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Temporal order of cancers and mental disorders in an adult population

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Background

Population-based examination of comorbidity is an emerging field of study.

Aims

The purpose of the present population level study is to expand our understanding of how cancer and mental illness are temporally associated.

Method

A sample of 83 648 056 physician billing records for 664 838 (56% female) unique individuals over the age of 18 was stratified on ages 19–49 years and 50+ years, with temporal order of mental disorder and cancer forming the basis of comparison.

Results

Mental disorders preceded cancers for both genders within each age strata. The full range of cancers and mental disorders preceding or following each pivot ICD class are described in terms of frequency of diagnosis and duration in days, with specific examples illustrated.

Conclusions

The temporal comorbidity between specific cancers and mental disorders may be useful in screening or clinical planning and may represent indicators of disease mechanism that warrant further screening or investigation.

Declaration of interest

None.

Keywords

Temporal comorbidity; cancer; mental disorder; physician diagnosis; population; adult; psychiatric disorder.

Importance of comorbidity

Comorbidity refers to disorders and diseases that occur in tandem with likelihoods greater than expected by chance alone.[1] The study of comorbidity has evolved rapidly in recent years since its formal description with respect to chronic disease by Feinstein *et al*.[2] Yet the study of comorbidity remains complex and challenging, even as the field of comorbidity medicine continues to progress.[1] Current definitions incorporate concepts such as multi-comorbidity in addition to simple two-diagnosis comorbidity, and the idea of etiological and non-etiological comorbidity, referring to its causal and independent forms, among others.[1] Its applicability to clinical practice is limited and, although common, it remains poorly understood.[1]

With respect to cancer, study most frequently focuses on constrained sets of disorders related to a specific type of cancer.[3–14] Other approaches often focus on proximal or prognostic comorbidity and employ comorbidity indices, such as the Charlson index.[5,15–25]

Current evidence on the comorbidity of cancer and mental disorders

Recent studies that examined the association between neoplasms, including cancer, and mental disorders focused on the association of mental morbidity in cancer patients and survivors, utilising diagnostic interviews and surveys to assess mental disorder status.[26,27] Others have examined mental health problems and needs for social support post-diagnosis.[28] While a population study approach is informative, especially when both mental and physical comorbidities are examined, studies are often cross-sectional[27] and are biased by recall in interviews to assess mental status in association with cancer.[29]

Population-based study

One recent large population study,[30] employing 10 years of data from Sweden's national registry of physician diagnoses, studied temporal data related to mental disorder, finding that mental disorder rates increased 10 months before cancer, peaking immediately after and remaining elevated for the study duration. Findings were strongest with cancers that had a poorer prognosis. The overall long-term co-occurrence in a population of any mental disorder and any cancer has not been reported in the reviewed literature.

While the temporal order of disorder and disease arising in any given patient is identified in terms of the progress of time, the population-based study of the temporal order of comorbid diseases may be bidirectional in time, given the advent of large data-sets, as the 10-year Swedish study[30] and others[31] have demonstrated. Such studies have formed the groundwork for better understanding the temporal relationship between cancers and mental disorders.

Potential mechanisms

There is a growing body of evidence showing that systemic inflammation mediated by pro-inflammatory cytokines can facilitate tumour growth and metastasis.[32–35] Inflammation-based prognostic scores have been found to be independently associated with survival in cancer, independent of tumour type. Furthermore, antipsychotic medications, in addition to stress and mental disorder, affect central nervous system cell–cell communication, it is possible that they also modulate immunity and inflammation.

Other research has shown that environmental factors can lead to epigenetic changes. Bioactive nutrients and gut microbiota can alter DNA methylation and modulate the 'gut–brain axis' via their influence on inflammatory cytokines and production of antimicrobial peptides.[36] It is biologically plausible that similar pathways or conditions drive the development of both cancer and mental illness;[37] however, the temporal association of such factors remains confounded by treatment and is largely unstudied.

Purpose of present study

The purpose of the current study was to expand our present understanding of comorbidity. Using a 16-year, regional population dataset, we examined, separately for males and females, the relationship between all neoplasms (cancers) before and after any mental disorder and all mental disorders before and after any neoplasm, where these physician-diagnosed main ICD classes co-occurred. We hypothesised that specific mental disorders and neoplasms would arise significantly in proportion before or after the pivot ICD classes of interest (neoplasm or mental disorder).

Method

To be paid for services, physicians must submit forms for each encounter to the Provincial government that include diagnosis (up to three per claim). All regional provincial physician billing records data from the Calgary Health Zone, Alberta, Canada, representing physician-diagnosed ICD-9 classification, age, gender and diagnosis date between Spring 1993 and Fall 2010 were analysed. The sample consisted of 75 944 698 records for 525 439 (55% female) unique individuals over the age of 18. The data represent the majority of the residing population over the period, including those that moved to and away from the region, or were deceased. Additional regional systems (emergency, in-patient, ambulatory) that also record physician diagnosis were not considered to avoid redundancy.

Data were grouped based on Boolean association within the two main ICD classes, with neoplasm and mental disorder independently linked to all associated ICD disorders. For the purpose of comparison between and within groups, odds ratios (OR). In addition to ORs, data were also grouped so that the first date of diagnosis of any disorder for each patient could be compared with the first date of diagnosis by class (any mental disorder or any neoplasm) and by specific main ICD diagnosis within the class (any mental disorder or neoplasm). It was rare for mental disorder and cancer to be diagnosed on the same visit day, and such cases were not included in the analysis (242 males/31 439 diagnoses and 267 females/45 826 diagnoses for all disorders). Age represents a potential confounder. Age (mean and standard deviation) was reported in addition to ORs for each group overall and within age stratification (19–49 years and 50+ years). Additional comorbidities (e.g., obesity and diabetes) while potentially influential, were not considered.

In addition, the duration between the first date of diagnosis for mental disorders associated with neoplasms and cancers was calculated. The total frequency of specific diagnoses arising for each diagnosis within the duration interval before and after the pivot diagnosis (any mental disorder or neoplasm) was also calculated for comparison. The proportions of the diagnostic frequencies for each specific diagnosis were calculated for comparison.

Statistical differences were estimated based on comparison of the 95% confidence intervals (CI). Non-overlapping 95% CIs with z set to 1.96 indicated a statistical difference ($P < 0.05$).

There are multiple ways to count different groups for the purpose of meaningful comparison: (a) number of unique individuals within defined groups or ICD classes, or individual diagnoses; (b) cumulative frequency of diagnoses for individuals within defined groups or ICD classes, or individual diagnoses; and (c) the temporal order of counts and frequencies comparing counts within defined groups or ICD classes, or individual diagnoses within diagnostic groups of main ICD diagnostic categories ($n = 1036$). In this analysis, there were two temporal groupings for each gender based on two pivot classes of ICD diagnoses (neoplasm and mental disorder), wherein counts of unique individuals, frequencies and average durations arising before and after each pivot diagnosis (before and after any neoplasm; before and after any mental disorder) were calculated overall for age and gender, and for each independent diagnosis by age and gender temporal grouping. Further, the base rate of mental disorder in the present sample was 54% over 16 years.[31]

After a general description of the sample and the overall relationships within and between groups, we examined the specific neoplasms arising before or after any mental disorder, and the specific mental disorders arising before or after any neoplasm. Specific examples are detailed (e.g., specific diagnoses within the pivot diagnosis account for the observed significance). The data were analysed using Stata 14. Each table result was verified using two independent algorithms: 'contract' *v.* 'unique' to verify counts of unique individuals within groupings, and 'collapse' for calculating cumulative frequency and duration within diagnoses by temporal grouping.

Results

Table 1 provides the unique individual counts and the associated cumulative frequencies of diagnoses within each condition. Note the increased counts under the condition of mental disorder before cancer for both genders. The proportion of those with any mental disorder before cancer was higher for males and females in both age groups. For example, for 58% of males and 63% of

Table 1 Gender and age for unique individuals over the age of 18 years

Gender	Condition	Age in years, mean (s.d.)	19–49 years		50+ years	
			Unique individuals	Records	Unique individuals	Records
Female	All	45.2 (17.6)	218 951	18 230 305	77 497	31 672 669
	No CA No MD	32.6 (23.9)	48 607	962 890	11 557	2 272 041
	No CA MD	41.6 (22.8)	76 112	4 835 023	22 258	10 658 944
	CA No MD	46.3 (22.5)	17 250	1 251 853	7787	1 800 661
	CA MD	60 (20.4)	76 982	11 180 539	35 895	16 941 023
	MD > CA	54.7 (20.3)	23 919	3 946 837	13 416	4 568 128
	MD < CA	51.5 (18.8)	52 913	7 213 045	22 390	12 350 571
Males	All	46.7 (16.6)	176 403	10 631 071	52 588	15 410 653
	No CA No MD	29.5 (23.1)	66 260	669 381	9715	2 248 147
	No CA MD	38.5 (22.7)	62 838	2 399 684	12 830	6 537 408
	CA No MD	47.1 (23.8)	14 706	1 028 681	6929	1 129 633
	CA MD	55.6 (22.2)	32 599	6 533 325	23 114	5 495 465
	MD > CA	61.2 (19.5)	11 112	2 637 453	9626	1 551 329
	MD < CA	56.7 (18)	21 366	3 880 494	13 396	3 930 110

CA, cancer; MD, mental disorder.

Table 2 Odds ratios by condition by gender by age strata

Gender	Condition	19–49 years (95% CI)	50+ years (95% CI)
Female	Overall	2.85 (2.79, 2.91)	2.39 (2.32, 2.47)
	MD > CA	0.89 (0.87, 0.91)	0.9 (0.86, 0.93)
	MD < CA	1.96 (1.92, 2)	1.49 (1.44, 1.55)
Male	Overall	2.34 (2.29, 2.39)	2.53 (2.43, 2.62)
	MD > CA	0.8 (0.78, 0.82)	1.05 (1.01, 1.1)
	MD < CA	1.53 (1.5, 1.57)	1.46 (1.41, 1.52)

CA, cancer; MD, mental disorder; >, after; <, before.

females aged 19–49 years, any mental disorder preceded any cancer. For 69% of males and 66% of females over 50 years of age, any mental disorder preceded any cancer.

Table 2 shows the overall ORs for each category by gender for the two age strata. Males and females were more likely to have both mental disorder and cancer compared to either one or neither, and for both genders, it was more likely that any neoplasm would follow any mental disorder. This was the case for each age category. When stratified by age, the ORs for the 19–49-year-old group are consistent within the age strata and slightly greater than those for the group over 50 years of age, even though the proportions of those with both mental disorder and neoplasm are greater in the over 50 years of age strata for both genders (Table 1).

Table 3 provides a comparison of average age, cumulative diagnostic frequency, average duration, and frequency proportions by pivot diagnosis by independent diagnoses. Examples of serious diagnoses for each pivot category for males and females include schizophrenic disorders (295), affective psychoses (296) and other nonorganic psychoses (298), representing ICD diagnoses that arise with considerable frequency – potentially reflecting intensity – within these patients. Note that this table represents the summed counts or frequency of diagnoses within each ICD main diagnosis under the condition of arising before and after each ICD pivot. ICD disorder 306 (psychological distress) was the only disorder arising significantly after neoplasm in both females and males. Only in males was there one non-significant disorder, ICD disorder 313 (emotional distress). Table 3 identifies the specific neoplasm and mental disorders underpinning the overall ORs shown in Table 2.

As shown in Table 3, for females, when any cancer was the pivot diagnosis, the average age was 51 years, the average time cancer arose before the specified mental disorders was 2191 days, and the average time after the specified mental disorders was 1378 days. For females, when any mental disorder was the pivot diagnosis, the average age was 59 years, the average time cancer arose before the specified mental disorders was 2311 days, and the average time after the specified mental disorders was 885 days. The specific mental disorder in females with the shortest duration (1423 days) before cancer was psycho-physiological gastro-intestinal disorder (306), and that with the longest duration (2894 days) was intellectual disability not otherwise specified (319). The specific cancer in females with the shortest duration (302 days) arising after any mental disorder was malignant neoplasm – pancreas (157), and that with the longest duration (1549 days) arising after any mental disorder was malignant neoplasm – major salivary (142).

As shown in Table 3, for males, when any cancer was the pivot diagnosis, the average age was 50 years, the average time cancer arose before the specified mental disorders was 2045 days, and the average time after the specified mental disorders was 1420 days. For males, when any mental disorder was the pivot diagnosis, the average age was 61 years, the average time cancer arose before the specified mental disorders was 2114 days, and the average time after the specified mental disorders was 868 days. The specific mental disorder in males with the shortest duration before cancer was senile/presenile psychosis (290), and that with the longest duration was other mental retardation (318). The specific cancer in males with the shortest duration arising after any mental disorder was malignant neoplasm of lip, oral cavity, and pharynx (140), and that with the longest duration arising after any mental disorder was haemangioma/lymphangioma (228).

Table 3 also shows a wide range of frequencies or counts of each diagnosis before or after the pivot diagnosis, as well as the frequency proportions of the total for each specific diagnosis that arose before and after each pivot diagnosis.

Summary of results

The results shown in the tables illustrate in detail the overall and temporal relationships between ICD mental disorders and cancers as categories of diagnosis. Table 3 provides more depth of temporal information about the specific temporal relationships of the ICD diagnoses associated with each pivot diagnosis (any cancer or mental disorder), where both mental disorder and cancer arose in the same person at different times. Mental disorders preceded cancers, independent of age, for both genders. Table 3 provides a basis for examining the relative intensity and the average durations before and after each pivot diagnosis to provide an index of sequence or order.

Discussion

Our findings support the study of comorbid disorders, advancing the field by comprehensively examining the relationship between neoplasms, including cancer, and mental disorder, information that until now was not available. The results represent an important advance detailing the 16-year relationship between all cancers and all mental disorders in a large population, supporting future laboratory research on plausible biological mechanisms potentially linking a variety of disorders – for example, the effect of antipsychotics on cadherin-mediated cell–cell adhesion.[38]

The results of the present study are most comparable to those of a Swedish national study of mental disorder and cancer.[30,39] Yet, the results of the present study are materially different. The Swedish study examined the relationship between cancer and mental disorder, noting an increase in relative risk from 2 years before the onset of cancer and finding that cancer predisposed people to psychological distress and mental disorder from 2 years before to after the onset of cancer for the study duration.[30] Our results are the opposite of the Swedish study results, showing that, if random, cancer and mental disorders had equal odds of arising either before or after one another, according to the null hypothesis. We observed a strong relationship between mental disorder and cancer, with mental disorder preceding cancer. The differences in findings may be due to the 16-year time-based approach, or the different analytical methods employed, or both.

The strength of the temporal relationship between mental disorder and cancer illustrated in this paper is similar to that shown by another study based on this data sample. In that study, the temporal relationship between mental disorder and ulcerative colitis[31] pointed to a potential mechanism for the onset of anxiety and depression preceding the onset of ulcerative colitis. This effect might be related to one or more of the principal medications used to treat these disorders, such as selective serotonin reuptake inhibitors. For example, there was no relationship with thought disorders or psychosis, for which a different class of medications is used in treatment. Psychotropic drugs probably do not only modulate cell

Table 3 Comparison of ICD diagnoses (frequency and average duration) by group arising before and after pivot diagnoses

Gender	Pivot diagnostic category	Age, years	Duration of diagnosis before pivot, days	Frequency	Duration of diagnosis after pivot, days	Frequency	Proportion before pivot	Proportion after pivot
Psychosis (290–299)								
F	Senile/presenile psychoses (290)	83	2574	148 264	742	19 662	0.88	0.12
F	Alcoholic psychoses (291)	64	2647	2668	1250	644	0.81	0.19
F	Drug psychoses (292)	47	2215	2798	1347	1230	0.69	0.31
F	Transient organic mental disorder (293)	66	2492	13 566	1089	2713	0.83	0.17
F	Other organic psychotic condition (294)	70	2241	10 357	1009	2191	0.83	0.17
F	Schizophrenic disorders (295)	50	2139	113 094	1418	54 195	0.68	0.32
F	Affective psychoses (296)	50	2183	181 036	1423	80 407	0.69	0.31
F	Paranoid states (297)	64	2139	6500	1421	3350	0.66	0.34
F	Other nonorganic psychoses (298)	52	2463	32 465	1103	8261	0.8	0.2
F	Psychoses of childhood (299)	49	1972	167	1525	120	0.58	0.42
Neurotic disorders, personality disorders, and other nonpsychotic mental disorders (300–316)								
F	Neurotic disorders (300)	51	2012	487 223	1516	271 633	0.64	0.36
F	Personality disorders (301)	41	2088	36 525	1442	17 293	0.68	0.32
F	Sexual disorders (302)	42	1732	1290	1566	726	0.64	0.36
F	Alcohol dependence syndrome(303)	49	2253	19 060	1422	8774	0.68	0.32
F	Drug dependence (304)	43	2458	27 353	1295	10 324	0.73	0.27
F	Nondependent drug abuse (305)	46	2099	13 338	1488	7377	0.64	0.36
F	Psycho-physiological gastro-intestinal disorder (306)	52	1423	6141	1560	7727	0.44	0.56
F	Special symptom (307)	42	2090	46 693	1470	24 077	0.66	0.34
F	Acute reaction to stress (308)	50	1929	79 187	1527	48 065	0.62	0.38
F	Adjustment reaction (309)	48	2083	123 687	1518	61 042	0.67	0.33
F	Nonpsychotic brain syndrome(310)	61	2354	7279	1262	1806	0.8	0.2
F	Depressive disorder (311)	50	2084	573 543	1487	290 981	0.66	0.34
F	Conduct disturbance (312)	55	2306	4198	1297	1670	0.72	0.28
F	Emotional disorder childhood/adolescence (313)	43	1721	2944	1738	2749	0.52	0.48
F	Hyperkinetic syndrome (314)	40	2181	5781	1330	1873	0.76	0.24
F	Specific developmental delays (315)	42	2167	1042	1305	317	0.77	0.23
F	Psychic factors associated with other disorder (316)	52	1808	10 545	1451	5423	0.66	0.34
Mental retardation (317–319)								
F	Mild intellectual disability (317)	47	2822	1154	1469	691	0.63	0.37
F	Other mental retardation (318)	46	2149	306	1415	227	0.57	0.43
F	Intellectual disability not otherwise specified (NOS) (319)	41	2894	243	1442	135	0.64	0.36

Gender	Any MD is pivot	Age, years	MD before CA, days	MD before CA Frequency	MD after CA, days	MD after CA Frequency	Proportion MD before	Proportion MD after
Malignant (mal) neoplasm (neo) of lip, oral cavity, and pharynx (140–149)								
F	Mal neo lip (140)	69	2260	3445	699	308	0.92	0.08
F	Mal neo tongue (141)	65	2563	1020	641	96	0.91	0.09
F	Mal neo major salivary (142)	57	2496	503	1549	128	0.8	0.2
F	Mal neo gum (143)	67	3141	206	419	19	0.92	0.08
F	Mal neo mouth floor (144)	60	2643	236	778	49	0.83	0.17
F	Mal neo of other and unspecified parts of mouth (145)	64	2645	959	676	179	0.84	0.16
F	Mal neo oropharynx (146)	61	2713	556	540	101	0.85	0.15

(*Continued*)

Table 3 (*Continued*)

Gender	Any MD is pivot	Age, years	MD before CA, days	MD before CA Frequency	MD after CA, days	MD after CA Frequency	Proportion MD before	Proportion MD after
F	Mal neo nasopharynx (147)	61	1744	554	1308	37	0.94	0.06
F	Mal neo hypopharynx (148)	66	2379	144	731	17	0.89	0.11
F	Other mal neo oropharynx (149)	71	2515	339	678	34	0.91	0.09
Malignant neoplasm of digestive organs and peritoneum (150–159)								
F	Mal neo oesophagus (150)	69	2409	2698	525	200	0.93	0.07
F	Mal neo stomach (151)	69	2113	3484	576	392	0.9	0.1
F	Mal neo small bowel (152)	63	2286	738	210	79	0.9	0.1
F	Mal neo colon (153)	70	2371	19 389	728	2701	0.88	0.12
F	Mal neo rectum/anus (154)	66	2278	7292	902	1219	0.86	0.14
F	Mal neo liver (155)	63	2443	4440	566	343	0.93	0.07
F	Mal neo gallbladder and extrahepatic bile ducts (156)	69	2240	1500	402	117	0.93	0.07
F	Mal neo pancreas (157)	71	2531	7918	308	409	0.95	0.05
F	Mal neo peritoneum (158)	62	2027	672	515	43	0.94	0.06
F	Other mal neo gastro-intestine /peritoneum (159)	66	1950	438	564	47	0.9	0.1
Malignant neoplasm of respiratory and intrathoracic organs (160–165)								
F	Mal neo of nasal cavities, middle ear, and accessory sinuses (160)	56	2849	770	564	113	0.87	0.13
F	Mal neo larynx (161)	69	2073	1300	800	199	0.87	0.13
F	Mal neo trachea/lung (162)	70	2492	35 892	431	2288	0.94	0.06
F	Mal neo pleura (163)	61	2840	468	590	55	0.89	0.11
F	Mal neo of thymus, heart, and mediastinum (164)	55	2378	834	488	92	0.9	0.1
F	Mal neo of other and ill-defined sites within the respiratory system and intrathoracic organs (165)	50	2445	1039	1241	233	0.82	0.18
Malignant neoplasm of bone, connective tissue, skin, and breast (170–175)								
F	Mal neo bone/artic cart (170)	59	2487	1136	925	210	0.84	0.16
F	Mal neo soft tissue (171)	54	2424	3297	937	496	0.87	0.13
F	Mal melanoma skin (172)	57	2454	7813	1107	1775	0.81	0.19
F	Other mal neo skin (173)	68	2500	53 882	1234	12 822	0.81	0.19
F	Mal neo female breast (174)	59	2435	82 325	891	9825	0.89	0.11
Mal neoplasm of genitourinary organs (179–189)								
F	Mal neo uterus NOS (179)	69	2365	1109	994	133	0.89	0.11
F	Mal neo cervix uteri (180)	50	1940	4750	734	810	0.85	0.15
F	Mal neo placenta (181)	54	1722	78	824	16	0.83	0.17
F	Mal neo uterus body (182)	67	2414	3207	801	590	0.84	0.16
F	Mal neo uterine adnexa (183)	61	2489	16 757	668	1736	0.91	0.09
F	Mal neo of other and unspecified female genital organs (184)	61	2075	1840	705	262	0.88	0.12
F	Mal neo bladder (188)	71	2339	10 142	1084	1913	0.84	0.16
F	Mal neo of kidney and other and unspecified urinary organs (189)	67	2472	5275	867	665	0.89	0.11
Malignant neoplasm of other and unspecified sites (190–199)								
F	Mal neo eye (190)	59	2236	844	1083	131	0.87	0.13
F	Mal neo brain (191)	58	2296	6344	535	534	0.92	0.08
F	Mal neo of other and unspecified parts of nervous system (192)	59	2171	516	997	77	0.87	0.13
F	Mal neo thyroid (193)	51	2161	4202	1077	872	0.83	0.17
F	Mal neo other endocrine (194)	58	1614	1202	1099	90	0.93	0.07
F	Mal neo other/ill-defined site (195)	64	1940	728	448	120	0.86	0.14
F	Mal neo lymph nodes (196)	63	2807	1444	757	240	0.86	0.14
F	Secondary mal neo of respiratory and digestive systems (197)	66	2568	2874	372	241	0.92	0.08
F	Sec mal neo other sites (198)	61	2661	1640	470	118	0.93	0.07

(*Continued*)

Table 3 (*Continued*)

Gender	Any MD is pivot	Age, years	MD before CA, days	MD before CA Frequency	MD after CA, days	MD after CA Frequency	Proportion MD before	Proportion MD after
F	Mal neo NOS (199)	67	2225	8094	522	681	0.92	0.08
Malignant neoplasm of lymphatic and hematopoietic tissue (200–208)								
F	Lymphosarcoma and reticulosarcoma (200)	62	2048	7115	763	1576	0.82	0.18
F	Hodgkin's disease (201)	51	2101	2397	609	514	0.82	0.18
F	Other mal neo lymph/histio (202)	64	2345	6072	715	715	0.89	0.11
F	Multiple myeloma and immunoproliferative neoplasms (203)	68	2352	5597	561	772	0.88	0.12
F	Lymphoid leukaemia (204)	66	2193	5114	770	972	0.84	0.16
F	Myeloid leukaemia (205)	57	2019	3238	713	435	0.88	0.12
F	Monocytic leukaemia (206)	56	2267	254	910	55	0.82	0.18
F	Other specified leukaemia (207)	60	2530	503	851	55	0.9	0.1
F	Leukaemia-unspecified cell (208)	65	2614	1105	680	94	0.92	0.08
Benign (ben) neoplasms (210–229)								
F	Ben neo of lip, oral cavity, and pharynx (210)	53	2121	3095	1213	934	0.77	0.23
F	Other ben neo gastro-intestine (211)	60	2603	23 689	1137	3952	0.86	0.14
F	Ben neo of respiratory and intrathoracic organs (212)	60	2097	1796	1143	468	0.79	0.21
F	Ben neo of bone and articular cartilage (213)	47	2329	1032	1128	286	0.78	0.22
F	Lipoma (214)	50	2234	10 405	1201	3143	0.77	0.23
F	Other ben neo soft tissue (215)	49	2233	7822	1214	2215	0.78	0.22
F	Ben neo of skin (216)	49	2296	149 562	1204	42 320	0.78	0.22
F	Ben neo breast (217)	50	2132	22 412	1204	7404	0.75	0.25
F	Uterine leiomyoma (218)	46	2198	12 972	1198	4017	0.76	0.24
F	Other ben neo uterus (219)	46	2427	977	1186	249	0.8	0.2
F	Ben neo ovary (220)	45	2389	4282	1103	929	0.82	0.18
F	Ben neo other fem genital (221)	46	2326	813	1190	228	0.78	0.22
F	Ben neo urinary (223)	57	2712	469	1013	56	0.89	0.11
F	Ben neo of eye (224)	59	2700	935	1135	147	0.86	0.14
F	Ben neo nervous system (225)	56	1912	2995	875	686	0.81	0.19
F	Ben neo thyroid (226)	49	2371	1093	1170	320	0.77	0.23
F	Ben neo other endocrine (227)	48	1772	840	1019	255	0.77	0.23
F	Haemangioma and lymphangioma, any site (228)	44	2168	4511	1205	1335	0.77	0.23
F	Ben neo of other and unspecified sites (229)	47	2074	1351	1289	439	0.75	0.25
Carcinoma *in situ* (230–234)								
F	Carcinoma *in situ* digestive org (230)	67	2167	1784	760	302	0.86	0.14
F	Carcinoma *in situ* respiratory (231)	70	2337	978	532	161	0.86	0.14
F	Carcinoma *in situ* skin (232)	70	2880	9098	1167	1273	0.88	0.12
F	Carcinoma *in situ* of breast and genitourinary system (233)	47	2259	6940	1050	1495	0.82	0.18
F	Carcinoma *in situ* of other and unspecified sites (234)	63	2163	1242	590	150	0.89	0.11
Neoplasms of uncertain behaviour (235–238)								
F	Neo of uncertain behaviour of digestive and respiratory systems (235)	60	2185	1327	946	295	0.82	0.18
F	Neo of uncertain behaviour of genitourinary organs (236)	52	2387	611	883	126	0.83	0.17
F	Neo of uncertain behaviour of endocrine glands and nervous system (237)	49	2175	865	800	166	0.84	0.16

(*Continued*)

Table 3 (*Continued*)

Gender	Any MD is pivot	Age, years	MD before CA, days	MD before CA Frequency	MD after CA, days	MD after CA Frequency	Proportion MD before	Proportion MD after
F	Neo of uncertain behaviour of other and unspecified sites and tissues (238)	55	2493	25 248	1170	5112	0.83	0.17
F	Unspecified neo (239)	54	2033	5725	1084	1623	0.78	0.22
Gender	**Any CA is Pivot**	**Age, years**	**CA before MD, days**	**CA before MD Frequency**	**CA after MD, days**	**CA after MD Frequency**	**Proportion CA before**	**Proportion CA after**
Psychosis (290–299)								
M	Senile/presenile psychoses (290)	80	2564	84 580	714	10 751	0.89	0.11
M	Alcoholic psychoses (291)	57	2087	4940	1015	1552	0.76	0.24
M	Drug psychoses (292)	42	2531	2716	1302	1124	0.71	0.29
M	Transient org mental disorder (293)	64	2236	11 165	1024	2394	0.82	0.18
M	Other organic psych condition (294)	65	1954	7979	1560	2900	0.73	0.27
M	Schizophrenic disorders (295)	44	1982	97 263	1614	63 650	0.6	0.4
M	Affective psychoses (296)	52	2228	72 092	1589	36 485	0.66	0.34
M	Paranoid states (297)	58	2269	4235	1412	1254	0.77	0.23
M	Other nonorganic psychoses (298)	49	2465	21 743	917	5739	0.79	0.21
M	Psychoses of childhood (299)	30	2355	1165	1122	81	0.93	0.07
Neurotic disorders, personality disorders, and other nonpsychotic mental disorders (300–316)								
M	Neurotic disorders (300)	54	1893	162 548	1521	98 138	0.62	0.38
M	Personality disorders (301)	44	1784	8795	1880	6694	0.57	0.43
M	Sexual disorders (302)	55	1980	13 929	1478	8231	0.63	0.37
M	Alcohol dependence syndrome(303)	50	1916	21 938	1368	13 052	0.63	0.37
M	Drug dependence (304)	42	2089	20 021	1250	8198	0.71	0.29
M	Nondependent drug abuse (305)	47	1916	8784	1465	5747	0.6	0.4
M	Psycho-physiological gastro-intestinal disorder (306)	56	1144	2630	1562	3633	0.42	0.58
M	Special symptom (307)	53	2002	15 892	1281	8388	0.65	0.35
M	Acute reaction to stress (308)	55	1837	22 896	1517	14 600	0.61	0.39
M	Adjustment reaction (309)	49	1937	47 373	1465	25 840	0.65	0.35
M	Nonpsychotic brain syndrome(310)	51	1607	7694	1246	3007	0.72	0.28
M	Depressive disorder (311)	54	2045	198 459	1468	103 753	0.66	0.34
M	Conduct disturbance (312)	52	2174	4065	1570	1821	0.69	0.31
M	Emotional disorder childhood/adolescence (313)	41	1613	1234	1386	1203	0.51	0.49
M	Hyperkinetic syndrome (314)	39	2080	4839	1463	1915	0.72	0.28
M	Specific developmental delays (315)	33	2407	807	1286	528	0.6	0.4
M	Psychic factor associated with other disorder (316)	57	2006	4011	1290	2363	0.63	0.37
Mental retardation (317–319)								
M	Mild intellectual disability (317)	40	2052	1032	1724	855	0.55	0.45
M	Other mental retardation (318)	37	2085	583	2460	798	0.42	0.58
M	Intellectual disability NOS (319)	42	2099	416	1650	217	0.66	0.34
Gender	**Any MD is pivot**	**Age, years**	**MD before CA, days**	**MD before CA Frequency**	**MD after CA, days**	**MD after CA Frequency**	**Proportion MD before**	**Proportion MD after**
Malignant neoplasm of lip, oral cavity, and pharynx (140–149)								
M	Mal neo lip (140)	69	2064	2377	991	285	0.89	0.11
M	Mal neo tongue (141)	58	2154	1377	344	203	0.87	0.13
M	Mal neo major salivary (142)	58	2342	343	891	90	0.79	0.21
M	Mal neo gum (143)	62	2019	112	801	11	0.91	0.09

(*Continued*)

Table 3 (*Continued*)

Gender	Any MD is pivot	Age, years	MD before CA, days	MD before CA Frequency	MD after CA, days	MD after CA Frequency	Proportion MD before	Proportion MD after
M	Mal neo mouth floor (144)	61	1855	281	524	31	0.9	0.1
M	Mal neo of other and unspecified parts of mouth (145)	61	2000	1015	508	158	0.87	0.13
M	Mal neo oropharynx (146)	61	2300	776	528	103	0.88	0.12
M	Mal neo nasopharynx (147)	59	2053	932	571	190	0.83	0.17
M	Mal neo hypopharynx (148)	59	1614	373	449	45	0.89	0.11
M	Other mal neo oropharynx (149)	61	1493	159	423	39	0.8	0.2
Malignant neoplasm of digestive organs and peritoneum (150–159)								
M	Mal neo oesophagus (150)	66	2498	5111	416	539	0.9	0.1
M	Mal neo stomach (151)	67	1957	3194	421	398	0.89	0.11
M	Mal neo small bowel (152)	65	2376	504	714	51	0.91	0.09
M	Mal neo colon (153)	68	2090	14 091	695	2387	0.86	0.14
M	Mal neo rectum/anus (154)	67	2110	6976	726	1900	0.79	0.21
M	Mal neo liver (155)	62	2144	4929	515	414	0.92	0.08
M	Mal neo/extrahepatic bile ducts (156)	65	1994	955	232	96	0.91	0.09
M	Mal neo pancreas (157)	69	2168	6034	367	520	0.92	0.08
M	Mal neo peritoneum (158)	65	2340	364	523	16	0.96	0.04
M	Other mal neo gastro-intestine/peritoneum (159)	67	1863	322	606	42	0.88	0.12
Malignant neoplasm of respiratory and intrathoracic organs (160–165)								
M	Mal neo nasal cavity/sinus (160)	55	2211	505	1054	90	0.85	0.15
M	Mal neo larynx (161)	66	2268	2378	794	488	0.83	0.17
M	Mal neo trachea/lung (162)	69	2159	24 863	428	3116	0.89	0.11
M	Mal neo pleura (163)	66	2046	720	456	84	0.9	0.1
M	Mal neo of thymus, heart, and mediastinum (164)	60	2414	553	349	105	0.84	0.16
M	Mal neo of other and ill-defined sites within the respiratory system and intrathoracic organs (165)	53	2242	605	996	130	0.82	0.18
Malignant neoplasm of bone, connective tissue, skin, and breast (170–175)								
M	Mal neo bone/artic cart (170)	54	1792	1206	532	181	0.87	0.13
M	Mal neo soft tissue (171)	55	2106	2376	592	528	0.82	0.18
M	Mal melanoma skin (172)	62	2245	5453	1090	1124	0.83	0.17
M	Other mal neo skin (173)	70	2407	46 374	1215	13 512	0.77	0.23
M	Mal neo male breast (175)	63	2049	146	1337	26	0.85	0.15
Malignant neoplasm of genitourinary organs (179–189)								
M	Mal neo prostate (185)	72	2074	41 723	1041	7643	0.85	0.15
M	Mal neo testis (186)	44	1769	1374	1072	425	0.76	0.24
M	Mal neo male genital (187)	63	2077	609	1070	108	0.85	0.15
M	Mal neo bladder (188)	72	2283	16 695	1059	3609	0.82	0.18
M	Mal neo of kidney and other and unspecified urinary organs (189)	66	2362	5503	833	772	0.88	0.12
Malignant neoplasm of other and unspecified sites (190–199)								
M	Mal neo eye (190)	59	2145	600	902	111	0.84	0.16
M	Mal neo brain (191)	55	1908	5222	433	630	0.89	0.11
M	Mal neo of other and unspecified parts of nervous system (192)	59	2521	328	1175	35	0.9	0.1
M	Mal neo thyroid (193)	59	1672	1359	857	223	0.86	0.14
M	Mal neo other endocrine (194)	59	2658	496	1137	67	0.88	0.12
M	Mal neo other/ill-defined site (195)	66	1977	682	521	83	0.89	0.11
M	Mal neo lymph nodes (196)	62	2303	1134	1061	199	0.85	0.15
M	Secondary (sec) mal neo of respiratory and digestive systems (197)	66	1798	1675	381	189	0.9	0.1
M	Sec mal neo other sites (198)	63	2146	760	428	61	0.93	0.07

(*Continued*)

Table 3 (*Continued*)

Gender	Any MD is pivot	Age, years	MD before CA, days	MD before CA Frequency	MD after CA, days	MD after CA Frequency	Proportion MD before	Proportion MD after
M	Mal neo NOS (199)	66	2104	5704	644	545	0.91	0.09
Malignant neoplasm of lymphatic and hematopoietic tissue (200–208)								
M	Lymphosarcoma/reticulosarcoma (200)	60	1771	5824	826	1473	0.8	0.2
M	Hodgkin's disease (201)	51	1942	1625	1180	377	0.81	0.19
M	Other mal neoplasms of lymphoid and Histiocytic tissue (202)	63	2170	4706	633	869	0.84	0.16
M	Multiple myeloma and immunoproliferative neoplasms (203)	67	2038	4472	563	656	0.87	0.13
M	Lymphoid leukaemia (204)	64	2010	5323	827	1615	0.77	0.23
M	Myeloid leukaemia (205)	55	1641	2883	581	828	0.78	0.22
M	Monocytic leukaemia (206)	55	1499	166	1119	53	0.76	0.24
M	other specified leukaemia (207)	66	2330	475	977	29	0.94	0.06
M	Leukaemia-unspecified cell (208)	65	2497	695	446	60	0.92	0.08
Benign neoplasms (210–229)								
M	Ben neo of lip, oral cavity, and pharynx (210)	53	1937	1641	1284	682	0.71	0.29
M	Other ben neo gastro-intestine (211)	62	2361	17 617	1184	4360	0.8	0.2
M	Ben neo respiratory system/thorax (212)	59	1835	1204	1358	343	0.78	0.22
M	Ben neo of bone and articular cartilage (213)	47	2045	527	1353	242	0.69	0.31
M	Lipoma (214)	48	2053	6643	1388	2831	0.7	0.3
M	Other ben neo soft tissue (215)	51	2040	3886	1286	1541	0.72	0.28
M	Ben neo of skin (216)	54	2166	55 868	1325	21 308	0.72	0.28
M	Ben neo breast (217)	53	1904	511	1382	214	0.7	0.3
M	Ben neo male genital (222)	63	2498	1324	1246	339	0.8	0.2
M	Ben neo urinary (223)	61	2465	224	1074	47	0.83	0.17
M	Ben neo of eye (224)	55	2479	390	895	77	0.84	0.16
M	Ben neo nervous system (225)	52	1650	1141	896	527	0.68	0.32
M	Ben neo thyroid (226)	52	2275	149	914	56	0.73	0.27
M	Ben neo other endocrine (227)	54	1796	476	1078	126	0.79	0.21
M	Haemangioma and lymphangioma, any site (228)	47	2000	1057	1492	506	0.68	0.32
M	Ben neo of other and unspecified sites (229)	51	1801	581	1139	252	0.7	0.3
Carcinoma *in situ* (230–234)								
M	Carcinoma *in situ* digestive org (230)	64	2021	1374	731	312	0.81	0.19
M	Carcinoma *in situ* respiratory (231)	68	2190	921	697	131	0.88	0.12
M	Carcinoma *in situ* skin (232)	71	2681	8804	1118	1711	0.84	0.16
M	Carcinoma *in situ* of breast and genitourinary system (233)	70	2167	910	777	156	0.85	0.15
M	Carcinoma *in situ* of other and unspecified sites (234)	65	2204	1052	873	104	0.91	0.09
Neoplasms of uncertain behaviour (235–238)								
M	Neo of uncertain behaviour of digestive and respiratory systems (235)	62	2039	1007	1378	297	0.77	0.23
M	Neo of uncertain behaviour of genitourinary organs (236)	67	1886	609	908	184	0.77	0.23
M	Neo of uncertain behaviour of endocrine glands and nervous system (237)	51	2036	360	618	132	0.73	0.27
M	Neo of uncertain behaviour of other and unspecified sites and tissues (238)	61	2369	14 968	1184	4113	0.78	0.22
M	Unspecified neo (239)	56	1848	2479	1156	877	0.74	0.26

signalling in the central nervous system, but also affect communication across all cellular systems, such as immune system regulation.[40]

Age represented a potential confounder of the results; hence, age was stratified into two groups, with the finding that the overall and temporal relationships of cancer and mental disorder were independent of age. This strengthens the idea that there may be a mechanism operating separately from the process of simple functional decline.[41–46]

In summary, this paper provides a description of the overall relationship between cancer and mental disorder in a large North American population. More directly related to clinical utility are descriptions of the frequencies and the average times in days with which specific diagnoses arise either following or in advance of cancer and mental disorder. For example, frequencies of specific cancers or mental disorders arising before or after the pivot class may represent an index of that specific disorder's intensity in patients, and may indicate the need for further screening or investigation.

Limitations, conclusion and next steps

We recognise that only cancer and mental disorder were considered in this paper. The relationships within and between the remaining classes of ICD disorders are also important and warrant more detailed study. Although the present work remains illuminating, and we contend that it is congruent with developments in laboratory and biological research, a complete list of disorders leading to and from a given pivot diagnosis is a worthy pursuit. Notwithstanding the complexity of conducting a metabolomics study at a population level, the main limitation of this contribution is the need to await the development of the algorithms required to develop the temporal roadmaps within and between the thousands of diagnoses underpinning the 18 main ICD classes of disorder. In such algorithms, the native patterns of the relationships arising in sequence among related disorders within patients would be preserved. Comparison of the average durations by specific diagnosis only provides a crude index of sequence; however, these calculations are independent for each specific diagnosis arising either before or after the pivot class diagnosis.

Another main limitation is that the present paper cannot resolve a clear understanding of the mechanism underpinning the temporal relationship between mental disorder and cancer. The results mainly introduce the additional confounder of psychiatric treatment. The relationship between brain function, the effects of antipsychotics and immune function is appealing in its simplicity in terms of basic research models testable in laboratory settings. Regardless, a great deal of work remains to design and implement studies that might resolve mechanistic issues such as treatment with antipsychotics and common constitutional and epigenetic vulnerability, as well as the influence of environmental and sociocultural factors.

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