ACTA ONCOLOGICA
2023, VOL. 62, NO. 12, 1653–1660
https://doi.org/10.1080/0284186X.2023.2270145

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ORIGINAL ARTICLE

Impact of multimorbidity and polypharmacy on mortality after cancer: a nationwide registry-based cohort study in Denmark 2005–2017

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ABSTRACT

Background: Concurrent chronic diseases and treatment hereof in patients with cancer may increase mortality. In this population-based study we examined the individual and combined impact of multimorbidity and polypharmacy on mortality, across 20 cancers and with 13-years follow-up in Denmark.

Materials and Methods: This nationwide study included all Danish residents with a first primary cancer diagnosed between 1 January 2005 and 31 December 2015, and followed until the end of 2017. We defined multimorbidity as having one or more of 20 chronic conditions in addition to cancer, registered in the five years preceding diagnosis, and polypharmacy as five or more redeemed medications 2–12 months prior to cancer diagnosis. Cox regression analyses were used to estimate the effects of multimorbidity and polypharmacy, as well as the combined effect on mortality.

Results: A total of 261,745 cancer patients were included. We found that patients diagnosed with breast, prostate, colon, rectal, oropharynx, bladder, uterine and cervical cancer, malignant melanoma, Non-Hodgkin lymphoma, and leukemia had higher mortality when the cancer diagnosis was accompanied by multimorbidity and polypharmacy, while in patients with cancer of the lung, esophagus, stomach, liver, pancreas, kidney, ovarian and brain & central nervous system, these factors had less impact on mortality.

Conclusion: We found that multimorbidity and polypharmacy was associated with higher mortality in patients diagnosed with cancer types that typically have a favorable prognosis compared with patients without multimorbidity and polypharmacy. Multimorbidity and polypharmacy had less impact on mortality in cancers that typically have a poor prognosis.

ARTICLE HISTORY
Received 15 September 2023
Accepted 4 October 2023

KEYWORDS
Mortality; multimorbidity; polypharmacy; prognosis

Introduction

Ageing populations are leading to increasingly challenging disease management across health system sectors [1,2]. Cancer treatment is complex in itself, but multimorbidity and polypharmacy further increases complexity [3]. Across the 20 most prevalent cancers in Denmark, Loeppentin et al. found that more than half of new cancer patients presented with one or more chronic diseases at the time of cancer diagnosis and one-third fulfilled criteria for polypharmacy (≥5 concurrent drugs) [4].

The most prevalent conditions in newly diagnosed cancer patients are well-known chronic conditions in the populations of industrialized countries, including cardiovascular disease, chronic obstructive pulmonary disease, diabetes, stroke and depression and anxiety disorders. Likewise, common pharmacological treatments in cancer patients mirror these diagnoses and include antihypertensives, anti-thrombotic agents, anti-hyperlipidemic agents, analgesics and diuretics [4]. Survival in cancer patients is strongly affected by tumor stage, genotype of the cancer and phenotypic characteristics of the patient, however, studies of individual cancer types have found that entering the cancer trajectory with concurrent multimorbidity and polypharmacy may also impact mortality [5–10]. A review on multimorbidity in patients with breast-, lung- and colon cancer, found that postoperative complications and mortality was higher in patients with comorbidities, even though having comorbidity did not seem to be linked to differences in tumor biology or aggressiveness [11]. The existing literature are limited by studies covering only a single cancer diagnosis, only advanced stage cancer [12] or early stage cancer [7,8,13], or only elderly cancer patients [14–16], studying a few selected comorbidities [7–9,13,17–20] or exclusively focusing on polypharmacy in

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/0284186X.2023.2270145.

isolation [21]. Thus, no comprehensive study including all major cancers and multiple comorbid conditions and pharmaceutical treatments has been reported before. Therefore, we aimed to estimate the effect of multimorbidity and polypharmacy on mortality in patients diagnosed with the 20 most common cancers in Denmark. We included 131 different comorbidities and redeemed drugs in this nationwide, population-based cohort study.

Materials and methods

Setting

The Danish healthcare system is characterized by a tax-paid health system with a universal coverage and central registration of healthcare use and expenses. The national Civil Registration System (CRS) assigns a unique 10-digit number to all residents in Denmark since 1968, which enables linkage between national registries [22].

Data sources

To identify the study cohort of cancer patients, we retrieved data from The Danish Cancer Registry, which was established in 1943 and includes diagnosis of all cancers diagnosed in Denmark [23].

We identified the comorbid conditions in the Danish National Patient Registry (DNPR), which was established in 1977, and contains the diagnoses for all somatic and psychiatric inpatient hospital admissions and, from 1995, all outpatient visits [24]. We obtained information on redeemed drug prescriptions from the Danish National Prescription Registry, which was established in 1995 and contains information on all prescription drugs dispensed at Danish community pharmacies, including for nursing home residents [21,25]. We used the Civil Registration System (CRS) [26], to link information across the included registries and identify the date of death or emigration.

Study cohort and design

We included all citizens $\geq$18 years and living in Denmark five years before the diagnosis of a first primary cancer from 1 January 2005 to 31 December 2015. We selected the 20 most prevalent cancer diagnoses in Denmark [4] using the International Classification of Diseases, 10th Revision (ICD-10). We combined brain cancer and central nervous system (CNS) tumors because of the small numbers of cases, leaving the following 19 groups for analysis: cancer of the breast (C50), or cancer in the lung (C34), prostate (C61), colon (C18), rectal (C19, C20), oesophagus (C15), stomach (C16), oropharynx (C10), liver (C22), pancreas (C25), bladder (C67), kidney (C64), uterus (C54), cervix (C53), ovary (C56), brain and central nervous system (C70–C72) as well as malignant melanoma (C43), non-Hodgkin lymphoma (C85), and leukaemia (C90–C95). All cancer patients were followed from date of diagnosis until date of death, migration, disappearance or end of follow-up at 31 December 2017 (3 to 13 years), whichever came first.

Multimorbidity and polypharmacy

As there are no international gold standard definitions or measures of multimorbidity or polypharmacy [27], we defined them from the literature and on clinical considerations. Following Ording & Sørensen, 2013, we defined multimorbidity as two or more coexisting conditions [1], in this case, multimorbidity was one or more chronic condition *in addition to* the cancer diagnosis.

We combined diseases identified in a systematic review of 39 studies of comorbidity indices, ranging from 4 to 102 (mean = 18) diseases included [27], with the following clinical criteria for multimorbidity:

- a chronic disease, thus excluding acute diseases such as pneumonia and conditions considered risk factors for diseases such as hypertension *and*
- temporal relevance for the cancer course, thus diagnosed within 5 years prior to the cancer diagnosis.

Multimorbidity was defined as hospitalization for one or more of 20 disease groups according to the International Classification of Diseases 10th Revision (131 specific diagnoses), in addition to specific drugs dispensed for these diseases when treated outside hospitals (Supplementary Table 1).

We defined polypharmacy as five or more different medications [25,28], and applied the following criteria for included drugs:

- temporal importance for the treatment of cancer and thus prescribed and redeemed within 2–12 months before the cancer diagnosis and
- in long-term use, thus medications that were redeemed at least twice

We included 90 different redeemed drugs from the following Anatomical Therapeutic Chemical (ATC) chapters: A, alimentary tract and metabolism (drugs for diabetes, antiemetics and other conditions); B, blood and blood-forming organs (anti-thrombotic and other haematological drugs); C, cardiovascular system (drugs for cardiac disease, hypertension and hyperlipidaemia, and anti-diuretic drugs); D, dermatological conditions; G, genitourinary system and reproductive hormones; H, systemic hormonal preparations, except reproductive hormones and insulin; J, systemic antibiotics; L, antineoplastic and immunomodulating agents; M, musculoskeletal system (anti-inflammatory and anti-rheumatic drugs); N, nervous system (analgesics, antiepileptic and anti-parkinsonism drugs, antipsychotics and antidepressants), P, insecticides and repellents; R, respiratory system; S, sensory organs (Supplementary Table 2).

More details on variable definitions are provided in our earlier publication on burden of disease in cancer patients [4].

Table 1. Study cohort characteristics according to age group, sex, cancer type, morbidity and drug prescriptions.

			Comorbidity				Polypharmacy			
			Number of comorbidities		More than 2 comorbidities		Prescriptions per patient		Polypharmacy (+5 drugs)	
		N	Mean	SD	n	Percent	Mean	SD	n	Percent
Total		261745	1.05	1.31	71571	(27.3 %)	6.40	5.22	147544	(56.4 %)
Sex	Male	129342	1.09	1.32	37067	(28.7 %)	6.24	4.98	72713	(56.2 %)
	Female	132403	1.01	1.29	34504	(26.1 %)	6.56	5.44	74831	(56.5 %)
Age group (years)	<55	42139	0.45	0.81	3875	(9.2 %)	3.71	3.77	12775	(30.3 %)
	55-65	61713	0.79	1.10	12033	(19.5 %)	5.26	4.68	28765	(46.6 %)
	65-75	84077	1.10	1.30	24381	(29.0 %)	6.66	5.10	50537	(60.1 %)
	75-85	56245	1.49	1.48	23059	(41.0 %)	8.39	5.50	41403	(73.6 %)
	85+	17571	1.69	1.53	8223	(46.8 %)	9.21	5.47	14064	(80.0 %)
Cancer type	Breast cancer	47262	0.80	1.14	9358	(19.8 %)	5.41	4.91	22119	(46.8 %)
	Lung cancer	39815	1.52	1.48	16603	(41.7 %)	8.36	5.79	28468	(71.5 %)
	Prostate cancer	4231	0.89	1.16	948	(22.4 %)	5.81	4.57	2259	(53.4 %)
	Colon cancer	27025	1.15	1.37	8297	(30.7 %)	6.73	5.21	16242	(60.1 %)
	Rectal cancer	14617	0.91	1.22	3406	(23.3 %)	5.42	4.61	7162	(49.0 %)
	Oesophagus cancer	4263	1.26	1.43	1428	(33.5 %)	6.82	5.11	2617	(61.4 %)
	Stomach cancer	5178	1.22	1.38	1698	(32.8 %)	7.11	5.23	3278	(63.3 %)
	Oropharynx cancer	973	1.09	1.37	275	(28.3 %)	5.62	4.60	488	(50.2 %)
	Liver cancer	331	1.98	1.61	179	(54.2 %)	8.80	5.87	245	(74.1 %)
	Pancreas cancer	8719	1.34	1.41	3191	(36.6 %)	8.28	5.68	6304	(72.3 %)
	Bladder cancer	8134	1.22	1.37	2668	(32.8 %)	7.24	5.31	5238	(64.4 %)
	Kidney cancer	6552	1.23	1.41	2156	(32.9 %)	7.49	5.46	4357	(66.5 %)
	Uterine cancer	7153	0.91	1.19	1645	(23.0 %)	6.32	4.91	4099	(57.3 %)
	Cervical cancer	3789	0.59	1.03	508	(13.4 %)	4.47	4.21	1421	(37.5 %)
	Ovarian cancer	4996	0.86	1.19	1074	(21.5 %)	6.35	5.19	2793	(55.9 %)
	Malignant melanoma	19007	0.62	1.03	2832	(14.9 %)	4.40	4.34	7147	(37.6 %)
	Brain & CNS cancer	4361	0.97	1.16	1086	(24.9 %)	5.27	4.74	2037	(46.7 %)
	Non-Hodgkin lymphoma	313	1.04	1.28	87	(27.7 %)	6.68	5.21	186	(59.4 %)
	Leukaemia	11151	1.09	1.30	3245	(29.1 %)	6.93	5.31	6802	(61.0 %)

Abbreviations: SD:standard deviation.

Statistical analyses

Initially, we examined the prevalence of multimorbidity and polypharmacy using descriptive statistics (mean, standard deviation (SD) and proportion). For each cancer type separately, we estimated hazard ratios (HRs) with 95% confidence intervals (CIs) of multimorbidity or polypharmacy on the hazard of death while considering variations over time, modelled as a continuous function of time using restricted cubic splines in Cox proportional hazards models, shown graphically. Baseline hazards were adjusted for age group at cancer diagnosis and sex. As the assumption of proportional hazards was violated in several analyses (i.e., the effect of multimorbidity varied according to time since diagnosis), we split the follow-up time in four-time bands (0–1, 1–2, 2–5, 5+ years after diagnosis) allowing different exposure effects in each time band. We further estimated HRs with 95% CIs for combinations of multimorbidity and polypharmacy, respectively and hazard of death using time since cancer diagnosis as the underlying time scale. To illustrate the absolute impact on survival, we examined the association between multimorbidity and polypharmacy and risk of death estimating the restricted mean survival time at five and ten years after cancer diagnosis. Pseudo observations [29] were used in regression model for the restricted mean survival time to estimate the effect of multimorbidity and polypharmacy respectively, adjusted for sex and age group (<55, 55-69, >70) at cancer diagnosis. The analyses were performed using Stata version 14.2.

Results

In total, 261,745 incident cancer patients were included in this study (Table 1). On average, they had 1.05 (SD 1.31) preexisting diseases at the time of cancer diagnosis, which increased with age. A proportion of 27.3% had more than two comorbidities at the time of cancer diagnosis. The mean number of preexisting diseases ranged from 0.59 in patients with cervical cancer to 1.98 in patient with liver cancer. The mean number of prescriptions in the 2–12 months before cancer diagnosis was 6.40 (SD 5.22), and 56.4% fulfilled the criteria for polypharmacy in this period (+5 drugs), but this ranged from 30.3% in persons <55 years to 80.0% in those 85+ years.

Overall, multimorbidity and polypharmacy at the time of cancer diagnosis were associated with decreased survival (Supplementary Table 3). We identified two different patterns according to the type of cancer and the time since diagnosis; for some cancers preexisting multimorbidity and polypharmacy were associated with increased mortality, while for other cancers they had a limited effect in the short term. Figures 1 and 2 shows these patterns for a sample of the included cancers.

Pre-existing multimorbidity and polypharmacy was associated with higher mortality in certain cancers

For cancers that typically have a favorable prognosis, exemplified by breast, prostate, and colon cancer, multimorbidity and polypharmacy at diagnosis were associated with higher

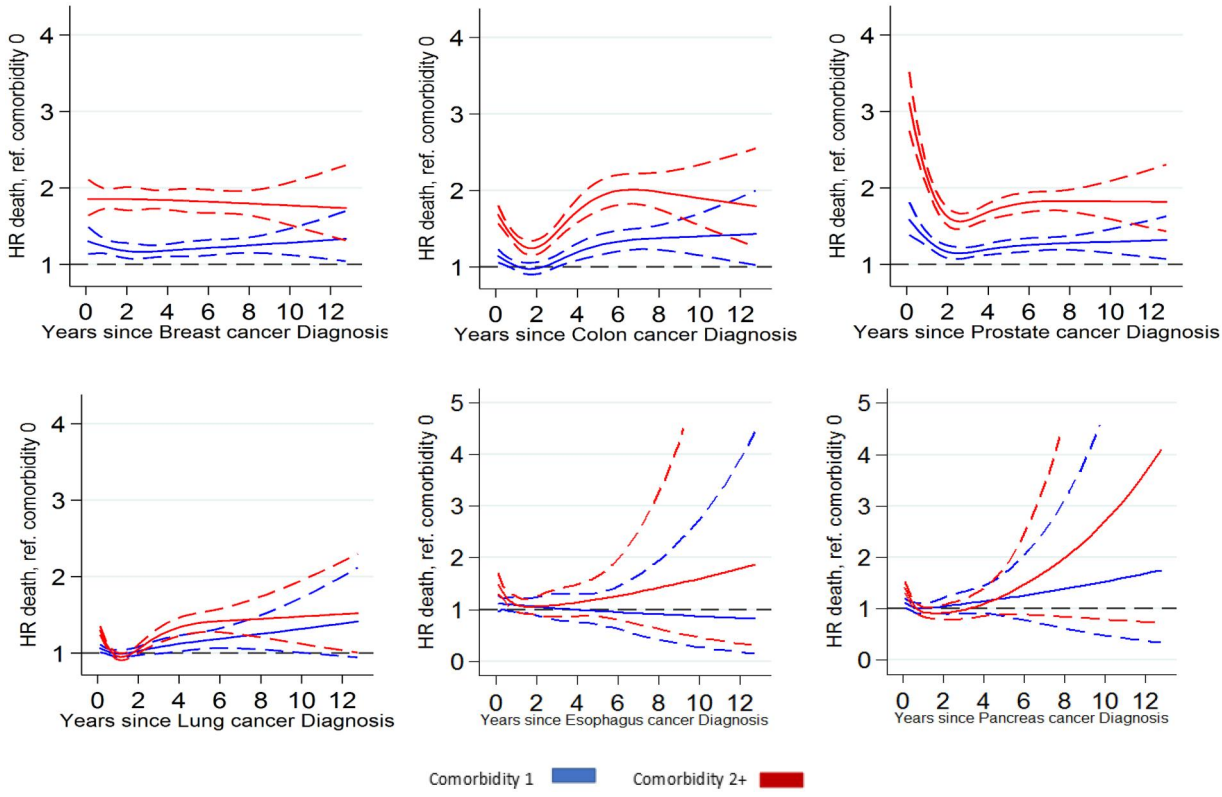

Figure 1. Hazard ratios by time since diagnosis for hazard of death according to comorbidity versus no comorbidity.
Note: adjusted for age at diagnosis and sex

mortality compared with patients with no multimorbidity or polypharmacy (Figures 1 and 2). The mortality increased as the number of chronic conditions increased (Figure 1). The same pattern was seen for polypharmacy (Figure 2). Patients with both multimorbidity and polypharmacy had the highest hazard of death throughout follow-up for, e.g., patients with colon, breast and prostate cancer, whereas, mortality was similar for combinations of multimorbidity/polypharmacy in the years after diagnosis (Supplementary Figure 1). Breast and prostate cancer patients with more than two pre-existing comorbidities had quite similar increased mortality with an HR; of 1.84 (95% CI; 1.76 – 1.92) and HR 1.86 (95% CI 1.79 – 1.39), respectively (Supplementary Table 3). Breast cancer patients followed up to five years after cancer diagnosis, and with two or more chronic conditions survived on average 127 days shorter (95% CI −140 to −115 days) than those without chronic conditions (Figure 3). The same pattern was seen in patients with prostate cancer, with those having two or more chronic conditions on average lost 178 days i.e. nearly 6 months of reduced survival during the first five years (95% CI −191 to −164 days) compared with prostate cancer patients with no chronic conditions (Figure 4).

In some cancers, pre-existing comorbidity and polypharmacy had limited effect in the short term

For cancers that typically have a poor prognosis, exemplified by lung, esophagus, and pancreas cancer in Figures1 and 2, multimorbidity and polypharmacy at cancer diagnosis had limited short-term impact on mortality and even with the presence of more than two comorbidities or polypharmacy mortality only increased slightly. For patients with these cancer types, the impact of multimorbidity and polypharmacy was strongest more than five years after diagnosis (Figures 1 and 2). In patients with lung, esophagus, and pancreas cancer the impact of multimorbidity was more pronounced more than 5 years after diagnosis, as illustrated in HRs close to a 50% increased mortality up to five years after cancer diagnosis (HR, 1,52; 1,47; 1,50, respectively) (Supplementary Table 3).

Discussion

In this nationwide cohort of Danish patients with a primary cancer, we observed that preexisting multimorbidity and polypharmacy associated variably with mortality. Thus, multimorbidity and polypharmacy in patients diagnosed with a cancer that typically have a favorable prognosis was associated with higher mortality. Concurrently, multimorbidity and polypharmacy had less impact on mortality in cancers that typically have a poor prognosis. Specifically, multimorbidity and use of many drugs was associated with shorter survival in cancers with relatively favorable prognoses, i.e., breast, prostate, colon, rectal, oropharynx, bladder, uterine and cervical cancer, malignant melanoma, non-Hodgkin lymphoma, and leukemia. The large decreases or increases after many years of follow-up observed for some cancers, hold considerable insecurity due to diminishing numbers, especially for cancers with low survival.

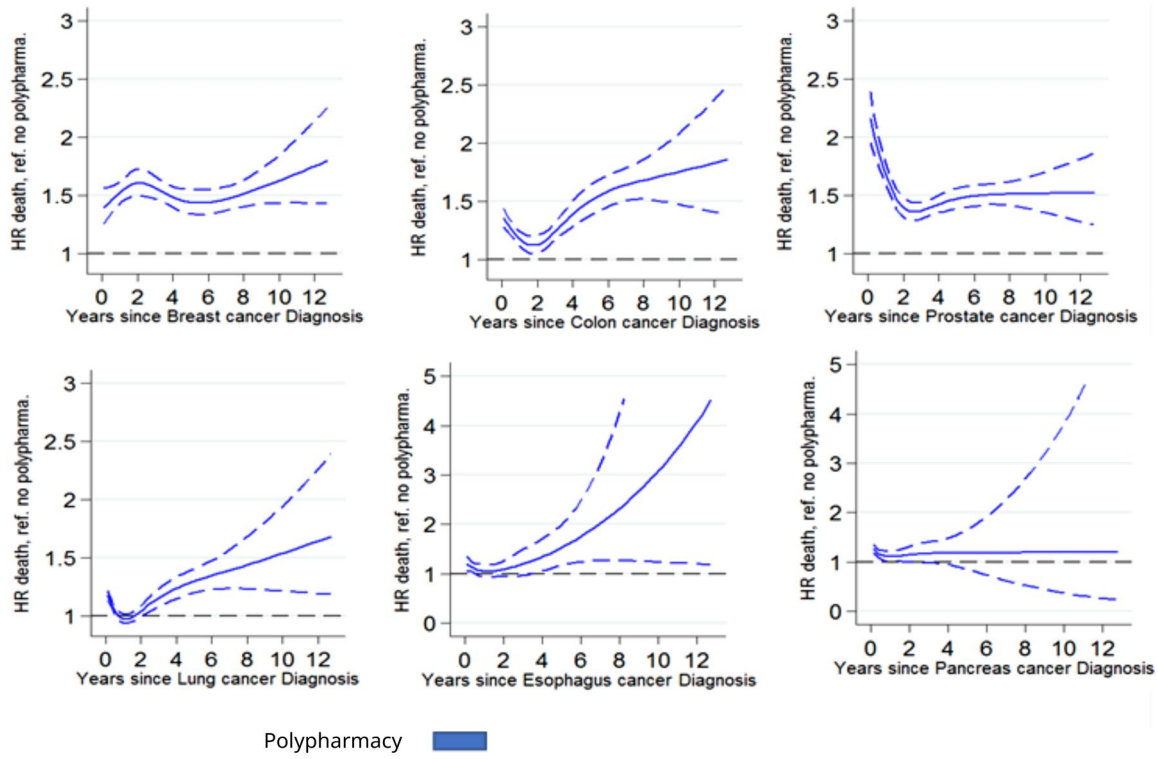

Figure 2. Hazard ratios with 95% confidence intervals by time since diagnosis for hazard of death according to polypharmacy versus no polypharmacy.

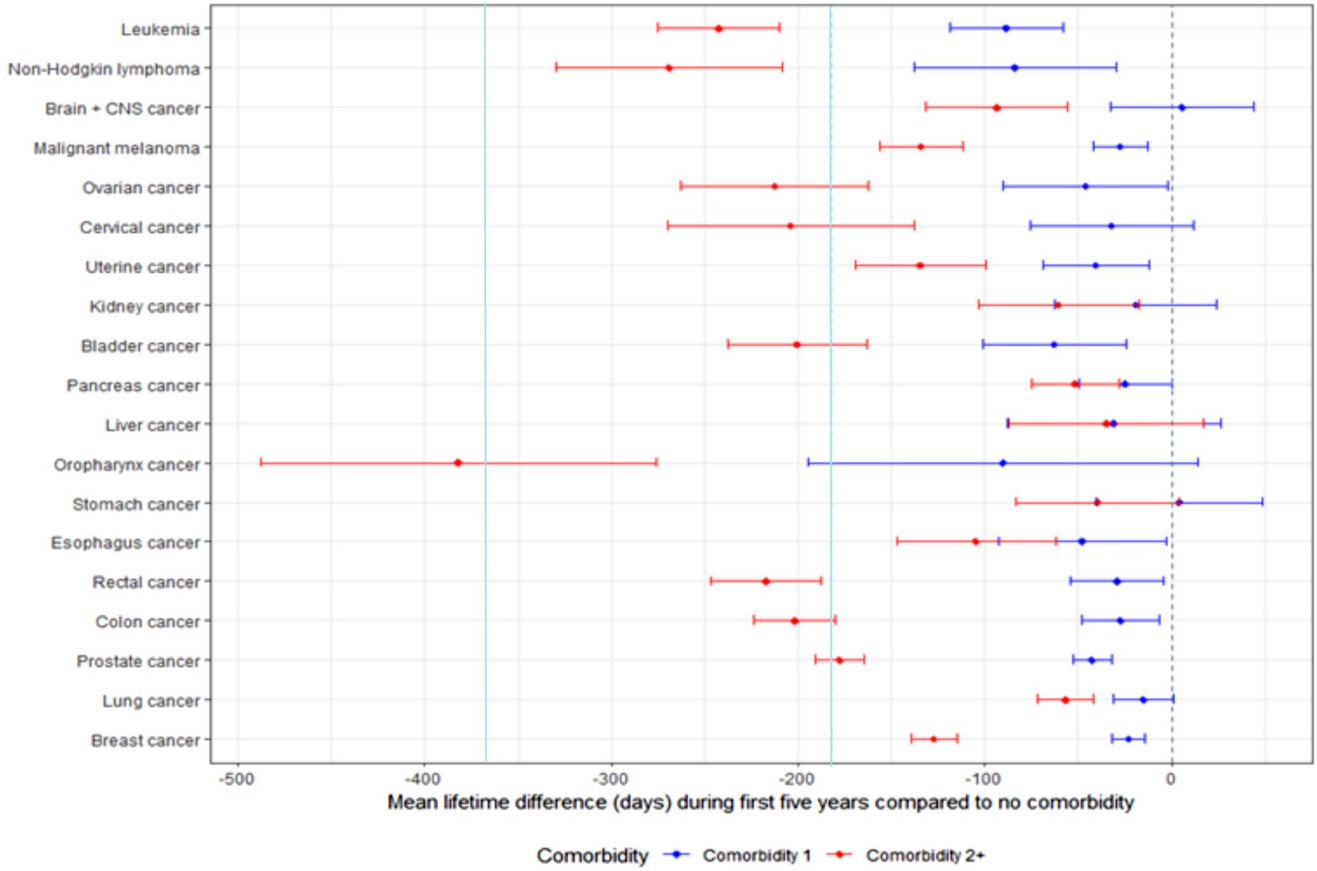

Figure 3. Days of life lost in the first five years after cancer diagnosis according to comorbidity versus no comorbidity, restricted mean survival time analysis.

Our results show that in some cancers multimorbidity and polypharmacy had limited impact on mortality which are partially in line with that reported by Read et al. [30] who found that comorbidity is most important when the tumor has little impact on patient survival. Together, these findings indicate that patients with an unfavorable cancer phenotype

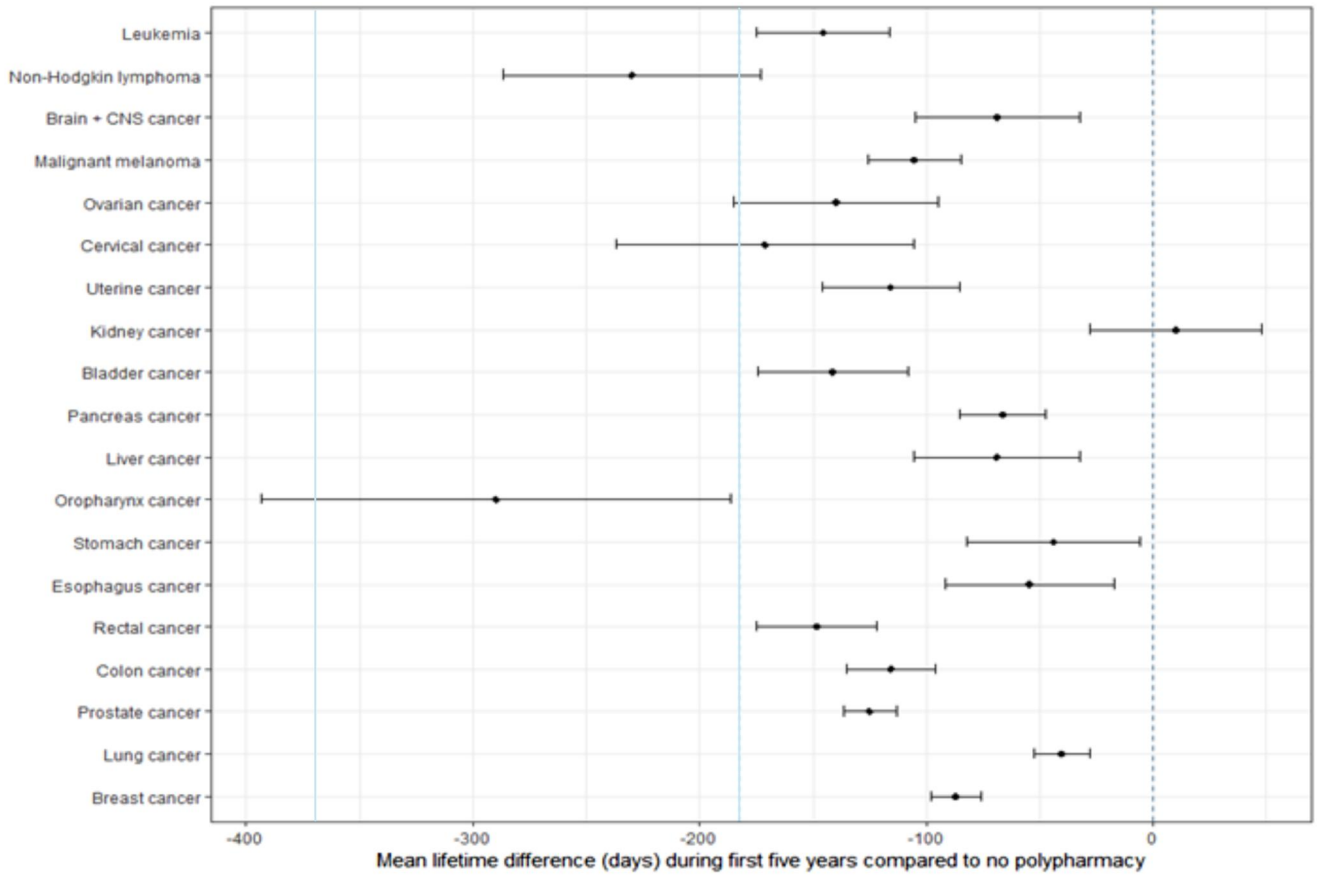

Figure 4. Days of life lost in the first 5 years after cancer diagnosis according to polypharmacy versus no polypharmacy, restricted mean survival time analysis.

or high tumor burden are characterized by having such a short remaining lifetime that neither multimorbidity nor polypharmacy has time to impact mortality.

The present study does not reveal the reasons for the increased mortality in patients with multimorbidity and cancer of the breast, prostate, colon, rectal, oropharynx, bladder, uterine and cervical cancer, malignant melanoma, Non-Hodgkin lymphoma, and leukemia. This finding may be explained by a number of mechanisms. Increasing research at both molecular and epidemiological level has shown that diseases progress and co-occurs due to underlying pathological mechanisms [31]; malfunctioning immune system and low-grade inflammation may impact mortality in several of cancers including gastrointestinal cancer, liver cancer, lung cancer and pancreatic cancer [32, 33], as well as conditions within the cardiovascular and metabolic system, i.e., hypertension, hyperglycemia and dyslipidemia [34], type 2 diabetes [35], chronic kidney disease [36], depression [37,38], and autoimmune diseases [39] which are all conditions existing in the present study population.

Other mechanisms may include a lower tolerance for the cancer treatment or less aggressive cancer treatment provided to these patients [8,9]. Thus, results from a population-based study of 6340 prostate cancer patients showed, that patients with comorbidity less frequently received aggressive treatment, and had poor survival compared with patients without comorbidity [5]. Lifestyle factors may furthermore represent an underlying mechanism. It is well-known that smoking causes damage to multiple organs contributing to lung cancer, chronic obstructive pulmonary disease, and cardiovascular disease [40] thereby establishing a cluster of diseases caused by the same factor leading to poorer survival.

The strengths of this study include the inclusion of both multimorbidity and polypharmacy, making it possible to document these coherent factors' association with mortality. The study includes register-based data and covers all Danish residents including 20 prevalent cancers, which makes the results generalizable to a large proportion of cancer patients. Furthermore, the data were compiled independent of social position as they were retrieved from nationwide health registries in which they were entered for administrative reasons also minimizing recall, selection, and information bias. We included a range of comorbidities and redeemed medication that makes it possible to present a comprehensive selection of comorbidities and drug use in cancer patients. Alternatively, a weighted index, such as Charlson Comorbidity Index [41], could have been employed to quantify the degree of multimorbidity. However, a simple count of concurrent diseases is a more precise assessment of multimorbidity and is in line with the definition [1].

However, administrative data may also have missing data or inaccurate information, although such misclassification is likely to be non-differential. Comorbidities were counted as a number of disease categories (out of the 20 defined), and it is true that patients may have more individual diagnoses within one category and still be classified as having one comorbidity. This is not an issue for, e.g., diabetes, but may cause some misclassification of the number of comorbidities

for, e.g., mental disorders. We did not include data on cause-specific mortality, however, cause-specific mortality is only available through death certificates and as less than 10% are autopsied the validity of the cause of death is minimal [42].

We did not have information of the patient's treatment and also lacked information on the severity of chronic conditions, which could have had an impact on mortality. Although polypharmacy is not necessarily inappropriate, it increases the risk of drug-drug interactions, adverse events, and hospitalization [28], and as such may impact survival.

Our results underscore the need to identify and handle comorbidities and polypharmacy throughout the course of cancer treatment and in cancer survivors.

Conclusion

In conclusion, we report that for a number of cancers that typically have a favorable prognosis, multimorbidity and polypharmacy at the time of cancer diagnosis are associated with increased mortality compared with cancer patients without multimorbidity and polypharmacy. However, multimorbidity and polypharmacy had less impact on mortality in cancers with poor prognosis.

Acknowledgment

The study was funded by the Capital Region of Denmark and the Agency for Digitalization

Ethical approval

The national register linkage was approved by the Danish Data protection agency (jr. nr. 2017-41-5054)

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The data are stored in a database at Statistics Denmark. According to Danish legislation, the data used in this study cannot be shared as they are derived from nationwide registers.

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