ACTA ONCOLOGICA
2023, VOL. 62, NO. 2, 103–109
https://doi.org/10.1080/0284186X.2023.2178325

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ORIGINAL ARTICLE

Seasonal effects on cancer incidence and prognosis

Ida Wikén[a], Therese M-L Andersson[a] and Cecilia Radkiewicz[b]

[a]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; [b]Upper Gastrointestinal Surgery/Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

ABSTRACT

Background: It is unknown if the reduction in the expected number of cancer cases diagnosed during Swedish holidays are due to diagnostic delays, how different cancers are affected, and if the season of diagnosis influences long-term cancer survival. We aimed to quantify seasonal trends in incidence and excess mortality for a wide range of malignancies, requiring more or less urgent clinical management.

Material and methods: This nationwide cohort study included all Swedish residents aged 20–84 in 1990–2019. Incidence and relative survival in pancreatic, colorectal, lung, urothelial, breast, and prostate cancer, together with malignant melanoma, non-Hodgkin lymphoma, and acute leukemia diagnosed during holiday and post-holiday were compared to working (reference) season. Incidence rate ratios (IRR) were estimated using Poisson regression and excess (cancer) mortality rate ratios using flexible parametric models.

Results: We identified 882,980 cancer cases. Incidence declined during holiday season for all malignancies and the IRR ranged from 0.58 (95% CI 0.57–0.59 in breast to 0.92 (95% CI 0.89–0.94) in pancreatic cancer. A post-holiday increase was noted for acute leukemia, pancreatic, and lung cancer. For all malignancies except lung cancer, non-Hodgkin lymphoma, and acute leukemia, the excess mortality at 2 years from diagnosis was higher among those diagnosed during the holiday season. A tendency toward elevated short-term (0.5 years) excess mortality was noted in the post-holiday group, but long-term effects only persisted in breast cancer.

Conclusion: This study demonstrates lower holiday detection rates and higher mortality rates in various cancer types diagnosed during holiday season. Healthcare systems should offer a uniform level of cancer care independent of calendar season.

ARTICLE HISTORY
Received 10 June 2022
Accepted 6 February 2023

KEYWORDS
Neoplasms/epidemiology; incidence; adult; registries; mortality/trends

Background

Timely detection at an early stage reduces cancer morbidity and mortality [1,2]. Diagnostic delays are dependent on appropriate clinical management by medical (often general) practitioners but also incorporate patient health awareness and the effectiveness of healthcare systems, including laboratory, pathology, radiology, and other specialized departments [3–8].

Sweden has a strict legislature regarding statutory holiday leave [9]. This contributes to strained medical workforces in the healthcare sector, accountable for the clinical management (diagnosis and treatment) of cancer, during holiday season [10,11]. The Swedish national breast cancer screening program reduces its capacity and routine medical checkups and screening, e.g. colonoscopy, skin examination, prostate-specific antigen (PSA) measurement, of asymptomatic patients and risk groups are typically postponed until working season. As a consequence, cancer numbers drop during holidays [12–15]. It is however not known whether subacute diagnostics and treatment of tumors presenting with cancer alarm symptoms during holidays are delayed, though there are indications that survival after cancer surgery performed during the holiday season is impaired [16,17].

We performed a nationwide, population-based cohort study to investigate whether the holiday season influences the incidence of and relative survival in nine malignancies selected to represent different levels of diagnostic and clinical management and cover a range of clinical presentations.

Material and methods

Design and data sources

This was a population-based cohort study including all cases of pancreatic, colorectal, lung, urothelial, breast, and prostate cancer, as well as malignant melanoma, non-Hodgkin lymphoma/chronic lymphocytic leukemia (NHL/CLL), and acute leukemia recorded in the Swedish National Cancer Register in year 1990–2019 and at age 20–84. It is mandatory for the responsible clinician and pathologist to report all incident malignant (and some benign) conditions to the Swedish

CONTACT Cecilia Radkiewicz cecilia.radkiewicz@ki.se Upper Gastrointestinal Surgery/Department of Molecular Medicine and Surgery, Karolinska Institutet, Retzius väg 13 a, level 4, SE-171 77, Stockholm, Sweden

Supplemental data for this article can be accessed online at https://doi.org/10.1080/0284186X.2023.2178325.

Cancer Register, resulting in a high coverage of around 96% [18]. Date of diagnosis is set as date of pathology (biopsy, excision, or resection) or cytology specimen collection or, if this is missing, clinical examination that led up to cancer diagnosis. Approximately 98% of all registered cancer cases are morphologically verified [19]. In addition to cancer data, the Swedish Cancer Register extracts information on migration from the National Total Population and the date and cause of death from the Cause of Death Registers, ensuring a complete and non-biased follow-up of basically all recorded cancer patients. Publicly available data on population counts and vital statistics by sex, age, and calendar year, to estimate incidence rates and relative survival, were retrieved from Statistics Sweden. The study was approved by the Swedish Ethical Review Authority: 2020-06617.

Cancer classification and staging

The nine cancer types were selected to represent different levels of diagnostic and clinical management and cover a range of presentations, from acute symptom onset (acute leukemia) to diffuse symptomatology (pancreatic and prostate cancer). Some malignancies typically present with classic alarm symptoms like jaundice (pancreatic cancer), cough and hemoptysis (lung cancer), change in bowel habits, rectal bleeding, or blood in the stool (colorectal cancer), visible hematuria (urinary bladder cancer), and B symptoms like fever, night sweats, and unintentional weight loss (NHL/CLL and acute leukemia). While others are more readily self-detected like visible skin lesions (malignant melanoma) or palpable lumps (breast cancer and NHL). Solid tumors and NHL/CLL were grouped according to anatomical location using the 7th edition of the International Classification of Diseases (ICD-7) and leukemia using ICD-8 [20,21]. When relevant, the World Health Organization Histological Classification of Neoplasms (CANC/24.1) was used to classify histology [22]. NHL and CLL were grouped as one disease entity due to overlapping clinical management. See Supplementary Table S1 for details regarding cancer classification. We excluded benign conditions, incident autopsy findings, breast cancer in men, and cancers of the same type if less than two years had passed between the dates of diagnosis, the latter to avoid duplicate registrations (Supplementary Figure S1). TNM stage was included in the Swedish National Cancer Register in year 2004 and the coverage of M stage (distant metastases at diagnoses) was acceptable for selected solid tumor types from year 2010 (Supplementary Table S2).

Statistical analysis

All analyses were, if not otherwise stated, stratified by cancer type. Calendar weeks were counted as seven consecutive days starting on January 1, except calendar week 52 which included 8 (or 9 if leap year) days. Holiday season was defined as the calendar weeks covering Christmas (week 52–1) and summer (week 25–34), post-holiday the succeeding 3 weeks (calendar week 2–4 and 35–37), while the remaining year constituted "working" season. Easter was not included in holiday season since the exact dates vary between calendar years, are placed in connection with ordinary weekend days, and typically does not result in a prolonged adjournment of societal functions.

The frequency distribution by cancer type, sex, and calendar period, were calculated for working, holiday, and post-holiday seasons and compared using the Pearson chi-square test. Age-standardized incidence rates (ASIR) were computed as the number of new cancer cases per 100,000 person-years and weighted according to the Swedish age distribution in year 2019. Poisson regression was used to calculate holiday-to-working and post-holiday-to-working season incidence rate ratios (IRR) with 95% confidence intervals (CI). Because publicly available population counts are aggregated over calendar year, and not season, it was not possible to adjust for age and sex. Acknowledging that the registration quality of TNM is questionable, we performed a subgroup analysis restricted to the incidence of metastasized (M1) pancreatic, colorectal, lung, breast, and prostate cancer diagnosed in year 2010–2019.

A graphical illustration to clarify the direct and indirect (mediated) effect of the season of diagnosis on cancer survival was made (Supplementary Figure S2). We hypothesized that suboptimal clinical management is chiefly a potential issue during holidays but that cancer stage is the dominant factor undermining survival among cancer patients diagnosed during the holiday and post-holiday season through an accumulation of advanced cases. Cancer survival was counted from date of diagnosis until the date of death, emigration, or end of follow-up (31 December 2020), whichever occurred first. We analyzed relative survival (excess mortality) to avoid issues with unreliable records of the cause of death and to account for direct as well as indirect cancer deaths. Relative survival is the ratio of the observed cancer patient survival and the expected survival in the general population of corresponding age, sex, and calendar year [23]. Flexible parametric models were used to estimate the excess mortality rate per 1,000 person-years and holiday-to-working and post-holiday-to-working season excess mortality rate ratios (EMR), adjusted for age (20–44, 45–54, 55–64, 65–74, or 75–84 years), sex (breast and prostate cancer excepted), and calendar year (1990–99, 2000–09, or 2010–19). "Lead-time bias" implies that even if the date of death would have remained the same if diagnosed earlier, postponed cancer diagnoses falsely have a reduced survival time. Using this definition, the lead time in the present study could amount to maximum 13 weeks (the length of the longest holiday + post-holiday period). To account for this, we decided to allow for the excess mortality rate and the EMR to vary over time from diagnosis using flexible parametric models [24]. Restricted cubic splines with 5 degrees of freedom were used for the baseline hazard function and, to allow for non-proportional hazards, a time-varying effect of season on excess mortality was fitted using three degrees of freedom. The EMR was plotted over follow-up and estimated at 0.5, 2, and 5 years after diagnosis. Excess mortality over follow-up was estimated for the reference categories; age 65–74,

female sex (male in prostate cancer), and calendar period 2010–2019. As a sensitivity analysis, to explore whether the smoothening effect of the restricted cubic splines falsely hides a true EMR decline after 13 weeks from diagnosis, we re-ran the same model but with a forced knot location of the time varying effect at 13 weeks from diagnosis with similar graphical output as the model with the default knot positions (i.e. the 25, 50, and 75 centiles of the distribution of uncensored log event times) [24].

The significance level was set to 0.05 and all tests of statistical significance were two-sided. All statistical analyses were performed using Stata Intercooled 17.1 (StataCorp, College Station, TX RRID: SCR_012763).

Results

We identified 882,980 incident cases of the included nine cancer types during the study period (Table 1). Prostate, breast, and colorectal cancer were the most common malignancies. The male proportion was marginally larger during the holiday (56.3%) and post-holiday (56.7%) compared to the working season (56.0%). The number of cancer cases increased but the seasonal distribution remained largely unchanged during the studied calendar periods. Mean age was slightly higher in patients diagnosed during holiday (67.1 years) compared to post-holiday and working season (both 66.8 years).

Incidence

Figure 1 presents the ASIR over calendar weeks 1–52. The seasonal variation in prostate, breast, and colorectal cancer was roughly similar and the incidence reduction was substantial during the holiday season. A similar pattern, although less pronounced, was seen in lung and urothelial cancer and NHL/CLL. The pancreas cancer and acute leukemia ASIR estimates were unstable due to lower numbers, but incidence tended to decline during holiday and peak post-holiday. Malignant melanoma was the only cancer type with a distinct peak occurring shortly before the beginning of the summer holiday.

Table 2 shows the mean ASIR during working, holiday, and post-holiday seasons together with the holiday-to-working and post-holiday-to-working IRR. All holiday incidence drops were statistically significant and the largest decline was seen in breast (IRR 0.58; 95% CI: 0.57–0.59) and prostate cancer (IRR 0.60; 95% CI: 0.60–0.61). The smallest relative decrease was seen in pancreatic cancer (IRR 0.92; 95% CI: 0.89–0.94). A small, but statistically significant, post-holiday peak was noted in pancreatic cancer (IRR 1.05; 95% CI: 1.01–1.09), lung cancer (IRR 1.02; 95% CI: 1.00–1.04), and acute leukemia (IRR 1.11; 95% CI: 1.04–1.18). Only breast cancer incidence failed to normalize to working season rates or above post-holiday. The pattern was similar in the subgroup analysis of primarily metastasized (M1) solid tumors in 2010–2019 (Supplementary Table S3). Though the holiday decline was less pronounced in M1 breast (IRR 0.87; 95% CI: 0.78–0.97) and prostate (IRR 0.79; 95% CI: 0.74–0.85) cancer. The tendency toward a post-holiday M1 cancer increase was noticeable in all sites but pancreatic and prostate cancer.

Table 1. Numbers (n) and proportions (%) of cases diagnosed during working, holiday, and post-holiday season by cancer type, sex, calendar period, and mean age (years) including standard deviation (SD).

			Working		Holiday		Post-holiday		
	n	%	*N*	%	N	%	*N*	%	*p*-value
Total:	882980	100	619692	70.2	154862	17.5	108426	12.3	
Cancer type									
Pancreatic			18100	2.9	5849	3.8	3359	3.1	
Colorectal			97297	15.7	27949	18.0	17239	15.9	
Lung			62719	10.1	19309	12.5	11298	10.4	
Urothelial			46654	7.5	12332	8.0	8197	7.6	
Melanoma skin			46551	7.5	12861	8.3	8036	7.4	
NHL/CLL[a]			38745	6.3	11065	7.1	6794	6.3	
Acute leukemia			6497	1.0	2088	1.3	1271	1.2	
Breast			134999	21.8	27669	17.9	22502	20.8	
Prostate			168130	27.1	35740	23.1	29730	27.4	<0.001
Sex									
men			346918	56.0	87241	56.3	61524	56.7	
women			272774	44.0	67621	43.7	46902	43.3	<0.001
Calendar period									
1990–1999			160511	25.9	41360	26.7	27966	25.8	
2000–2009			206377	33.3	50334	32.5	35961	33.2	
2020–2019			252804	40.8	63168	40.8	44499	41.0	<0.001
Mean age			Years	SD	years	SD	Years	SD	
			66.8	11.4	67.1	11.7	66.8	11.5	

[a]Non-Hodgkin lymphoma/chronic lymphocytic leukemia.

Survival

In all cancers except breast, the excess (cancer) mortality peaked within 2 years from diagnosis and regardless of season of diagnosis (Supplementary Figure S3). An increase in excess mortality in patients diagnosed outside the working season was chiefly seen within 2 years from diagnosis (Supplementary Figure S3). Holiday and post-holiday EMR were plotted over 5 years from diagnosis (Figure 2) together with presenting the EMR estimates at 0.5, 2, and 5 years after diagnosis (Table 3). All cancer types diagnosed during holiday season, except for pancreatic cancer and acute leukemia, had significantly increased excess (cancer) mortality at 0.5 years from diagnosis with EMR ranging from 1.09 (95% CI: 1.07–1.12) in lung cancer to 1.53 (95% CI: 1.40–1.67) in breast cancer. At 2 years after diagnosis, those diagnosed during holiday season still experienced higher excess mortality in colorectal (EMR 1.08; 95% CI: 1.04–1.11), urothelial (EMR 1.09; 95% CI: 1.01–1.18), pancreatic (EMR 1.09; 95% CI: 1.02–1.17), breast (EMR 1.29; 95% CI: 1.22–1.38), prostate cancer (EMR 1.31; 95% CI: 1.23–1.40), and malignant melanoma (EMR 1.17; 95% CI: 1.04–1.33). Pancreatic, breast, and prostate cancer had a statistically significant higher cancer death rate also after 5 years if diagnosed during holiday season. Focusing on cancer patients diagnosed post-holiday, trends were less consistent, but a tendency toward higher 0.5-year excess mortality was seen in all tumor types except for malignant melanoma and acute leukemia. Only breast cancer patients diagnosed post-holiday had statistically significant EMR at 2 and 5 years from diagnosis (Table 3).

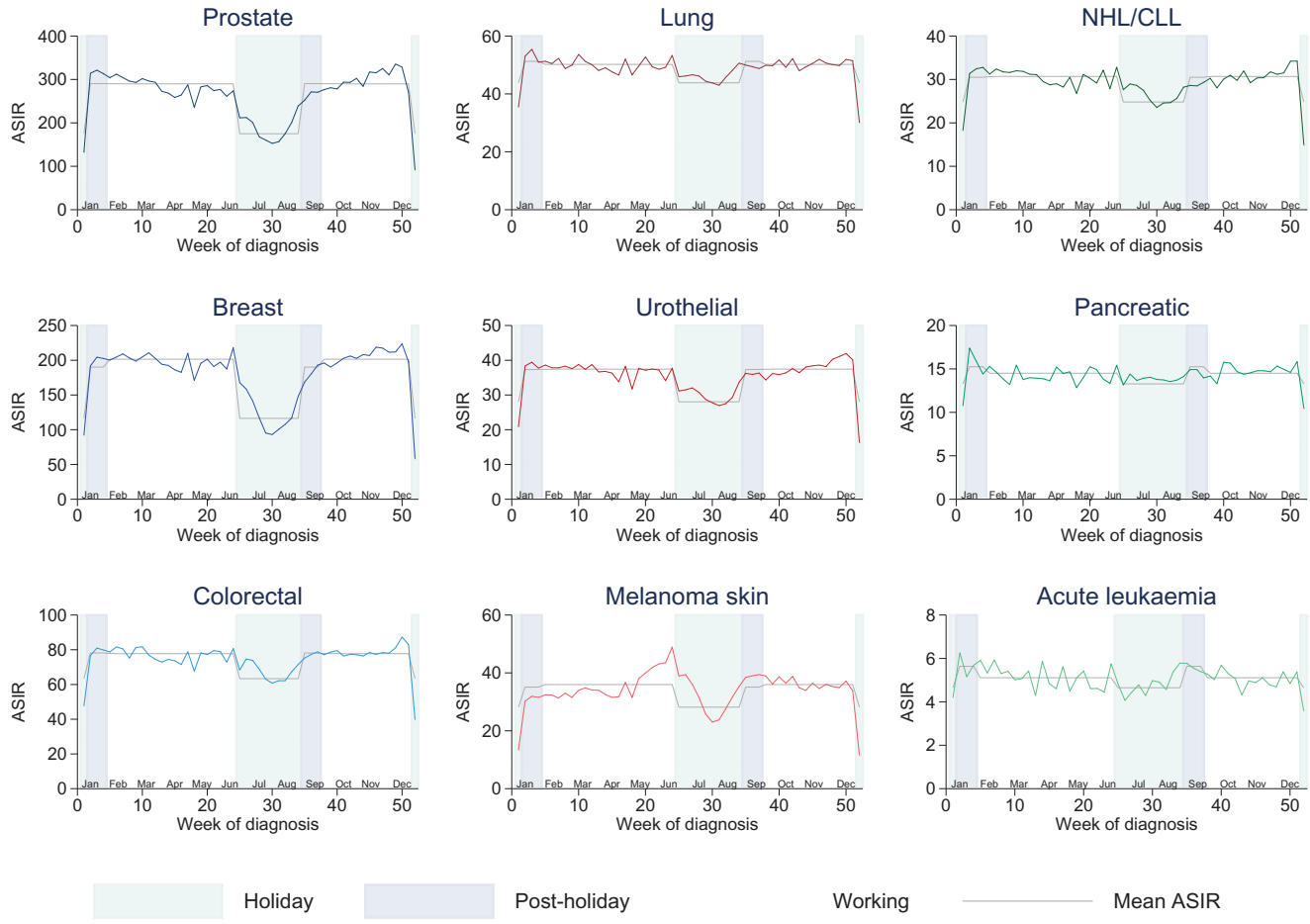

Figure 1. Age-standardized incidence rate (ASIR) over calendar week 1–52, and mean ASIR over season, by cancer type.

Table 2. Age-standardized incidence rate (ASIR) per 100 000 person-years during working, holiday, and post-holiday season together with incidence rate ratios (IRR) with 95% confidence intervals (CI), comparing holiday and post-holiday to working season (reference), by cancer type.

	ASIR			IRR (95% CI)		
Cancer type	Working	Holiday	Post-holiday	Working	Holiday	Post-holiday
Pancreatic	14.5	13.3	15.3	1 (ref)	0.92 (0.89–0.94)	1.05 (1.01–1.09)
Colorectal	77.8	63.4	78.2	1 (ref)	0.81 (0.80–0.82)	1.00 (0.99–1.02)
Lung	50.2	43.8	51.3	1 (ref)	0.87 (0.86–0.89)	1.02 (1.00–1.04)
Urothelial	37.5	28.0	37.3	1 (ref)	0.75 (0.73–0.76)	1.00 (0.97–1.02)
Melanoma skin	36.0	28.2	35.1	1 (ref)	0.78 (0.77–0.80)	0.98 (0.96–1.00)
NHL/CLL[a]	30.7	24.8	30.5	1 (ref)	0.81 (0.79–0.83)	0.99 (0.97–1.02)
Acute leukemia	5.11	4.65	5.64	1 (ref)	0.91 (0.87–0.96)	1.11 (1.04–1.18)
Breast	202	116	190	1 (ref)	0.58 (0.57–0.59)	0.94 (0.93–0.96)
Prostate	290	175	291	1 (ref)	0.60 (0.60–0.61)	1.00 (0.99–1.01)

[a]Non-Hodgkin lymphoma/chronic lymphocytic leukemia.

Discussion

This study reports decreased incidence rates of all nine malignancies, selected to represent different degrees of clinical urgency, during holiday compared to working season. Acute leukemia, pancreatic, and lung cancer incidence also increased slightly in the post-holiday period. After 2 years from diagnosis, the excess cancer death rate among patients diagnosed during holiday season had dropped but remained elevated in all malignancies except for lung cancer, NHL/CLL, and acute leukemia.

Several limitations are worth mentioning. Even if data were prospectively collected, the observational design implies risks of information bias and confounding. A possible bias is if reporting to the cancer register was systematically delayed during holiday seasons. Date of diagnosis is however set to date of histological sample collection and not date of reporting, counteracting this bias. There is also a risk of cancer misclassification, this error should however not vary over calendar season and would therefore drive risk estimates toward the null. Observational in nature, this study cannot claim causality, but rather aims to be hypothesis-generating. Moreover, we lacked information on important drivers including reliable data on tumor stage, treatment, and waiting times to initiate treatment, as well as other prognostic factors and supposedly effect modifiers like socio-economy,

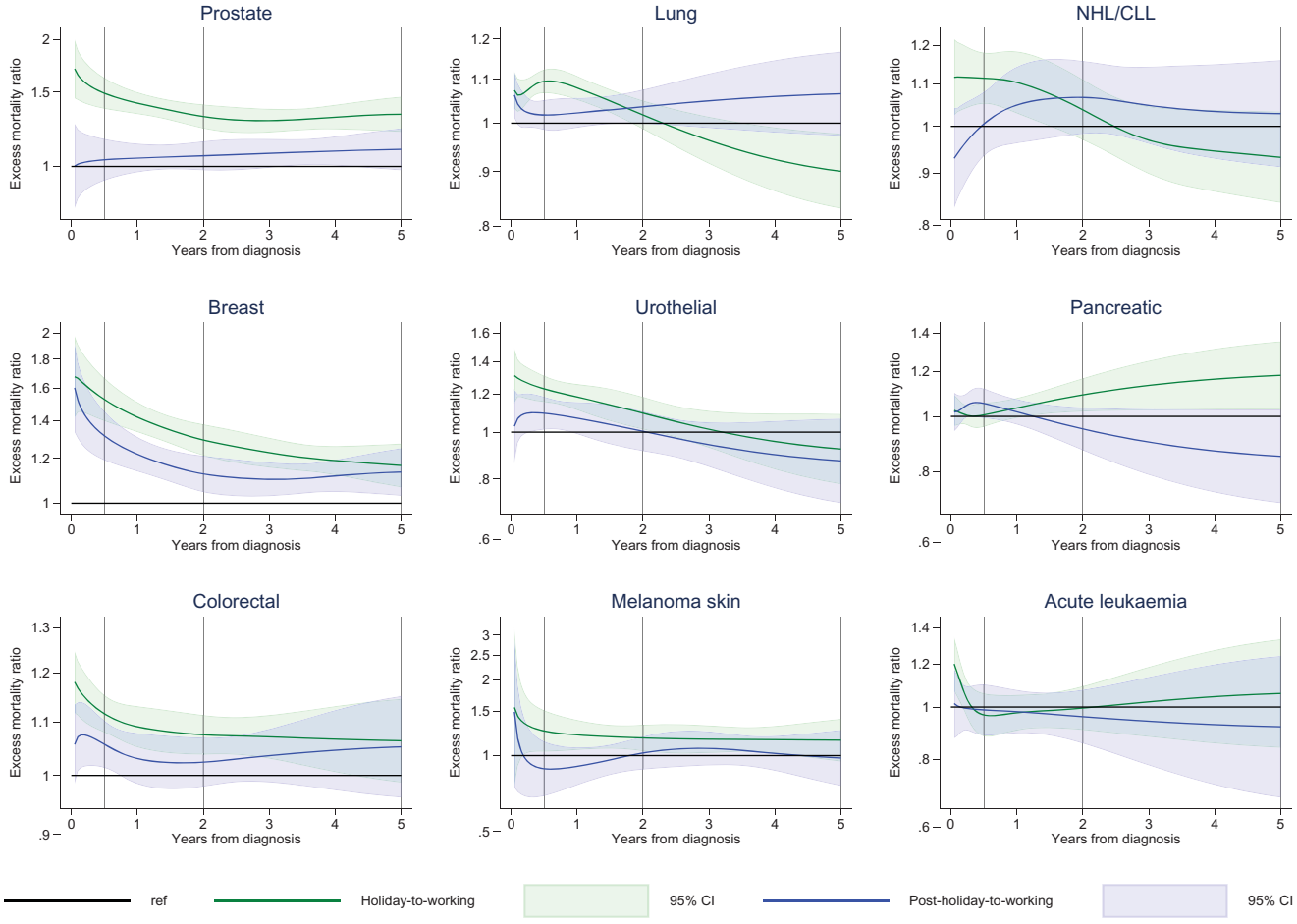

Figure 2. Adjusted excess mortality ratios with 95% confidence intervals (CI) (shaded area) over 5 years from diagnosis in holiday (green line) and post-holiday (blue line) compared to reference working season (black line).

Table 3. Adjusted excess mortality ratios (EMR) with 95% confidence intervals (CI) at 0.5, 2, and 5 years from cancer diagnosis comparing holiday and post-holiday to working season (reference), by cancer type.

		Holiday EMR (95% CI)			Post-holiday EMR (95% CI)		
Cancer type	Working	0.5 years	2 years	5 years	0.5 years	2 years	5 years
Pancreatic	1 (ref)	1.01 (0.96–1.06)	1.09 (1.02–1.17)	1.18 (1.03–1.36)	1.05 (0.99–1.12)	0.95 (0.87–1.04)	0.85 (0.70–1.03)
Colorectal	1 (ref)	1.12 (1.08–1.15)	1.08 (1.04–1.11)	1.06 (0.99–1.15)	1.06 (1.01–1.10)	1.02 (0.98–1.07)	1.05 (0.96–1.15)
Lung	1 (ref)	1.09 (1.07–1.12)	1.02 (0.99–1.05)	0.90 (0.83–0.98)	1.02 (0.99–1.05)	1.04 (1.00–1.08)	1.07 (0.97–1.17)
Urothelial	1 (ref)	1.23 (1.15–1.31)	1.09 (1.01–1.18)	0.92 (0.78–1.09)	1.09 (1.01–1.18)	1.00 (0.91–1.10)	0.87 (0.71–1.07)
Melanoma skin	1 (ref)	1.25 (1.04–1.51)	1.17 (1.04–1.33)	1.15 (0.95–1.40)	0.89 (0.69–1.14)	1.02 (0.88–1.19)	0.98 (0.76–1.26)
NHL/CLL[a]	1 (ref)	1.11 (1.05–1.18)	1.04 (0.97–1.11)	0.93 (0.84–1.03)	1.01 (0.93–1.08)	1.07 (0.98–1.16)	1.03 (0.91–1.16)
Acute leukemia	1 (ref)	0.97 (0.88–1.06)	1.00 (0.91–1.09)	1.06 (0.84–1.33)	0.99 (0.89–1.10)	0.96 (0.86–1.08)	0.92 (0.68–1.24)
Breast	1 (ref)	1.53 (1.40–1.67)	1.29 (1.21–1.38)	1.17 (1.07–1.28)	1.32 (1.19–1.46)	1.13 (1.05–1.21)	1.14 (1.03–1.25)
Prostate	1 (ref)	1.49 (1.37–1.62)	1.31 (1.23–1.40)	1.33 (1.21–1.46)	1.04 (0.92–1.16)	1.06 (0.98–1.15)	1.10 (0.98–1.23)

[a]Non-Hodgkin lymphoma/chronic lymphocytic leukemia.

comorbidity, and performance status, complicating inferences on the effect of season on diagnostic delays and cancer prognosis.

The strengths lie in the large sample size granting power to investigate also rarer malignancies and the population-based approach minimizing the risk of selection bias. The Swedish National Cancer Register records basically all incident cancer cases in the population independent of sex, region, or socioeconomic status. Moreover, the use of the national registration number, assigned to all Swedish residents, yields an unbiased and basically complete follow-up. To investigate the season of diagnosis in relation to cancer mortality, we handled potential misclassification of the cause of death and lead-time bias by using relative survival to estimate net survival and flexible parametric models to allow for the excess mortality to vary over follow-up, respectively.

Studies on seasonal variation in cancer incidence and prognosis are sparse, but our findings are in line with previous reports of decreased numbers of malignant melanoma, breast, and prostate cancer cases being diagnosed during Swedish summer season [12,13]. Moreover, we detected seasonal variations of additionally six cancer types. The discrepancy is probably driven by different definitions of holiday season together with the larger sample size and more recent data. The metastasized solid tumor incidence variation over calendar season, especially the tendency toward a post-

holiday peak, is startling and this has to our knowledge not been reported previously.

The EMR peaked within the first 0.5 years from diagnosis but the excess mortality among those diagnosed during holiday season remained elevated also after 2 years in most cancers. The sustained effect cannot be solely driven by lead time, since this could only bias excess mortality within a shorter time frame. A poorer stage distribution (and consequently survival) in patients diagnosed with breast and prostate cancer during the summer has been reported previously [13]. While this probably reflects the removal of screening-detected low-risk cases, we demonstrate similar survival losses in holiday-diagnosed pancreatic, colorectal, urothelial, melanoma skin cancer, and NHL/CLL. A combination of patient, doctor, and system delay in response to cancer alarm symptoms forms one explanation. Patients might be less prone to seek medical advice, healthcare providers less accessible, and waiting times may be longer during holidays. At worst, the mortality rate increase among cancer patients diagnosed during holidays is partly a consequence of impaired quality of care, including treatment delays and limited access to specialized expertise. Poorer outcomes after cancer surgery performed during holidays have been reported previously and remained significant despite careful adjustments for prognostic factors [18]. Patients diagnosed during holiday season are probably less likely to be asymptomatic or detected incidentally and even the most fine-grained data on adverse prognostic factors including stage, could not fully adjust for this. As an example, the proportion of colorectal patients presenting with acute bowel obstruction, an independent negative prognostic factor, has been reported to be larger during holidays when cases detected investigating indolent symptoms are removed [25,26]. Even though some contamination after holiday cannot be ruled out, the tendency toward a solid tumor M1 peak and poorer survival in the post-holiday setting indicates healthcare system vacation delays. This was however mostly noticeable shortly (<0.5 years) from diagnosis in a handful of malignancies, and a sustained (5 year), statistically significant mortality elevation over follow-up was limited to patients diagnosed with post-holiday breast cancer.

This study reports incidence declines during holidays in a wide range of malignancies and also sites not included in screening programs. Moreover, a higher excess mortality was seen in cancer patients diagnosed during and, to a limited extent, the weeks after holiday season. However, the present study did not address underlying drivers or population groups at increased risk. Future studies should focus on whether tumor stage, clinical management, and quality of care, differ between calendar seasons as well as if certain subpopulations, based on socio-economy, psychiatric comorbidity, geographical region, or ethnicity, are more vulnerable to holiday delays. Even though the cancer mortality rate increase among those diagnosed post-holiday was modest, any avoidable premature cancer death is unacceptable and resources should be allocated to buffer working conditions including a granted holiday leave to supply a consistent level of high-quality healthcare all year around.

In conclusion, this study reports decreased cancer incidence rates during holiday season together with increased cancer mortality rates in those diagnosed outside working season, for a wide range of different tumor types. Findings were not limited to cancers included in screening programs but aggressive malignancies like pancreatic cancer and acute leukemia as well as metastasized cancers also varied over season. Healthcare should provide the same accessibility and quality throughout the year and unfavorable timing of clinical presentation must never affect cancer prognosis.

Disclosure statement

The authors declare no potential conflicts of interest.

Funding

This work was not supported by any funding agency. CR received funding from Region Stockholm, [grant number: FoUI-963792].

ORCID

Ida Wikén http://orcid.org/0000-0003-0697-0588

Data availability statement

Cancer data was generated by the Swedish National Board of Health and Welfare, is considered sensitive, and is not publicly available due to Swedish laws and regulations. Derived, aggregated data supporting the study findings is available upon request.

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