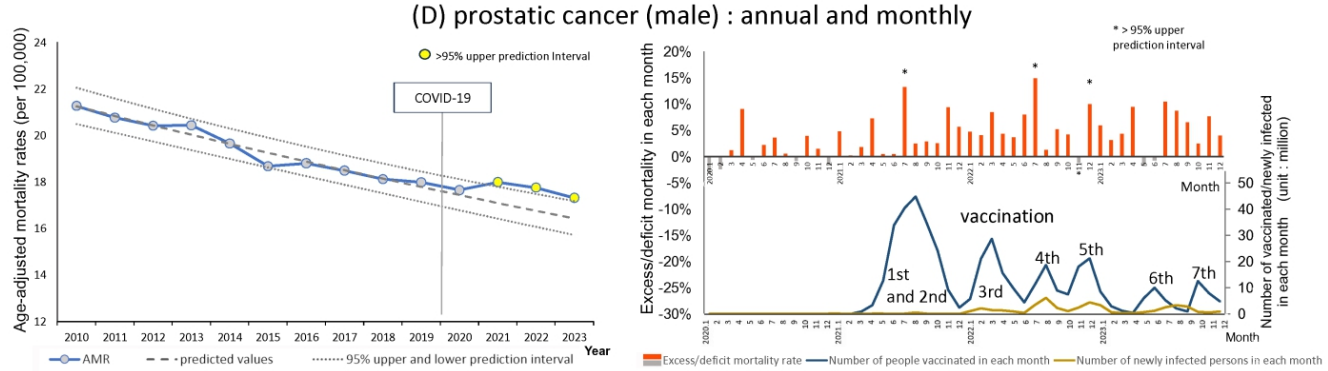
(B) leukemia : annual and monthly



(C) lip/oral/pharyngeal cancer : annual and monthly



(D) prostatic cancer (male) : annual and monthly



(E) pancreatic cancer : annual and monthly

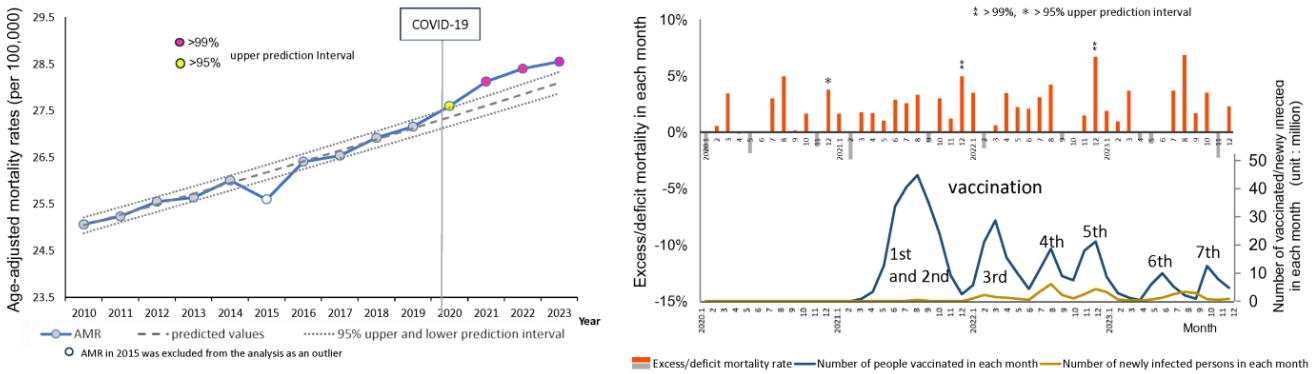


Figure 6. Age-adjusted mortality rates (AMR) over time and monthly excess mortality: cancers with excess mortality between 2020 and 2023

See Figure 1 to explain the axes, units, and other elements of Figure 6.

(A) Ovarian cancer

There was a gradual downward trend in AMR from 2010, followed by a slight increase from 2020. However, there was significant excess mortality that exceeded the 99% upper prediction intervals (PIs) for 2021, 2022, and 2023. Monthly excess mortality was observed from 2021.

(B) Leukemia

The annual AMR for leukemia had been slowly declining or plateauing since 2010 but showed excess mortality above the 95% upper PI in 2022 and 2023. The monthly AMR exceeded 99% upper PI in January 2022 and 2023, and 95% upper PI in December 2022.

(C) Lip/oral/pharyngeal cancer

The annual AMR over time was on a gradual downward trend but increased in 2022 and 2023 above the 95% upper PI. The monthly excess mortality was found to be more clearly and statistically significant in several months between 2021 and 2023.

(D) Prostatic cancer

There was a gradual downward trend in annual AMR from 2010, which exceeded the 95% upper PI from 2021 to 2023. Monthly excess mortality was seen through 2021 and 2023, exceeding the 95% upper PI in several months.

(E) Pancreatic cancer

The AMR in 2015 was excluded from the analysis because it was an apparent outlier for unknown reasons.

The annual AMR for pancreatic cancer increased from 2010, began to exceed the 95% upper PI in 2020, and then deviated further and increased between 2021 and 2023, exceeding the 99% upper PI. Monthly excess mortality was observed from 2020, exceeding the 95% upper PI in December 2020, and showed even greater excess in December 2021 and 2022, exceeding the 99% upper PI.

Discussion

Scherb and Hayashi used logistic regression analysis to calculate predicted mortality rates and intervals from pre-pandemic mortality trends and to detect deviations in mortality rates during the pandemic. The authors state: “In this model, the hypotheses concerning trends and change-points can be visualized naturally, and possible effects can be tested and quantified by point- and interval-estimation using a wide range of methods.” According to their method, the crude excess mortality rates for all causes were estimated to be −2.84% (95% CI: −4.46, −1.25) in 2020, 0.80% (−0.83, 2.40) in 2021, and 8.37% (6.74, 9.97) in 2022 in Japan [7].

In our study, when deaths were age-adjusted and analyzed in the same way as by Scherb et al., the age-adjusted excess mortality rate from all causes was −2.3% (−2.7, −1.9) in 2020, but 2.1% (1.6, 2.6) in 2021, 9.6% (9.0, 10.2) in 2022, and 9.5% (8.5, 10.4) in 2023 (Fig 7A). The results were similar to those of Scherb et al. There was a lower mortality rate in 2020, the first year of the pandemic, than predicted from the previous trend in mortality, but this changed to a slight excess in 2021, with excess deaths in 2022 and 2023 deviating from the previous trend in mortality by nearly 10%.

This finding is mirrored in the official life expectancy data published by MHLW, which show that life expectancy in Japan suddenly started to shorten in 2021, shortened further in 2022, and remained almost the same in 2023 (Fig 7B) [25]. This indicates that a significant anomaly in national health occurred after 2021, which also coincides with the period from 2021 to 2023 when Japan recommended vaccination for most of its population (Fig. 3).

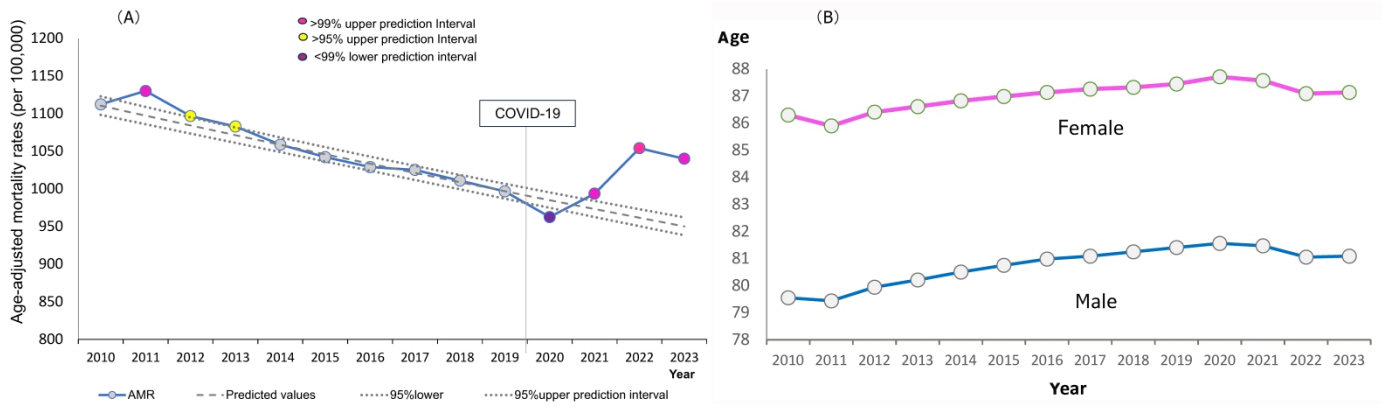


Figure 7 (A) Age-adjusted mortality rates (AMRs) over time: all causes. (B) Life expectancy in Japan [25]

(A) The predicted mortality rates and intervals from the pre-pandemic age-adjusted mortality (AMR) for all causes for 2010–2019, excluding 2011–2013, when the mortality rates were exceptionally high due to the major earthquake and tsunami, were compared with the AMR during the pandemic, from 2020–2023. The AMR in 2020 was under the 99% lower prediction interval (PI), but from 2021 it was above the 99% upper PI, with a further excess in 2022 and a slight downward trend in 2023, but still significantly above the 99% PI.

(B) Before the pandemic, with the exception of 2011, the year of earthquake and tsunami, life expectancy grew steadily, and the same was true in 2020, the first year of the pandemic. However, it began to turn downwards from 2021, shortened further in 2022, and remained almost the same in 2023.

The findings in 2020, during the first year of the pandemic

In 2020, there was no increase in all cancer mortality. The only statistically significant deviations from the predicted AMRs in 2020 were a 3.9% excess in all cancer deaths among those aged 75–79, a very small (0.9%) excess in pancreatic cancer deaths, and a 3.8% deficit in breast cancer deaths (for breast cancer, there was also a 4.3% deficit in 2021).

In 2020, highly virulent strains of SARS-CoV-2 entered Japan, but there were relatively few deaths attributed to COVID-19 in Japan [26]. Declarations of a pandemic emergency were issued three times up to September 2021, requesting people to refrain from going out and securing hospitalization for COVID-19 patients. The number of screenings for gastric, lung, colorectal, breast, and uterine cancers in the community decreased by 24.4%, whereas only a 0.9% decrease in the workplace, in 2020, and they appeared to return to their original trends in 2021. The number of significant surgeries for cancer in digestive organs decreased by 6.2% in 2020 and 5.1% in 2021 compared to those in 2018 and 2019 [27]. We found excess cancer mortality among the 75–79 age group in 2020 in our research, and the decline in such cancer care could be the reason for this.

Modeling studies in some countries have been conducted to estimate the impact of the pandemic on cancer mortality [11,12]. In fact, during the first wave of COVID-19 in Belgium in March and April 2020, cancer deaths increased by 10% and 33%, respectively, compared to the number of deaths predicted using data from 2013 to 2018 [13]. In Madurai, a city in southern India, deaths attributed to cancer increased by 109% during the first weeks of lockdown [14]. In Brazil, during the first wave in March through May 2020, the number of biopsies, colonoscopies, mammograms, and oncological surgeries decreased by 29%, 57%, 55%, and 9%, respectively, compared to pre-pandemic figures. As a result, the number of hospitalizations for cancer decreased by 21%, whereas the mortality rate in hospitalized patients with cancer increased by 14% [28].

The findings in 2021, 2022, and 2023

The AMR for all cancer deaths stopped its previous decline and plateaued, surpassing the 95% PI in 2021. The AMR remained above the 99% PI with further deviation in 2022, and was still above

the 95% PI in 2023, although following the original downward trend. In addition, monthly observations showed significant excesses after August 2021, whereas large-scale vaccination of the general population began around April 2021. There were statistically significant excess deaths among those aged 75–79 in 2021, 75–84 in 2022, and 50–54 and 75–84 in 2023, with gradual trends in excess mortality across several other age groups. Of those over 65, 92% received the third vaccination dose, compared with 64% of 12–64 year olds. Alegria et al. reported excess mortality for all cancer in 2021 and 2022 among those aged 15–44 in the UK and USA [29,30]. These findings of excess cancer deaths in the younger generation may align with our finding of significant excess cancer deaths for the 50–54 age group in 2023.

The most common types of cancer, including lung, colorectal, stomach, and liver cancer, showed similar downward trends to the pre-pandemic period, within the 95% PIs between 2021 and 2023. On the other hand, it was found that among the 20 types of cancer, ovarian cancer, prostatic, and pancreatic cancer showed statistically significant excess mortality in 2021. Excess mortality in ovarian cancer, leukemia, lip/oral/pharyngeal, prostatic, and pancreatic cancer escalated in 2022, and continued in 2023. All these five cancer types showed statistically significant excess deaths in 2022 and 2023, and the trend in excess deaths in these cancer types was robust. Excess deaths for breast cancer exceeded the 95% confidence interval in August 2022, but in 2023, annual AMR was below the predicted rate, and there was no month with statistically significant excess deaths.

According to a report on domestic cancer medical care [27] and in the absence of an emergency declaration from October 2021 onwards, the restrictions on access to cancer screening or treatment seem to have been relaxed after late 2021. Reduced cancer screening or medical care in the first half of the pandemic period does not seem to explain the later presence of excess mortality for only five types of cancer. Regarding the incidence during this period, the crude number of all patients registered from base hospitals for cancer treatment showed an increasing trend for prostatic cancer in men and breast cancer in women in 2021, and especially in 2022 [31]. However, these numbers are not age-adjusted, and the increases cannot be evaluated.

The influences of multiple doses of mRNA-LNP SARS-CoV-2 vaccine

Vaccination with the first and second doses of vaccine started in early 2021, and the number of people vaccinated soon peaked in the summer of 2021, at 80% of the population. The number receiving the third dose peaked in the spring of 2022, at 68% of the population, and even the eighth round, including self-amplifying mRNA SARS-CoV-2 vaccine, is currently being administered, making Japan the country with the highest vaccination rates.

Researchers have reported that the mRNA-LNP SARS-CoV-2 vaccine may increase the risk of the development and progression of cancer [32-35]. In addition, several case reports of cancer developing or worsening after vaccination have been published, which discuss possible causal links between cancer and mRNA-LNP SARS-CoV-2 vaccination [36-41].

Based on the molecular weight of BNT162b2 mRNA (Pfizer-BioNTech), the number of mRNA molecules per dose is estimated at 13 trillion, and for mRNA-1273 (Moderna), the estimate is 40 trillion mRNA molecules per dose [42, 43]. The total number of cells in the human body is estimated to be 37.2 trillion [44], so the number of mRNA molecules is very high in comparison, ranging from one-third to the equivalent of the total cell number. After inoculation, the mRNA-LNPs are delivered to various organs, especially the liver, spleen, adrenal glands, ovaries, and bone marrow [45]. In one study, vaccine mRNA was detected by hybridization with an mRNA-LNP SARS-CoV-2 vaccine-specific probe 7–60 days after the second dose of mRNA-1273 or BNT162b2 [46]. Modified mRNA containing N1-methyl-pseudouridine has been shown to facilitate the translation of a large amount of SARS-CoV-2 spike protein (S-protein) [47]. The S-protein has been detected on the surface of exosomes in the blood of vaccinated people [48]. Fragments of vaccine-specific recombinant S-protein were found in blood samples from 50% of vaccine recipients and were

detectable 3–6 months later [49]. By immunostaining 15 months after the third mRNA-LNP SARS-CoV-2 vaccination, S-protein was detected in the cornified and spinous layers of the epidermis and within the eccrine sweat glands in a prolonged skin lesion [50].
On the other hand, in the case of COVID-19, which is basically a respiratory infection, reports suggest the viral S-protein can only be detected in the serum for up to 10–20 days, even in severely ill patients [51-53]. The attenuated Omicron strains emerged in Japan in early 2022 and have been prevalent at various points since then. As the graphs in Figures 1 and 6 show, the cumulative number of vaccination doses given up to the end of 2023 (436 million) was nine times the number of newly confirmed infections (47 million), suggesting that the vaccine may have had a greater impact on the Japanese population than the infections themselves.
A 26-week study was conducted on more than 50,000 employees at a medical institution in the United States to observe the incidence of COVID-19 during the Omicron variant phases of the pandemic, including in the analysis the number of vaccine doses received (0, 1, 2, 3, and 4 or more doses). The study found that the higher the number of vaccines previously received, the higher the cumulative incidence of COVID-19 [54].
The susceptibility of those who have received multiple vaccinations against COVID-19 may be enhanced by immune imprinting [46,55] and immunosuppression. This can result in risks from exposure to viral S-protein in addition to vaccine S-protein for the multiply vaccinated [32-34, 56]. These reports suggest that the vaccine may significantly impact people, due to the large number of mRNA-LNPs that are injected, their rapid and widespread distribution, particularly into specific organs, the amount of S-protein produced, its long persistence in the body, and increased susceptibility to the infection.
Next, we consider one by one the possible explanations for how mRNA-LNP SARS-CoV-2 vaccine may be involved in the excess mortality for all cancers and some specific cancer types.

Thrombogenic effects of spike protein and LNP

Because cancer often leads to the activation of coagulation via various mechanisms, one of the major causes of mortality in patients with cancer is cancer-associated thrombosis (CAT) [57-59], manifesting as disseminated intravascular coagulation (DIC) in its most extreme form [60]. So, the additional thrombus-forming tendency noted with the mRNA-LNP SARS-CoV-2 vaccine is likely to be extremely dangerous. The viral and vaccine S-protein of SARS-CoV-2, especially in the Omicron lineages, with its solid electropositive potential, could attach to electronegative glycoconjugates on the surfaces of red blood cells (RBCs), other blood cells, and endothelial cells [61]. The S-protein of SARS-CoV-2 alone has been reported to bind to angiotensin-converting enzyme 2 (ACE2) and activate the angiotensin II type 1 receptor (AT1) signal, which promotes interleukin-6 (IL-6) trans-signaling [62], induces vascular wall thickening via activation of the protein kinases [63], impairs mitochondrial function [64], and generates reactive oxygen species (ROS) [65]. A recent study revealed that certain segments of the S-protein have the ability to induce the formation of amyloid, a fibrous protein that is insoluble in water. Amyloid plays a significant role in blood coagulation and fibrinolytic disturbances [66]. The anti-S-protein antibodies bind to the S-protein that emerges on cell surfaces, leading to autoimmune inflammatory reactions [67-71]. In addition, injection of LNPs into mice has been reported to cause strong inflammation [72].
All these findings suggest the mRNA-LNP SARS-CoV-2 vaccine increases the risk of thrombosis in individuals with cancer. Cancer deaths are likely to occur sometime after the assumed causes due to multistep carcinogenesis. However, certain cases classified as cancer death in Vital Statistics might be considered to be due to thrombosis or inflammation, which may have brought forward the death of people with cancer.

Suppression of cancer immunosurveillance

Some studies have shown that type I interferon (IFN) responses, which play an essential role in cancer immunosurveillance, are suppressed after mRNA-LNP SARS-CoV-2 vaccination [73, 74]. A large number of exosomes containing microRNA (miRNA)-148a and miRNA-590 are released from cells where S-protein has been translated in large quantities, and each miRNA suppresses the ubiquitin-specific peptidase 33 (USP33)–interferon regulatory factor (IRF9) axis in microglia that internalize these exosomes [75]. Seneff et al. explained in their review that this results in the suppression of the function of type I IFN and BRCA2, which are critical factors protecting against cancer [33].

One study showed that individuals vaccinated with the SARS-CoV-2 vaccine, including BNT162b2, had a statistically significant increase in expression of PD-L1 on the surfaces of peripheral granulocytes and monocytes [76]. Programmed death-ligand1 (PD-L1)/programmed cell death 1 (PD-1) expression in the tumor microenvironment is reported to suppress cancer immunosurveillance profoundly [77].

Some studies have reported that anti-S-protein IgG4 levels rose in the sera of recipients of the mRNA SARS-CoV-2 vaccine after the second dose and increased further after a third dose [78,79], but were not detected in the sera of unvaccinated patients with COVID-19 [79]. Non-cancer-specific IgG4 is reported to inhibit the antibody effector functions mediated via cancer-specific IgG1. This has been demonstrated by local administration of non-cancer-specific IgG4, which dramatically accelerated the growth of implanted colorectal and breast tumors and skin papillomas caused by carcinogens [80]. According to a meta-analysis, in overall cancer, pancreatic cancer, and lymphoma, the standardized incidence ratios of patients with IgG4-related disease (IgG4-RD) compared to the general population were 2.57 (95% CI: 1.72, 3.84), 4.07 (1.04, 15.92), 69.17 (3.91, 1223.04), respectively [81]. A review of IgG4 described that long-term exposure to large amounts of specific antigens, such as those found in mRNA-LNP SARS-CoV-2 vaccines, may cause uncontrolled growth of cancer cells through a class switch from IgG1 to IgG4 [82].

Another study showed that IL-10 release with non-specific stimulation in fresh whole blood from recipients of the second dose of BNT162b2 or mRNA-1273 increased within two weeks [83]. These findings might explain the excess mortality for all cancers, especially excess deaths from pancreatic cancer, in our study.

Possible effects of spike protein on development and progression of specific cancers

In our study, the AMRs for ovarian cancer, leukemia, lip/oral/pharyngeal, prostatic, and pancreatic cancers showed statistically significant excess mortality beyond the predicted rates from 2021 to 2023. They are known as estrogen- and estrogen receptor alpha (ERα)-sensitive cancers [84-89].

Recent research by Solis et al. [90] on the binding ability of S-protein of SARS-CoV-2 to >9000 human proteins has shown that S-protein binds specifically to and interacts with ERα. The addition of estradiol (E2) to human breast cancer cells causes these cells to proliferate, whereas the addition of raloxifene, a selective ERα modulator, inhibits proliferation. The breast cancer cells grow when S-protein is added instead of E2, and the addition of raloxifene inhibits their growth. They also reported the finding of S-protein-ERα cytosolic colocalization, which may lead to potentiation of membrane-bound ERα signaling. Membrane-bound ERα has reportedly been implicated in many pathways, including the activation of c-Myc that promotes the cell cycle and impacts carcinogenesis [91]. Activation of ERα bound to estrogen is reported to induce DNA damage in ER-sensitive cancer cells [92-96]. A similar DNA damage might occur when S-protein binds to and stimulates ERα.

Nuclear translocation of mRNA and S-protein with the nuclear localization signal (NLS) on S-protein has been reported [97], and S-protein localized in the nucleus was found to inhibit DNA damage repair by impeding recruitment of key DNA repair proteins BRCA1 and 53BP1 to the

damage site [98]. The simultaneous occurrence of a high requirement for BRCA1 to repair DNA damage that might be caused by activated ERα bound to S-protein and the dysfunction of BRCA1 caused by S-protein may raise concerns about the increased risk of cancer in ERα-sensitive cells in mRNA-LNP SARS-CoV-2 vaccine recipients.

Cancers associated with impaired BRCA1 activity are reported to include breast, uterine, and ovarian cancer in women, prostatic cancer in men, and a modest increase in pancreatic cancer for both men and women [99]. Dysfunction due to BRCA1 mutation has been reported to cause Fanconi anemia, which leads to acute myeloid leukemia [100]. These findings could explain our results of excess mortality for these specific cancer types after widespread mRNA-LNP SARS-CoV-2 vaccination. The observation that injected LNPs accumulate particularly in the ovaries and bone marrow [45] could also explain more plausibly our findings of excess mortality for ovarian cancer and leukemia, which are estrogen-sensitive and may be influenced by S-protein produced by mRNA with LNPs.

According to a review on sex hormone receptors in head and neck squamous cell carcinoma (HNSCC), ERα is involved in the biopathology of HNSCC, particularly oropharyngeal cancer with human papillomavirus (HPV) infection. These effects include promoting DNA hypermutation, facilitating HPV integration, and cooperating with the epithelial growth factor receptor (EGFR) [88]. Given the immunosuppression and the ERα-stimulating effect of S-protein, this finding may explain the increased mortality from lip/oral/pharyngeal cancer in 2022 and 2023.

Concerns regarding effects of residual DNA fragments on development and progression of cancer

Recently, several researchers have reported that fragments of DNA from residual plasmid vectors that were used for the production of mRNA exist in several lots of Pfizer-BioNTech and Moderna vaccines. Most of these studies showed that the amount of residual DNA exceeded 10ng/dose, the regulatory limit set by the U.S. Food and Drug Administration (FDA) [101-107] (Fig. S1). The number of residual DNA fragments per inoculation is estimated to be in the region of billions to hundreds of billions [102,103]. The FDA states in its guidance for industry, “There are several potential mechanisms by which residual DNA could be oncogenic, including insertional mutagenesis following DNA integration” [108]. The simian virus 40 (SV40) enhancer/promoter DNA sequence has been detected in BNT162b2 vials [101-103,105,106]. DNA sequences such as S-protein and SV40 enhancer/promoter were confirmed by Polymerase Chain Reaction (PCR) from HEK293 cells transfected with BNT162b2 and washed twice 6 hours after the trasfection [106]. Since transfection is efficient enough when the substance is encapsulated in LNPs,, the regulatory limits established before introducing LNP formulations are no longer suitable and should be reevaluated. The study showed that the SV40 enhancer/promoter had the DNA nuclear targeting sequence (DTS), which binds to proteins with the nuclear localization signal (NLS) [109]. Consequently, DNA fragments containing the SV40 enhancer would more likely be transported into the nuclei even when cells were not dividing. One in vitro study showed that linear DNA fragments were integrated into the genome in a somewhat proportion of transfected mammalian host cells [110]. Avian leukosis virus (ALV), which has no transforming oncogene but has enhancer sequences, is known to integrate next to the host’s myc proto-oncogene, subsequently inducing hyperexpression of the host’s myc and carcinogenesis in chickens [111]. Even in the absence of integration into the genome, cGAS‐STING signaling induced by the presence of foreign DNA in the cells is reported to have a tumor-promoting function [112]. SV40 enhancer has been reported to be bound by p53, preventing p53 from conserving gene stability [113] and to have strong somatic hypermutation activity in several cell types [114], which may result in carcinogenesis. Given these findings, further investigation is required to determine whether the observed excess cancer deaths following mass vaccination were linked to reported residual DNA in the vaccine.

Conclusions

Statistically significant excess age-adjusted mortality for all cancers and some specific types of cancer, including ovarian cancer, leukemia, lip/oral/pharyngeal, prostatic, and pancreatic cancers, was found not in 2020, but emerged in 2021, escalated in 2022 and continued in 2023. The large-scale mRNA-LNP SARS-CoV-2 vaccination started in 2021 and has been implemented to date especially with one or more booster injections in 2022 and 2023. The particular excess mortality rates for these specific cancers might be accounted for by several mechanisms following mRNA-LNP SARS-CoV-2 vaccination. The causal relationship between excess cancer deaths and large-scale vaccination cannot be assessed in this study. Still, the coincidence of the timing requires an urgent and rigorous investigation, including analyses by vaccination status and clinical validation.

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Figure S1

Figure S1. Verifications of mRNA Vaccine DNA Contamination around the World (As of 2024-12-28)

Summarized by Fujikawa K.

Researcher	Affiliation, Country	Pharma Company	# of Vials	First reported	Methods	DNA/dose (limit 10ng)	DNA/RNA ratio (limit 1/3030)	Concerns	Publication etc
McKernan K, et al.	Medicinal Genomics, US	Pfizer, Moderna	a dozen	Feb-23	Electrophoresis (Agilent)	2250ng -- 3390ng [1]	1/8 -- 1/2	Adverse events, Gene integration	Preprint [101] Reported to and presented at FDA Presented at the World Council for Health ※Found gene integration in OvCar3 cancer cells transfected by Kämmerer ※Found SV40 enhancer in tumors of vaccinated (※reported in Substack)
					Fluorometer (Qubit)	312ng -- 843ng [1]	1/47 -- 1/8		
					qPCR/RT-qPCR	12ng	1/161 -- 1/43		
		Pfizer, Moderna, Daiichi-Sankyo (Japan)	5	Nov-23	Fluorometer (Qubit)	17.5 -- 61.8ng (after Tritton-X/RNaceA)			
					qPCR	88.8ng (Pfizer)			
Buckhaults PJ	USC, US	Pfizer, Moderna	some	Jul-23	qPCR	0.6ng -- 18.7ng		Adverse events, Gene integration	Presented in South Caloraina Senate [102] ※Presented gene integration to normal human epithelial stem cells
		Pfizer 2020, Pfizer 2023, Moderna 2020, Moderna 2023	4	Apr-24	qPCR	7.7ng (SV40e, Pfizer) 4.5 -- 5.5ng (Neo/Kan, Pfizer) 1.5 -- 9.0ng (ORI, Pfizer) 2.5 -- 18.7ng (Spike, Pfizer) 0.002 -- 0.004ng (ORI, Moderna 2023)			
König B, Kirchner JO	Magdeburg Molecular Detections, Germany Indep., Germany	Pfizer, Moderna	7	Sep-23	Fluorometer (Qubit)	3600ng -- 5340ng	1/12 -- 1/7	Adverse events, Gene integration	Reported to the German Ministry of Health Published in Methods Protoc [104]
Speicher DJ, McKernan K, et al.	University of Guelph, Canada Medicinal Genomics, US	Pfizer, Moderna	27	Oct-23	Fluorometer (Qubit)	1896ng -- 5100ng		Adverse events, Gene integration	Preprint [103] Presented at the World Council for Health
					qPCR	0.22ng -- 2.43ng (Spike) 0.01ng -- 4.27ng (ORI)			
Speicher DJ	University of Guelph, Canada	Pfizer, Moderna (Australia)	3	Jun-24	Fluorometer (Qubit)	451ng -- 1420ng (after RNaceA/DNaceI)		Adverse events, Gene integration	Reported to Therapeutic Goods Administration (TGA, Australia) Under litigation
					qPCR	6.46ng -- 163.68ng (Spike) 0.54ng -- 12.97ng (ORI) 3.70ng -- 14.69ng (SV40e, Pfizer)			
Raoult D	Aix-Marseille Univ (Former Prof), France	Pfizer	some	Nov-24	Fluorometer (Qubit)	216ng (Avg) 5160ng (Avg, after Triton-X-100)		Gene integration	Preprint [105]
Kämmerer U, et al.	Univ. Hospital of Würzburg, Germany	Pfizer	4	Dec-24	Fluorometer (Qubit)	2712 -- 3683ng (after Triton-X-100) 32.71 -- 42.09ng (after Triton-X-100/RNaceA)		Adverse events, Gene integration	Published in Science, public health policy and the law [106]
Wang TJ, Kim A, Kim K	Centreville High School, technically supported by the FDA researchers, US	Pfizer	6	Dec-24	Fluorometer (Qubit)	41.4-109.5ng (extracted by Monarch Plasmid DNA Miniprep, which includes RNaseA)		Gene integration	Published in Journal of High School Science [107]

[1] Multiplied the value by 300 for ul

[2] From the description of DNA 44x10fg to mRNA 400ng, the calculation for Moderna 1-dose as mRNA 100ug