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Title

Comorbidity trajectories in working age cancer survivors: a national study of Swedish men

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Abstract

Background A large proportion of cancer survivors are of working age, and maintaining health is of interest both for their working and private life. However, patterns and determinants of comorbidity over time among adult cancer survivors are incompletely described. We aimed to identify distinct comorbidity trajectories and their potential determinants.

Methods In a cohort study of Swedish men born between 1952 and 1956, men diagnosed with cancer between 2000 and 2003 (n= 878) were matched with cancer-free men (n=4,340) and followed over five years after their first year of survival. Comorbid diseases were identified using hospital diagnoses and included in the analysis using group-based trajectory modelling. The association of socioeconomic and developmental characteristics were assessed using multinomial logit models.

Results Four distinct comorbidity trajectories were identified. As many as 84% of cancer survivors remained at very low levels of comorbidity, and the distribution of trajectories was similar among the cancer survivors and the cancer-free men. Increases in comorbidity were seen among those who had comorbid disease at baseline and among those with poor summary disease scores in adolescence. Socioeconomic characteristics and physical, cognitive and psychological function were associated with types of trajectory in unadjusted models but did not retain independent relationships with them after simultaneous adjustment.

Conclusions Among working-age male cancer survivors, the majority remained free or had very low levels of comorbidity. Those with poorer health in adolescence and pre-existing comorbid diseases at cancer diagnosis may, however, benefit from follow-up to prevent further increases in comorbidity.

Key words

Cancer; survivor; comorbidity; trajectory; adolescence; longitudinal; risk factor

Highlights:

- Four trajectories were found in cancer survivors and cancer-free men.
- Over 80% of men remained free or had low levels of comorbidity in both cohorts.
- The distribution of trajectories was similar in the two cohorts.
- Having higher comorbidity after cancer was linked with poor health prior to baseline.
- Those with higher risk of developing disease may benefit from increased follow-up.

1 Introduction

Approximately 40% of cancer diagnoses are made in individuals of working age [1], and health after surviving cancer is a concern for both work and private life. Cancer and cancer treatments can have a substantial physical and psychological impact that may persist over time [2, 3]. This may include increased risks for hypothyroidism, osteoporosis, diabetes, cardiovascular diseases and problems of cognitive dysfunction, pulmonary, urinary and bowel function [4-8]. However, studies monitoring long-term comorbidity have often focused on presence or absence of specific diseases [9] or treatments [10], but not on the accumulation of disease. Also, previous studies have examined on specific cancer types, such as testicular and breast cancer among adults [8], or childhood cancer survivors [11-13] for whom chronic disease risk is different from adult-onset cancer. Patients with more serious illness may be underrepresented due to loss to follow-up in surveys [14]. Little is known about heterogeneity in comorbidity trajectory, i.e. whether there may be distinct subgroups that follow different courses of disease accumulation after surviving adult-onset cancer. There is a social gradient in the risk of cancer in general [15], so socioeconomic characteristics may also increase the risk of health problems following cancer treatment particularly for more disadvantaged individuals. On the other hand, higher physical, cognitive and psychological capacity may buffer some of the disease risk [16-19]. Characterising types and predictors of comorbidity trajectories may help to identify individuals at high risk of an unfavourable prognosis.

The aim of this study is first to identify and compare trajectories for accumulation of comorbidity over five years in working-age cancer survivors and cancer-free individuals. A secondary aim is to examine whether individual socioeconomic and developmental characteristics (physical, cognitive and psychological function) predict trajectory membership, as these factors have been found to influence cancer risk [15] and comorbidity [20].

2 Materials and Methods

Using Swedish registers, data from a cohort of men born from 1952 to 1956 was analysed using group-based trajectory modelling and multinomial regression analysis. A first lifetime cancer diagnosis was identified between 2000 and 2003, and follow-up started one year after cancer diagnosis and ended at five years, death or emigration, whichever occurred first.

2.1 Cancer diagnosis

The *Cancer Register*, with a recorded high completeness [21], holds information of all cancer diagnoses in Sweden since 1958, coded according to the International Classification of Diseases [ICD]-7. To reduce the heterogeneity in cancer type, treatment and prognosis, we focused on colorectal (ICD-7 153, 154), male genitourinary system (including kidney and urinary tract) (177-

181), skin (190-191) and lung cancers (including bronchus) (162-163), as well as leukaemia (204-207 excluding 204.1), and thyroid cancer (194). These diagnoses were chosen as they are relatively common. The five-year survival rate varied, with approximately 90% survival for skin, thyroid and male genital system cancers, around 60-80% for cancers of the kidney, urinary system, colon, rectum and leukaemia, and fewer than 20% for lung cancer [22, 23]. Lung, leukaemia and thyroid cancers were combined due to data scarcity.

2.2 *Comorbidity*

Common comorbidities including depression, anxiety, osteoporosis and infectious disease [5, 6, 8, 24] were identified using the Patient Register. We also included diseases used for the Charlson comorbidity index – myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, chronic renal failure, mild liver disease, diabetes with and without chronic complication, renal disease, hemiplegia or paraplegia, moderate or severe liver disease, and acquired immunodeficiency syndrome (AIDS/HIV) [25-28]. The Swedish versions of ICD-9 and 10 were used to identify comorbidities (codes are shown in appendix). Comorbidity at the start of follow-up was the summary of incident primary diagnoses recorded in the Patient Register (from 1987 for inpatient diagnoses and from 2001 for outpatient diagnoses). Follow-up was limited to five years as the patient register data were available up to the end of 2009. During follow-up, comorbidity was summarised every three months; for example, an incident diagnosis of one of the diseases increased the comorbidity count by one. The count is carried forward until another incident disease is identified [29, 30]. As we focused on chronic conditions diagnoses viewed as acute events, such as peptic ulcer and infectious disease [30], were not carried forward.

2.3 *Developmental and socioeconomic characteristics*

Emotional regulation [31] and physical activity patterns [32] that have developed by late adolescence may persist into adult life; and cognitive ability in childhood correlates with mid-life cognition, socioeconomic position and behaviour [33, 34]. Thus, physical, cognitive and psychological function and health characteristics in adolescence may have profound implications for future health. These measures were assessed in the conscription examination in the early 1970s when most of these men were 18-19 years of age. Trained psychologists produced ratings for psychological and cognitive function by combining evaluations using questionnaires, interviews and tests [35]. A normally distributed nine-level scale for stress resilience was constructed as a compound variable derived by combining evaluations of psychological dimensions such as social maturity, level and direction of interests, psychological energy and emotional stability [16]. Similarly, a normally distributed nine-level scale for cognitive function summarised the examination of linguistic understanding, spatial recognition, general knowledge and the ability to follow mechanical instructions. Physical function

was assessed using an electronically braked bicycle ergometer with gradually increasing load. These variables were used as continuous measures with higher values indicating lower function. The disease score summarised medical examination and record review results and consisted of 0-9 categories, and this was collapsed into: 0=no diagnosis, 1=no serious health problems and 2= fairly significant to significant health problems.

The Longitudinal Integration Database for Health Insurance and Labour Market Studies [36] in 1990 provided the most recent information on socioeconomic measures before cancer diagnosis. Individual disposable income after subtracting taxes [37] was used as an indicator of socioeconomic position (hereafter, it is expressed as income). It was divided into ten equally sized groups by decile points from the highest (=0) to the lowest (=9) and used as a continuous variable. Marital status was categorised as: married, single and divorced or widowed, and the married was the reference category. Age at cancer diagnosis [38] and cancer type [12] were included in the analysis.

2.4 Analytical sample

Among 284,257 men, 1,125 were diagnosed with one of the defined cancer types as a first cancer between January 1, 2000 and December 31, 2003. We excluded those who died (n=133), had a history of emigration (n=32), or emigrated (n=1) within a year after the diagnosis. Each of the remaining 959 men was matched at the time of the cancer diagnosis with five cancer-free subjects who were alive at the time of diagnosis and born in the same year. The most recent available information on county of residence (24 counties) was in 1985 and this was also used for matching [39]. Among the 4,795 cancer-free men, we excluded 37 record duplicates and 16 individuals who died, emigrated or developed the incident cancer before the start of follow-up. Another 81 and 402 subjects were excluded from the survivor and cancer-free cohorts, respectively, due to missing data in relevant variables or an ill-defined summary disease score in the conscription assessment. Thus, 878 and 4,340 subjects with and without cancer, respectively, were included in the analysis.

2.5 Analysis

Group-based trajectory modelling [40] identifies distinct trajectories for groups of individuals approximately following the same developmental course over time. Membership probability for all trajectory groups and individuals is calculated using maximum likelihood estimation, and subjects are assigned to a group that showed the highest membership probability. A zero-inflated Poisson distribution model was employed as the proportions of individuals without a comorbid diagnosis was high. The number of groups and the order of polynomial functions (whether the shape of trajectory was constant, linear or quadratic) was determined by the Bayesian Information Criterion [40]. Based on a preceding study [41], we started from testing a three-group model, and for both cohorts, four-group models were selected. The average probability of membership for all groups exceeded 95%, which was well above the recommended 70% [40]. The confidence intervals for the mean count of

comorbid diseases were obtained by using 500 bootstrapped samples. The extent to which exposure variables predict the likelihood of belonging to a particular trajectory group was examined using multinomial logit models. Unadjusted and adjusted estimates were produced by controlling for socioeconomic, demographic and developmental characteristics and the type of cancer for the survivor cohort. Sensitivity analysis was conducted by excluding those who had a diagnosis of any cancer after the start of follow-up. All analyses were conducted using Stata/SE version 14. This study has been approved by Uppsala Regional Ethics Committee (Dnr 2014/324).

3 Results

The four comorbidity trajectories identified were similar in the cancer survivor and cancer-free cohorts: 1) **a constant low trajectory**, 2) **a low start and an acute increase trajectory**, 3) **a medium start and a slow increase trajectory**, and 4) **a high start and a slow increase trajectory** (**Figure 1**). For each trajectory, the observed and predicted values were similar, apart from the acute increase trajectory around the end of follow-up. For ease of understanding, observed comorbidity for five randomly sampled individuals from each trajectory in the survivor cohort is presented (**Figure 2**).

Estimated intercept and slope coefficients (**Table 1**) and the characteristics of the two cohorts (**Table 2**) by the trajectory groups are displayed. At the start of follow-up, the overall means for the number of diagnoses was higher in the survivor cohort than the cancer-free cohort (0.13 (SD 0.40) and 0.08 (0.32), respectively). The difference was slightly increased at the end of follow-up and the means of the number of diagnoses were 0.24 (0.67) for the survivor cohort and 0.15 (0.49) for the cancer-free cohort.

Although stress resilience and the summary disease score measured in adolescence showed slightly more favourable values for the general population cohort, the differences between the cohorts were only marginal. Physical and cognitive function in adolescence and income in 1990 were similar in both cohorts or slightly higher for the survivor cohort. Those who were excluded from the cancer survivor cohort (n=81, 8%) and the cancer-free cohort (n=404, 8%) tended to have poorer health in adolescence and had lower income in adulthood.

Within each cohort, the constant low trajectories showed the most favourable developmental and socioeconomic characteristics. Conversely, the highest comorbidity trajectory followed by the acute increase trajectory were characterised by having the least favourable attributes. In the survivor cohort, the distribution of trajectories was similar for colorectal, genitourinary and skin cancers, and about 85% were classified in the constant low trajectory (**Figure 3**). For lung and thyroid cancer, and to a lesser extent for leukaemia, the majority were still in the constant low trajectory, with around 20-30% in the medium start trajectory.

Compared with the constant low trajectory, in unadjusted analysis, lower stress resilience, and to a lesser extent lower cognitive and physical function, income and poorer disease score, tended to be associated with membership of the acute or high trajectories in both cohorts (**Table 3**). Only the cancer group that includes lung, leukaemia and thyroid cancers was associated with membership of the medium or high trajectories. When all variables were included in the model for both the survivor and the cancer-free cohorts, only poor disease score in adolescence, and the cancer group for the survivor cohort, were associated with trajectory membership. Developmental and socioeconomic characteristics hardly retained independent associations with trajectories. The results did not change notably when those who had a cancer diagnosis during follow-up were excluded (n=60 in the cancer survivor cohort and n=59 in the cancer-free cohort).

4 Discussion

In this Swedish register-based study, we identified four distinct trajectories to describe the accumulation of comorbidity over five years following the first year after cancer diagnosis. The findings indicate that, despite the notion of increased risk of adverse sequelae due to cancer and cancer treatments, 84% of cancer survivors remained free (or had very low levels) of comorbidity. The distribution of trajectories was not substantially different between the cancer survivors and cancer-free cohort. The trajectories were distributed similarly between colorectal, genitourinary and skin cancers, with approximately 85% of subjects in the constant low trajectory. For lung, leukaemia and thyroid cancer, about 60-70% of subjects were in the constant low trajectory, and 20-30% were in the medium-start trajectory. Physical, cognitive and psychological characteristics in adolescence and income in adulthood predicted trajectory group membership in the unadjusted but not multivariable analysis. Only the summary disease score in adolescence retained some independent associations.

Despite concerns about adverse health sequelae after surviving cancer, little was known about the course of comorbidity accumulation. We found that there was heterogeneity in comorbidity trajectory after surviving cancer. Also, more than 80% of the cancer survivors lived with generally very few or no diseases (apart from cancer) for five years after the first year following the cancer diagnosis. The pattern may of course be different for older people with cancer, as this is a study of people of working age. The prevalence of comorbidity-free cancer survivors has previously been reported to be about 30% to 60% in other countries [5, 42-44]. Our cohort members were younger than the subjects in these studies, which may explain the observed higher proportion of comorbidity-free subjects. However, the results belie the notion that cancer and cancer treatments necessarily always lead to adverse health sequelae. This is not to deny the burden of comorbidity for survivors, but the experience differed by trajectory groups. Those who started without comorbidity tended to continue at a very low level or free of comorbidity. In contrast, those who had comorbid diseases at baseline experienced some increase in disease burden, approximating to one additional disease. It may be

reasonable therefore to expect further increases with time. The presence of comorbidity has implications for the prognosis of cancer, treatment decisions and ultimate survival, while the evidence-base for the impact of comorbidity in the context of cancer is currently limited [45]. Further research on recurrence, treatment and survival outcomes in relation to accumulation of comorbidity, preferably with longer follow-up, will be informative for outcomes among cancer survivors.

Notwithstanding the expected inverse associations between socioeconomic position and cancer risk in general [15], we found that physical, cognitive and psychological function in adolescence and adult socioeconomic position were not necessarily more favourable in the cancer-free cohort than in the survivor cohort. Individuals with an advantageous position may make more use of medical services and therefore have a higher probability of being detected with some cancers such as prostate [46] and skin cancer [47]. Also, those who did not survive the first year after their diagnosis had on average lower income than those who survived. As a result of such selection effects, individuals in the survivor cohort may not necessarily be disadvantaged compared with those in the cancer-free cohort. Within each cohort, in the unadjusted analysis, unfavourable developmental and socioeconomic characteristics tended to be associated with the trajectories that had started with a higher number of comorbid diseases and where the number of diseases increased subsequently. This is consistent with earlier studies that have reported the risk of depression, anxiety, infection and the number of diseases [16-19] to be higher for socially disadvantaged individuals and had lower cognitive and physical function. However, most of the associations, apart from poor disease score in adolescence, diminished in magnitude in models adjusted for all variables in both cohorts. Adulthood socioeconomic position may in part be a consequence of earlier experiences and psychological, cognitive and physical function. Adjustment for these variables, therefore, might have been over-adjustment.

Our study has potential limitations. First, as the identification of comorbidity was limited to inpatient and outpatient diagnoses, meaning that some conditions that were treated in primary care (such as many depressions) were not included. Second, the models taking the different reasons for censorship (including for mortality) into account did not converge and therefore were not used. However, this should only have limited impact on the results since the estimated trajectories did not show notable differences when models were tested in the preliminary analysis, both before and after accounting for censorship. Most of the exclusions were due to common missingness in variables for characteristics in adolescence. Using all available data, the direction and magnitude of associations for income were similar to that of the complete case analysis, apart from the statistically significant association of income with the high start trajectory in the survivor cohort. Third, cancer stage may be important for predictions of trajectory, but this information was unfortunately not available before 2004. Fourth, the number of subjects was limited in some groups, and this may be of concern, particularly in the adjusted models. In analyses of the cancer-free cohort, which has a larger sample size, the statistically significant associations diminished for physical, cognitive and psychological function when the model

included the summary health score in adolescence. Similar patterns of change in the associations were observed for the cancer-survivor cohort, and this may provide some indication that the result may not be due solely to lack of statistical power. However, replication of the study would be advisable, with a larger sample size. Fifth, developmental characteristics, income and marital status were measured several years before the cancer diagnosis. These characteristics predicted various disease risks in adult life, indicating stable associations with the health outcomes investigated here. However, changes in characteristics that occurred before the start of follow-up may have resulted in reduced precision of some estimates. Finally, as our subjects were limited to men and aged in their late 40s to early 50s when diagnosed with cancer, the results may not be generalizable to women, or other cancer types and periods.

Strengths of this study pertain to the use of nationwide register data that enables inclusion of essentially all men who met our eligibility criteria, regardless of health conditions after cancer survival. Also, underestimation of comorbidity in the current study is of less concern than in studies relying on surveys, where subjects with an unfavourable prognosis are less likely to participate. Unlike earlier studies focusing on childhood cancer survivors, this study shows patterns of long-term comorbidity accumulation among adult-onset cancer patients in the working-age male population.

This study identified four distinct trajectories of comorbidity after cancer survival for men in their late 40s to early 50s at the time of cancer diagnosis. The distribution of trajectories appeared not to differ substantially from those in the cancer-free cohort. The majority of men, who started without comorbidity, stayed without comorbidity or experienced a very low level of comorbidity. Some increases in comorbidity were seen among those who already had some diseases other than cancer, which were linked to unfavourable socioeconomic and developmental characteristics, in particular, poor health in adolescence.

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Table 1 Estimated intercept and slope coefficients for trajectory groups over the five-year follow-up for cancer survivor and cancer-free cohorts

	Lowest and constant morbidity	Low start and an acute increase	Medium start and a slow increase	High start and a slow increase
	Cancer survivor cohort			
Intercept (log) (95% CI)	-5.65 (-5.97, -5.34)	-4.40 (-5.13,-3.67)	-0.16 (-0.26, -0.05)	0.69 (0.53, 0.85)
Slope coefficient (log) (95% CI)	Not applicable	0.23 (0.19, 0.28)	0.02 (0.01, 0.03)	0.02 (0.01, 0.03)
	Cancer-free cohort			
Intercept (log) (95% CI)	-6.14 (-6.42, -5.86)	-3.90 (-4.22, -3.57)	-0.17 (-0.22, -0.12)	0.69 (0.62, 0.76)
Slope coefficient (log) (95% CI)	0.02 (0.00, 0.05)	0.22 (0.20, 0.23)	0.02 (0.01, 0.02)	0.02 (0.01, 0.02)

CI: confidence interval

Table 2 The distribution of socioeconomic, physical, cognitive and psychological characteristics by trajectory groups over the five-year follow-up for cancer survivor and cancer-free cohorts

		Cancer survivor cohort					Cancer-free cohort				
		Total	Lowest and constant morbidity	Low start and an acute increase	Medium start and a slow increase	High start and a slow increase	Total	Lowest and constant morbidity	Low start and an acute increase	Medium start and a slow increase	High start and a slow increase
Total		878 (100%)	734 (84%)	28 (3%)	91 (10%)	25 (3%)	4,340 (100%)	3,851 (89%)	119 (3%)	298 (7%)	72 (2%)
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age at the start of follow-up		48.9 (1.9)	48.9 (1.9)	49.3 (1.8)	49.0 (1.8)	48.7 (1.9)	48.9 (1.9)	48.9 (1.9)	49.1 (1.6)	49.3 (1.8)	49.5 (1.9)
Stress resilience		5.0 (1.9)	4.9 (1.9)	5.5 (2.1)	5.4 (2.0)	6.1 (2.0)	4.9 (1.9)	4.9 (1.9)	5.4 (1.9)	5.0 (2.0)	5.7 (2.3)
Cognitive function		4.8 (2.0)	4.7 (2.0)	5.0 (1.9)	5.0 (2.0)	5.6 (1.6)	4.8 (2.0)	4.7 (2.0)	5.1 (1.7)	4.7 (2.0)	5.3 (2.0)
Physical fitness		3.7 (1.8)	3.7 (1.8)	4.5 (1.9)	4.0 (1.9)	4.0 (1.7)	3.8 (1.8)	3.7 (1.8)	4.1 (1.7)	3.8 (1.9)	4.0 (1.6)
Income		5.1 (2.9)	5.0 (2.8)	5.6 (3.0)	5.7 (3.0)	6.0 (2.6)	5.2 (2.8)	5.2(2.8)	5.7 (2.9)	5.0 (2.8)	6.3 (2.7)
		freq (column %)	freq (row %)	freq (row %)	freq (row %)	freq (row %)	freq (column %)	freq (row %)	freq (row %)	freq (row %)	freq (row %)
Disease summary score											
No diagnosis		355 (40)	310 (87)	7 (2)	30 (8)	8 (2)	1,904 (44)	1,718 (90)	45 (2)	124 (7)	17 (1)
No serious health problems		352 (40)	298 (85)	10 (3)	37 (11)	7 (2)	1,694 (39)	1,504 (89)	46 (3)	113 (7)	31 (2)
Fairly to significant health problems		171 (19)	126 (74)	11 (6)	24 (14)	10 (6)	742 (17)	629 (85)	28 (4)	61 (8)	24 (3)
Marital status											
Married		511 (58)	441 (86)	11 (2)	46 (9)	13 (3)	2,479 (57)	2,235 (90)	62 (3)	156 (6)	26 (1)
Single		317 (36)	252 (80)	13 (4)	41 (13)	11 (3)	1,615 (37)	1,407 (87)	48 (3)	122 (8)	38 (2)
Divorced or widowed		50 (6)	41 (82)	4 (8)	4 (8)	1 (2)	246 (6)	209 (85)	9 (4)	20 (8)	8 (3)
Cancer type											
Colorectal		188 (21)	158 (84)	6 (3)	19 (10)	5 (3)					
Genitourinary		306 (35)	266 (87)	10 (3)	25 (8)	5 (2)					
Skin		303 (35)	255 (84)	10 (3)	29 (10)	9 (3)					
Other	Lung	32 (4)	23 (72)	0 (0)	6 (19)	3 (9)					
	Leukaemia	33 (4)	20 (61)	1 (3)	9 (27)	3 (9)					
	Thyroid	16 (2)	12 (75)	1 (6)	3 (19)	0 (0)					

Lower values in stress resilience (1-9), cognitive function (1-9), physical fitness (1-10) and income decile (1-10) indicate high resilience, function and income level, and ascending the number the function/income declines.

Table 3 Risk ratio for trajectories of comorbidity disease development in the cancer survivor and cancer-free cohorts

	Cancer survivor cohort			Cancer-free cohort		
	Low start and an acute increase	Medium start and a slow increase	High start and a slow increase	Low start and an acute increase	Medium start and a slow increase	High start and a slow increase
Unadjusted model						
Stress resilience	1.17 [0.96, 1.43]	1.14 [1.01, 1.28]*	1.40 [1.12, 1.75]**	1.15 [1.05, 1.27]**	1.03 [0.97, 1.09]	1.25 [1.11, 1.42]***
Cognitive function	1.08 [0.89, 1.31]	1.07 [0.96, 1.20]	1.28 [1.04, 1.57]*	1.09 [0.99, 1.19]	0.99 [0.94, 1.06]	1.17 [1.04, 1.32]*
Physical function	1.27 [1.03, 1.58]*	1.11 [0.98, 1.25]	1.09 [0.87, 1.36]	1.12 [1.02, 1.24]*	1.03 [0.96, 1.10]	1.08 [0.95, 1.23]
Summary disease score						
No diagnosis	Reference	Reference	Reference	Reference	Reference	Reference
No serious health problems	1.49 [0.56, 3.96]	1.28 [0.77, 2.13]	0.91 [0.33, 2.54]	1.17 [0.77, 1.77]	1.04 [0.80, 1.36]	2.08 [1.15, 3.78]*
Fairly to significant health problems	3.87 [1.47, 10.20]**	1.97 [1.11, 3.50]*	3.08 [1.19, 7.97]*	1.70 [1.05, 2.75]*	1.34 [0.98, 1.85]	3.86 [2.06, 7.23]***
Income	1.08 [0.95, 1.24]	1.10 [1.02, 1.18]*	1.13 [0.98, 1.30]	1.06 [0.99, 1.13]	0.98 [0.94, 1.02]	1.15 [1.06, 1.25]***
Cancer type						
Colorectal	Reference	Reference	Reference			
Genitourinary	0.99 [0.35, 2.78]	0.78 [0.42, 1.46]	0.59 [0.17, 2.08]			
Skin	1.03 [0.37, 2.90]	0.95 [0.51, 1.74]	1.12 [0.37, 3.39]			
Other	0.96 [0.19, 4.88]	2.72 [1.33, 5.56]**	3.45 [1.01, 11.74]*			
Adjusted model						
Stress resilience	0.97 [0.77, 1.23]	1.05 [0.91, 1.20]	1.23 [0.94, 1.60]	1.08 [0.96, 1.22]	1.00 [0.93, 1.08]	1.06 [0.91, 1.23]
Cognitive function	0.98 [0.80, 1.21]	1.00 [0.89, 1.13]	1.12 [0.90, 1.40]	1.03 [0.93, 1.14]	1.00 [0.93, 1.06]	1.06 [0.93, 1.20]
Physical function	1.18 [0.94, 1.49]	1.04 [0.91, 1.18]	0.96 [0.76, 1.20]	1.07 [0.96, 1.19]	1.01 [0.94, 1.09]	0.97 [0.84, 1.12]
Summary disease score						
No diagnosis	Reference	Reference	Reference	Reference	Reference	Reference
No serious health problems	1.43 [0.53, 3.88]	1.16 [0.69, 1.96]	0.74 [0.26, 2.12]	1.07 [0.70, 1.63]	1.04 [0.79, 1.36]	1.90 [1.04, 3.48]*
Fairly to significant health problems	3.24 [1.09, 9.64]*	1.67 [0.87, 3.21]	1.79 [0.57, 5.57]	1.25 [0.72, 2.14]	1.31 [0.92, 1.87]	2.66 [1.31, 5.44]**
Income	1.03 [0.89, 1.18]	1.07 [0.98, 1.16]	1.07 [0.91, 1.26]	1.03 [0.96, 1.10]	0.96 [0.92, 1.01]	1.08 [0.99, 1.19]
Cancer type						
Colorectal	Reference	Reference	Reference			
Genitourinary	0.91 [0.32, 2.59]	0.81 [0.43, 1.52]	0.65 [0.18, 2.32]			
Skin	1.12 [0.39, 3.19]	1.01 [0.54, 1.88]	1.21 [0.39, 3.73]			
Other	0.96 [0.19, 5.01]	2.88 [1.39, 5.95]**	3.87 [1.10, 13.60]*			

Lowest morbidity group is the reference group for each cohort.

The square brackets show 95% confidence intervals.

*: p-value <0.05; **: p-value < 0.01; ***: p-value <0.001

All variables as well as marital status and age of cancer diagnosis (or age or matching) are mutually adjusted in the adjusted model.

Figure 1 Trajectory of comorbid disease development

Left: cancer survivor cohort; right: cancer-free cohort

Dot and dashed line: observed values and 95% confidence intervals (bootstrapped)

Solid line with light grey: predicted values and 95% confidence intervals

Figure 2 Changes in the comorbidity for five individuals for each trajectory group in the cancer survivor cohort

Observed comorbidity for five randomly sampled individuals from each trajectory group in the survivor cohort. Each line, solid (—), dash (---), dot (.....) short-dash (---) and long-dash (—) represents an individual.

Figure 3 Proportion of the type of incident cancer diagnosis by trajectory groups in the cancer survivor cohort

Light grey: constant low group

Black: acute increase group

Dark grey: medium start and a slow increase group

Grey: high start and a slow increase group

Appendix

Swedish version of the International Classification of Diseases version 9 and 10 codes for the identification of diagnosis

Myocardial infarction

ICD-9: 410*, 412*

ICD-10: I21*, I22*, I252*

Congestive heart failure

ICD-9: 398X*, 402A*, 402B*, 402X*, 404A*, 404B*, 404X*, 414W*, 425E*, 425F*, 425H*, 425W*, 425X*, 428*

ICD-10: I099*, I110*, I130*, I132*, I255*, I420*, I425*, I426*, I427*, I428*, I429*, I43*, I50*, P29*

Peripheral vascular disease

ICD-9: 093A*, 437D*, 440*, 441*, 443B*, 443W*, 443X*, 447B*, 557B*, 557X*, V43C*, V43E*

ICD-10: I70*, I71*, I731*, I738*, I739*, I771*, I790*, I792*, K551*, K558*, K559*, Z958*, Z959*

Cerebrovascular disease

ICD-9: 362D*, 430*, 431*, 432*, 433*, 434*, 435*, 436*, 437*, 438*

ICD-10: G45*, G46*, H340*, I60*

Dementia

ICD-9: 290*, 294B*, 331C*

ICD-10: F00*, F01*, F02*, F03*, F051*, G30*, G311*

Chronic pulmonary disease

ICD-9: 416W*, 416X*, 49*, 500*, 501*, 502*, 503*, 504*, 505*, 506E*, 508B*, 508W*

ICD-10: I278*, I279*, J40*, J41*, J42*, J43*, J44*, J45*, J46*, J47*, J60*, J61*, J62*, J63*, J64*, J65*, J66*, J67*, J684*, J701*, J703*

Rheumatic disease

ICD-9: 446F*, 710A*, 710B*, 710C*, 710D*, 710E*, 714A*, 714B*, 714C*, 714W*, 725*

ICD-10: M05*, M06*, M315*, M32*, M33*, M34*, M351*, M353*, M360*

Mild liver disease

ICD-9: 070C*, 070D*, 070E*, 070F*, 070G*, 070X*, 570*, 571*, 573D*, 573E*, 573W*, 573X*, V42H* ICD-10: B18*, K700*, K701*, K702*, K703*, K709*, K713*, K714*, K715*, K717*, K73*, K74*, K760*, K762*, K763*, K764*, K768*, K769*, Z944*

Diabetes without chronic complication

ICD-9: 250A*, 250B*, 250C*, 250D*, 250H*, 250X*

ICD-10: E100*, E101*, E106*, E108*, E109*, E110*, E111*, E116*, E118*, E119*, E120*, E121*, E126*, E128*, E129*, E130*, E131*, E136*, E138*, E139*, E140*, E141*, E146*, E148*, E149*

Diabetes with chronic complication

ICD-9: 250D*, 250E*, 250F*, 250G*

ICD-10: E102*, E103*, E104*, E105*, E107*, E112*, E113*, E114*, E115*, E117*, E122*, E123*, E124*, E125*, E127*, E132*, E133*, E134*, E135*, E137*, E142*, E143*, E144*, E145*, E147*

Renal disease

ICD-9: 403A*, 403B*, 403X*, 404A*, 404B*, 404X*, 582*, 583A*, 583B*, 583C*, 583E*, 583G*, 583H*, 585*, 586*, 588A*, V42A*, V45B*, V56*

ICD-10: I120*, I131*, N032*, N033*, N034*, N035*, N036*, N037*, N052*, N053*, N054*, N055*, N056*, N057*, N18*, N19*, N250*, Z490*, Z491*, Z492*, Z940*, Z992*

Hemiplegia or paraplegia

ICD-9: 334B*, 342*, 343*, 344A*, 344B*, "344C*", 344D*, 344E*, 344F*, 344G*, 344X*

ICD-10: G041*, G114*, G801*, G802*, G81*, G82*, G830*, G831*, G832*, G833*, G834*, G839*

Moderate or severe liver disease

ICD-9: 456A*, 456B*, 456C*, 572C*, 572D*, 572E*, 572W*

ICD-10: I850*, I859*, I864*, I982*, K704*, K711*, K721*, K729*, K765*, K766*, K767*

AIDS/HIV

ICD-9: 279K

ICD-10: B20*, B21*, B22*, B24*

Depression

ICD-9: 296B, 298A, 296B, 296W, 311X, 300E, 300F, 309A, 309B

ICD-10: F32*, F33*, F34*, F381*, F488, F4321

Anxiety

ICD-9: 300A, 300D

ICD-10: F41*, F42

Osteoporosis

ICD-9: 733A

ICD-10: M80*

Gastrointestinal, urogenital disease and recurrent serious infection

ICD-9: 00*(excluding 009*), 01*(excluding 011E), 02*, 03*(excluding 034A), 04*(excluding 040C), 05*, 06*, 07*, 08*, 09*(excluding 099D), 10*, 11*, 12*, 13*(excluding 135*, 136A, 136B), 320*, 321*, 324*, 460*, 461*, 462*, 463*, 464*, 465*, 466*, 468*, 48*, 473*, 474*, 711A*, 684*, 680*, 686*, 382*, 595

ICD-10: A*, B*, G00*, G01*, G02*, G06*, G07*, J0*, J1*, J20*, J21*, J22*, J32*, J35*, J36*, J37*, M00*, M01*, L00*, L01*, L02*, L08*, H66*, N10*, N30*

Reference for codes

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