



Excess Mortality in a Nationwide Cohort of Cancer Patients during the Initial Phase of the COVID-19 Pandemic in Belgium

Geert Silversmit, Freija Verdoodt, Nancy Van Damme, Harlinde De Schutter, and Liesbet Van Eycken

ABSTRACT

Background: Most studies investigating the impact of coronavirus infectious disease-19 (COVID-19) on mortality among patients with cancer were performed in a hospital setting, and the evidence is thus based on a selected and frail subset of patients. This study evaluates the excess mortality during the first wave of COVID-19 in a nationwide, prevalent cancer cohort in Belgium.

Methods: Mortality was studied among almost 240,000 patients with cancer diagnosed between 2013 and 2018 and alive on January 1, 2020. The observed number of deaths in the months January to June 2020 was compared with the expected number of deaths applying the monthly mortality rates observed in the cancer cohort during the previous years. A comparison using the excess mortality rates from the general population was performed.

Results: An excess number of deaths of about 400 was observed in the month of April, coinciding with a peak of COVID-19 diagnoses in Belgium and corresponding to a 33% rise in mortality. A comparable number of excess deaths was estimated if the COVID-19 excess mortality rates from the general Belgian population were applied to the cancer cohort, stratified by age and sex.

Conclusions: A considerable excess mortality in the Belgian cancer cohort was observed during the initial peak of COVID-19 in Belgium. The pattern of excess mortality was, however, not markedly different from that observed in the general population.

Impact: These results suggest that the susceptibility of prevalent cancer patients to COVID-19–induced mortality during the first wave of the pandemic was comparable with the general population.

Introduction

Since December 2019, the spread of severe acute respiratory syndrome coronavirus-2 (SARSCoV-2) and the associated coronavirus infectious disease-19 (COVID-19) has led to substantial mortality worldwide (1, 2). In Belgium, all-cause mortality started to exceed expected levels around the end of March 2020, coinciding with increasing numbers of confirmed COVID-19 cases. Mortality peaked in the second week of April with about 600 deaths per day, roughly doubling the expected daily number of deaths (3). Excess mortality observed in the Belgian population during March and April was in line with the number of deaths that was reported to be COVID-19 related in Belgium (3, 4).

Patients with cancer have been designated as a particularly vulnerable subgroup during the pandemic (5–7). Several studies among COVID-19 patients have indeed reported that a history of cancer is associated with an increased risk of severe morbidity and mortality, when controlling for important confounding factors such as age, sex, and comorbidities (8–12). In Belgium, a large registry-based study among more than 10,000 hospitalized patients found increased in-

hospital mortality within 30 days after COVID-19 diagnosis for patients with a history of solid cancer ($n = 892$) compared with those without such history (11).

Much of the evidence on cancer and COVID-19 is based on patients who are hospitalized for COVID-19 or other causes at the time of study, are often older and present with underlying comorbidities, thus representing a selected and frail subgroup of patients with cancer. Nonetheless, cancer patients represent a heterogeneous population and, in the same way, individuals contracting SARSCoV-2 present with highly diverse phenotypes. Categorizing all patients with cancer as “COVID-19 vulnerable” may thus not be informative (13). The impact of the COVID-19 pandemic on the overall population of patients with cancer remains, however, understudied.

These considerations prompted us to evaluate excess mortality in a nationwide cohort of almost 240,000 prevalent cancer patients during the first half of 2020, covering the initial wave of the COVID-19 pandemic in Belgium. Using data from the nationwide Belgian Cancer Registry (BCR; refs. 14–16) and Statbel (Directorate General Statistics - Statistics Belgium; ref. 17), the number of excess all-cause deaths in the cancer cohort between January and June 2020 was estimated and compared with the excess mortality observed in the general population in Belgium. Excess all-cause mortality was used as an indicator for the burden of the pandemic in a large, nationwide cohort of patients with cancer, which can provide information on the impact of COVID-19 as well as on the effects of a disruption of the health care system.

Materials and Methods

Excess mortality rates in the general population

Statbel (17), the Belgian statistical office, estimated the daily number of excess deaths in the general population during the COVID-19 period as the difference between the observed number of deaths and the number of expected deaths. The latter was calculated using the

Belgian Cancer Registry, Brussels, Belgium.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (<http://cebp.aacrjournals.org/>).

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average daily mortality from previous years (3). The same approach was used in our study to estimate the monthly crude excess mortality rates in the general population for January to June 2020.

Capital letters are used for quantities related to the general population, whereas small letters will be used further on for quantities related to the cancer cohort. The observed number of deaths, $D_{y,msa}$ in a given month (m) of a calendar year (y) by broad age group (a) and sex (s) at the national level, was obtained from Statbel open data (18). The broad age groups available were: 0 to 24, 25 to 44, 45 to 64, 65 to 74, 75 to 84, 85+ year. The expected number of deaths for a given month in 2020 was considered as the average number of deaths for the same month within the period 2012 to 2019, $E_{msa} = \sum_{y=2012}^{2019} D_{y,msa} / 8$. The excess number of deaths by month in 2020 equals the difference between the observed number of deaths, $D_{y=2020,msa}$, and the expected number of deaths, E_{msa} . The monthly excess mortality rates, R_{msa} in the general population by sex and age group were obtained by dividing the excess number of deaths by the population size alive at the start of the month (PT), which was taken as the person months at risk: $R_{msa} = (D_{y=2020,msa} - E_{msa}) / PT_{y=2020,msa}$.

The population numbers by age and sex are available at Statbel, however only at the start of a given calendar year (19). A linear interpolation was therefore applied to estimate the population alive at the start of each calendar month: $PT(\text{year} = y, \text{month} = i) = PT(y, 1) + (i - 1)[PT(y + 1, 1) - PT(y, 1)] / 12$. The monthly increment observed in 2019 was used for 2020, as the population size at the start of 2021 is not yet known.

These excess mortality rates observed during the COVID-19 pandemic in the general population were applied to the cancer cohort in 2020 to estimate the expected excess number of deaths in case the cancer population would have the same vulnerability as the general population.

Cancer patient cohort and follow-up

From the BCR (14–16) which holds information on all new cancer diagnoses in Belgium since 2004, all patients with a primary cancer diagnosis during 2013 to 2018 were identified; 2018 being the most recent year with complete information on cancer incidence. All invasive tumors were selected except nonmelanoma skin cancers (ICD-10: C00.0–43.9, C45.0–96.9, and chronic myeloid neoplasms). If a person had more than one primary cancer diagnosis during 2013 to 2018, the earliest occurring diagnosis was retained. No restriction on age at diagnosis was applied.

Patients without a national social security identification number (NSSN) were excluded, as well as patients who were lost to follow-up or died at the date of diagnosis. Patients lost to follow-up after the diagnosis date were censored at the time of the last known contact alive. Observed all-cause mortality of the cancer cohort was calculated on the basis of vital status and date of death which were obtained from the Belgian Crossroads Bank for Social Security (20) and linked using the NSSN. Follow-up was available until June 30, 2020.

Expected mortality rates in the cancer cohort

The monthly number of expected deaths in the cancer cohort from January to June 2020 was estimated on the basis of the average monthly mortality rates observed within the 2013 to 2018 cancer cohort during the same months in the previous years. Similar to the analyses for the general population, the crude mortality rates were stratified by sex, age, calendar year, and time since diagnosis; the latter being an important indicator for survival as, in general, the conditional survival improves with longer time since diagnosis. “Attained year” was defined as 0 in

the year of diagnosis, 1 in the subsequent calendar year, and so on. Patients diagnosed in 2013, the earliest year of diagnosis in the cancer cohort, had an attained year of 7 in 2020. However, when calculating expected deaths in 2020 based on mortality in previous years the maximum attained year realised by the 2013 to 2018 cancer cohort is six for patients diagnosed in 2013 surviving until 2019. To achieve mortality rates with attained year 7, the diagnosis year 2012 was therefore added for the calculation of the expected mortality rates. The expected crude mortality rates were thus estimated on the basis of the observed mortality for the 2012 to 2018 cancer cohort in the calendar period 2012 to 2019 and applying that to the person time at risk in 2020 for the 2013 to 2018 cancer cohort. A schematic representation of attained year as related to diagnosis year and calendar year is provided in the online supplement (Supplementary Fig. S1).

Person time at risk was calculated per attained year, calendar month, sex, and broad age group by splitting the observation time per patient by calendar month, using the %lexis SAS macro developed by Bendix Carstensen (21). The contribution of a patient in a specific month equalled the ratio of the number of days the patient contributed to that month divided by the number of days in that month. For example, a patient diagnosed at an age of 65 years on the April 10, 2015, and who died on the January 3, 2016, contributed 21/30 of a month to April 2015 and full months for May till December 2015 with attained year 0 and finally 3/31 to January 2016 with attained year 1. All these person months and the number of observed deaths were then summed over attained year (t), month (m), sex (s), and attained age stratum (a), respectively noted as $pt_{tmsa}(\text{incidence } 2012-2018)$ and d_{tmsa} . Attained age equalled the age at diagnosis in the year of diagnosis and was incremented by 1 for each subsequent calendar year. Finally, the ratio of the number of deaths and the person time in a stratum provided the observed crude mortality rate in that stratum: $r_{tmsa} = d_{tmsa} / pt_{tmsa}(\text{incidence } 2012-2018)$. These rates were then multiplied with the person time observed in 2020 for the 2013 to 2018 cancer cohort to obtain the expected number of deaths in a stratum: $e_{tmsa} = r_{tmsa} \cdot pt_{tmsa}(y = 2020, \text{incidence } 2013-2018)$. The total expected number of deaths in a calendar month in 2020, e_m , was obtained as the independent sum in each age- to sex-attained year stratum, using the same age categories as for the general population.

Excess number of deaths in the cancer cohort

The validity of the calculation of the expected number of deaths in the cancer cohort was evaluated by applying the same methodology to the years 2017, 2018, and 2019 and comparing the estimated expected number of deaths with the observed number of deaths per month, d_m , in those years. The expected number consistently overestimated the observed number, results are given in (Supplementary Fig. S2). This could be attributed to the gradually improving survival probability with incidence year in the 2012 to 2018 cohort as shown in (Supplementary Fig. S3), overall for all cancer types and particularly for lung cancer in Belgium (15). The average ratio between expected and observed number of deaths over these 36 months was used as calibration factor, f , for the expected number of deaths in 2020. The calibrated results for 2017, 2018, and 2019 are presented in (Supplementary Fig. S2). Finally, the difference between the observed and calibrated expected number of deaths results in the excess number of deaths, $d_{e,m}$, in a specific month m for 2020: $d_{e,m} = d_m - f \cdot e_m$.

Because the distribution of specific cancer sites is fairly constant during the diagnosis period included in the study (Supplementary Fig. S4, ≤ 3 percentage points change), stratification according to cancer sites was deemed unnecessary for overall excess calculations.

When site-specific excess results are reported, site-specific rates and calibration factors were determined.

Expected excess number of deaths in the cancer cohort

The excess mortality rates from the general population during January to June 2020 were applied to the cancer cohort to estimate the number of excess deaths one would have expected supposing the same underlying vulnerability to COVID-19 mortality as in the general population, taking sex and age into account. This number of deaths was named the expected excess number of deaths, d_e^* .

The expected excess number of deaths in the cancer cohort equals the product of the excess mortality rates from the general population and the person time at risk in the cancer cohort in the calendar year 2020: $d_{e,msa}^* = R_{msa} \cdot pt_{y=2020,msa}$. The total expected excess number of deaths in a calendar month in 2020, $d_{e,m}^*$, was obtained as the independent sum over the age-sex strata.

Statistical analysis

Standard errors on the excess number of deaths and mortality rates were calculated assuming a Poisson distribution for the observed number of deaths. The mathematical derivation is given in (Supplementary Materials and Methods). A significance level of 5% was applied and 95% confidence intervals are reported. All analyses were performed with SAS version 9.4 (SAS Institute).

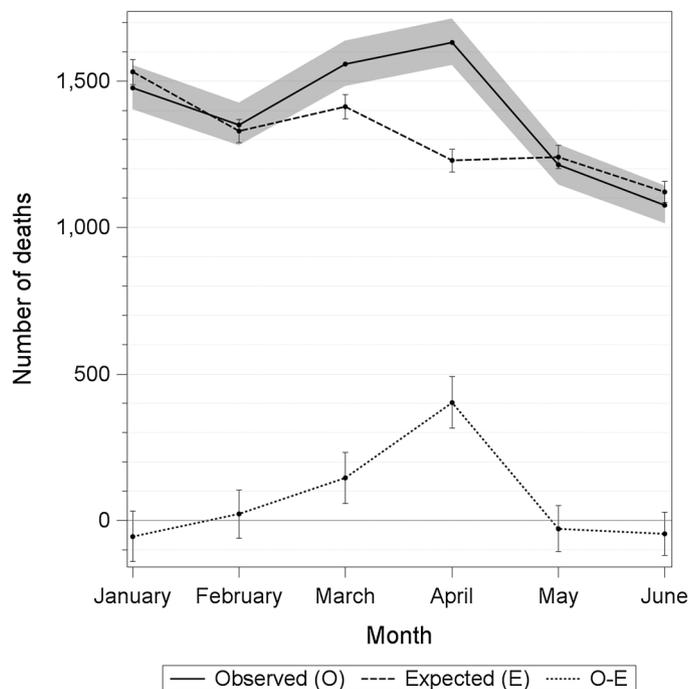
Results

The 2013 to 2018 cancer cohort consisted of 395,168 individuals, of which 7,062 (1.8%) were excluded due to non-NSSN and 1,423 (0.4%) due to lost to follow-up or death at the date of incidence. Finally, 386,683 individuals remained for the analysis, of which 238,665 were alive at the start of the calendar year 2020.

The observed and expected number of deaths per month in the 2013 to 2018 cancer cohort during January to June 2020 are given in Fig 1.

Figure 1.

Observed (full line) and expected (dashed line) number of deaths in the calendar year 2020 for the cancer incidence cohort 2013 to 2018. The lower pointed line represents the excess mortality, that is, the difference of the observed and expected number of deaths.



Excess mortality was noted during March and April, and we estimated 145 (95% CI, 57–233) excess deaths in March and 403 (95% CI, 315–492) in April. With an expected number of deaths in March and April 2020 of 1,413 and 1,229, this corresponded with a relative increase in mortality of 10% and 33%, respectively, compared with previous years.

The expected excess number of deaths in the 2013 to 2018 cancer cohort, based on the excess mortality observed in the general population, was 94 (95% CI, 79–109) for March 2020 and 435 (95% CI, 418–452) for April 2020.

Excess number of deaths during April 2020 are provided for a number of individual cancer types in (Supplementary Table S1), together with the group of haematologic malignancies and the group of solid tumors. Significant numbers of excess deaths were observed for cancer of the oesophagus and gastroesophageal junction, pancreas and peri-pancreas, lung, breast (female), kidney, bladder, haematological malignancies, and the solid tumors. However, except for breast cancer in females (101 excess deaths), the estimated number of excess deaths per cancer site was small (≤ 50). The number of expected excess deaths using the excess mortality rates from the general population lies within the 95% CI for the observed excess number of deaths, except for colorectal and prostate cancer for which a higher excess number was expected.

Discussion

In a nationwide cohort of almost a quarter million patients with cancer in Belgium, we found 10% excess mortality in March and 33% in April 2020. Mortality rates restored to normal levels of previous years in May 2020. The observed excess mortality coincided with the peak of COVID-19 during the first half of 2020 in Belgium (4), and was not markedly different from the excess mortality observed in the general Belgian population during the same period, when taking age and gender into account. Our results do not indicate that cancer patients who were diagnosed at least one year prior to the onset of the pandemic

were impacted differently with regard to overall mortality, compared with the general population. Excess mortality by individual cancer type appeared not markedly different from the expected excess, however, we found some evidence of lower-than-expected excess mortality among patients with colorectal and prostate cancer. Due to small numbers, cautious interpretation of tumor type specific results is needed.

In a *post hoc* analysis, we evaluated the excess mortality among patients with more than one primary cancer diagnosis over the incidence period 2004 to 2018. No indication towards a higher excess mortality among patients with more than one primary invasive tumor diagnosis compared with patients with only one primary tumor has been observed. However, the low number of excess deaths in the patient group with more than one primary invasive diagnosis ($N = 29$ in April 2020) does not allow to draw strong conclusions.

The most important strength of our study is the large, population-based cohort of patients with cancer, which virtually alleviates selection bias, and prevents recall bias of cancer history and confounding by indication.

Our estimates of excess mortality capture the net burden of mortality during the first wave of COVID-19 in Belgium, which includes deaths that are directly and indirectly related to COVID-19. Any observed difference between cancer patients and the general population could have been explained by several components, including differences in the risk of SARS-CoV-2 infection and of severe complications upon infection, as well as differences in the exposure to the virus (22–24). In addition, follow-up of the cancer may have been impacted due to measures of confinement and altered prioritization of clinical care and resources, which initiated in Belgium during the second week of March. Given the data that was available for this study at national level, these subcomponents could not be evaluated separately, and we cannot exclude that combined effects biased our results towards a null finding. Our study aimed to evaluate the impact of the pandemic on a large prevalent cancer population, and conclusions may therefore not be generalisable to patients with a recent cancer diagnosis at time of the pandemic.

Generic advice designating patients with cancer to be at high risk for developing severe and lethal complications upon SARS-CoV-2 infection has contributed to changes in the clinical management of cancer during the course of 2020 (13, 25). Somewhat alarming observations of altered management of COVID-19 in patients with cancer compared with non-cancer patients have been reported (6, 7, 11). In the Belgian registry-based study among hospitalized patients with COVID-19, individuals with a history of solid cancer were less likely to receive COVID-19 directed treatment, less frequently admitted to an intensive care unit, and less likely to receive invasive ventilation, whereas at higher risk for in-hospital 30-day mortality (11). Although it should be

noted, as discussed by the authors, that the study evaluated all-cause mortality and patients may thus have died because of their malignancy, these observations need further attention. As researchers are starting to unravel the interplay between cancer and the novel coronavirus, many questions remain unanswered. Overcoming the challenges to collect and combine large high-quality datasets will facilitate evaluating the impact of COVID-19 on patients with cancer and trajectories.

In conclusion, in a nationwide cohort of prevalent patients with cancer, we find considerable excess mortality during the initial wave of COVID-19 in Belgium. The pattern of excess mortality was, however, not markedly different from that observed in the general population. Continuation of efforts to collect and combine real-world data sources is warranted, allowing further research into the various pathways through which the COVID-19 pandemic affects patients with cancer.

Authors' Disclosures

G. Silversmit reports grants from Foundation Against Cancer, Brussels, Belgium (Stichting Tegen Kanker) during the conduct of the study. F. Verdoodt reports grants from Foundation Against Cancer, Brussels, Belgium (Stichting Tegen Kanker) during the conduct of the study. N. Van Damme reports grants from Foundation Against Cancer, Brussels, Belgium (Stichting Tegen Kanker) during the conduct of the study. H. De Schutter reports grants from Foundation Against Cancer, Brussels, Belgium (Stichting Tegen Kanker) during the conduct of the study. L. Van Eycken reports grants from Foundation against Cancer, Brussels, Belgium (Stichting tegen Kanker) during the conduct of the study.

Authors' Contributions

G. Silversmit: Conceptualization, data curation, software, formal analysis, investigation, visualization, methodology, writing—original draft, writing—review and editing. **F. Verdoodt:** Conceptualization, supervision, investigation, methodology, writing—original draft, project administration, writing—review and editing. **N. Van Damme:** Conceptualization, validation, investigation, methodology, writing—review and editing. **H. De Schutter:** Conceptualization, validation, investigation, methodology, writing—review and editing. **L. Van Eycken:** Conceptualization, resources, supervision, funding acquisition, validation, investigation, methodology, writing—review and editing.

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