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Preventive drugs in the last year of life of older adults with cancer: is there room for deprescribing?

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Preventive drugs in the last year of life of older adults with cancer: is there room for deprescribing?

Running head: *Preventive drugs at the end of life*

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Abstract

Background: The continuation of preventive drugs for older patients with advanced cancer has come under scrutiny since these drugs are unlikely to achieve their clinical benefit during the patients' remaining lifespan.

Patients and methods: nationwide cohort study of older adults (≥65 years) with solid cancer who died between 2007 and 2013 in Sweden, using routinely collected data with record linkage. We calculated the monthly utilization and cost of preventive drugs throughout the last year before death.

Results: Among 151 201 older patients who died with cancer (mean age 81.3 [SD, 8.1] years), the average number of drugs increased from 6.9 to 10.1. Preventive drugs were frequently continued until the final month of life, including antihypertensives, platelet aggregation inhibitors, anticoagulants, statins, and oral antidiabetics. Median drug costs amounted to $1482 (interquartile range [IQR] $700–$2896]) per person, including $213 (IQR $77–$490) for preventive therapies. Compared to older adults who died with lung cancer ($205, IQR $61–$523), costs for preventive drugs were higher among older adults who died with pancreatic cancer (adjusted median difference [AMD] $13, 95% CI $5–$22), or gynecological cancers (AMD $27, 95% CI $18–$36). There was no decrease in the cost of preventive drugs throughout the last year of life.

Conclusion: preventive drugs are commonly prescribed during the last year of life of older adults with cancer and are often continued until the final weeks before death. Adequate deprescribing strategies are warranted to reduce the burden of drugs of limited clinical benefit near the end of life.

Keywords: palliative care; end-of-life; drug prescribing; deprescribing

Introduction

In high-income countries, people aged 70 years and older now account for almost two-thirds of cancer-related deaths.[1] Chronic multimorbidity has thus become the norm rather than the exception in oncology[2], and is associated with poorer chances of survival and with a higher burden of functional impairments and physical symptoms.[3] Multimorbidity also comes with a higher burden of long-term pharmacological treatments. In the United States and in Europe, about 40% of people aged 65 years or older use 5 or more drugs concomitantly.[4,5] This polypharmacy is particularly problematic among older people with advanced cancer[6], since the potential to develop serious drug–drug interactions is amplified by the use of anticancer agents and complementary medicines.[7,8] Moreover, the probability of experiencing adverse drug reactions increases because the main pharmacokinetic parameters are affected not only by age but also by the physiological impact of cancer (e.g. modified drug absorption due to gastrointestinal symptoms or to impairments in the gut wall function, decrease in the volume of distribution caused by weight loss, renal impairment due to the nephrotoxicity of chemotherapy).[9,10]

Beyond pharmacology, polypharmacy in the context of advanced cancer also raises important questions from a clinical and ethical viewpoint. As cancer progresses and prognosis worsens, the net benefit of each additional medicine gradually decreases while the risk of harm increases. This "law of diminishing returns" makes the continuation or initiation of long-term treatments particularly questionable for older patients with advanced cancer. Preventive drugs are prescribed either to avert or delay the onset of a disease among individuals who are considered at high risk of developing that disease in the future (*primary prevention*), or to avoid the recurrence of a condition that the patient experienced in the past (*secondary prevention*). These drugs typically need several years before the physiological and biological changes that they produce translate into measurable and clinically meaningful health outcomes. Thus, the time-until-benefit of preventive agents is often much longer than the remaining lifespan of older adult with serious illness.[11] Recent randomized controlled trials show that lipid-lowering medications can safely be deprescribed among older adults with limited life expectancy, and that the discontinuation of antihypertensives among individuals without cardiovascular disease is safe

in the short term.[12,13] Other long-term treatments such as bisphosphonates retain their effect 3 to 5 years after their withdrawal.[14] Nevertheless, a handful of observational studies have reported that preventive medications are prescribed during the last year of life of patients with life-limiting disease, and have cast doubt upon the benefit of these treatments.[15] There is limited investigation to date of the continuation and discontinuation of medications throughout the last months of life and with little information about the costs of these medications and about potential variation across cancer types. The aim of the current study was therefore to evaluate the prescribing of preventive drugs throughout the final year of life of older adults who died with cancer across Sweden, and to estimate the direct costs of preventive drugs.

Methods

Study design and data

This was a retrospective cohort study based on routinely collected data in Sweden, a country with a universal healthcare system. Data from the National Cause of Death Register were linked through deterministic matching to the Total Population Register, the National Patient Register, the Swedish Prescribed Drugs Register, the Social Services Register, and the Swedish Register of Education. The Regional Ethical Review Board in Stockholm approved the study.

Study population

We included older adults aged ≥65 years who died in Sweden between 2007 and 2013, as these were the most recent available data. Decedents were considered as eligible for inclusion if a diagnosis of solid cancer (International Classification of Diseases [ICD], 10th revision codes C00–C76 and C80) was reported either in a hospital discharge report during the last 2 years of life, or as an underlying or contributing cause of death. We decided *a priori* to exclude decedents with missing cause of death, those with missing drug prescription history throughout the last 6 months of life, and those who remained hospitalized continuously during the last 3 months before death. Older adults with concomitant hematological malignancies (ICD-10 codes C81–C95) were also excluded, in order to select a homogenous population of individuals diagnosed only with solid cancer. Previous studies have indeed shown that persons with hematological malignancies experience a rapid functional decline at the end of life, which makes survival prediction particularly challenging. The potential for cure until late in the course of the disease trajectory differentiates these older patients from those dying with solid cancer.[16,17]

Outcomes

Utilization and cost of preventive drugs during the last 12 months of life were the main study outcomes. Preventive drugs with questionable benefit near the end of life have been identified in a recent

systematic review of the literature[15], and include drugs for diabetes, vitamins, mineral supplements, antithrombotic agents, antihypertensives, statins, bisphosphonates, and medications for chronic anemia. The list of corresponding Anatomical Therapeutic Chemical (ATC) classification codes is available in Supplementary eTable 1.

We computed monthly exposure to specific drug classes based on data from the Swedish Prescribed Drugs Register, which contains detailed information about all prescription drugs delivered in community pharmacies in Sweden since 2005 (including drugs dispensed to nursing home residents, at the exception of a few facilities with their own drug storeroom). Methods for constructing periods of drug exposure have been presented in detail elsewhere [5,18], and are illustrated in eFigure 1A. *Continuation* of preventive drugs was calculated as the proportion of older adults who were still using preventive drugs during the last month before death among those exposed one year before, while *initiation* was calculated the proportion of older adults who started using preventive drugs during the last year of life. Drug costs were estimated through a two-step approach, as described in eFigure 1B. We first divided the total cost of each purchase by the number of days covered to obtain the average daily cost. Second, we multiplied this average daily cost by the expected number of days of exposure during a given month, which allowed for distributing drug costs according to the assumed length of exposure. This approach provides a more realistic estimate of the costs, instead of artificially concentrating all expenditures at the purchase date. Drug costs were standardized using the harmonized index of consumer prices (HICP) with 2013 as reference year in order to correct for inflation over time and were then converted from the Swedish currency SEK into US dollars (USD) based on the European Central Bank average exchange rate from 1 January to 31 December 2013 to facilitate international comparisons (1 SEK = 0.1535 USD).

Assessment of individual characteristics

Sex and date of birth were extracted from the Total Population Register and cross-validated with data reported on study participants' death certificates. We categorized solid malignancies into 14 distinct locations. Details about the corresponding ICD-10 codes are presented in eTable 2. The overall burden

of chronic multimorbidity was measured with a recently validated tool that captures a set of 60 distinct chronic diseases based on different data sources (contributing causes of deaths, inpatients and outpatients diagnoses reported during the last 3 years of life, and specific drugs unequivocally linked to chronic conditions).[19] Living arrangement at time of death was defined as "community" or "nursing home", while the place of death was reported as either "hospital" or "usual place of living". The decedents' level of education was categorized into "primary", "secondary", and "tertiary" education in accordance with the International Standard for Classification of Education.

Statistical analysis

Multivariable quantile regressions were used to model drug costs across different cancer types, while controlling for sex, age, number of chronic diseases, living arrangement, and level of education. While linear regression allows for modeling the mean of an outcome, quantile regression is used to model quantiles of the outcome when the distribution of the outcome is highly skewed.[20] Beta coefficients obtained from quantile regression models can be interpreted as the adjusted median difference (AMD) in costs compared with the reference group, and are reported together with their 95% CIs. We compared the results with estimates drawn from generalized linear models with log link function and gamma distribution, to ensure that the average median effects reported in our study are concordant (in both direction and magnitude) with average mean effects.[21] Variations in the cost of preventive drugs were then represented graphically in a series of contour graphs plotting the average cost by age at death and number of comorbidities. Two sets of sensitivity analyses were performed to mitigate the risk of bias due to the potentially unpredictable time of death of older adults with cancer, which would explain why preventive drugs were continued until the very end of life: we first excluded patients whose underlying cause of death suggested an acute and sudden fatal event ~~who died from acute and possibly unpredictable causes~~ (eTable 4); ~~then,~~ we then stratified the main analyses according to the time between cancer diagnosis and death, separating decedents who were diagnosed more than 12 months before death from those who were diagnosed during the last 6 months of life. Individuals with missing data for the time between diagnosis and death (n=7863, 5.2%) were excluded from this~~e~~ sensitivity

analysis. Statistical analyses were performed using JMP version 13.0 (SAS Institute Inc) and Stata version 14.1 (StataCorp LP). This study adheres to the RECORD guidelines (Supporting file).[22]

Results

Characteristics of the study population

Among a total of 165 821 older adults who died with cancer in Sweden between 2007 and 2013, 151 201 (91.2%) met our eligibility criteria (Figure 1). Mean age at time of death was 81.3 years (SD, 8.1), 45% of decedents were women, 18% lived in nursing home facilities, and 47% died in hospitals. As shown in Table 1, the most common cancer types affected male genital organs (17%), respiratory organs (12%), and colon-rectum (11%). A large majority of patients had been diagnosed with cancer more than 12 months (60%), or between 6 to 12 months (12%) before death. Hypertension, ischemic heart disease, heart failure, atrial fibrillation, and type 2 diabetes were the most commonly diagnosed comorbidities. Older adults who died without cancer reported as cause of death on their death certificate (n=29 984, 19.8%) were, on average, older, lived more often in nursing homes, and had a greater number of chronic comorbidities than those who died *from* cancer (eTable4).

Use of preventive drugs

Throughout the last year of life, the mean number of prescribed drugs increased from 6.9 to 10.1 (mean difference 2.1, 95% CI 2.0–2.2) and the proportion of individuals using ≥10 drugs rose from 26% to 52%. Preventive drugs were frequently prescribed near the end of life (Table 2). Antihypertensives were prescribed to 60.1% of the decedents during their last month of life, including beta-blockers (38.2%), angiotensin-converting-enzyme inhibitors (18.5%), and calcium channel blockers (15.9%). Antithrombotic agents, anti-anemics, lipid-lowering drugs, mineral supplements, and drugs for diabetes were also commonly prescribed. We observed little change in the use of preventive drugs over the course of the last year before death. The proportion of older adults who continued therapy until the final month of life ranged from 56.6% for bisphosphonates, to 65% for statins and vitamins, up to ≥80% for insulin, beta-blockers, and vitamin B12 or folic acid. Overall, 28.2% of decedents initiated antithrombotic agents (including 13.4% platelet aggregation inhibitors) during their last year of life, 23.2% initiated high-blood pressure medications (including 13.3% beta-blockers), and 4.9% started

statins. Differences in the use of preventive drugs across cancer types are reported in eTable 5. In sensitivity analyses, results remained very similar after excluding individuals who died from acute and possibly unpredictable causes of death (eTable 6), or while comparing patients who had been diagnosed with cancer >-12 months before death to individuals who were diagnosed closer to death (eTable 7).

Drug costs during the last year of life

The median drug cost during the last year of life was $1482 (interquartile range [IQR] $700–$2896]) per person, ranging from $961 among decedents with cancers of unknown primary site, to $1811 among women with breast cancer, up to $3073 among men with cancers affecting male genital organs (Table 3). After adjusting for multiple confounders, we found significantly higher costs for patients with breast cancer, gynecological cancers, cancers of male genital organs, and multiple solid tumors, compared with individuals who died with lung cancer. Median monthly drug costs increased from $80 to $153 over the course of the last year of life, although there was significant variation according to the type of cancer (eTable 8).

The median cost for preventive drugs during the last year of life amounted to $213 (IQR $77–$490) in the total study population and varied across cancer types. Compared to older adults who died with lung cancer ($205, IQR $61–$523), those who died with pancreatic cancer (adjusted median difference [AMD] $19, 95% CI $7–$31), breast cancer (AMD $19, 95% CI $11–$28), and gynecological cancers (AMD $27, 95% CI $18–$36) had the highest costs per person. Throughout the last year of life, the proportion of total drug costs corresponding to preventive drugs was 20.2%; this proportion decreased from 20.5% during the 12th month before death to 18.5% during the last month before death. However, despite this relative reduction, we found an absolute increase in the costs owing to preventive drugs (eTable 9). Overall, costs were highest among older adults aged less than 80 years and among those who had ≥5 chronic comorbidities, although our data shows that women with breast cancer had significantly higher costs for preventive drugs even with a low burden of chronic multimorbidity (eFigure 2). In sensitivity analyses, we found only marginal differences according to the time between diagnosis and death (eTable 10).

Discussion

This large nationwide study has three main findings. First, a substantial share of older adults who die with solid cancer continues to receive preventive drugs until the final month of life. Second, preventive drugs account for around one fifth of the total costs of prescribed drugs, and this proportion decreases only slightly as death approaches. Third, there are important differences between cancer types in the use and costs of preventive drugs, which can only partly be explained by age and chronic multimorbidity.

Our study builds on previous work exploring the utilization of preventive drugs in terminally ill patients.[23,24] In Australia, Currow *et al*. showed that, patients were prescribed on average 2.6 drugs for managing comorbid conditions at the time of palliative care referral.[25] Many patients who receive preventive cardiovascular drugs continue to do so until the very end of life.[26,27] For instance, the prescribing of antihypertensive agents and platelet aggregation inhibitors is commonplace among hospice patients with advanced cancer.[28] Recent studies have also shown that polypharmacy increases near the end of life, which is fueled not only by symptomatic drugs but also by the continuation of preventive agents until the very last weeks of life.[18,24]

The frequent continuation of long-term preventive drugs is indicative of insufficient deprescribing strategies at the end of life. Although the preventive drugs reported in our study are most often pharmacologically and clinically appropriate in the general population, their use in the context of limited life expectancy and palliative goals of care should be examined critically.[29,30] Preventive medicines are not necessarily inappropriate at the end of life, as some may have palliative indications to avert distressing symptoms or to avoid serious complications (e.g. anticoagulants for managing cancer-related venous thrombosis). However, the large proportion of older adults with cancer who continue to receive statins, antihypertensives, vitamins and mineral supplements throughout the last year of life does suggest the existence of routine-based prescribing practices that contribute to low-value care. Our finding that older adults with poor-prognosis cancers (e.g. brain, lung, liver, pancreas)

were just as likely as those with less aggressive disease to use preventive drugs during their last month of life suggests that there is room for deprescribing.

The question of whether drug treatments should be initiated or continued near the end of life is at the center of the *Choosing Wisely* campaign, which has been endorsed by the American Society of Clinical Oncology, the American Geriatrics Society, and the American Medical Directors Association. It is, for instance, explicitly recommended to refrain from using lipid-lowering agents in older patients with limited life expectancy. Evidence from a recent randomized controlled trial shows that discontinuing statins in this population is safe and can result in improved quality of life.[12] Three components seem essential to reduce the burden of preventive drugs of limited benefit. First, timely physician-patient communication is needed to evaluate whether the prescribed treatments are concordant with the patient goals of care. Second, physicians should carefully consider whether the prescribed drugs are likely to achieve their benefit within the patients' remaining lifetime. Third, the decision to initiate, continue or discontinue preventive treatments should account for the risk of the patient coming to harm.

From a health economics perspective, it can be argued that drugs account for only small share of the total healthcare expenditure, with hospital and long-term care being the major sources of medical spending at the end of life. In the United States, drugs-related costs (including drugs administered during hospital stays) amount to around 4% of the entire medical expenditure during the last year of life.[31] However, at the patient level, these costs are substantial and may contribute to the 'financial toxicity' of treatments, especially in countries with no universal healthcare insurance coverage.[32] It is worth noting that drug prices are generally much lower in Europe than in the United States, owing for the most part to strong price regulation within the European Union. In 2017, pharmaceutical expenditures amounted to $1162 per capita in the United States compared with $479 in Sweden.[33] Moreover, indirect costs (e.g. cost of International Normalized Ratio-testing associated with use of warfarin) and induced costs (e.g. hospital expenditures caused by severe adverse drug reactions) of drug prescribing also contribute to the overall burden of drug costs.

This is the first nationwide study that has explored drug utilization in the last year of life according to cancer type, and that has investigated the costs associated with these drugs. However, we acknowledge a number of limitations. First, it is possible that a fraction of patients included in the cohort died from sudden and totally unexpected deaths, which could explain why preventive drugs were continued until the time of death. Retrospective cohorts of decedents are indeed prone to confounding-by-indication bias and tend to underestimate the prognostic uncertainty surrounding end-of-life decisions.[34] However, sensitivity analyses were performed in an attempt to separate sudden from non-sudden deaths, and showed only marginal differences regarding patterns of drug utilization at the end of life. Second, routinely collected data about drug dispensing do not allow for assessing whether drugs are actually consumed by patients, and do not provide information about dosage modifications that may occur between two refills. It is possible that some drugs were tapered off near the end of life, which our data would not reflect. Moreover, the estimations of drug costs relied on the assumption that patients used their treatments according to the prescribed daily dose. Although this assumption is unlikely at the individual level, it is reasonable to assume that, at a population level, variations from one patient to another cancel each other out. Also, since drugs administered during hospitalizations are not collected in the Swedish Prescribed Drugs Register, the costs attributable to cancer-directed therapy are largely underestimated. Third, although this study relies on routinely collected healthcare and administrative data with nationwide coverage in Sweden, the generalizability of our findings may be limited to countries with universal health coverage and wide access to preventive drugs. Finally, we did not assess appropriateness of prescribing: some preventive drugs reported in this study may in specific cases and for specific indications have a meaningful clinical value. For instance, the frequent use of bisphosphonates among women with breast cancer ~~can~~ could stem from an effort to prevent and control bone metastases.

Conclusion

The use of preventive drugs in the last year of life is common among older adults with cancer, although there is considerable variation in use according to cancer type. In this context, the use of preventive drugs should be reconsidered in light of patient goals of care, values and preferences. Reducing the therapeutic burden in people with advanced cancer has the potential to not only reduce unnecessary adverse effects and improve patient quality of life, it also has the potential to reduce the financial burden for patients.

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Figure 1 – Study population flowchart

Table 1 – Characteristics of older adults who died with solid cancer in Sweden, 2007–2013

Sex, No. (%)	
Men	83 429 (55.2)
Women	67 772 (44.8)
Age at time of death, years	
Mean (SD)	81.3 (8.1)
65 to 74 years	35 690 (23.6)
75 to 84 years	56 950 (37.7)
85 to 94 years	52 474 (34.7)
95 years and older	6087 (4.0)
Level of education, No. (%)	
Primary education	71 661 (48.9)
Secondary education	57 937 (39.5)
Tertiary education	17 030 (11.6)
Living arrangement, No. (%)	
Community	123 702 (81.8)
Nursing home	27 499 (18.2)
Place of death, No. (%)	
Usual place of living	80,439 (53.2)
Hospital facility	70,762 (46.8)
Primary malignancy, No. (%)	
Respiratory organs	18 435 (12.2)
Esophagus and stomach	5014 (3.3)
Colon-rectum	16 102 (10.6)
Liver and intrahepatic bile duct	3711 (2.5)
Pancreas	7808 (2.5)
Other digestive organs	3643 (2.4)
Breast	9920 (6.6)
Urinary tract	10 231 (6.8)
Male genital organs	25 642 (17.0)
Female genital organs	6868 (4.5)
Melanoma of skin	2651 (1.8)
Brain and meninges	2266 (1.5)
Unknown primary site	4030 (2.7)
Other primary malignancy	16 502 (10.9)
Multiple solid tumors	18 378 (12.2)
Time between diagnosis and death, No. (%)	
More than 12 months	86 032 (60.0)
6 to 12 months	16 440 (11.5)
Less than 6 months	40 866 (28.5)
Number of chronic comorbidities, No. (%)	
Mean (SD)	4.5 (2.8)
0	6216 (4.1%)
1	14 242 (9.4%)
2	19 570 (12.9%)
3	22 039 (14.6%)
4	21 529 (14.2%)
≥5	67 605 (44.7%)
Main chronic comorbidities, No. (%)	
Hypertension	66 553 (44.0%)
Ischemic heart disease	50 896 (33.7%)
Heart failure	42 049 (27.8%)
Atrial fibrillation	36 584 (24.2%)

Diabetes	31 279 (20.7%)
Cerebrovascular disease	28 730 (19.0%)
Cataract and other lens diseases	24 388 (16.1%)
COPD, emphysema, chronic bronchitis	22 465 (14.9%)
Dementia	17 784 (11.8%)

Missing values: education (n=4573, 3%), time from diagnosis to death (n=7863, 5.2%).

Table 2 – Use of preventive drugs during the last year of life of older adults (≥65 years) with solid cancer in Sweden, 2007–2013

	Prevalence (n=151 201)			Continuation[b] until the final month of life	Initiation[c] during the last year of life
	12th month before death	Last month before death	Absolute change		
	Percent	Percent	Percent points (95%CI)[a]	Percent (95%CI)	Percent (95%CI)
Drugs used in diabetes	**14.0%**	**14.9%**	**+0.9 (0.6 to 1.2)**	**87.3 (86.8 to 87.7)**	**3.6 (3.5 to 3.7)**
Insulin and analogues	7.6%	10.0%	+2.4 (2.2 to 2.6)	89.3 (88.8 to 89.9)	4.0 (3.9 to 4.1)
Blood glucose-lowering drugs	8.7%	7.1%	-1.6 (-1.8 to -1.4)	68.2 (67.4 to 69.0)	1.8 (1.7 to 1.9)
Vitamins	**8.2%**	**9.2%**	**+1.0 (0.8 to 1.2)**	**64.9 (64.1 to 65.7)**	**6.7 (6.6 to 6.8)**
Mineral supplements	**14.7%**	**19.2%**	**+4.5 (4.2 to 4.8)**	**68.4 (67.7 to 69.9)**	**14.2 (14.0 to 14.4)**
Calcium	10.5%	11.1%	+0.6 (0.4 to 0.8)	65.7 (64.9 to 66.4)	6.5 (6.4 to 6.7)
Potassium	4.6%	7.8%	+3.2 (3.0 to 3.4)	64.5 (63.3 to 65.6)	6.8 (6.6 to 6.9)
Antithrombotic agents	**46.6%**	**48.1%**	**+1.5 (1.1 to 1.9)**	**79.2 (78.9 to 79.5)**	**28.2 (27.9 to 28.5)**
Vitamin K antagonists	7.7%	5.6%	-2.1 (-2.3 to -1.9)	47.6 (46.7 to 48.5)	3.8 (3.7 to 3.9)
Heparin group	2.7%	10.0%	+7.3 (7.1 to 7.5)	49.3 (47.8 to 51.9)	14.9 (14.6 to 15.9)
Platelet aggregation inhibitors	37.7%	36.2%	-1.5 (-1.8 to -1.2)	77.4 (77.1 to 77.8)	13.4 (13.2 to 13.6)
Drugs used in the treatment of hypertension	**60.4%**	**60.1%**	**-0.3 (-0.6 to 0.0)**	**86.4 (86.2 to 86.7)**	**23.2 (22.9 to 23.6)**
Low-ceiling diuretics	6.3%	5.2%	-1.1 (-1.3 to -0.9)	61.2 (60.2 to 62.1)	1.9 (1.8 to 1.9)
Potassium-sparing agents	7.3%	11.2%	+3.9 (3.7 to 4.1)	69.0 (68.1 to 69.9)	7.6 (7.5 to 7.8)
Beta blocking agents	37.5%	38.2%	+0.7 (0.4 to 1.0)	82.9 (82.6 to 83.3)	13.3 (13.1 to 13.6)
Calcium channel blockers[d]	18.9%	15.9%	-3.0 (-3.3 to -2.7)	68.8 (68.2 to 69.3)	4.9 (4.7 to 5.7)
ACE inhibitors	20.3%	18.5%	-1.8 (-2.1 to -1.5)	71.8 (71.3 to 72.3)	6.6 (6.4 to 6.7)
Angiotensin II antagonists	11.7%	9.9%	-1.8 (-2.0 to -1.6)	71.3 (70.6 to 71.9)	2.4 (2.3 to 2.4)
Lipid modifying agents	**21.5%**	**16.8%**	**-4.7 (-5.0 to -4.4)**	**65.0 (64.4 to 65.5)**	**5.4 (5.3 to 5.5)**
HMG CoA reductase inhibitors	21.0%	16.3%	-4.7 (-5.0 to -4.4)	64.9 (64.4 to 65.4)	4.9 (4.7 to 5.6)
Bisphosphonates	**4.2%**	**3.9%**	**-0.3 (-0.4 to -0.2)**	**56.6 (55.3 to 57.8)**	**2.8 (2.7 to 2.9)**
Anti-anemic preparations	**25.7%**	**30.4%**	**+4.7 (4.4 to 5.0)**	**79.7 (79.3 to 82.1)**	**17.6 (17.4 to 17.8)**
Iron preparations	7.4%	11.0%	+3.6 (3.4 to 3.8)	55.8 (54.9 to 56.8)	11.1 (11.0 to 11.3)
Vitamin B12 and folic acid	21.0%	23.2%	+2.2 (1.9 to 2.5)	82.4 (82.0 to 82.8)	8.9 (8.7 to 9.1)

Abbreviations: CI, confidence interval; ACE, angiotensin-converting-enzyme

[a] *Difference in proportions*

[b] *Proportion of older adults who received drugs during the last month before death, among those exposed 12 months before death*

[c] *Proportion of older adults who received drugs during the last year of life, among those not exposed 12 months before death*

[d] *Excluding selective calcium channel blockers with direct cardiac effects (ATC code C08D)*

Table 3 – Drug costs during the final year of life, by cancer type

	Decedents, No.	Total costs for prescription drugs, per capita, US $[a]		Costs for preventive drugs, per capita, US $[b]		Proportion of total drug costs dedicated to preventive agents, %		
		Median (IQR)	ß (95% CI)[c]	Median (IQR)	ß (95% CI)[c]	Total last year of life	12th month	Last month
Respiratory organs	18 435	1371 (662-2619)	Ref	205 (61-523)	Ref	23.6%	24.6%	21.8%
Esophagus and stomach	5014	1145 (552-2267)	-122 (-178 to -65)	199 (68-479)	6 (-4 to 16)	22.9%	28.1%	15.2%
Colorectal	16 102	1074 (538-2107)	-161 (-199 to -122)	209 (72-479)	11 (4 to 18)	26.5%	28.3%	21.1%
Liver and intrahepatic bile duct	3711	1079 (505-2117)	-224 (-288 to -161)	222 (82-514)	19 (7 to 31)	23.7%	23.9%	23.6%
Pancreas	7808	1263 (627-2353)	-47 (-94 to 1)	213 (69-520)	13 (5 to 22)	23.0%	24.8%	20.6%
Other digestive organs	3643	1041 (500-2110)	-162 (-227 to -98)	191 (65-426)	-7 (-19 to 5)	12.8%	12.5%	13.0%
Breast	9920	1811 (851-3410)	528 (482 to 575)	218 (81-528)	19 (11 to 28)	26.3%	26.5%	24.1%
Urinary tract	10 231	1221 (626-2274)	-113 (-158 to -69)	232 (93-508)	11 (3 to 19)	25.1%	26.1%	21.1%
Male genital organs	25 642	3073 (1593-4559)	1826 (1790 to 1863)	209 (80-450)	13 (6 to 19)	13.3%	13.2%	12.7%
Female genital organs	6868	1350 (675-2568)	39 (-12 to 91)	239 (86-573)	27 (18 to 36)	26.5%	26.2%	23.3%
Melanoma of skin	2651	1015 (520-1944)	-165 (-239 to -91)	200 (68-458)	12 (-2 to 25)	25.6%	27.1%	22.8%
Brain and meninges	2266	1216 (640-2190)	-149 (-227 to -70)	205 (63-572)	3 (-11 to 17)	27.7%	28.6%	24.1%
Unknown primary site	4030	961 (475-1816)	-224 (-286 to -162)	203 (82-431)	12 (0 to 23)	22.6%	22.2%	23.5%
Other primary malignancy	16 502	1185 (627-2234)	-81 (-120 to -42)	221 (93-444)	4 (-3 to 12)	19.8%	20.4%	19.1%
Multiple solid tumors	18 378	1746 (796-3409)	342 (305 to 379)	219 (74-545)	13 (7 to 20)	18.9%	18.8%	16.9%
Total cohort	**151 201**	**1482 (700-2986)**		**213 (77-490)**		**20.2%**	**20.5%**	**18.5%**

Abbreviation: IQR, Inter-quartile range.

a Expenditures for all prescription drugs dispensed in community pharmacies (ATC codes A to S)

b Expenditures for the prescription drugs mentioned in Table 2 (ATC codes available in Appendix eTable 2)

c Quantile regression model adjusted for sex, age at death, number of chronic diseases, living arrangement, and education (missing values: 4573). β coefficients can be interpreted as the adjusted median difference in costs compared to decedents with cancer of the respiratory organs.

Preventive drugs in the last year of life of older adults with cancer: is there room for deprescribing?

Running head: *Preventive drugs at the end of life*

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Abstract

Background: The continuation of preventive drugs for older patients with advanced cancer has come under scrutiny since these drugs are unlikely to achieve their clinical benefit during the patients' remaining lifespan.

Patients and methods: nationwide cohort study of older adults (≥65 years) with solid cancer who died between 2007 and 2013 in Sweden, using routinely collected data with record linkage. We calculated the monthly utilization and cost of preventive drugs throughout the last year before death.

Results: Among 151 201 older patients who died with cancer (mean age 81.3 [SD, 8.1] years), the average number of drugs increased from 6.9 to 10.1. Preventive drugs were frequently continued until the final month of life, including antihypertensives, platelet aggregation inhibitors, anticoagulants, statins, and oral antidiabetics. Median drug costs amounted to $1482 (interquartile range [IQR] $700–$2896]) per person, including $213 (IQR $77–$490) for preventive therapies. Compared to older adults who died with lung cancer ($205, IQR $61–$523), costs for preventive drugs were higher among older adults who died with pancreatic cancer (adjusted median difference [AMD] $13, 95% CI $5–$22), or gynecological cancers (AMD $27, 95% CI $18–$36). There was no decrease in the cost of preventive drugs throughout the last year of life.

Conclusion: preventive drugs are commonly prescribed during the last year of life of older adults with cancer and are often continued until the final weeks before death. Adequate deprescribing strategies are warranted to reduce the burden of drugs of limited clinical benefit near the end of life.

Keywords: palliative care; end-of-life; drug prescribing; deprescribing

Introduction

In high-income countries, people aged 70 years and older now account for almost two-thirds of cancer-related deaths.[1] Chronic multimorbidity has thus become the norm rather than the exception in oncology[2], and is associated with poorer chances of survival and with a higher burden of functional impairments and physical symptoms.[3] Multimorbidity also comes with a higher burden of long-term pharmacological treatments. In the United States and in Europe, about 40% of people aged 65 years or older use 5 or more drugs concomitantly.[4,5] This polypharmacy is particularly problematic among older people with advanced cancer[6], since the potential to develop serious drug–drug interactions is amplified by the use of anticancer agents and complementary medicines.[7,8] Moreover, the probability of experiencing adverse drug reactions increases because the main pharmacokinetic parameters are affected not only by age but also by the physiological impact of cancer (e.g. modified drug absorption due to gastrointestinal symptoms or to impairments in the gut wall function, decrease in the volume of distribution caused by weight loss, renal impairment due to the nephrotoxicity of chemotherapy).[9,10]

Beyond pharmacology, polypharmacy in the context of advanced cancer also raises important questions from a clinical and ethical viewpoint. As cancer progresses and prognosis worsens, the net benefit of each additional medicine gradually decreases while the risk of harm increases. This "law of diminishing returns" makes the continuation or initiation of long-term treatments particularly questionable for older patients with advanced cancer. Preventive drugs are prescribed either to avert or delay the onset of a disease among individuals who are considered at high risk of developing that disease in the future (*primary prevention*), or to avoid the recurrence of a condition that the patient experienced in the past (*secondary prevention*). These drugs typically need several years before the physiological and biological changes that they produce translate into measurable and clinically meaningful health outcomes. Thus, the time-until-benefit of preventive agents is often much longer than the remaining lifespan of older adult with serious illness.[11] Recent randomized controlled trials show that lipid-lowering medications can safely be deprescribed among older adults with limited life expectancy, and that the discontinuation of antihypertensives among individuals without cardiovascular disease is safe

in the short term.[12,13] Other long-term treatments such as bisphosphonates retain their effect 3 to 5 years after their withdrawal.[14] Nevertheless, a handful of observational studies have reported that preventive medications are prescribed during the last year of life of patients with life-limiting disease, and have cast doubt upon the benefit of these treatments.[15] There is limited investigation to date of the continuation and discontinuation of medications throughout the last months of life and with little information about the costs of these medications and about potential variation across cancer types. The aim of the current study was therefore to evaluate the prescribing of preventive drugs throughout the final year of life of older adults who died with cancer across Sweden, and to estimate the direct costs of preventive drugs.

Methods

Study design and data

This was a retrospective cohort study based on routinely collected data in Sweden, a country with a universal healthcare system. Data from the National Cause of Death Register were linked through deterministic matching to the Total Population Register, the National Patient Register, the Swedish Prescribed Drugs Register, the Social Services Register, and the Swedish Register of Education. The Regional Ethical Review Board in Stockholm approved the study.

Study population

We included older adults aged ≥65 years who died in Sweden between 2007 and 2013, as these were the most recent available data. Decedents were considered as eligible for inclusion if a diagnosis of solid cancer (International Classification of Diseases [ICD], 10th revision codes C00–C76 and C80) was reported either in a hospital discharge report during the last 2 years of life, or as an underlying or contributing cause of death. We decided *a priori* to exclude decedents with missing cause of death, those with missing drug prescription history throughout the last 6 months of life, and those who remained hospitalized continuously during the last 3 months before death. Older adults with concomitant hematological malignancies (ICD-10 codes C81–C95) were also excluded, in order to select a homogenous population of individuals diagnosed only with solid cancer. Previous studies have indeed shown that persons with hematological malignancies experience a rapid functional decline at the end of life, which makes survival prediction particularly challenging. The potential for cure until late in the course of the disease trajectory differentiates these older patients from those dying with solid cancer.[16,17]

Outcomes

Utilization and cost of preventive drugs during the last 12 months of life were the main study outcomes. Preventive drugs with questionable benefit near the end of life have been identified in a recent

systematic review of the literature[15], and include drugs for diabetes, vitamins, mineral supplements, antithrombotic agents, antihypertensives, statins, bisphosphonates, and medications for chronic anemia. The list of corresponding Anatomical Therapeutic Chemical (ATC) classification codes is available in Supplementary eTable 1.

We computed monthly exposure to specific drug classes based on data from the Swedish Prescribed Drugs Register, which contains detailed information about all prescription drugs delivered in community pharmacies in Sweden since 2005 (including drugs dispensed to nursing home residents, at the exception of a few facilities with their own drug storeroom). Methods for constructing periods of drug exposure have been presented in detail elsewhere [5,18], and are illustrated in eFigure 1A. *Continuation* of preventive drugs was calculated as the proportion of older adults who were still using preventive drugs during the last month before death among those exposed one year before, while *initiation* was calculated the proportion of older adults who started using preventive drugs during the last year of life. Drug costs were estimated through a two-step approach, as described in eFigure 1B. We first divided the total cost of each purchase by the number of days covered to obtain the average daily cost. Second, we multiplied this average daily cost by the expected number of days of exposure during a given month, which allowed for distributing drug costs according to the assumed length of exposure. This approach provides a more realistic estimate of the costs, instead of artificially concentrating all expenditures at the purchase date. Drug costs were standardized using the harmonized index of consumer prices (HICP) with 2013 as reference year in order to correct for inflation over time and were then converted from the Swedish currency SEK into US dollars (USD) based on the European Central Bank average exchange rate from 1 January to 31 December 2013 to facilitate international comparisons (1 SEK = 0.1535 USD) .

Assessment of individual characteristics

Sex and date of birth were extracted from the Total Population Register and cross-validated with data reported on study participants' death certificates. We categorized solid malignancies into 14 distinct locations. Details about the corresponding ICD-10 codes are presented in eTable 2. The overall burden

of chronic multimorbidity was measured with a recently validated tool that captures a set of 60 distinct chronic diseases based on different data sources (contributing causes of deaths, inpatients and outpatients diagnoses reported during the last 3 years of life, and specific drugs unequivocally linked to chronic conditions).[19] Living arrangement at time of death was defined as "community" or "nursing home", while the place of death was reported as either "hospital" or "usual place of living". The decedents' level of education was categorized into "primary", "secondary", and "tertiary" education in accordance with the International Standard for Classification of Education.

Statistical analysis

Multivariable quantile regressions were used to model drug costs across different cancer types, while controlling for sex, age, number of chronic diseases, living arrangement, and level of education. While linear regression allows for modeling the mean of an outcome, quantile regression is used to model quantiles of the outcome when the distribution of the outcome is highly skewed.[20] Beta coefficients obtained from quantile regression models can be interpreted as the adjusted median difference (AMD) in costs compared with the reference group, and are reported together with their 95% CIs. We compared the results with estimates drawn from generalized linear models with log link function and gamma distribution, to ensure that the average median effects reported in our study are concordant (in both direction and magnitude) with average mean effects.[21] Variations in the cost of preventive drugs were then represented graphically in a series of contour graphs plotting the average cost by age at death and number of comorbidities. Two sets of sensitivity analyses were performed to mitigate the risk of bias due to the potentially unpredictable time of death of older adults with cancer, which would explain why preventive drugs were continued until the very end of life: we first excluded patients whose underlying cause of death suggested an acute and sudden fatal event (eTable 4); we then stratified the main analyses according to the time between cancer diagnosis and death, separating decedents who were diagnosed more than 12 months before death from those who were diagnosed during the last 6 months of life. Individuals with missing data for the time between diagnosis and death (n=7863, 5.2%) were excluded from this sensitivity analysis. Statistical analyses were performed using JMP version 13.0

(SAS Institute Inc) and Stata version 14.1 (StataCorp LP). This study adheres to the RECORD guidelines (Supporting file).[22]

Results

Characteristics of the study population

Among a total of 165 821 older adults who died with cancer in Sweden between 2007 and 2013, 151 201 (91.2%) met our eligibility criteria (Figure 1). Mean age at time of death was 81.3 years (SD, 8.1), 45% of decedents were women, 18% lived in nursing home facilities, and 47% died in hospitals. As shown in Table 1, the most common cancer types affected male genital organs (17%), respiratory organs (12%), and colon-rectum (11%). A large majority of patients had been diagnosed with cancer more than 12 months (60%), or between 6 to 12 months (12%) before death. Hypertension, ischemic heart disease, heart failure, atrial fibrillation, and type 2 diabetes were the most commonly diagnosed comorbidities. Older adults who died without cancer reported as cause of death on their death certificate (n=29 984, 19.8%) were, on average, older, lived more often in nursing homes, and had a greater number of chronic comorbidities than those who died *from* cancer (eTable4).

Use of preventive drugs

Throughout the last year of life, the mean number of prescribed drugs increased from 6.9 to 10.1 (mean difference 2.1, 95% CI 2.0–2.2) and the proportion of individuals using ≥10 drugs rose from 26% to 52%. Preventive drugs were frequently prescribed near the end of life (Table 2). Antihypertensives were prescribed to 60.1% of the decedents during their last month of life, including beta-blockers (38.2%), angiotensin-converting-enzyme inhibitors (18.5%), and calcium channel blockers (15.9%). Antithrombotic agents, anti-anemics, lipid-lowering drugs, mineral supplements, and drugs for diabetes were also commonly prescribed. We observed little change in the use of preventive drugs over the course of the last year before death. The proportion of older adults who continued therapy until the final month of life ranged from 56.6% for bisphosphonates, to 65% for statins and vitamins, up to ≥80% for insulin, beta-blockers, and vitamin B12 or folic acid. Overall, 28.2% of decedents initiated antithrombotic agents (including 13.4% platelet aggregation inhibitors) during their last year of life, 23.2% initiated high-blood pressure medications (including 13.3% beta-blockers), and 4.9% started

statins. Differences in the use of preventive drugs across cancer types are reported in eTable 5. In sensitivity analyses, results remained very similar after excluding individuals who died from acute and possibly unpredictable causes of death (eTable 6), or while comparing patients who had been diagnosed with cancer >12 months before death to individuals who were diagnosed closer to death (eTable 7).

Drug costs during the last year of life

The median drug cost during the last year of life was $1482 (interquartile range [IQR] $700–$2896]) per person, ranging from $961 among decedents with cancers of unknown primary site, to $1811 among women with breast cancer, up to $3073 among men with cancers affecting male genital organs (Table 3). After adjusting for multiple confounders, we found significantly higher costs for patients with breast cancer, gynecological cancers, cancers of male genital organs, and multiple solid tumors, compared with individuals who died with lung cancer. Median monthly drug costs increased from $80 to $153 over the course of the last year of life, although there was significant variation according to the type of cancer (eTable 8).

The median cost for preventive drugs during the last year of life amounted to $213 (IQR $77–$490) in the total study population and varied across cancer types. Compared to older adults who died with lung cancer ($205, IQR $61–$523), those who died with pancreatic cancer (adjusted median difference [AMD] $19, 95% CI $7–$31), breast cancer (AMD $19, 95% CI $11–$28), and gynecological cancers (AMD $27, 95% CI $18–$36) had the highest costs per person. Throughout the last year of life, the proportion of total drug costs corresponding to preventive drugs was 20.2%; this proportion decreased from 20.5% during the 12th month before death to 18.5% during the last month before death. However, despite this relative reduction, we found an absolute increase in the costs owing to preventive drugs (eTable 9). Overall, costs were highest among older adults aged less than 80 years and among those who had ≥5 chronic comorbidities, although our data shows that women with breast cancer had significantly higher costs for preventive drugs even with a low burden of chronic multimorbidity (eFigure 2). In sensitivity analyses, we found only marginal differences according to the time between diagnosis and death (eTable 10).

Discussion

This large nationwide study has three main findings. First, a substantial share of older adults who die with solid cancer continues to receive preventive drugs until the final month of life. Second, preventive drugs account for around one fifth of the total costs of prescribed drugs, and this proportion decreases only slightly as death approaches. Third, there are important differences between cancer types in the use and costs of preventive drugs, which can only partly be explained by age and chronic multimorbidity.

Our study builds on previous work exploring the utilization of preventive drugs in terminally ill patients.[23,24] In Australia, Currow *et al*. showed that, patients were prescribed on average 2.6 drugs for managing comorbid conditions at the time of palliative care referral.[25] Many patients who receive preventive cardiovascular drugs continue to do so until the very end of life.[26,27] For instance, the prescribing of antihypertensive agents and platelet aggregation inhibitors is commonplace among hospice patients with advanced cancer.[28] Recent studies have also shown that polypharmacy increases near the end of life, which is fueled not only by symptomatic drugs but also by the continuation of preventive agents until the very last weeks of life.[18,24]

The frequent continuation of long-term preventive drugs is indicative of insufficient deprescribing strategies at the end of life. Although the preventive drugs reported in our study are most often pharmacologically and clinically appropriate in the general population, their use in the context of limited life expectancy and palliative goals of care should be examined critically.[29,30] Preventive medicines are not necessarily inappropriate at the end of life, as some may have palliative indications to avert distressing symptoms or to avoid serious complications (e.g. anticoagulants for managing cancer-related venous thrombosis). However, the large proportion of older adults with cancer who continue to receive statins, antihypertensives, vitamins and mineral supplements throughout the last year of life does suggest the existence of routine-based prescribing practices that contribute to low-value care. Our finding that older adults with poor-prognosis cancers (e.g. brain, lung, liver, pancreas)

were just as likely as those with less aggressive disease to use preventive drugs during their last month of life suggests that there is room for deprescribing.

The question of whether drug treatments should be initiated or continued near the end of life is at the center of the *Choosing Wisely* campaign, which has been endorsed by the American Society of Clinical Oncology, the American Geriatrics Society, and the American Medical Directors Association. It is, for instance, explicitly recommended to refrain from using lipid-lowering agents in older patients with limited life expectancy. Evidence from a recent randomized controlled trial shows that discontinuing statins in this population is safe and can result in improved quality of life.[12] Three components seem essential to reduce the burden of preventive drugs of limited benefit. First, timely physician-patient communication is needed to evaluate whether the prescribed treatments are concordant with the patient goals of care. Second, physicians should carefully consider whether the prescribed drugs are likely to achieve their benefit within the patients' remaining lifetime. Third, the decision to initiate, continue or discontinue preventive treatments should account for the risk of the patient coming to harm.

From a health economics perspective, it can be argued that drugs account for only small share of the total healthcare expenditure, with hospital and long-term care being the major sources of medical spending at the end of life. In the United States, drugs-related costs (including drugs administered during hospital stays) amount to around 4% of the entire medical expenditure during the last year of life.[31] However, at the patient level, these costs are substantial and may contribute to the 'financial toxicity' of treatments, especially in countries with no universal healthcare insurance coverage.[32] It is worth noting that drug prices are generally much lower in Europe than in the United States, owing for the most part to strong price regulation within the European Union. In 2017, pharmaceutical expenditures amounted to $1162 per capita in the United States compared with $479 in Sweden.[33] Moreover, indirect costs (e.g. cost of International Normalized Ratio-testing associated with use of warfarin) and induced costs (e.g. hospital expenditures caused by severe adverse drug reactions) of drug prescribing also contribute to the overall burden of drug costs.

This is the first nationwide study that has explored drug utilization in the last year of life according to cancer type, and that has investigated the costs associated with these drugs. However, we acknowledge a number of limitations. First, it is possible that a fraction of patients included in the cohort died from sudden and totally unexpected deaths, which could explain why preventive drugs were continued until the time of death. Retrospective cohorts of decedents are indeed prone to confounding-by-indication bias and tend to underestimate the prognostic uncertainty surrounding end-of-life decisions.[34] However, sensitivity analyses were performed in an attempt to separate sudden from non-sudden deaths, and showed only marginal differences regarding patterns of drug utilization at the end of life. Second, routinely collected data about drug dispensing do not allow for assessing whether drugs are actually consumed by patients, and do not provide information about dosage modifications that may occur between two refills. It is possible that some drugs were tapered off near the end of life, which our data would not reflect. Moreover, the estimations of drug costs relied on the assumption that patients used their treatments according to the prescribed daily dose. Although this assumption is unlikely at the individual level, it is reasonable to assume that, at a population level, variations from one patient to another cancel each other out. Also, since drugs administered during hospitalizations are not collected in the Swedish Prescribed Drugs Register, the costs attributable to cancer-directed therapy are largely underestimated. Third, although this study relies on routinely collected healthcare and administrative data with nationwide coverage in Sweden, the generalizability of our findings may be limited to countries with universal health coverage and wide access to preventive drugs. Finally, we did not assess appropriateness of prescribing: some preventive drugs reported in this study may in specific cases and for specific indications have a meaningful clinical value. For instance, the frequent use of bisphosphonates among women with breast cancer could stem from an effort to prevent and control bone metastases.

Conclusion

The use of preventive drugs in the last year of life is common among older adults with cancer, although there is considerable variation in use according to cancer type. In this context, the use of preventive drugs should be reconsidered in light of patient goals of care, values and preferences. Reducing the therapeutic burden in people with advanced cancer has the potential to not only reduce unnecessary adverse effects and improve patient quality of life, it also has the potential to reduce the financial burden for patients.

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Figure 1 – Study population flowchart

Table 1 – Characteristics of older adults who died with solid cancer in Sweden, 2007–2013

Sex, No. (%)	
Men	83 429 (55.2)
Women	67 772 (44.8)
Age at time of death, years	
Mean (SD)	81.3 (8.1)
65 to 74 years	35 690 (23.6)
75 to 84 years	56 950 (37.7)
85 to 94 years	52 474 (34.7)
95 years and older	6087 (4.0)
Level of education, No. (%)	
Primary education	71 661 (48.9)
Secondary education	57 937 (39.5)
Tertiary education	17 030 (11.6)
Living arrangement, No. (%)	
Community	123 702 (81.8)
Nursing home	27 499 (18.2)
Place of death, No. (%)	
Usual place of living	80,439 (53.2)
Hospital facility	70,762 (46.8)
Primary malignancy, No. (%)	
Respiratory organs	18 435 (12.2)
Esophagus and stomach	5014 (3.3)
Colon-rectum	16 102 (10.6)
Liver and intrahepatic bile duct	3711 (2.5)
Pancreas	7808 (2.5)
Other digestive organs	3643 (2.4)
Breast	9920 (6.6)
Urinary tract	10 231 (6.8)
Male genital organs	25 642 (17.0)
Female genital organs	6868 (4.5)
Melanoma of skin	2651 (1.8)
Brain and meninges	2266 (1.5)
Unknown primary site	4030 (2.7)
Other primary malignancy	16 502 (10.9)
Multiple solid tumors	18 378 (12.2)
Time between diagnosis and death, No. (%)	
More than 12 months	86 032 (60.0)
6 to 12 months	16 440 (11.5)
Less than 6 months	40 866 (28.5)
Number of chronic comorbidities, No. (%)	
Mean (SD)	4.5 (2.8)
0	6216 (4.1%)
1	14 242 (9.4%)
2	19 570 (12.9%)
3	22 039 (14.6%)
4	21 529 (14.2%)
≥5	67 605 (44.7%)
Main chronic comorbidities, No. (%)	
Hypertension	66 553 (44.0%)
Ischemic heart disease	50 896 (33.7%)
Heart failure	42 049 (27.8%)
Atrial fibrillation	36 584 (24.2%)

Diabetes	31 279 (20.7%)
Cerebrovascular disease	28 730 (19.0%)
Cataract and other lens diseases	24 388 (16.1%)
COPD, emphysema, chronic bronchitis	22 465 (14.9%)
Dementia	17 784 (11.8%)

Missing values: education (n=4573, 3%), time from diagnosis to death (n=7863, 5.2%).

Table 2 – Use of preventive drugs during the last year of life of older adults (≥65 years) with solid cancer in Sweden, 2007–2013

	Prevalence (n=151 201)			Continuation[b] until the final month of life	Initiation[c] during the last year of life
	12th month before death	Last month before death	Absolute change		
	Percent	Percent	Percent points (95%CI)[a]	Percent (95%CI)	Percent (95%CI)
Drugs used in diabetes	**14.0%**	**14.9%**	**+0.9 (0.6 to 1.2)**	**87.3 (86.8 to 87.7)**	**3.6 (3.5 to 3.7)**
Insulin and analogues	7.6%	10.0%	+2.4 (2.2 to 2.6)	89.3 (88.8 to 89.9)	4.0 (3.9 to 4.1)
Blood glucose-lowering drugs	8.7%	7.1%	-1.6 (-1.8 to -1.4)	68.2 (67.4 to 69.0)	1.8 (1.7 to 1.9)
Vitamins	**8.2%**	**9.2%**	**+1.0 (0.8 to 1.2)**	**64.9 (64.1 to 65.7)**	**6.7 (6.6 to 6.8)**
Mineral supplements	**14.7%**	**19.2%**	**+4.5 (4.2 to 4.8)**	**68.4 (67.7 to 69.9)**	**14.2 (14.0 to 14.4)**
Calcium	10.5%	11.1%	+0.6 (0.4 to 0.8)	65.7 (64.9 to 66.4)	6.5 (6.4 to 6.7)
Potassium	4.6%	7.8%	+3.2 (3.0 to 3.4)	64.5 (63.3 to 65.6)	6.8 (6.6 to 6.9)
Antithrombotic agents	**46.6%**	**48.1%**	**+1.5 (1.1 to 1.9)**	**79.2 (78.9 to 79.5)**	**28.2 (27.9 to 28.5)**
Vitamin K antagonists	7.7%	5.6%	-2.1 (-2.3 to -1.9)	47.6 (46.7 to 48.5)	3.8 (3.7 to 3.9)
Heparin group	2.7%	10.0%	+7.3 (7.1 to 7.5)	49.3 (47.8 to 51.9)	14.9 (14.6 to 15.9)
Platelet aggregation inhibitors	37.7%	36.2%	-1.5 (-1.8 to -1.2)	77.4 (77.1 to 77.8)	13.4 (13.2 to 13.6)
Drugs used in the treatment of hypertension	**60.4%**	**60.1%**	**-0.3 (-0.6 to 0.0)**	**86.4 (86.2 to 86.7)**	**23.2 (22.9 to 23.6)**
Low-ceiling diuretics	6.3%	5.2%	-1.1 (-1.3 to -0.9)	61.2 (60.2 to 62.1)	1.9 (1.8 to 1.9)
Potassium-sparing agents	7.3%	11.2%	+3.9 (3.7 to 4.1)	69.0 (68.1 to 69.9)	7.6 (7.5 to 7.8)
Beta blocking agents	37.5%	38.2%	+0.7 (0.4 to 1.0)	82.9 (82.6 to 83.3)	13.3 (13.1 to 13.6)
Calcium channel blockers[d]	18.9%	15.9%	-3.0 (-3.3 to -2.7)	68.8 (68.2 to 69.3)	4.9 (4.7 to 5.7)
ACE inhibitors	20.3%	18.5%	-1.8 (-2.1 to -1.5)	71.8 (71.3 to 72.3)	6.6 (6.4 to 6.7)
Angiotensin II antagonists	11.7%	9.9%	-1.8 (-2.0 to -1.6)	71.3 (70.6 to 71.9)	2.4 (2.3 to 2.4)
Lipid modifying agents	**21.5%**	**16.8%**	**-4.7 (-5.0 to -4.4)**	**65.0 (64.4 to 65.5)**	**5.4 (5.3 to 5.5)**
HMG CoA reductase inhibitors	21.0%	16.3%	-4.7 (-5.0 to -4.4)	64.9 (64.4 to 65.4)	4.9 (4.7 to 5.6)
Bisphosphonates	**4.2%**	**3.9%**	**-0.3 (-0.4 to -0.2)**	**56.6 (55.3 to 57.8)**	**2.8 (2.7 to 2.9)**
Anti-anemic preparations	**25.7%**	**30.4%**	**+4.7 (4.4 to 5.0)**	**79.7 (79.3 to 82.1)**	**17.6 (17.4 to 17.8)**
Iron preparations	7.4%	11.0%	+3.6 (3.4 to 3.8)	55.8 (54.9 to 56.8)	11.1 (11.0 to 11.3)
Vitamin B12 and folic acid	21.0%	23.2%	+2.2 (1.9 to 2.5)	82.4 (82.0 to 82.8)	8.9 (8.7 to 9.1)

Abbreviations: CI, confidence interval; ACE, angiotensin-converting-enzyme

[a] *Difference in proportions*

[b] *Proportion of older adults who received drugs during the last month before death, among those exposed 12 months before death*

[c] *Proportion of older adults who received drugs during the last year of life, among those not exposed 12 months before death*

[d] *Excluding selective calcium channel blockers with direct cardiac effects (ATC code C08D)*

Table 3 – Drug costs during the final year of life, by cancer type

	Decedents, No.	Total costs for prescription drugs, per capita, US $[a]		Costs for preventive drugs, per capita, US $[b]		Proportion of total drug costs dedicated to preventive agents, %		
		Median (IQR)	ß (95% CI)[c]	Median (IQR)	ß (95% CI)[c]	Total last year of life	12th month	Last month
Respiratory organs	18 435	1371 (662-2619)	Ref	205 (61-523)	Ref	23.6%	24.6%	21.8%
Esophagus and stomach	5014	1145 (552-2267)	-122 (-178 to -65)	199 (68-479)	6 (-4 to 16)	22.9%	28.1%	15.2%
Colorectal	16 102	1074 (538-2107)	-161 (-199 to -122)	209 (72-479)	11 (4 to 18)	26.5%	28.3%	21.1%
Liver and intrahepatic bile duct	3711	1079 (505-2117)	-224 (-288 to -161)	222 (82-514)	19 (7 to 31)	23.7%	23.9%	23.6%
Pancreas	7808	1263 (627-2353)	-47 (-94 to 1)	213 (69-520)	13 (5 to 22)	23.0%	24.8%	20.6%
Other digestive organs	3643	1041 (500-2110)	-162 (-227 to -98)	191 (65-426)	-7 (-19 to 5)	12.8%	12.5%	13.0%
Breast	9920	1811 (851-3410)	528 (482 to 575)	218 (81-528)	19 (11 to 28)	26.3%	26.5%	24.1%
Urinary tract	10 231	1221 (626-2274)	-113 (-158 to -69)	232 (93-508)	11 (3 to 19)	25.1%	26.1%	21.1%
Male genital organs	25 642	3073 (1593-4559)	1826 (1790 to 1863)	209 (80-450)	13 (6 to 19)	13.3%	13.2%	12.7%
Female genital organs	6868	1350 (675-2568)	39 (-12 to 91)	239 (86-573)	27 (18 to 36)	26.5%	26.2%	23.3%
Melanoma of skin	2651	1015 (520-1944)	-165 (-239 to -91)	200 (68-458)	12 (-2 to 25)	25.6%	27.1%	22.8%
Brain and meninges	2266	1216 (640-2190)	-149 (-227 to -70)	205 (63-572)	3 (-11 to 17)	27.7%	28.6%	24.1%
Unknown primary site	4030	961 (475-1816)	-224 (-286 to -162)	203 (82-431)	12 (0 to 23)	22.6%	22.2%	23.5%
Other primary malignancy	16 502	1185 (627-2234)	-81 (-120 to -42)	221 (93-444)	4 (-3 to 12)	19.8%	20.4%	19.1%
Multiple solid tumors	18 378	1746 (796-3409)	342 (305 to 379)	219 (74-545)	13 (7 to 20)	18.9%	18.8%	16.9%
Total cohort	**151 201**	**1482 (700-2986)**		**213 (77-490)**		**20.2%**	**20.5%**	**18.5%**

Abbreviation: IQR, Inter-quartile range.

a Expenditures for all prescription drugs dispensed in community pharmacies (ATC codes A to S)

b Expenditures for the prescription drugs mentioned in Table 2 (ATC codes available in Appendix eTable 2)

c Quantile regression model adjusted for sex, age at death, number of chronic diseases, living arrangement, and education (missing values: 4573). β coefficients can be interpreted as the adjusted median difference in costs compared to decedents with cancer of the respiratory organs.

Supplementary materials

eFigure 1 – Calculation of monthly drug exposure and costs

eTable 1 – List of International Classification of Diseases, 10th revision (ICD-10) codes corresponding to solid malignancies

eTable 2 – List of Anatomical Therapeutic Chemical (ATC) codes corresponding to preventive drugs

eTable 3 – List of International Classification of Diseases, 10th revision (ICD-10) codes used to identify acute and possibly unpredictable deaths in older adults

eTable 4 – Characteristics of older adults who died *with* and *without* cancer as cause of death on their death certificate

eTable 5 – Use of preventive medications during the final month of life, by cancer type

eTable 6 – Sensitivity analysis: use of preventive medications during the last year of life of older adults (≥65 years) with cancer, after excluding individuals who died from acute and possibly unpredictable causes

eTable 7 – Sensitivity analysis: use of preventive medications during the last year of life of older adults (≥65 years) with cancer, according to the time between cancer diagnosis and death

eTable 8 – Change in medication costs throughout the final year of life, by cancer type

eTable 9 – Change in the preventive medication costs throughout the final year of life, by cancer type

eFigure 2 – Mean costs for preventive medications during the final year of life, by cancer type, age at death and number of chronic comorbidities, in US$

eTable 10 – Sensitivity analysis: preventive medication costs during the final year of life, by cancer type and according to the time between cancer diagnosis and death

eFigure 1 – Calculation of monthly drug exposure and costs

A. Calculation of monthly drug exposure

Drug	Amount purchased	Prescribed daily dose	No. of days covered	Month 1	Month 2	Month 3	Month 4
Drug A							
Purchase 1	15g	0.5g	30				
Purchase 2	6g	0.2g	30				
Purchase 3	30g	1.0g	30				
Drug B							
Purchase 1	15g	0.25g	60				
Exposure Drug A				15 days	**30 days**	30 days	15 days
Exposure Drug B				15 days	**30 days**	15 days	0 day

B. Calculation of monthly drug costs

Drug	Purchase cost in US$	No. days covered	Daily cost in US$	Month 1	Month 2	Month 3	Month 4
Drug C	50	45	1.11				
Drug D	10.5	70	0.15				
Drug E	35	63	0.55				
Drug F	210	30	7.00				
Drug G	6	30	0.20				
Costs of drugs *purchased* during the month				$60.5	**$251**	$0	
Costs of drugs *used* during the month				$30.2	**$140**	$142	

eTable 1 – List of Anatomical Therapeutic Chemical (ATC) codes corresponding to preventive drugs

Drug class	ATC code
Drugs used in diabetes	A10
Insulin and analogues	A10A
Blood glucose lowering drugs	A10B
Vitamins	A11
Mineral supplements	A12
Calcium	A12A
Potassium	A12B
Antithrombotic agents	B01A
Vitamin K antagonists	B01AA
Heparin group	B01AB
Platelet aggregation inhibitors	B01AC
Drugs used in the treatment of hypertension	C02, C03A, C03B, C07, C08 (excl. C08D), C09
Low-ceiling diuretics	C03A, C03B
Potassium-sparing agents	C03D
Beta blocking agents	C07
Calcium channel blockers	C08, excl. C08D
ACE inhibitors	C09A, C09B
Angiotensin II antagonists	C09C, C09D
Lipid modifying agents	C10
HMG CoA reductase inhibitors	C10AA
Bisphosphonates	M05BA, M05BB
Anti-anemic preparations	B03
Iron preparations	B03A
Vitamin B12 and folic acid	B03BA, B03BB

Note: combinations of blood glucose-lowering drugs and lipid modifying agents are classified in A10B (e.g. combination of sitagliptin and simvastatin).

eTable 2 – List of International Classification of Diseases, 10th revision (ICD-10) codes corresponding to solid malignancies

Solid malignancy	ICD-10 codes
Respiratory organs (incl. lung and bronchus)	C30-C39
Esophagus and stomach	C15-C16
Colorectal	C18-C20
Liver and intrahepatic bile duct	C22
Pancreas	C25
Other digestive organs	C15-C26
Breast	C50
Urinary tract	C64-C68
Male genital organs	C60-C63
Female genital organs	C51-C58
Melanoma of skin	C43
Brain and meninges	C70-C71
Unknown primary site	C80
Other primary malignancy	C00-14, C40-41, C44-49, C69, C72-C75
Multiple tumor sites	Individuals with ≥2 distinct primary sites

eTable 3 – List of International Classification of Diseases, 10th revision (ICD-10) codes used to identify acute and possibly unpredictable deaths in older adults

ICD Chapter	Main criteria	Conditional argument
	ICD-10 codes listed as underlying cause of death	*Inpatient or specialized outpatient care admission in the past 5 years*
Certain infectious and parasitic diseases	A00; A01; A02; A03; A04; A05; A06; A07; A08; A09; A39; A40; A41; A499; A80; A81; A87; B371; B375; B377; B440; B441; B448; B449; B99	
Diseases of the blood and blood-forming organs	D611; D619; D649	
Endocrine, nutritional and metabolic diseases	E86	
Diseases of the nervous system	G000; G001; G002; G003; G009; G039; G040; G048; G049; G060; G062; G931; G936	
Ischaemic and pulmonary heart diseases	I20; I21; I23; I25; I249; I249; I255; I26; I28	No history of ischemic heart disease (I20-I25) or pulmonary embolism (I26)
Other forms of heart disease	I30; I33; I40; I461; I469	
Cerebrovascular diseases	I60; I61; I62; I63; I64; I65; I66; I67	No history of cerebrovascular disease (I60-I69)
Diseases of arteries, arterioles and capillaries	I71; I72; I74; I97	
Diseases of the respiratory system	J069; J09; J10; J11; J12; J13; J14; J15; J18; J22; J690; J81; J851; J852; J93; J958; J960	
Diseases of the digestive system	K250; K251; K252; K253; K254; K255; K256; K257; K259; K260; K261; K263; K264; K265; K266; K269; K550; K65; K720; K810; K859	
Diseases of the musculoskeletal system and connective tissue	M726	
Diseases of the genitourinary system	N00; N04; N10; N17; N390; N990; N998	No history of diabetes (E10-14) or renal failure (N18-19)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	R02; R572; R570; R571	
Injury, poisoning and certain other consequences of external causes	S065; S066; S068; S069; S071; S10-99; T00-T99	
External causes of morbidity and mortality	V00-V99; X60-79; X80-84	

eTable 4 – Characteristics of older adults who died *with* and *without* cancer reported as cause of death

	Total cohort (n=151 201)	Cancer as cause of death (n=121 217)	No cancer as cause of death (n=29 984)	P-value
Sex, No. (%)				<.001
Men	83 429 (55.2)	65583 (54.1%)	17846 (59.5%)	
Women	67 772 (44.8)	55634 (45.9%)	12138 (40.5%)	
Age at time of death, years				
Mean (SD)	81.3 (8.1)	80.4 (8.0)	85.0 (7.5)	<.001
65 to 74 years	35 690 (23.6)	32449 (26.8%)	3241 (10.8%)	<.001
75 to 84 years	56 950 (37.7)	47443 (39.1%)	9507 (31.7%)	
85 to 94 years	52 474 (34.7)	37673 (31.1%)	14801 (49.4%)	
95 years and older	6087 (4.0)	3652 (3.0%)	2435 (8.1%)	
Level of education[b], No. (%)				<.001
Primary education	71 661 (48.9)	56733 (48.1%)	14928 (51.9%)	
Secondary education	57 937 (39.5)	47266 (40.1%)	10671 (37.1%)	
Tertiary education	17 030 (11.6)	13871 (11.8%)	3159 (11.0%)	
Living arrangement, No. (%)				<.001
Community	123 702 (81.8)	102376 (84.5%)	21326 (71.1%)	
Nursing home	27 499 (18.2)	18841 (15.5%)	8658 (28.9%)	
Place of death, No. (%)				<.001
Usual place of living	80,439 (53.2)	67609 (55.8%)	16170 (53.9%)	
Hospital facility	70,762 (46.8)	53608 (44.2%)	13814 (46.1%)	
Primary malignancy, No. (%)				<.001
Respiratory organs	18 435 (12.2)	17334 (14.3%)	1101 (3.7%)	
Esophagus and stomach	5014 (3.3)	4751 (3.9%)	263 (0.9%)	
Colon-rectum	16 102 (10.6)	14460 (11.9%)	1642 (5.5%)	
Liver and intrahepatic bile duct	3711 (2.5)	3486 (2.9%)	225 (0.8%)	
Pancreas	7808 (2.5)	7548 (6.2%)	260 (0.9%)	
Other digestive organs	3643 (2.4)	3387 (2.8%)	256 (0.9%)	
Breast	9920 (6.6)	8216 (6.8%)	1704 (5.7%)	
Urinary tract	10 231 (6.8)	7406 (6.1%)	2825 (9.4%)	
Male genital organs	25 642 (17.0)	19556 (16.1%)	6086 (20.3%)	
Female genital organs	6868 (4.5)	5972 (4.9%)	896 (3.0%)	
Melanoma of skin	2651 (1.8)	1915 (1.6%)	736 (2.5%)	
Brain and meninges	2266 (1.5)	1720 (1.4%)	546 (1.8%)	
Unknown primary site	4030 (2.7)	3907 (3.2%)	123 (0.4%)	
Other primary malignancy	16 502 (10.9)	4251 (3.5%)	12251 (40.9%)	
Multiple solid tumors	18 378 (12.2)	17308 (14.3%)	1070 (3.6%)	
Number of chronic comorbidities, No. (%)				
Mean (SD)	4.5 (2.8)	4.2 (2.7)	5.9 (3.0)	<.001
0	6 216 (4.1%)	5 914 (4.9%)	302 (1.0%)	<.001
1	14 242 (9.4%)	13 093 (10.8%)	1 149 (3.8%)	
2	19 570 (12.9%)	17 321 (14.3%)	2 249 (7.5%)	
3	22 039 (14.6%)	18 810 (15.5%)	3 229 (10.8%)	
4	21 529 (14.2%)	17 611 (14.5%)	3 918 (13.1%)	
≥5	67 605 (44.7%)	48 468 (40.0%)	19 137 (63.8%)	
Chronic comorbidities, No. (%)				
Hypertension	66 553 (44.0%)	51 519 (42.5%)	15 034 (50.1%)	<.001
Ischemic heart disease	50 896 (33.7%)	35 468 (29.3%)	15 428 (51.5%)	<.001
Heart failure	42 049 (27.8%)	27 563 (22.7%)	14 486 (48.3%)	
Atrial fibrillation	36 584 (24.2%)	25 531 (21.1%)	11 053 (36.9%)	<.001
Diabetes	31 279 (20.7%)	24 520 (20.2%)	6 759 (22.5%)	<.001
Cerebrovascular disease	28 730 (19.0%)	19 320 (15.9%)	9 410 (31.4%)	<.001

	Total cohort (n=151 201)	Cancer as cause of death (n=121 217)	No cancer as cause of death (n=29 984)	P-value
Sex, No. (%)				<.001
Cataract and other lens diseases	24 388 (16.1%)	18 789 (15.5%)	5 599 (18.7%)	<.001
COPD, emphysema, chronic bronchitis	22 465 (14.9%)	17 349 (14.3%)	5 116 (17.1%)	<.001
Dementia	18 629 (12.3%)	12 451 (10.3%)	6 178 (20.6%)	<.001

eTable 5 – Use of preventive drugs during the final month of life, by cancer type

	Drugs used in diabetes	Vitamins	Mineral supplements	Antithrombotic agents	Drugs used in the treatment of hypertension	Lipid modifying agents	Bisphosphonates	Anti-anemic preparations
	%	%	%	%	%	%	%	%
Respiratory organs	13.3%	8.5%	18.1%	47.1%	58.3%	20.7%	4.6%	23.7%
Esophagus and stomach	12.6%	7.8%	14.1%	40.9%	53.6%	15.4%	1.6%	37.1%
Colorectal	13.9%	8.6%	18.1%	43.1%	57.9%	15.2%	2.5%	34.0%
Liver and intrahepatic bile duct	25.2%	8.8%	16.7%	43.5%	70.1%	18.2%	3.2%	23.3%
Pancreas	28.1%	6.6%	18.8%	46.7%	60.6%	18.3%	2.4%	20.4%
Other digestive organs	14.1%	8.3%	19.2%	42.4%	59.4%	14.5%	2.8%	29.9%
Breast	13.3%	8.9%	25.2%	45.7%	59.8%	10.2%	9.0%	27.6%
Urinary tract	15.2%	11.0%	17.4%	50.1%	63.8%	19.2%	2.9%	34.7%
Male genital organs	13.5%	9.9%	17.4%	53.6%	60.4%	17.8%	3.3%	33.3%
Female genital organs	12.7%	9.0%	21.8%	46.2%	57.1%	12.7%	4.0%	27.9%
Melanoma of skin	14.4%	8.2%	16.4%	49.2%	63.3%	18.6%	3.5%	25.8%
Brain and meninges	20.0%	4.6%	25.1%	41.4%	54.9%	17.8%	6.9%	15.7%
Unknown primary site	15.3%	9.3%	20.3%	51.6%	65.0%	18.4%	4.0%	33.2%
Other primary malignancy	13.3%	12.4%	23.5%	55.5%	65.4%	16.5%	4.3%	35.9%
Multiple solid tumors	14.4%	8.0%	17.9%	44.6%	56.9%	16.6%	3.4%	26.9%
Total cohort	**14.9%**	**9.2%**	**19.2%**	**48.1%**	**60.1%**	**16.8%**	**3.9%**	**30.4%**

eTable 6 – Sensitivity analysis: use of preventive drugs during the last year of life of older adults (≥65 years) with cancer, after excluding individuals who died from acute and possibly unpredictable causes (n= 102 515)

	12th month before death	Last month before death	Absolute change
	Percent	Percent	Percent points (95%CI)
Drugs used in diabetes	13.8%	14.9%	1.04 (0.7 to 1.3)
Insulin and analogues	7.4%	10.2%	2.78 (2.5 to 3)
Blood glucose-lowering drugs	8.8%	7.1%	-1.71 (-1.9 to -1.5)
Vitamins	7.5%	8.5%	0.99 (0.8 to 1.2)
Mineral supplements	13.9%	18.5%	4.55 (4.2 to 4.9)
Calcium	10.0%	10.4%	0.41 (0.1 to 0.7)
Potassium	4.2%	7.6%	3.32 (3.1 to 3.5)
Antithrombotic agents	44.3%	45.6%	1.25 (0.8 to 1.7)
Vitamin K antagonists	7.2%	4.8%	-2.4 (-2.6 to -2.2)
Heparin group	3.0%	11.2%	8.2 (8 to 8.4)
Platelet aggregation inhibitors	35.6%	33.3%	-2.33 (-2.7 to -1.9)
Drugs used in the treatment of hypertension	58.9%	58.3%	-0.59 (-1 to -0.2)
Low-ceiling diuretics	6.5%	5.2%	-1.31 (-1.5 to -1.1)
Potassium-sparing agents	6.8%	11.3%	4.55 (4.3 to 4.8)
Beta blocking agents	36.4%	36.6%	0.23 (-0.2 to 0.6)
Calcium channel blockers[d]	18.5%	15.2%	-3.3 (-3.6 to -3)
ACE inhibitors	19.7%	17.3%	-2.39 (-2.7 to -2.1)
Angiotensin II antagonists	11.6%	9.5%	-2.14 (-2.4 to -1.9)
Lipid modifying agents	21.6%	16.2%	-5.46 (-5.8 to -5.1)
HMG CoA reductase inhibitors	21.1%	15.6%	-5.51 (-5.8 to -5.2)
Bisphosphonates	4.1%	3.9%	-0.23 (-0.4 to -0.1)
Anti-anemic preparations	23.5%	27.4%	3.89 (3.5 to 4.3)
Iron preparations	6.8%	10.1%	3.25 (3 to 3.5)
Vitamin B12 and folic acid	19.3%	21.1%	1.74 (1.4 to 2.1)

eTable 7 – Sensitivity analysis: use of preventive drugs throughout the last year of life of older adults (≥65 years) with cancer, according to the time between cancer diagnosis and death

	Time from cancer diagnosis to death					
	More than 12 months		6 to 12 months		Less than 6 months	
	12th month	Last month	12th month	Last month	12th month	Last month
	Percent	Percent	Percent	Percent	Percent	Percent
Drugs used in diabetes	13.9%	14.4%	13.4%	14.3%	14.6%	16.5%
Insulin and analogues	8.1%	9.9%	6.7%	10.1%	7.1%	10.6%
Blood glucose-lowering drugs	8.0%	6.4%	9.3%	6.4%	10.3%	9.2%
Vitamins	8.9%	9.4%	7.2%	8.5%	6.7%	8.3%
Mineral supplements	16.1%	19.9%	12.3%	18.2%	12.3%	17.8%
Calcium	11.2%	11.9%	9.0%	9.4%	9.2%	10.0%
Potassium	5.2%	8.0%	3.6%	8.0%	3.5%	7.2%
Antithrombotic agents	48.8%	49.0%	43.2%	44.7%	43.3%	47.8%
Vitamin K antagonists	8.1%	5.8%	8.0%	4.4%	7.2%	5.7%
Heparin group	4.1%	9.8%	1.6%	12.2%	0.5%	10.6%
Platelet aggregation inhibitors	38.4%	36.9%	35.2%	31.4%	36.5%	36.1%
Drugs used in the treatment of hypertension	61.3%	59.9%	58.7%	57.2%	60.1%	62.7%
Low-ceiling diuretics	5.9%	4.7%	6.7%	4.9%	7.4%	6.4%
Potassium-sparing agents	7.8%	11.2%	5.8%	11.0%	6.5%	11.2%
Beta blocking agents	38.5%	38.7%	35.9%	35.6%	36.7%	39.1%
Calcium channel blockers[d]	18.6%	15.1%	19.3%	14.8%	20.1%	18.7%
ACE inhibitors	20.3%	18.2%	20.5%	16.7%	20.8%	20.2%
Angiotensin II antagonists	11.6%	9.6%	12.2%	9.1%	12.4%	11.4%
Lipid modifying agents	21.1%	16.1%	23.6%	15.5%	23.2%	20.3%
HMG CoA reductase inhibitors	20.5%	15.5%	23.1%	15.1%	22.7%	19.7%
Bisphosphonates	4.5%	4.3%	3.7%	3.4%	3.7%	3.6%
Anti-anemic preparations	27.3%	30.4%	22.3%	27.6%	20.9%	27.9%
Iron preparations	8.4%	10.9%	7.0%	10.8%	5.0%	10.6%
Vitamin B12 and folic acid	22.3%	24.0%	17.9%	20.7%	18.1%	21.1%

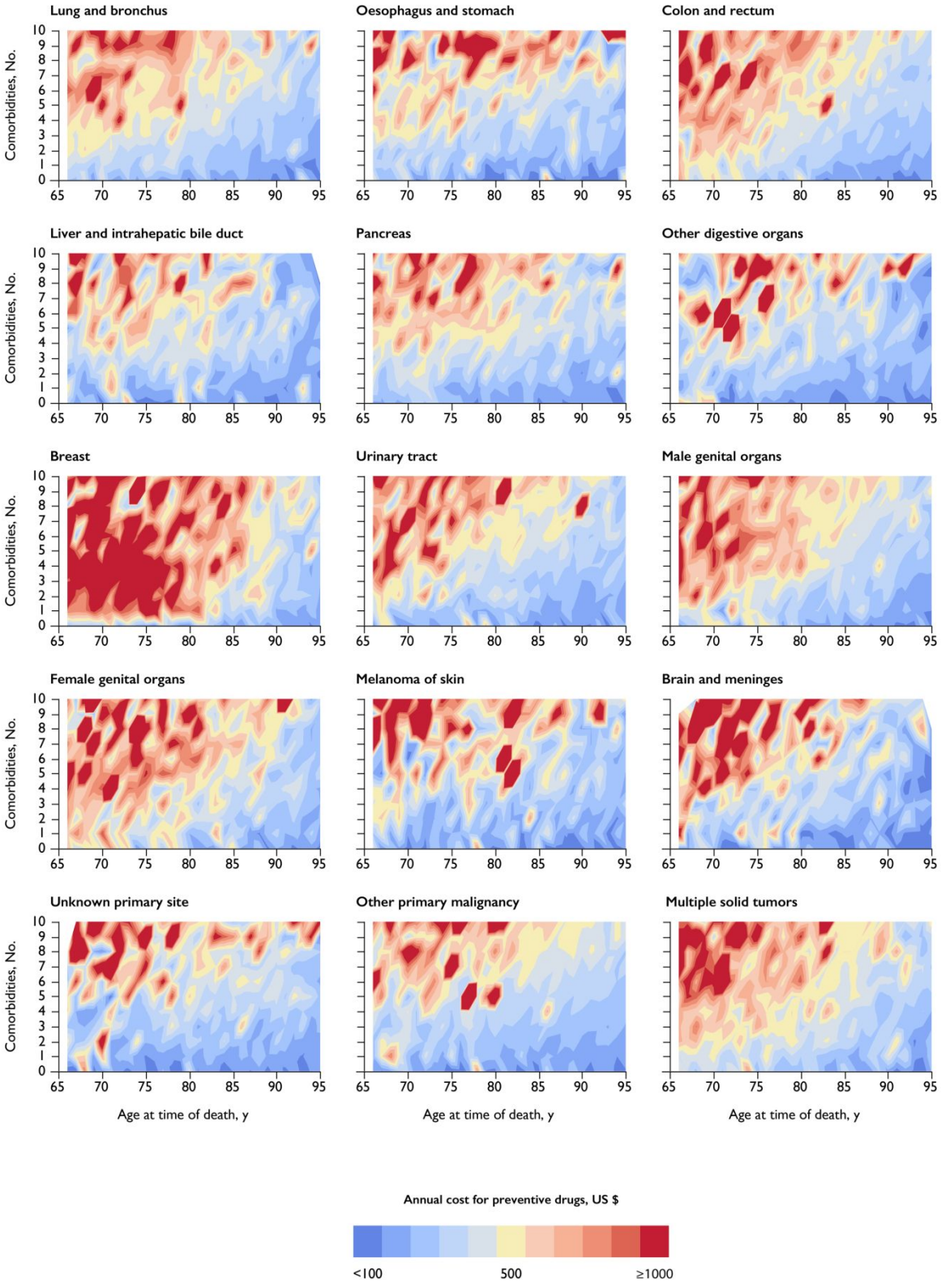
eTable 8 – Change in the costs of all prescription drugs throughout the final year of life, by cancer type

Primary malignancy	Decedents, No.	12th month	Last month	Median difference (US $), 95% CI	P value
		Median (IQR), US $	Median (IQR), US $		
Respiratory organs	18 435	66 (20 to 162)	160 (72 to 305)	+94.3 (90.8 to 97.8)	<0.001
Esophagus and stomach	5014	52 (16 to 124)	132 (56 to 293)	+80.0 (74.0 to 86.0)	<0.001
Colorectal	16 102	58 (21 to 132)	119 (54 to 243)	+61.1 (58.1 to 64.0)	<0.001
Liver and intrahepatic bile duct	3711	62 (22 to 136)	123 (55 to 247)	+60.9 (54.1 to 67.7)	<0.001
Pancreas	7808	57 (19 to 134)	161 (74 to 329)	+104.5 (98.9 to 110.1)	<0.001
Other digestive organs	3643	55 (19 to 133)	123 (55 to 267)	+68.1 (61.3 to 74.8)	<0.001
Breast	9920	112 (43 to 258)	173 (73 to 330)	+61.0 (54.2 to 67.8)	<0.001
Urinary tract	10 231	70 (27 to 152)	127 (59 to 255)	+56.5 (52.4 to 60.5)	<0.001
Male genital organs	25 642	183 (63 to 363)	251 (110 to 452)	+67.4 (62.2 to 72.6)	<0.001
Female genital organs	6868	71 (27 to 159)	138 (61 to 292)	+66.5 (61.1 to 71.9)	<0.001
Melanoma of skin	2651	59 (20 to 131)	117 (56 to 229)	+58.6 (51.4 to 65.9)	<0.001
Brain and meninges	2266	49 (12 to 125)	159 (75 to 297)	+109.6 (100.6 to 118.5)	<0.001
Unknown primary site	4030	58 (22 to 130)	108 (52 to 209)	+50.5 (45.2 to 55.7)	<0.001
Other primary malignancy	16 502	80 (36 to 165)	110 (55 to 216)	+30 (27.1 to 32.8)	<0.001
Multiple solid tumors	18 378	83 (28 to 216)	180 (79 to 366)	+97.7 (93.4 to 101.9)	<0.001
Total cohort	**151 201**	**80 (29 to 195)**	**153 (68 to 314)**	**+73.1 (71.7 to 74.4)**	**<0.001**

eTable 9 – Change in the costs of preventive drugs throughout the final year of life, by cancer type

Primary malignancy	Decedents, No.	12th month	Last month	Median difference (US $), 95% CI	P value
		Median (IQR), US $	Median (IQR), US $		
Respiratory organs	18 435	11 (0-31)	13 (3-38)	+1.89 (1.35 to 2.43)	<0.001
Esophagus and stomach	5014	12 (1-31)	12 (3-33)	-0.16 (-1.09 to 0.77)	0.732
Colorectal	16 102	12 (2-31)	14 (3-34)	+1.33 (0.80 to 1.86)	<0.001
Liver and intrahepatic bile duct	3711	14 (3-34)	15 (5-38)	+1.74 (0.53 to 2.94)	<0.001
Pancreas	7808	11 (0-29)	14 (3-42)	+2.42 (1.61 to 3.24)	<0.001
Other digestive organs	3643	12 (2-28)	12 (3-34)	+0.71 (-0.30 to 1.73)	0.168
Breast	9920	13 (3-34)	14 (4-35)	+0.17 (-0.51 to 0.85)	0.620
Urinary tract	10 231	15 (4-35)	15 (5-36)	+0.23 (-0.47 to 0.94)	0.515
Male genital organs	25 642	14 (4-32)	14 (4-32)	-0.24 (-0.65 to 0.16)	0.236
Female genital organs	6868	13 (2-34)	15 (3-45)	+1.69 (0.76 to 2.63)	<0.001
Melanoma of skin	2651	13 (3-31)	13 (4-34)	+0.71 (-0.58 to 2.00)	0.280
Brain and meninges	2266	9 (0-30)	13 (2-40)	+3.59 (2.14 to 5.03)	<0.001
Unknown primary site	4030	13 (3-30)	15 (5-35)	+1.48 (0.48 to 2.48)	<0.001
Other primary malignancy	16 502	16 (5-34)	16 (5-35)	-0.20 (-0.71 to 0.32)	0.451
Multiple solid tumors	18 378	12 (1-33)	13 (3-37)	+1.01 (0.48 to 1.53)	<0.001
Total cohort	**151 201**	**13 (3–32)**	**14 (4–36)**	**+0.78 (0.60 to 0.95)**	**<0.001**

eFigure 2 – Mean costs for preventive drugs during the final year of life, by cancer type, age at death and number of chronic comorbidities, in US $



eTable 10 – Sensitivity analysis: preventive drugs costs during the final year of life, by cancer type and according to the time between cancer diagnosis and death

Primary malignancy	Total	Time from cancer diagnosis to death			P value
		More than 12 months	6 to 12 months	Less than 6 months	
	Median, US $ (P25-P75)	Median (IQR), US $	Median (IQR), US $	Median (IQR), US $	
Respiratory organs	205 (61-523)	219 (71-562)	228 (71-665)	192 (51-480)	<0.001
Esophagus and stomach	199 (68-479)	217 (80-543)	209 (85-535)	187 (51-439)	<0.001
Colorectal	209 (72-479)	217 (76-529)	213 (77-539)	204 (65-430)	<0.001
Liver and intrahepatic bile duct	222 (82-514)	229 (89-531)	240 (99-596)	222 (76-510)	0.0305
Pancreas	213 (69-520)	208 (69-511)	222 (64-620)	216 (70-510)	0.1337
Other digestive organs	191 (65-426)	198 (72-472)	198 (58-513)	196 (61-422)	0.2278
Breast	218 (81-528)	238 (88-610)	235 (92-535)	202 (72-404)	<0.001
Urinary tract	232 (93-508)	236 (99-515)	252 (95-570)	222 (82-480)	<0.001
Male genital organs	209 (80-450)	213 (84-461)	210 (74-449)	206 (75-428)	0.0102
Female genital organs	239 (86-573)	252 (89-635)	279 (113-723)	230 (79-491)	<0.001
Melanoma of skin	200 (68-458)	204 (73-468)	213 (64-545)	187 (70-414)	<0.001
Brain and meninges	205 (63-572)	191 (47-721)	251 (76-855)	205 (67-494)	<0.001
Unknown primary site	203 (82-431)	215 (87-448)	217 (70-617)	211 (88-437)	0.5715
Other primary malignancy	221 (93-444)	226 (98-449)	224 (90-456)	212 (83-437)	0.009
Multiple solid tumors	219 (74-545)	224 (78-557)	236 (81-632)	190 (52-439)	<0.001
Total cohort	**213 (77-490)**	**221 (84-509)**	**225 (80-560)**	**204 (66-459)**	**<0.001**

P-values were calculated with non-parametric Wilcoxon rank sum tests stratified by primary malignancy.

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Abstract, line 6 Abstract, lines 5-6 Abstract, line 6
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			Page 4
Objectives	3	State specific objectives, including any prespecified hypotheses			Page 5, line 6
Methods					
Study Design	4	Present key elements of study design early in the paper			Page 6, lines 2-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			Page 6, lines 2-17

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Page 6, lines 8-17 Page 6, lines 10-15 Page 6, line 5 + Figure 1
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Page 6 +Appendix eTable 1
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group			Pages 6-7

Bias	9	Describe any efforts to address potential sources of bias			Page 8, lines 1-17
Study size	10	Explain how the study size was arrived at			N.A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			Page 8, lines 1-17
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			Page 8, lines 1-17 Appendix eTables 5, 6, 7, 8, 9 and 10 + eFigure 2 No loss to follow-up by design (retrospective cohort of decedents)
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	Page 6, lines 2-7

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Page 6, line 5
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Figure 1
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			Page 9, lines 2-12 + Table 1
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure			Page 9-10 Table 2

		category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			Pages 9-10 Tables 2, 3
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			Page 10, lines 1-4 Page 10, lines 25-26
Discussion					
Key results	18	Summarise key results with reference to study objectives			Page 11, lines 2-7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Page 12, from line 22 onwards
Interpretation	20	Give a cautious overall interpretation of results considering objectives,			Pages 11-12

		limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results			Page 13, lines 10-12
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			Page 2
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Page 2

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

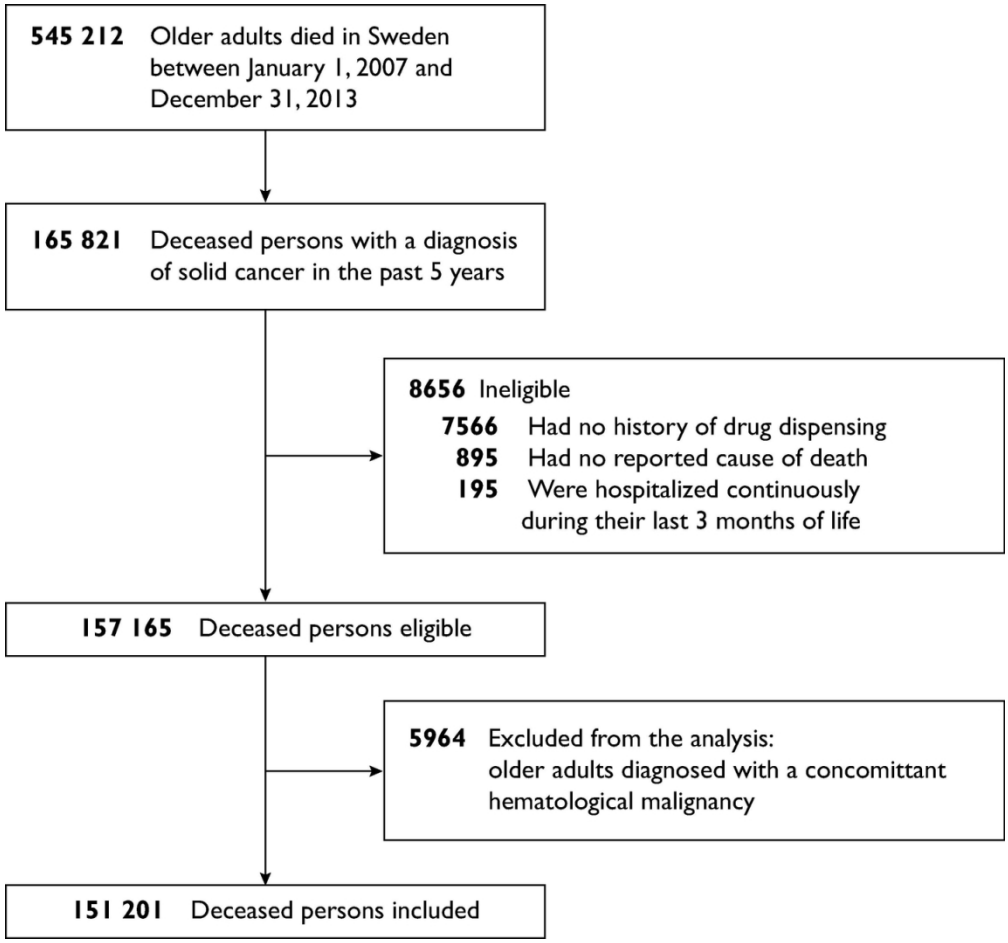


Figure 1

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