Increased Age-adjusted Cancer Mortality after the 3rd mRNA-Lipid Nanoparticle Vaccine Dose during the COVID-19 Pandemic in Japan

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Abstract

Purpose:
Excess deaths during the COVID-19 pandemic have become an issue in Japan, which has a rapidly aging population, and we conducted this study to evaluate how age-adjusted mortality rates for individual cancers shifted during the pandemic.

Methods:
Using published national data, we compared age-adjusted mortality rates for each cancer type between the first 3 years of the pandemic (2020-2022) and the 3 years before the pandemic (2017-2019), and also compared mortality rates in 2022 after nationwide mRNA-LNP vaccination to rates in 2020 before vaccination began. In addition, we identified trends in mortality from 2012 to 2019 to assess excess/deficit mortality during the pandemic.

Results:
Age-adjusted mortality rates decreased from the pre-pandemic period to the pandemic period for stomach, liver, lung, gallbladder/biliary tract, colon, and esophageal cancers, which account for a large proportion of cancer deaths in Japan, but this decreasing trend slowed from 2021 to 2022. Age-adjusted mortality rates for breast, pancreatic, lip/oral/pharyngeal cancers and leukemia increased significantly in 2022 after much of the Japanese population had received the third mRNA-LNP vaccine dose, compared to 2020, the first year of the pandemic when no vaccinations were administered. There were also marginally significant increases for ovarian and uterine cancers between 2020 and 2022.

Data interpretations:
As previously described in a molecular biological study, the increased mortality rates for these cancers might be caused by cell proliferation mediated by binding of spike protein to estrogen receptors, and the spike protein might originate from mRNA-LNP vaccination rather than COVID-19 infection itself. The significance of this possibility warrants further studies.

Conflict of Interest

The authors declare no potential conflicts of interest.

Funding Statement

This study did not receive any funding.

Introduction

The coronavirus disease 2019 (COVID-19) emerged in Wuhan, China in November 2019 and has resulted in a global pandemic. COVID-19 was first identified in January 2020, and various health care and socioeconomic restrictions were imposed to prevent the spread of the disease in Japan. Since February 2021, mass vaccination with a mRNA-lipid nanoparticle (mRNA-LNP) vaccine approved for emergency use has been recommended for all people aged 6 months and older, especially high-risk groups. As of March 2023, 80% of the population had received their first and second dose, 68% had received their third dose, and 45% had received their fourth dose.The report of the Ministry of Health, Labour and Welfare shows that more than 99.9% of formulations administered were mRNA-LNPs.
(data available from: https://www.mhlw.go.jp/content/10601000/001125498.pdf)
Despite these national measures, 33.8 million people in Japan had been infected and 74,500 had died of COVID-19 as of the end of April 2023.
The COVID-19 pandemic has had a profound impact on health care as a whole, beyond the immediate impact of the virus. Cancer care is no exception. Some researchers have reported that interruptions in cancer screening and delays in diagnosis and treatment resulting from lockdown restrictions on behavior and routine medical care have caused cancer deaths to increase [1–8]. There is also concern that mRNA-LNP vaccines may promote cancer development and progression [9-12]. However, large-scale epidemiologic data on cancer mortality, including data for individual types of cancer, after mRNA-LNP vaccination have not been reported. We conducted overall and age-adjusted statistical analysis of published Japanese mortality statistics on epidemiological trends in mortality for all cancers collectively and for individual cancers during the pandemic period from 2020 to 2022.

Methods

Statistical data

The data used in this analysis are listed below and are all publicly available national data. The number of deaths were taken from the Vital Statistics, which include monthly deaths (reflected in statistics after a 5-month review period following death certificate submission) and confirmed annual deaths by cause, sex, and age (5-year age groups). The target samples were limited to Japanese individuals living in Japan. Population estimates by age group required for the age-adjusted analysis are from the Statistics Bureau of the Ministry of Internal Affairs and Communications.

Age adjustment

Mortality rates for each cause of death during the COVID-19 pandemic were assessed using age-adjusted mortality rates to eliminate the effects of the aging population. The Ministry of Health, Labour and Welfare in Japan reportedly uses direct age adjustment with smoothed standard population data from 2015 (125.32 million), and the same approach was used in this study. Age adjustment for female-specific cancers was performed using the “sex-specific smoothed standard population dataset 1”.

$$\text{age-adjusted mortality rate}(/100{,}000) = \left(\Sigma(d_i/p_i \times p_{si}) \right) / \Sigma p_{si} \times 100{,}000$$

i=age group, d_i=number of deaths in that age group,
p_i=number in that age group in the observed population,
p_{si}=number in that age group in the standard population

Excess and deficit mortality during the COVID-19 pandemic

In this analysis, the mean number of age-adjusted deaths and the mortality rates from the pre-pandemic period of 2017 to 2019 were used as the baseline for evaluation. The ratios of the baseline age-adjusted mortality rate to age-adjusted mortality rate (rate ratios; RR) in 2020, 2021, and 2022 were calculated, and RR-1 was defined as either excess mortality or deficit mortality. RRs for 2021 and 2022 relative to 2020 were calculated similarly. For significance tests, the 95% or 99% confidence interval (CI) was determined using a method recommended for direct standardization (age-adjusted death rates) by the CDC (Centers for Disease Control and Prevention)/National Center for Health in the United States. Excess mortality was defined as when the lower limit of the CI for the mortality rate in the target year was greater than the upper limit of the CI for the mortality rate at baseline or in 2020, and deficit mortality as when the upper limit of the CI for the mortality rate in the target year was less than the lower limit of the CI for the mortality rate at baseline or in 2020. The standard deviation was calculated using the following formula published in "Direct Standardization (Age-Adjusted Death Rates). March 1995; Healthy People 2000 Statistical Notes Number 6 ー Revised, CDC/National Center for Health Statistics" which is available from: https://www.cdc.gov/nchs/data/statnt/statnt06rv.pdf.

$$\text{standard deviation (SD)} = (\Sigma w_{si}^2 \times m_i \times (1-m_i)/p_i)^{1/2} \times 100{,}000 \quad \text{(per 100,000 population)}$$

the age-specific death rate, $m_i = d_i/p_i$
the standard weight, $w_{si} = p_{si}/\Sigma p_{si}$

Trends of secular change in mortality rates for the pre-pandemic years 2012 to 2019, with regression lines calculated by linear approximation with the least squares method, were compared against the target year to assess for deviation.

Data Availability

The data analyzed in this study were obtained from the following official websites.
Total number of vaccinations to date. Japanese Prime Minister's Official Residence Website: https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html
The Vital Statistics. Ministry of Health, Labour and Welfare. e-Stat "Japan in Statistics. Demographic Survey" available from:
https://www.e-stat.go.jp/stat-search/files?page=1&layout=datalist&toukei=00450011&tstat=000001028897&cycle=1&tclass1=000001053058&tclass2=000001053060&cycle_facet=tclass1&tclass3val=0
Estimated population by age. Statistics Bureau, Ministry of Internal Affairs and Communications available from: https://www.stat.go.jp/data/jinsui/2.html#monthly
The Standard Population for Age-Adjusted Mortality Rates. Website of the Ministry of Health, Labour and Welfare : https://www.mhlw.go.jp/toukei/saikin/hw/jinkou/kakutei20/dl/14_nencho.pdf
Sex-specific smoothed standard population dataset 1. Website of the Ministry of Health, Labour and Welfare, available from: https://www.mhlw.go.jp/content/10700000/000557741.pdf

Ethics

Since only published data were used, it was determined that submission of a research plan to an ethics committee was not required in Japan.

Results

Age-adjusted deaths/mortality rates for all causes and all cancers

The mean annual number of age-adjusted deaths from all causes was 1,266,408 before the pandemic (2017 to 2019) and 1,209,403, 1,244,976, and 1,320,768 during the pandemic in 2020, 2021, and 2022, respectively. In 2020 and 2021, deaths decreased by 56,978 (−4.5%) and 21,431 (−1.7%), which was a statistically significant deficit compared to the pre-pandemic period. In contrast, deaths increased significantly by 54,360 (4.3%) in 2022 (Table 1).

The mean annual number of age-adjusted deaths from all cancers was 355,710 before the pandemic and 346,193, 345,625, and 344,114 during the pandemic in 2020, 2021, and 2022, respectively. In 2020, 2021, and 2022, deaths decreased by 9,517 (−2.7%), 10,085 (−2.8%), and 11,597 (−3.3%) compared to the pre-pandemic number, with a significance level of < 0.01 for each of the three years (Table 1).

Figure 1 shows trends in age-adjusted mortality from all cancers from 2012 to 2022. The mortality rate decreased until 2020, but this decreasing trend slowed from 2021 to 2022, slightly exceeding the regression line.

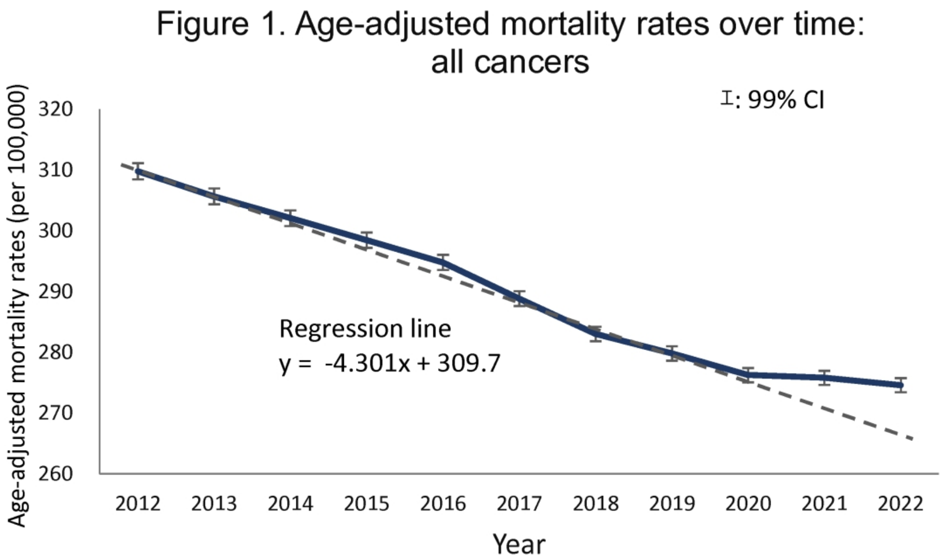


Figure 1. The horizontal axis indicates the year (2012-2022) and the vertical axis the age-adjusted mortality rate (per 100,000 population) for all cancers. The regression line estimated from the pre-pandemic period (2012-2019) using linear approximation with the least squares method is drawn with a dashed straight line, along with its equation. The 99% confidence interval (CI) for each year was added to the line.

There was a decreasing trend until 2020, but the rate of decline slowed after 2021, exceeding the regression line.

Number of age-adjusted deaths / mortality rates by cancer type

Table 1 compares the numbers of age-adjusted deaths for each type of malignancy before and during the pandemic, showing the numbers and rates of excess and deficit mortality for each year. The results of statistical tests are highlighted in pink with a ↗** symbol for "significantly increased at <0.01 level", in yellow with a ↗* symbol for "significantly increased at <0.05 level", in light blue with a ↘** symbol for "significantly decreased at <0.01 level" and in green with a ↘* symbol for "significantly decreased at <0.05 level". Similarly, excess and deficit mortality rates in 2021 and 2022 compared to 2020 are shown. Trends of secular change in mortality rates by malignancy before the pandemic were classified by the slope of the regression line for each trend, with a negative slope indicating a decreasing trend and a positive slope an increasing trend.

Figure 2 graphically depicts the excess or deficit mortality rates from baseline.

Some cancers had deficit mortality and others excess mortality. Stomach cancer (ICD-10 code C16) had the greatest deficit mortality, followed by liver/intrahepatic bile duct cancer (C23 and C24), trachea/bronchus/lung cancer (C33 and C34), gallbladder/biliary tract cancer (C23 and C24), colon cancer (C18–C20), esophageal cancer (C15), other cancers of the lymphatic and hematopoietic tissues (C88–C90, C96), and laryngeal cancer (C32), in that order. Conversely, pancreatic cancer (C25) had the greatest excess mortality, followed by breast cancer (C50), leukemia (C91–C95), lip/oral/pharyngeal cancer (C00–C14), malignant lymphoma (C81–C86), ovarian cancer (C56), central nervous system malignant tumor (C70–C72, C75.1–C75.3), and uterine cancer (C53–C55), in that order.

Table 1. Excess/Deficit Mortality for All Causes, All Cancers, and Each Cancer Type During the Pandemic

	Cause of death and ICD-10 codes, in decreasing order in 2022	Mean annual number of deaths at baseline (2017–2019)	Excess/deficit mortality numbers compared to baseline			Rate Ratio-1 (RR-1) to baseline			Statistical significance to baseline **<0.01, *<0.05			Rate Ratio-1 (RR-1) to 2020		Statistical significance to 2020 **<0.01, *<0.05		Slope of regress-ion line before pandemic
			2020	2021	2022	2020	2021	2022	2020	2021	2022	2021	2022	2021	2022	
	All cause of death	1,266,408	-56,978	-21,431	54,360	-4.5%	-1.7%	4.3%	↘**	↘**	↗**	2.9%	9.2%	↗**	↗**	-14.22
	Malignant neoplasms C00-C97	355,710	-9,517	-10,085	-11,597	-2.7%	-2.8%	-3.3%	↘**	↘**	↘**	-0.2%	-0.6%	N.S.	N.S.	-4.36
Subclassification	Malignant neoplasm of pancreas C25	33,688	996	1,561	1,905	3.0%	4.6%	5.7%	↗**	↗**	↗**	1.6%	2.6%	N.S.	↗*	0.239
	Malignant neoplasm of breast C50	14,442	-280	-260	624	-1.9%	-1.8%	4.3%	N.S.	N.S.	↗**	0.4%	6.9%	N.S.	↗**	0.271
	Leukemia C91–C95	8,349	-46	48	519	-0.6%	0.6%	6.2%	N.S.	N.S.	↗**	1.1%	6.8%	N.S.	↗**	-0.008
	Malignant neoplasm of lip, oral cavity and pharynx C00–C14	7,291	-14	73	345	-0.2%	1.0%	4.7%	N.S.	N.S.	↗**	0.2%	4.9%	N.S.	↗*	-0.042
	Malignant lymphoma C81–C86	12,151	475	356	286	3.9%	2.9%	2.4%	↗**	↗*	N.S.	-0.9%	-1.5%	N.S.	N.S.	0.028
	Malignant neoplasm of ovary C56	4,666	40	219	276	0.9%	4.7%	5.9%	N.S.	↗*	↗**	3.9%	5.1%	N.S.	↗<0.125	-0.058
	Malignant neoplasm of central nervous system C70–C72, C75.1–C75.3	2,708	29	236	258	1.1%	8.7%	9.5%	N.S.	↗**	↗**	7.6%	8.4%	↗<0.055	↗*	0.054
	Malignant neoplasm of uterus C53–C55	6,595	-61	-63	207	-0.9%	-1.0%	3.1%	N.S.	N.S.	↗*	0.0%	4.4%	N.S.	↗<0.055	0.081
	Other remaining malignant neoplasm in C00–C97	26,161	-66	-96	112	-0.3%	-0.4%	0.4%	N.S.	N.S.	N.S.	-0.1%	0.7%	N.S.	N.S.	-0.429
	Malignant neoplasm of prostate C61	11,359	-130	90	14	-1.1%	0.8%	0.1%	N.S.	N.S.	N.S.	2.2%	1.1%	N.S.	N.S.	-0.479
	Malignant melanoma of skin C43–C44	1,539	-3	-27	7	-0.2%	-1.8%	0.4%	N.S.	N.S.	N.S.	-1.6%	0.7%	N.S.	N.S.	-0.018
	Malignant neoplasm of bladder C67	8,158	-76	38	-43	-0.9%	0.5%	-0.5%	N.S.	N.S.	N.S.	1.4%	0.4%	N.S.	N.S.	0.004
	Malignant neoplasm of larynx C32	816	-100	-95	-109	-12.2%	-11.6%	-13.4%	↘*	↘*	↘**	0.7%	-1.3%	N.S.	N.S.	-0.005
	Other malignant neoplasms of lymphoid, hematopoietic,etc. C88–C90, C96	4,147	-279	-259	-296	-6.7%	-6.2%	-7.1%	↘**	↘**	↘**	0.5%	-0.5%	N.S.	N.S.	-0.039
	Malignant neoplasm of esophagus C15	11,145	-819	-896	-1,039	-7.3%	-8.0%	-9.3%	↘**	↘**	↘**	-0.8%	-2.1%	N.S.	N.S.	-0.150
	Malignant neoplasm of colon, sigmoid, and rectum C18-C20	48,465	-1033	-967	-1127	-2.1%	-2.0%	-2.3%	↘**	↘**	↘**	0.1%	-0.2%	N.S.	N.S.	-0.324
	Malignant neoplasm of gallbladder and other parts of biliary tract C23–C24	16,927	-1,073	-937	-1,624	-6.3%	-5.5%	-9.6%	↘**	↘**	↘**	0.9%	-3.5%	N.S.	↘*	-0.386
	Malignant neoplasm of trachea, bronchus and lung C33–C34	70,672	-1,763	-1,840	-2,380	-2.5%	-2.6%	-3.4%	↘**	↘**	↘**	-0.1%	-0.9%	N.S.	N.S.	-0.863
	Malignant neoplasm of liver and intrahepatic bile ducts C22	24,688	-2,065	-2,980	-3,729	-8.4%	-12.1%	-15.1%	↘**	↘**	↘**	-4.0%	-7.4%	↘**	↘**	-1.07
	Malignant neoplasm of stomach C16	41,743	-3,249	-4,284	-5,803	-7.8%	-10.3%	-13.9%	↘**	↘**	↘**	-2.7%	-6.6%	↘**	↘**	-0.150

Table1. This table compares the numbers of age-adjusted deaths for all causes, all cancers, and each type of cancer in the baseline period (2017-2019) and each year during the pandemic (2020, 2021, and 2022), showing the numbers and rates of excess and deficit mortality.

Results for statistical significance using a method recommended for direct standardization (age-adjusted death rates) by the CDC/National Center for Health are highlighted in pink with a ↗** symbol for "significantly increased at <0.01 level ", yellow with a ↗* symbol for "significantly increase at <0.05 level ", in light blue with a ↘** symbol for "significantly decreased at <0.01 level " and green with a ↘* symbol for "significant decrease at <0.05 level".

Results for excess and deficit mortality rates in 2021 and 2022 compared to in 2020 are represented similarly.

Trends in mortality rates for each cancer type during the 8 years before the pandemic（2012-2019） were referenced for the slope of the regression line for each trend. A negative slope indicates a decreasing trend; a positive slope indicates an increasing trend.

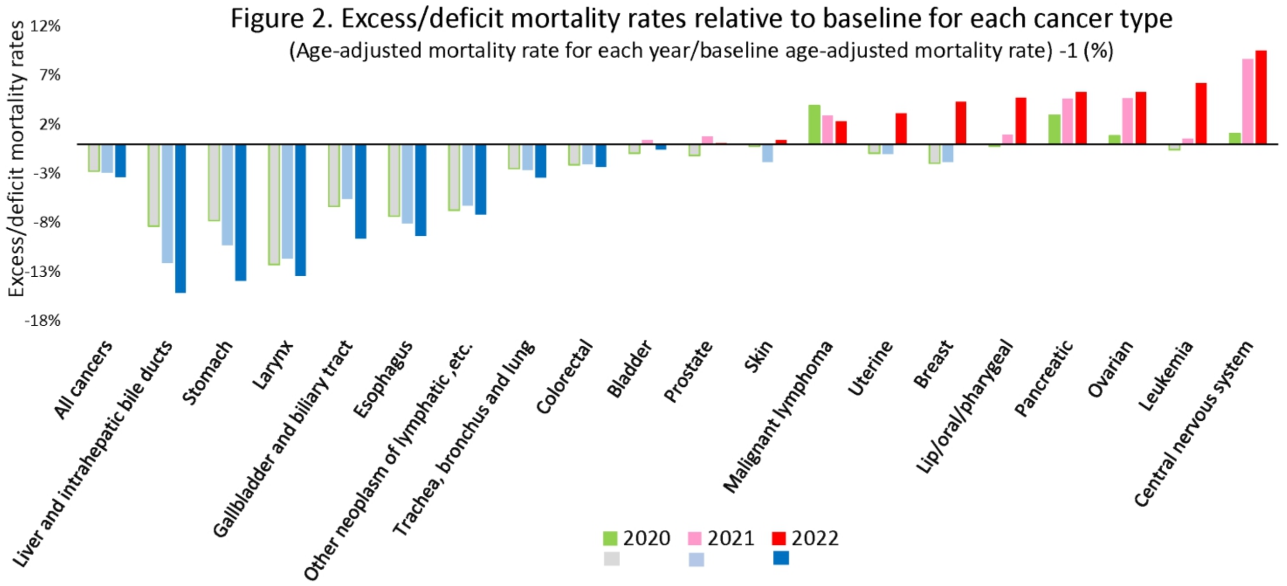


Figure 2. Excess/deficit mortality RR-1 for each cancer type during the pandemic in 2020, 2021, and 2022.
Rate ratio(RR)= the age-adjusted mortality rate for each year/the age-adjusted mortality rate for baseline (2017-2019). Excess/deficit mortality is expressed as RR minus 1.
The ratio relative to all cancers is on the far left, showing reduced mortality from the baseline in both 2020-2022. Of the 19 types of cancers, 8 showed a deficit of deaths and 8 showed excess deaths.
Cancers with a deficit in 2022, in descending order, were liver cancer, stomach cancer, laryngeal cancer, gall bladder/ biliary tract cancer, esophageal cancer, malignant tumors of lympho/hematopoietic organs other than leukemia and malignant lymphoma, lung cancer, and colorectal cancer. Cancers with excess deaths, in descending order of the excess death rate, were malignant tumors of the central nervous system, leukemia, ovarian cancer, pancreatic cancer, lip/oral/pharyngeal cancer, breast cancer, uterine cancer, and malignant lymphoma.

Cancers with deficit mortality

Mortality rates over time were calculated for the four cancers with a significant decrease in age-adjusted deaths from baseline to the pandemic period: stomach, liver, and lung, and colorectal cancer (Fig. 3-1 to 3-4). Each of these cancers showed the same decreasing trend observed for all cancers collectively, but mortality rates for these cancers have been above the regression line since 2021, and the rate of decrease has slowed.

Cancers with excess mortality

Deviation of age-adjusted mortality rates between 2020 and 2022 from the pre-pandemic trend of mortality rates over time were evaluated for the eight cancers with significantly higher mortality during the pandemic compared to just before the pandemic (2017-2019). Based on the result, cancers were divided into three mortality trend groups: (1) increasing before the pandemic and increasing at the same rate between 2020 and 2022 (malignant lymphoma, malignant central nervous system tumor); (2) increasing before the pandemic and at a higher or deviating rate between 2020 and 2022 (pancreatic cancer, breast cancer, uterine cancer); and (3) decreasing before the pandemic but shifting to increasing between 2020 and 2022 (ovarian cancer, leukemia, and lip/oral/pharyngeal cancer). Age-adjusted mortality rates of these eight cancers from 2012 to 2022 are shown below.

1. Cancers whose mortality was increasing before the pandemic and increasing at the same rate between 2020 and 2022

The mortality rate of malignant lymphoma has gradually increased since 2012, and tracked the regression line from 2021 to 2022, increasing within the range of the previous trend (Figure 4-1). From 2020 to 2022, monthly mortality rates exceeded the mortality rates in the same month at the

baseline (2017-2019) before the start of mRNA-LNP vaccination (Suppl. Fig. S1-1).
The mortality rate of malignant central nervous system tumors increased between 2020 and 2022, continuing the pre-pandemic trend (Figure 4-2). The excess in monthly mortality rates between 2020 and 2022 became more apparent after the start of mRNA-LNP vaccination (Suppl. Fig. S1-2).

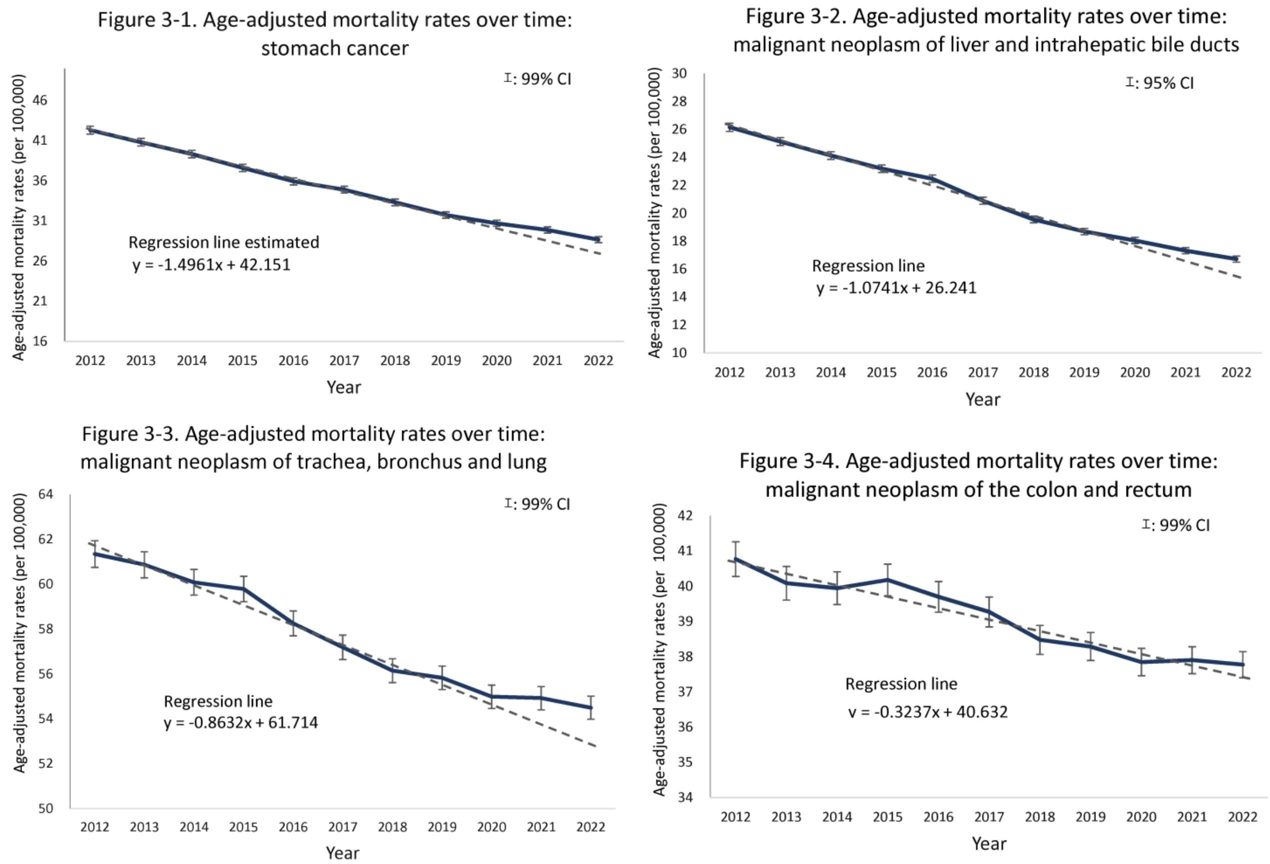


Figure 3-1,3-2,3-3,3-4 The horizontal axis indicates years (2012-2022) and the vertical axis indicates the age-adjusted mortality rates (per 100,000 population) for stomach cancer (Fig.3-1), liver cancer (Fig.3-2), lung cancer (Fig.3-3), and colorectal cancer (Fig.3-4).
The regression lines estimated from prepandemic period (2012-2019) using linear approximation with the least squares method are added by dashed straight lines, along with their equations. The 95/99% confidence interval (CI) for each year was added to the line.
There were decreasing trends until 2020, but the decline slowed down after 2021, exceeding the regression lines.

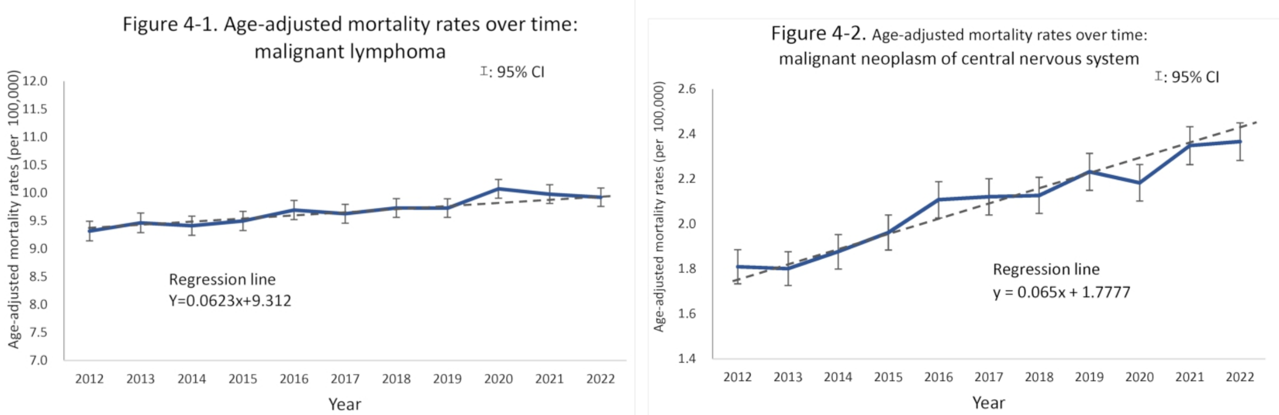


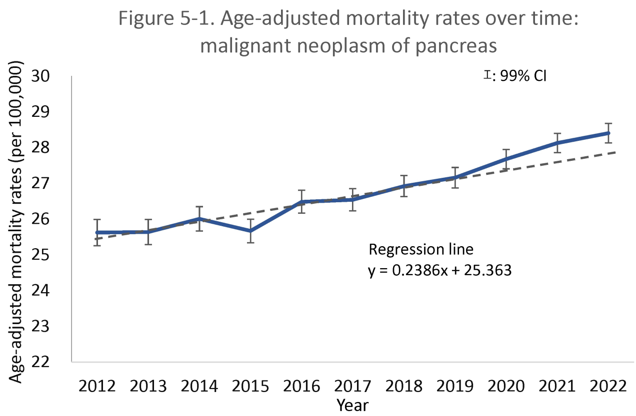
Figure 4-1,4-2. The horizontal axis indicates years (2012-2022) and the vertical axis indicates the age-adjusted mortality rates (per 100,000 population) for malignant lymphoma (Fig.4-1) and malignant neoplasms of the central nervous system (Fig.4-2). The regression lines estimated from the pre-pandemic period (2012-2019) using linear approximation with the least squares method are added by dashed straight lines, along with their equations. The 95% confidence interval (CI) for each year was added to the line. There were increasing trends throughout 2012-2022.

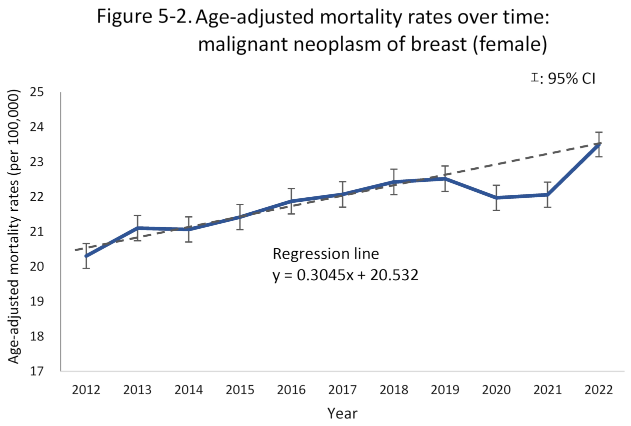
2. Cancers whose mortality was increasing before the pandemic and increasing at a higher rate between 2020 and 2022

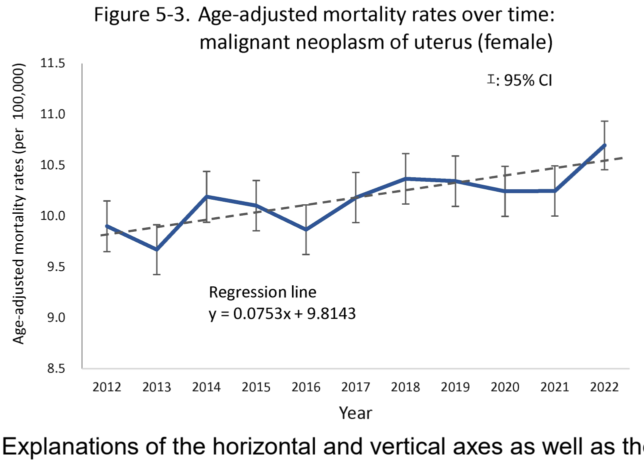
The mortality rate of pancreatic cancer increased from 2012, began to exceed the regression line in 2020, and then further exceeded the line between 2021 and 2022 (Figure 5-1). From 2020 to 2022, monthly mortality rates exceeded the mortality rates in the same month at the baseline (2017-2019) before the start of mRNA-LNP vaccination and increased further after the start of vaccination (Suppl. Fig. 2-1).

The mortality rate of breast cancer, which had been increasing since 2012, declined between 2020 and 2021, and increased steeply in 2022, though it remained below the regression line (Figure 5-2). The excess in monthly mortality rates became prominent after March 2022 (Suppl. Fig. 2-2).

The mortality rate of uterine cancer, as with that of breast cancer, had been increasing since 2012, decreased slightly between 2020 and 2021, and increased sharply in 2022 (Figure 5-3). The excess in monthly mortality rates increased or decreased in tandem with mRNA-LNP vaccination (Suppl. Fig. 2-3).







Explanations of the horizontal and vertical axes as well as the regression lines, CI,and equations are the same as above.

Figure 5-1. The mortality rates of pancreatic cancer were increasing from 2012, began to exceed the regression line in 2020, and then deviated further and increased between 2021 and 2022.

Figure 5-2. The mortality rates of breast cancer, which had been increasing since 2012, conversely declined between 2020 and 2021 and increased at a steep rate in 2022, although it remained below the regression line.

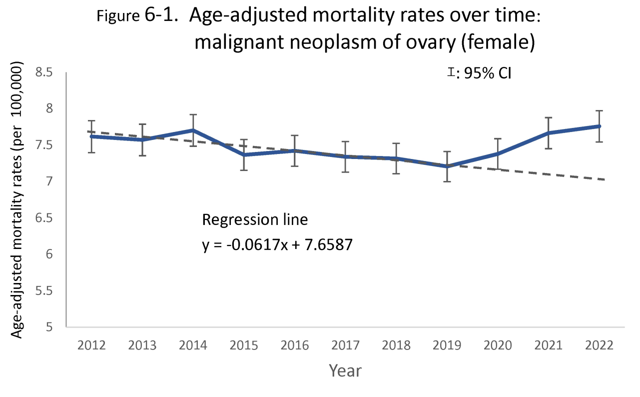
Figure 5-3. The mortality rates of uterine cancer, as with that of breast cancer, had been increasing since 2012, decreased slightly between 2020 and 2021, and increased sharply in 2022.

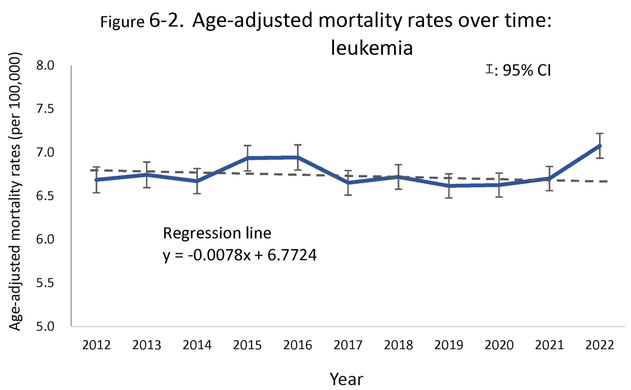
3. Cancers whose mortality was decreasing before the pandemic but began increasing between 2020 and 2022

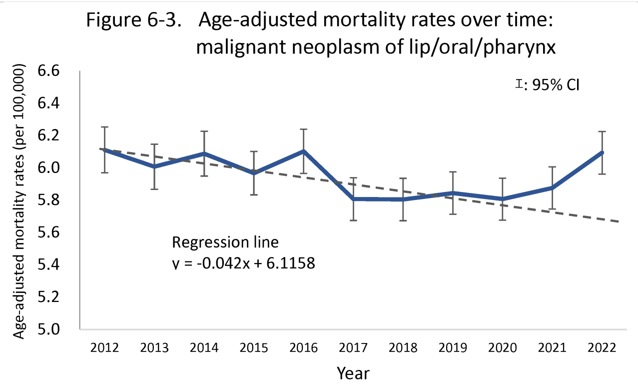
The mortality rate of ovarian cancer gradually decreased from 2012, slightly increased in 2020, and substantially increased from 2021 to 2022, with the lower limit of the 95% CI exceeding the regression line (Figure 6-1). The monthly mortality rates between 2020 and 2022 increased more significantly after the start of mRNA-LNP vaccination (Suppl. Fig. 3-1).

The mortality rate of leukemia had been slowly declining or leveling off since 2012, but increased in 2022 (Figure 6-2). The excess in monthly mortality rates between 2020 and 2022 became prominent after January 2022 (Suppl. Fig. 3-2).

For lip/oral/pharyngeal cancer, mortality rates over time were decreasing gradually, but increased in 2022 (Fig. 6-3). The excess in monthly mortality rates became more prominent after January 2022 (Suppl. Fig. 3-3).







Explanations of the horizontal and vertical axes as well as the regression lines, CI, and equations are the same as above.
Figure 6-1. The mortality rates of ovarian cancer showed a gradual downward trend from 2012, a slight increase from 2020, and a substantial increase from 2021 to 2022, with the lower limit of the 95% C.I. exceeding the regression line.
Figure 6-2. The mortality rates of leukemia have been slowly declining or plateauing since 2012, but increased in 2022.
Figure 6-3. For lip/oral/pharyngeal cancer, mortality rates over time were on a gradual downward trend, but increased in 2022.

Age-adjusted mortality rates in 2021 and 2022 compared to 2020 (Table 1)

No cancer had a significantly increased mortality rate in 2021 compared with the first year of the pandemic in 2020. However, in 2022, the third year of the pandemic, there were statistically significant increases in five types of cancer: pancreatic cancer, breast cancer, leukemia, lip/oral/pharyngeal cancer, and malignant central nervous system tumors. Also, there were marginally significant increases in mortality rates of uterine and ovarian cancers. Six cancers among these, excluding malignant central nervous system tumors, had an increase in mortality rate deviating from their pre-pandemic trend.

Mortality rates of stomach, liver, and gallbladder/biliary tract cancers decreased statistically significantly in 2021 and/or 2022 compared with those in 2020.

Discussion

The COVID-19 pandemic, which began in December 2019, resulted in excess mortality worldwide from 2020 to 2021 [13,14]. All 29 high-income countries except New Zealand, Norway and Denmark had excess mortality [15]. In our analysis of age-adjusted mortality data from 2020 to 2022 in this study, we found no excess all-cause mortality in 2020 and 2021, but excess mortality of 4.3% in 2022.

Attributed causes of excess mortality have also been examined. In particular, several countries have reported the impact of the pandemic on cancer mortality. The United Kingdom has indicated that delays in diagnosis and treatment can increase the number of deaths from breast cancer by 7.9%–9.6% and from colon cancer by 15.3%–16.6% within 5 years of diagnosis [1]. In the United States, 2487 excess deaths from breast cancer are expected to occur by 2030 due to decreased screening rates and delays in diagnosis and treatment [2]. 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 from 2013 to 2018 [3]. In Brazil, during the first wave in March through May 2020, the numbers 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 of hospitalized patients with cancer increased by 14% [4]. In Japan, the impact of the pandemic on cancer screening was also examined. The number of cancer screenings decreased by 25.7% and 13.2% in 2020 and 2021, respectively, compared to that in 2019, and the number of major surgeries decreased by 15% in 2020 compared to those in 2018 and 2019, cited from "Impact of new coronavirus infection on cancer screening and treatment (evaluation in FY2021), The National Cancer Center" available from:
https://www.mhlw.go.jp/content/10901000/001046961.pdf.

Most of these reports on the impact of the pandemic on cancer care are from the early stages of the pandemic in 2020, with only scattered reports in 2021 and few reports after 2022.

There is also another concern that receiving multiple mRNA-LNP vaccinations may reduce immune surveillance, leading to increased incidence and progression of cancer [9-12], but this has not been studied epidemiologically.

In Japan, mRNA-LNP vaccination started in February 2021, and by the end of December 2022, 68.2% of the population had received the third dose. To assess the impact of the pandemic on cancer care, we examined changes in mortality for 20 types of cancers as well as for all cancers collectively. In addition, we set the time frame for evaluation to include not just the early period of the pandemic in 2020, but rather a 3-year period to the end of 2022.

Comparison to pre-pandemic baseline

In 2020, 2021, and 2022, the rates of age-adjusted all-cancer deaths significantly decreased by 2.7%, 2.8%, and 3.3%, respectively, compared to the pre-pandemic baseline. This may reflect the decreasing trend in cancer mortality rates in Japan over the 8 years before the pandemic.

Typically, these trends were seen in the following types of cancer (in descending order by magnitude of decrease): stomach, liver, lung, gallbladder/biliary tract, colon and esophageal cancers, other malignancies of lymphoid, hematopoietic, and related tissues, and laryngeal cancer.

However, the declines in mortality rates seen before the pandemic have slowed down, both for all cancers and for cancers with the highest number of deaths, such as stomach, liver, lung, and colorectal cancer. This might be explained by the decrease in the number of cancer screenings and surgeries in Japan since the beginning of the pandemic and reduction of the body's immune surveillance mechanisms due to the mRNA-LNP vaccine [9-12].

Of great concern is that while cancers with the highest number of deaths have been decreasing during the pandemic, there were statistically significant increases in some types of cancers. Compared to the pre-pandemic baseline (2017-2019), the only cancers with significant increases were pancreatic cancer and malignant lymphoma in 2020. However, ovarian cancer and central nervous system tumors joined the list in 2021, and breast, uterine, lip/oral/pharyngeal cancers and leukemia in 2022. The increases in deaths from the first two cancers, malignant lymphoma and central nervous system tumors, were considered to be in line with pre-pandemic trends, whereas the increases in the other six cancers, namely, pancreatic, ovarian, breast, uterine, lip/oral/pharyngeal cancers and leukemia, deviated from the conventional trends.

Comparison of years after the start of mRNA-LNP vaccination (2021 and 2022) to 2020

Because age-adjusted mortality rates of some cancers changed during the first 3 years of the COVID-19 pandemic, rate ratios (RR) were calculated for 2021 and 2022 compared to 2020.

Significant deficit mortality (RR-1) of stomach, liver, and gallbladder/biliary tract cancers was observed in 2022.

For pancreatic, breast, lip/oral/pharyngeal cancers, leukemia, and malignant central nervous system tumors, significant excess-mortality (RR-1) was observed in 2022 compared to 2020. Also, marginally significant excess mortality was observed for ovarian and uterine cancers. Six of these, with the exception of malignant central nervous system tumors, showed excess mortality deviating from their pre-pandemic trends.

Recent research has shown that the SARS-CoV-2 spike protein binds to estrogen receptor alpha as well as ACE2 receptor and activates transcription [16].

Breast cancers express estrogen receptor alpha. Addition of estradiol to cell line culture medium causes breast cancer cells to proliferate, whereas addition of raloxifene, a selective estrogen receptor alpha modulator, inhibits proliferation. Breast cancer cell lines grow when spike protein instead of estradiol is added to the culture medium, and addition of raloxifene inhibits their growth. This raises the concern that if there are breast cancer cells in the body, the spike protein will bind to the estrogen receptor alpha on those breast cancer cells and become transcriptionally active as well, accelerating the progression of the disease. This mechanism may explain the statistically significant increase in breast cancer mortality in 2022, when mass vaccination progressed and 68% of the population received the third dose, compared to 2020, when the pandemic began and mRNA-LNP vaccination was not yet underway.

Vaccinated individuals receive an estimated 13 trillion molecules/dose of mRNA-LNPs, based on the molecular weight of BNT162b2 mRNA (1.39×10^6 g/mol) (Pfizer-BionTech) and a dose of 30 µg (by Iwahashi, J.; data available from: https://ameblo.jp/toonomikado/entry-12667109507.html). Consequently, vaccination results in massive production of spike protein in the body, and spike protein in exosomes circulates in the blood of vaccine recipients for more than 4 months [17]. After vaccination, mRNA-LNPs are transfected into various cells (the data from the Pharmaceuticals and Medical Devices Agency of Japan:
https://www.pmda.go.jp/drugs/2021/P20210212001/672212000_30300AMX00231_I100_2.pdf)
and produce spike proteins for a long period. Consequently, reduction of immunity and cancer surveillance by vaccine-derived spike proteins and continued stimulation of estrogen receptor alpha may result in progression of breast cancer and several other types of cancers with estrogen receptor alpha. Omicron strains emerged in Japan in early 2022, and have been prevalent at various points since then, but most infected individuals are protected by innate and acquired immunity in the respiratory tract, which means that they are unlikely to experience viremia and dissemination of spike protein throughout the body [18,19]. Therefore, the impact of spike protein binding to estrogen receptors appears to be focused on vaccine origin rather than infection origin.

Ovarian and uterine cancers also express estrogen receptor alpha in their cells [20-22], and as with breast cancers, binding of the spike protein to estrogen receptor alpha in cancer cells may mediate progression of these cancers, leading to this trend of increased mortality.

The study also found statistically significant increases in deaths in 2022 from leukemia, lip/oral/pharyngeal cancer, and pancreatic cancer.

Estrogen receptor alpha is also expressed in acute myelogenous leukemia cells, and estrogen is known to promote cancer cell proliferation and invasion [23], which may have contributed to the increased mortality rates.

Expression of estrogen receptor alpha has also been reported in lip/oral/pharyngeal cancers. Also, recent studies suggest that estrogen and estrogen receptor alpha complex may promote human papillomavirus (HPV)-induced host cell carcinogenesis in lip/oral/pharyngeal cancers as well as cervical cancer [24,25]. Our observation that the trend in age-adjusted mortality rate for lip/oral/pharyngeal cancers shifted from decreasing before the pandemic to increasing in 2022 may be explained by a combination of factors, namely, reactivation of latent HPV due to immunosuppression [26] and the series of phenomena caused by binding of spike protein to estrogen receptor alpha resulting from massive booster vaccination in 2022.

The expression of estrogen receptor beta has been identified as an unfavorable prognostic factor in pancreatic cancer [27,28]. Moreover, the spike protein has been shown to bind to estrogen receptor beta and may induce transcriptional activity in the nucleus [16]. However, the specific biological mechanisms remain to be clarified in future research.

The mortality rate of malignant central nervous system tumors also increased after the pandemic, following the same trend that started in 2012. However, there is evidence of high expression of estrogen receptor alpha in some glioblastoma, which are highly malignant brain tumors [29], and careful follow-up is needed.

On the other hand, stomach cancer and liver cancer, whose mortality rates decreased significantly, also express estrogen receptor alpha. Some studies quite interestingly show that expression of estrogen receptor alpha in cancer cells of these organs may suppress cell proliferation and invasion [30,31].

Conclusion

Statistically significant increases in age-adjusted mortality rates of breast, pancreatic, lip/oral/pharyngeal cancers and leukemia, as well as marginally significant increases for ovarian and uterine cancers, were observed in 2022 after much of the Japanese population had received the third or later mRNA-LNP vaccine dose. One possible mechanism of the increases for these cancers is cell proliferation mediated by binding of spike protein to estrogen receptor alpha(or beta), which suggests that excess mortality was related to mRNA-LNP vaccination rather than the effects of COVID-19 infection itself.

The significance of this possibility warrants further studies.

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