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Mortality in cancer patients previously diagnosed with herpes zoster in the hospital setting: a nationwide cohort study

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Background: Herpes zoster (HZ) is associated with underlying immunodeficiency and may thereby predict mortality of subsequent cancer.

Methods: By using Danish nationwide medical databases, we identified all cancer patients with a prior hospital-based HZ diagnosis during 1982–2011 ($n = 2754$) and a matched cancer cohort without prior HZ ($n = 26\,243$). We computed adjusted mortality rate ratios (aMRRs) associating prior HZ with mortality following cancer.

Results: Prior HZ was associated with decreased mortality within the year after cancer diagnosis (aMRR 0.87; 95% confidence interval (CI): 0.81–0.93), but not thereafter (aMRR 1.07; 95% CI: 0.99–1.15). However, prior HZ predicted increased mortality throughout the entire follow-up among patients aged <60 years (aMRR 1.39; 95% CI: 1.15–1.68) and those with disseminated HZ (aMRR 1.18; 95% CI: 1.01–1.37). The increased mortality rates were observed primarily for haematological and immune-related cancers.

Conclusions: Overall, HZ was not a predictor of increased mortality following subsequent cancer.

Herpes zoster (HZ) may be a marker of occult cancer (Sørensen *et al.*, 2004; Ho *et al.*, 2011; Liu *et al.*, 2012; Wang *et al.*, 2012; Chiu *et al.*, 2013; Cotton *et al.*, 2013; Iglar *et al.*, 2013) and some authors have advocated increased work-up for cancer in patients with HZ (Zaha *et al.*, 1993; Yamamoto *et al.*, 2003; Cotton *et al.*, 2013). However, limited data are available on whether HZ may be used to predict mortality in patients presenting with subsequent cancer in clinical practice. The two previous studies on the topic overall showed no association (Sørensen *et al.*, 2004; Cotton *et al.*, 2013), but were limited by small sample sizes and lacked information on key prognostic factors, such as cancer stage and comorbidities. The first study, which was conducted by our research group, was furthermore restricted to in-patient HZ diagnoses (Sørensen *et al.*, 2004).

Our objective was to provide updated and more detailed analyses of the association between HZ and mortality following a subsequent cancer by extending the period of follow-up, by including inpatient, outpatient and emergency room HZ diagnoses, and by obtaining information on cancer stage, comorbidities and use of immunosuppressive drugs.

MATERIALS AND METHODS

We conducted this nationwide matched cohort study by using Danish nationwide medical databases. The source population comprised 829 787 cancer patients. A detailed description of data

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sources and variable definitions is provided in the Supplementary Table S1.

We identified all patients with a diagnosis of first-time cancer in the Danish Cancer Registry (Statens Serum Institut, 2012) between 1982 and 2011, who had a prior hospital-based (i.e., inpatient, outpatient (ambulatory), or emergency room) HZ diagnosis recorded in the Danish National Patient Registry (DNPR) (Lynge *et al.*, 2011). We considered all available primary and secondary registry diagnoses and used the date of discharge or end of outpatient follow-up as the diagnosis date for HZ. By grouping the diagnosis codes, we differentiated between severity (uncomplicated or complicated) and extent (localised or disseminated) of HZ. For each HZ patient with subsequent cancer, we sampled up to 10 cancer patients with no prior HZ diagnosis individually matched by sex, birth year, cancer type and calendar period of cancer diagnosis (5-year interval).

From the Danish National Health Service Prescription Database (Johannesdottir *et al.*, 2012) and the DNPR, we retrieved information on the following covariates recorded before cancer diagnosis: treatment with immunosuppressive drugs within the first 6 months, comorbidities associated with immune dysregulation and comorbidity level categorised as none (0), moderate (1), severe (2) or very severe ($\geqslant 3$) using the Charlson Comorbidity Index score (Charlson *et al.*, 1987).

By using the Civil Registration System (Schmidt et al., 2014), we followed patients from the date of cancer diagnosis until death, emigration, or 31 December 2012, whichever came first. We computed the mortality rate per 1000 person-years for cancer patients with prior HZ and for the matched cancer cohort. Taking the matching variables into account, we used stratified Cox regression (Hosmer et al., 2008) to compute unadjusted mortality rate ratios (MRRs) with 95% confidence intervals (CIs) associating prior HZ with mortality following subsequent cancer. Then, we adjusted for comorbidity level and cancer stage (localised, regional, distant or unknown/missing). Because plots of the log(-log(survival)) vs log of survival time indicated non-proportionality, we divided follow-up time into 0–1 year and >1 year. We performed analyses for all cancers combined, cancer subgroups (haematological cancers, immune-related cancers, smoking- and alcohol-related cancers and cancers at all other sites), and individual cancers (Boyle, 1997; Nasca, 2001; Boffetta and Hashibe, 2006). Finally, we examined if the association depended on the included covariates through stratified analyses. As this analysis required dissolving of the matching, we used conventional Cox regression with additional adjustments for matching variables, cancer stage and comorbidity level in each subgroup analysis. All analyses were pre-specified.

RESULTS

We identified 2795 cancer patients with a prior HZ diagnosis and 26 243 cancer comparison cohort members without this diagnosis. Of these, 41 (1.5%) cancer patients with prior HZ were excluded because no matching cancer patients could be identified.

Cancer patients with prior HZ had a median age of 78 years and 56.9% were women (Table 1). Compared with the matched cancer cohort, HZ patients had a higher prevalence of comorbidities and were more frequently users of immunosuppressive drugs before cancer diagnosis. Cancer stage at time of diagnosis was similar. The observed differences remained when cancer subtypes were examined separately (Supplementary Table S2).

The unadjusted MRR within the first year after cancer diagnosis was 0.95 (95% CI: 0.89–1.02), but decreased to 0.87 (95% CI: 0.81–0.93) in the full model, which was mainly explained by adjustment for comorbidity level (Table 2). However, the stratified analysis

Table 1. Selected characteristics of persons diagnosed with herpes zoster and subsequent cancer and a matched cancer cohort, Denmark 1982–2011

	All malignant neoplasms	
	Herpes zoster patients	Matched cohort
	n (%)	*n* (%)
Total	2754 (100.0)	26 243 (100.0)
Age at cancer diagnosis (years)		
Range	18–100	16–102
Median (interquartile range)	78 (70–84)	77 (70–84)
Age groups		
15–59	256 (9.3)	2259 (8.6)
60–69	436 (15.8)	4344 (16.6)
70–79	915 (33.2)	9105 (34.7)
⩾80	1147 (41.6)	10 535 (40.1)
Sex		
Women	1566 (56.9)	14 897 (56.8)
Men	1188 (43.1)	11 346 (43.2)
Calendar period of cancer diagnosis		
1982–1994	1020 (37.0)	9738 (37.1)
1995–2011	1734 (63.0)	16 505 (62.9)
Cancer stage at diagnosis[a]		
Localised	1193 (43.3)	11 489 (43.8)
Regional	446 (16.2)	4151 (15.8)
Distant	466 (16.9)	4592 (17.5)
Unknown/missing	649 (23.6)	6011 (22.9)
Charlson Comorbidity Index level[b]		
None	1236 (44.9)	16 999 (64.8)
Moderate	699 (25.4)	5366 (20.4)
Severe	406 (14.7)	2362 (9.0)
Very severe	413 (15.0)	1516 (5.8)
Comorbidities with immune dysregulation, overall	581 (21.1)	2223 (8.5)
Any autoimmune disease	514 (18.7)	2123 (8.1)
Solid organ transplantation	46 (1.7)	15 (0.1)
Stem cell or bone marrow transplantation	1 (0.0)	3 (0.0)
Human immunodeficiency virus infection	30 (1.1)	41 (0.2)
Primary immunodeficiency	8 (0.3)	16 (0.1)
Other[c]	15 (0.5)	58 (0.2)
Immunosuppressive drugs overall[d]	128 (4.6)	760 (2.9)
Systemic glucocorticoids	116 (4.2)	663 (2.5)
TNF-alpha inhibitors	—	2 (0.0)
Other	31 (1.1)	163 (0.6)
Setting of herpes zoster diagnosis[e]		
Inpatient	2284 (82.9)	—
Outpatient	289 (10.5)	—
Emergency room	181 (6.6)	—
Severity of herpes zoster		
Complicated	712 (25.9)	—
Uncomplicated	2042 (74.1)	—
Extent of herpes zoster		
Disseminated	262 (9.5)	—
Localised	2492 (90.5)	—
Follow-up (years)		
Median (interquartile range)	1.71 (0.33–4.96)	1.88 (0.30–5.47)
Range	0–30.71	0–30.71
Total	9470	100 830

[a]Stage defined according to summary staging as follows: localised (T1-4, N0, M0; Ann Arbour I); regional (T1-4, N1-3, M0; Ann Arbour IIs, II-IIe); distant (T1-4, N1-3, M1; Ann Arbour IIs, III-IV); and unknown or missing.
[b]Four levels of comorbidity were defined based on Charlson Comorbidity Index scores of 0 (none), 1 (moderate), 2 (severe) and 3 or more (very severe).
[c]Other immunosuppressive conditions include lymphopenia, leukopenia, agranulocytosis, aplastic anemia and Felty's syndrome.
[d]Among patients diagnosed with cancer in July 2004 or later. The group of other immunosuppressive drugs included, for example, methotrexate, azathioprine, calcineurin inhibitors, other biological agents, and intestinal-acting aminosalicylic acid. See Supplementary Material for a list of included drugs.
[e]Among patients diagnosed with zoster in 1995 or later.

Table 2. Mortality associated with a prior diagnosis of herpes zoster in cancer patients compared with a matched cancer cohort without herpes zoster, Denmark, 1982–2011

	0–1 Year of follow-up				>1 Year of follow-up			
	Mortality rate (per 1000 PY)				Mortality rate (per 1000 PY)			
	Herpes zoster	Matched cohort	Unadjusted MRR (95% CI)[a]	Adjusted MRR (95% CI)[b]	Herpes zoster	Matched cohort	Unadjusted MRR (95% CI)[a]	Adjusted MRR (95% CI)[b]
All cancers combined	535 (503–567)	539 (528–549)	0.95 (0.89–1.02)	0.87 (0.81–0.93)	153 (144–162)	122 (120–125)	1.20 (1.12–1.29)	1.07 (0.99–1.15)
Haematological cancers	641 (520–761)	639 (599–679)	0.98 (0.80–1.20)	0.88 (0.71–1.08)	197 (160–234)	144 (134–153)	1.27 (0.99–1.61)	1.22 (0.96–1.57)
Immune-related cancers	133 (106–161)	109 (102–117)	1.15 (0.92–1.44)	0.94 (0.75–1.19)	114 (102–125)	86 (83–89)	1.30 (1.16–1.47)	1.12 (1.00–1.27)
Smoking- and alcohol-related cancers	1007 (925–1088)	1092 (1063–1120)	0.90 (0.83–0.99)	0.84 (0.77–0.92)	220 (196–244)	198 (191–206)	1.03 (0.89–1.19)	0.94 (0.81–1.10)
All other sites	511 (452–570)	500 (481–520)	1.00 (0.88–1.13)	0.91 (0.79–1.03)	158 (141–175)	132 (127–136)	1.22 (1.06–1.39)	1.05 (0.91–1.20)

Abbreviations: CI = confidence interval; MRR = mortality rate ratio; PY = person-years.
[a]Mortality rate ratios calculated with stratified Cox proportional hazard regression and thus adjusted for age at diagnosis, sex, calendar period at cancer diagnosis and cancer type by study design.
[b]Additionally adjusted for Charlson Comorbidity Index level and cancer stage.

revealed an increased mortality rate among cancer patients under the age of 60 years (adjusted MRR (aMRR) 1.31; 95% CI: 0.98–1.74) and among those who had experienced disseminated HZ (aMRR 1.18; 95% CI: 0.96–1.44) (Table 3). This increase was explained primarily on the basis of the results for haematological cancers (Supplementary Tables S3–S6). The lowest aMRR was observed for patients recently treated with immunosuppressive drugs (aMRR 0.62; 95% CI: 0.44–0.87 for all cancers combined).

The aMRR was 1.07 (95% CI: 0.99–1.15) after the first year of follow-up (Table 3). Again, an increased mortality rate was observed primarily for patients under the age of 60 years (aMRR 1.39; 95% CI: 1.07–1.79) and those with disseminated HZ (aMRR 1.21; 95% CI: 0.97–1.51) (Table 3). Thus, the youngest patients and patients with prior disseminated HZ had an increased mortality throughout the entire follow-up period (aMRRs 1.39; 95% CI: 1.15–1.68 and 1.18; 95% CI: 1.01–1.37, respectively). The increased estimates were particularly high among the patients with haematological or immune-related cancers (Supplementary Tables S3–S6). The MRRs for individual cancers were imprecise but supported the findings from the main analyses (Supplementary Table S7).

Finally, we observed no substantial difference or specific patterns when stratifying by time between HZ and cancer diagnoses (Table 3 and Supplementary Tables S3–S6).

DISCUSSION

We found that a hospital-based HZ diagnosis predicted an increased mortality in subsequent haematological and immune-related cancers, particularly among patients aged <60 years and among those who had experienced disseminated HZ. For the remaining cancer patients, a prior HZ diagnosis was associated with a slightly decreased 1-year mortality.

In an earlier study, we found no overall association between HZ and mortality of subsequent cancer except for a potentially increased the mortality (MRR 1.38; 95% CI: 0.83–2.28) among patients with haematological malignancies diagnosed within a year after HZ (Sørensen *et al.*, 2004). In a British study, median survival was 1197 days among 573 cancer patients (87% of those identified) with prior HZ diagnosed in general practice compared with 1201 days among matched cancer patients without HZ (Cotton *et al.*, 2013). Our data suggest that prior studies may have been confounded by unmeasured comorbidity level. Also, our study allowed us to perform detailed subgroup analyses that revealed potentially important associations.

An intact immune system is essential both for withstanding carcinogenesis (Ershler, 1993; Penn, 2000) and varicella-zoster virus reactivation (Wilson, 2011). HZ could therefore serve as a marker of underlying immune incompetence, possibly explaining the increased mortality of subsequent cancer. However, our results support this hypothesis in only a subgroup of patients. It is possible that disseminated infection and recrudescence in younger patients is a stronger marker of underlying immune incompetence. Indeed, disseminated HZ occurs more frequently in immunosuppressed individuals and HZ may be a presenting symptom of human immunodeficiency virus infection (Wilson, 2011; Søgaard *et al.*, 2012). Also, our estimates were driven by haematological and immune-related cancers, which are observed more frequently among immunosuppressed patients (Penn, 2000). Because viruses have been implicated in the development of several of these cancers (Penn, 2000; Alibek *et al.*, 2014), we speculate whether the mechanisms behind immunological evasion of oncogenic viruses and the varicella-zoster virus are closely related. The slightly decreased mortality observed during the first year of follow-up is difficult to reconcile with our *a priori* hypothesis. Similar stage distribution argues against increased cancer surveillance among HZ patients as an explanation.

Strength of our study is the nationwide setting in a uniform healthcare system with complete follow-up data (Schmidt *et al.*, 2014). Also, the Danish Cancer Registry has high completeness, maintained by notifications from multiple sources of the healthcare system. High validity (i.e., positive predictive value) is supported by a high proportion of histologically verified tumours (over 90% for major cancers) and a low proportion (0.1%) of diagnoses based on death certificates only (Statens Serum Institut, 2012).

We believe that the clinical picture of HZ confers a high diagnostic accuracy (Wilson, 2011) and thus positive predictive value in the DNPR. However, it is possible that physicians underreport HZ in elderly hospital patients, because they often have other diseases requiring greater clinical attention. Such misclassification could explain the lack of an association among patients aged ⩾60 years. Unmeasured confounding by lifestyle factors, for example, smoking, could also explain the unexpected results if HZ is underreported in patients with lifestyle-related comorbidities or if cancer patients with previous HZ represent healthier persons as they have survived competing diseases after their HZ diagnosis in order to be diagnosed with cancer and thus included in our study. We also lacked data on cancer treatment,

Table 3. Mortality following cancer among patients with a prior diagnosis of herpes zoster compared with a matched cancer cohort, by study characteristics, Denmark 1982–2011

	0–1 Year of follow-up			>1 Year of follow-up		
	Mortality rate (per 1000 PY)			Mortality rate (per 1000 PY)		
	Herpes zoster	Matched cohort	Adjusted MRR (95% CI)[a]	Herpes zoster	Matched cohort	Adjusted MRR (95% CI)[a]
Time between herpes zoster and cancer diagnoses						
0–365 Days	572 (481–664)	602 (572–633)	0.86 (0.72–1.03)	152 (128–177)	125 (119–132)	1.13 (0.92–1.39)
>365 Days	529 (495–563)	529 (518–540)	0.87 (0.81–0.94)	153 (144–163)	122 (119–124)	1.06 (0.97–1.14)
Sex						
Women	511 (469–552)	514 (501–528)	0.91 (0.84–0.99)	144 (133–154)	115 (112–118)	1.08 (0.99–1.17)
Men	568 (517–618)	571 (555–588)	0.87 (0.79–0.96)	170 (154–185)	135 (131–139)	1.11 (1.00–1.22)
Age at cancer diagnosis						
15–59 Years	294 (222–366)	192 (173–212)	1.31 (0.98–1.74)	62 (48–75)	36 (33–39)	1.39 (1.07–1.79)
60–69 Years	332 (272–391)	347 (328–366)	0.85 (0.71–1.03)	103 (88–118)	78 (74–82)	1.09 (0.93–1.28)
70–79 Years	557 (500–614)	566 (548–584)	0.86 (0.77–0.96)	152 (137–167)	129 (124–133)	1.03 (0.93–1.14)
⩾80 Years	680 (622–739)	713 (693–733)	0.88 (0.81–0.97)	262 (239–285)	224 (217–231)	1.08 (0.98–1.19)
Calendar period of cancer diagnosis						
1982–1994	706 (642–769)	698 (678–719)	0.91 (0.83–1.00)	160 (146–173)	136 (132–140)	1.06 (0.97–1.16)
1995–2011	448 (412–484)	456 (445–468)	0.87 (0.80–0.95)	148 (137–160)	112 (109–115)	1.12 (1.03–1.22)
Stage at cancer diagnosis						
Local	225 (196–253)	188 (180–196)	0.97 (0.84–1.11)	129 (119–139)	99 (96–101)	1.13 (1.04–1.23)
Regional	582 (498–665)	657 (628–687)	0.84 (0.72–0.97)	182 (155–208)	165 (157–174)	1.03 (0.89–1.20)
Metastatic	1958 (1757–2159)	1993 (1928–2058)	0.92 (0.82–1.02)	421 (330–511)	365 (340–390)	1.02 (0.81–1.28)
Unknown/missing	635 (561–709)	694 (668–719)	0.85 (0.75–0.96)	185 (161–209)	150 (143–157)	1.09 (0.95–1.25)
Charlson Comorbidity Index level						
None	422 (381–463)	447 (436–459)	0.92 (0.83–1.02)	126 (115–136)	105 (103–108)	1.10 (1.01–1.20)
Moderate	604 (536–673)	659 (632–685)	0.89 (0.79–1.01)	172 (152–193)	172 (164–179)	1.06 (0.94–1.20)
Severe	673 (574–771)	771 (726–815)	0.86 (0.74–1.01)	198 (168–229)	196 (183–210)	1.04 (0.88–1.23)
Very severe	665 (570–760)	993 (926–1059)	0.79 (0.68–0.93)	225 (189–260)	260 (236–284)	1.03 (0.85–1.24)
Comorbidity with immune dysregulation						
Yes	517 (449–585)	576 (538–613)	0.85 (0.73–0.98)	150 (131–170)	136 (126–146)	1.01 (0.87–1.18)
No	540 (504–576)	535 (524–546)	0.90 (0.84–0.97)	154 (144–164)	121 (119–124)	1.11 (1.03–1.18)
Immunosuppressive drugs[b]						
Yes	427 (293–561)	646 (574–719)	0.62 (0.44–0.87)	130 (82–179)	149 (124–175)	0.75 (0.49–1.15)
No	337 (290–385)	336 (321–351)	0.87 (0.75–1.01)	129 (109–149)	107 (101–113)	0.98 (0.83–1.16)
Setting of herpes zoster diagnosis[c]						
Inpatient	469 (405–534)	421 (401–441)	0.98 (0.84–1.13)	148 (127–170)	110 (105–116)	1.09 (0.93–1.27)
Outpatient clinic	388 (304–471)	411 (382–439)	0.89 (0.70–1.11)	124 (95–152)	103 (95–111)	1.02 (0.80–1.31)
Emergency room	296 (207–384)	345 (314–376)	0.76 (0.56–1.04)	107 (78–136)	89 (81–98)	1.05 (0.78–1.40)
Severity of herpes zoster						
Uncomplicated	531 (494–568)	549 (537–562)	0.86 (0.80–0.92)	157 (147–168)	123 (120–125)	1.10 (1.02–1.18)
Complicated	545 (482–609)	508 (488–528)	0.97 (0.86–1.10)	141 (125–158)	122 (117–126)	1.06 (0.94–1.21)
Extent of herpes zoster						
Localised	531 (498–565)	544 (533–555)	0.87 (0.81–0.93)	153 (144–162)	122 (120–125)	1.08 (1.01–1.15)
Disseminated	569 (460–677)	486 (454–517)	1.18 (0.96–1.44)	158 (125–191)	123 (115–132)	1.21 (0.97–1.51)

Abbreviations: CI = confidence interval; MRR = mortality rate ratios; PY = person-years.

[a]Mortality rate ratios were calculated with Cox proportional hazard regression adjusting for the same set of variables (age at diagnosis, sex, Charlson Comorbidity Index level, cancer stage and calendar period at cancer diagnosis) in each stratified analysis.

[b]Restricted to cancer diagnoses made in 2005 or later because of the availability of prescription data. See Supplementary Material for a list of included drugs.

[c]Restricted to herpes zoster patients diagnosed in 1995 or later and their corresponding matched cancer cohort members because of the availability of outpatient clinic and emergency room diagnoses.

but because major determinants of treatment choice (i.e., age, stage and comorbidity) were included, we do not believe that it had major impact on our results. However, residual confounding because of missing information on stage is possible, in particular for haematological cancers. Nevertheless, inclusion of this variable in the model did not suggest that it was a major confounder.

Because the observed association depended on HZ severity, our findings may not be applicable to mild HZ treated in general practice. Furthermore, members of the comparison cohort may have had HZ treated in general practice, possibly resulting in bias towards the null. Misclassification in subgroups of severity and extent of HZ is another limitation as some ICD-8 codes are unspecific. Because we grouped such codes as uncomplicated and localised, it cannot explain the increased MRRs observed for disseminated HZ.

Finally, we performed several subgroup analyses, which may have resulted in some spurious findings. However, the particularly increased MRRs found for the youngest age group and disseminated HZ were consistent for both haematological and immune-related cancers.

In conclusion, hospital-based HZ did not predict increased mortality of subsequent cancer except in patients with haematological or immune-related cancer, particularly among patients aged <60 years and those with disseminated infection.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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