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Abstract

Objective: Prior evidence on the relative risk of cancer among people with psychotic disorders is equivocal. The objective of this study was to compare incidence and stage at diagnosis of cancer for people with psychotic disorders relative to the general population.

Method: We constructed a retrospective cohort of people with a first diagnosis of non-affective psychotic disorder and a comparison group from the general population using linked health administrative databases in Ontario, Canada. The cohort was followed for incident diagnoses of cancer over a 25-year period. We used Poisson and logistic regression models to compare cancer incidence and stage at diagnosis between people with psychotic disorders and the comparison group, adjusting for confounding factors.

Results: People with psychotic disorders had an 8.6% higher incidence (IRR=1.09, 95%CI=1.05,1.12) of cancer overall relative to the comparison group, with effect modification by sex and substantial variation across cancer sites. People with psychotic disorders also had 23% greater odds (OR=1.23, 95%CI=1.13,1.34) of being diagnosed with more advanced stage cancer relative to the comparison group.

Conclusions: We found evidence of elevated cancer incidence in people with non-affective psychotic disorders relative to the general population. The higher odds of more advanced stage cancer diagnoses in people with psychotic disorders represents an opportunity to improve patient participation in recommended cancer screening, as well as timely access to services for cancer diagnosis and treatment. Future research should examine confounding effects of lifestyle factors and antipsychotic medications on the risk of developing cancer among people with psychotic disorders.

Keywords: cancer, incidence, oncology, psychotic disorders, schizophrenia

1 Introduction

The incidence of cancer in people with psychotic disorders has been an area of significant controversy.[1] Several studies have found a higher incidence of cancer among those with psychotic disorders relative to the general population, whereas others have found a lower incidence.[2] Prior meta-analyses have reported lower risk of melanoma, prostate cancer, and colorectal cancer, as well as higher risk of breast, cervical, and uterine cancers in people with schizophrenia.[2–4] Results of the studies included in these meta-analyses varied significantly, depending on the age of participants and duration of follow-up, and some studies provided evidence of effect modification by age and sex.[5] Relatedly, another meta-analysis found that people with prior diagnoses of serious mental illness, compared to those without, had higher odds of presenting with metastases at cancer diagnosis and shorter duration of survival following diagnosis.[6] However, the included studies had issues regarding representativeness of cohorts, reporting of follow-up periods, and adjustment for explanatory variables.[6]

In Canada, health administrative databases from the provincial healthcare systems provide an opportunity to obtain population-based estimates of cancer in people with psychotic disorders, along with detailed information on confounding variables. Although a recent Canadian study examined the relationship between psychotic disorders and colorectal cancer in terms of staging and survival,[7] there has been no research to date on the overall incidence of cancer among people with psychotic disorders in Canada. The primary objective of this study was to examine the incidence of cancer following a first diagnosis of non-affective psychotic disorder (NAPD), relative to the general population, using health administrative data from Ontario, Canada.[8] As a secondary objective, we sought to compare stage at cancer diagnosis between people with NAPD and the general population. We hypothesized that we would observe significant heterogeneity in relative risk by cancer site, and that people with NAPD would have greater likelihood of more advanced stage cancer at diagnosis.

2 Methods

2.1 Study Design and Data Sources

We conducted a retrospective cohort study using population-based health administrative data from Ontario, Canada. ICES is a prescribed entity under Ontario's Personal Health Information Protection Act (PHIPA). Section 45 of PHIPA authorizes ICES to collect personal health information, without consent, for the purpose of analysis or compiling statistical information with respect to the management of, evaluation or monitoring of, the allocation of resources to, or planning for all or part of the health system. Projects that use data collected by ICES under section 45 of PHIPA, and use no other data, are exempt from REB review. The use of the data in this project is authorized under section 45 and approved by ICES' Privacy and Legal Office. This manuscript followed the Reporting of studies Conducted using Observational Routinely collected Data (RECORD) guidelines,[9] as described in Appendix A1. We used health administrative databases from ICES, which contain information on hospital admissions, emergency department visits, and outpatient physician billings, as well as characteristics of patients and physicians. Databases were linked at the patient level using unique, encoded identifiers and analyzed onsite at ICES. A brief description of the databases used in this study can be found in Appendix A2.

2.2 Cohort Creation

Using an algorithm validated for identifying chronic cases of NAPD (Table 1), we identified people aged 14 to 59 with a first diagnosis of NAPD between January 1995 and December 2004.[10] A diagnosis of NAPD was classified as either schizophrenia spectrum disorder (i.e., schizophrenia, schizoaffective disorder, schizophreniform) or psychosis not otherwise specified. The case definition excluded affective psychoses, which require information that cannot be identified in outpatient physician billings. The index date was defined as either the date of discharge from hospital or the date of first visit to an emergency department or outpatient clinic. We used a lookback window of five years prior to the

index date to identify and exclude prevalent cases of NAPD. For our comparison group, we selected a random sample from the general population who had not previously received a diagnosis of NAPD, frequency matched by age and sex at a ratio of 4:1; index dates were assigned at random.

We excluded people who were younger than age 14 at the index date due to low incidence of psychotic disorders, as well as those older than age 60 to avoid misclassified cases of dementia. We also excluded non-residents of Ontario and those ineligible for provincial health insurance in the year prior to the index date to improve continuity and completeness of data. Moreover, we excluded people diagnosed with cancer prior to the index date so that only incident cases of cancer were identified.

2.3 Variable Definitions

A detailed description of the variables used in this study can be found in Appendix A3.

2.3.1 Outcome

The primary outcome of this study was person-time from the index date of NAPD to the date of first cancer diagnosis. Incident cases of cancer were identified via linkage to the Ontario Cancer Registry. For each first recorded cancer diagnosis, data pertaining the site and stage of primary malignancy were collected. Cancer site was based on International Classification of Diseases for Oncology (3rd Edition) topography codes for the primary tumor site. Cancer stage at diagnosis was classified using the Tumour, Node, and Metastases (TNM) American Joint Classification of Cancer Staging criteria for the primary tumour site. The cohort was followed until the outcome, death, a new onset of NAPD in the comparison group, or the end of the follow-up period (December 2019), at which point observations were censored.

2.3.2 Covariates

We assessed several confounding variables at baseline, based on their demonstrated associations with cancer.[2,11,12] Age and sex were obtained from the Registered Persons Database (RPDB), and were defined

as continuous and binary variables, respectively. Neighborhood-level income quintile was obtained from the RPDB and was based on the average household income for each postal code according to census data. Rurality of residence was obtained from the RPDB and based on the Rurality Index of Ontario, with rurality defined as communities in and above the 40th percentile. Access to a family physician was obtained from the ICES Physician Database and Primary Care Population Database and was based on whether a person was assigned to a family physician as of the index date.

2.4 Statistical Analyses

We summarized descriptive characteristics of the cohort using frequencies and proportions, as well as means and standard deviations. Standardized differences were calculated to compare baseline characteristics between people with NAPD and the comparison group. Standardized differences greater than 10% were considered to be indicative of significant between-group differences.[13]

Our primary objective was to compare the incidence of cancer between people with NAPD and the general population. We determined the crude incidence rates of all cancers, as well as site-specific cancers, for both groups. We used univariate and multivariable Poisson regression models to compare the time from the index date to the first cancer diagnosis among people with NAPD and the comparison group. We adjusted for age, sex, neighbourhood-level income, rurality of residence, and access to a family physician. We also conducted *post-hoc* stratified analyses by sex and age group for overall cancer incidence, as previous research suggests that these variables are effect modifiers in the relationship between schizophrenia and overall cancer risk.[5]

Additionally, we ran separate Poisson regression models for the incidence of cancer at each specific site. Those who developed cancer at sites other than the site of interest were censored at the time of that cancer diagnosis. Analyses of sex-specific cancers – including breast, cervical, ovarian, uterine, testicular, and prostate – were restricted to the relevant sex. Breast cancer was treated as a sex-specific

cancer for females, as males account for only 1% of all cases;[14] sensitivity analyses were performed to examine the effect of including males in the analysis of breast cancer incidence. To examine the influence of sex-specific cancers on the overall incidence of cancer in people with psychotic disorders, we also performed post-hoc sensitivity analyses by excluding sex-specific cancers from the model of overall cancer incidence.

Our secondary objective was to compare stage at diagnosis among those who developed cancer between people with NAPD and those without NAPD. A proportional odds model for stage at diagnosis was fit on the binary variable of NAPD diagnosis, with adjustment for age, sex, neighbourhood-level income, access to a family physician, and cancer site; people with missing data on staging were excluded from this analysis. Cancer site was included to control for the varying aggressiveness of cancer at different sites,[15] which would influence the likelihood of presenting with advanced staging at diagnosis. We found a large proportion of missing data on stage at cancer diagnosis (52%), and we performed a post-hoc analysis to examine whether people with psychotic disorders had higher odds of missing data. A logistic regression model of missing stage at diagnosis was fit on the binary variable of NAPD diagnosis, with adjustment for age, sex, neighbourhood-level income, access to family physician, and cancer site.

All statistical analyses were performed using STATA v16, and results were presented as incidence rate ratios (IRR) and odds ratios (OR) with corresponding 95% confidence intervals (CI).

3 Results

3.1 Cohort

The characteristics of the cohort at the index date are presented in Table 2, and a detailed breakdown of the cohort composition can be found in Appendix A4. We identified 63,410 cases of NAPD between January 1995 and December 2004 and derived an age- and sex-matched comparison group of 260,539

people from the general population. For both groups, the mean age was 36.0 years (SD = 11.9) and 45% of the sample was female. There was an even distribution across neighborhood-level income quintiles in the comparison group, as they were sampled from the general population, whereas a higher proportion of people with NAPD were in the lowest neighborhood-level income quintile (31% vs. 20%). Similar proportions of people with NAPD and the comparison group lived in rural areas (13% vs. 10%) and had access to a family physician (89% vs. 84%). With respect to psychiatric diagnoses among people with NAPD, 60% had an index diagnosis of schizophrenia spectrum disorder and 40% had an index diagnosis of psychosis not otherwise specified. The mean observation times for people with NAPD and the comparison group were approximately 19 and 18 years, respectively.

3.2 Incidence

The number and incidence rates of cancers are presented in Figure 1, along with results of the Poisson regression models. People with NAPD had an 8.6% higher incidence (IRR = 1.09, 95% CI: 1.05 – 1.12) of cancer overall relative to the comparison group in the fully adjusted model. People with NAPD also had higher incidence of breast cancer (IRR = 1.09, 95% CI: 1.01 – 1.17), cervical cancer (IRR = 1.43, 95% CI: 1.10 – 1.87), esophageal cancer (IRR = 1.72, 95% CI: 1.29 – 2.29), leukemia (IRR = 1.23, 95% CI: 1.08 – 1.40), liver cancer (IRR = 1.70, 95% CI: 1.31 – 2.21), lung cancer (IRR = 1.52, 95% CI: 1.40 – 1.65), and uterine cancer (IRR = 1.19, 95% CI: 1.02 – 1.38). In addition, people with NAPD had lower incidence of melanoma (IRR = 0.66, 95% CI: 0.55 – 0.79), thyroid cancer (IRR = 0.84, 95% CI: 0.72 – 0.98), and prostate cancer (IRR = 0.59, 95% CI: 0.53 – 0.66).

The results of the post-hoc stratified analyses by age and sex can be found in Appendix A5. Sex was found to be an effect modifier on the association between NAPD and incidence of cancer. Females with NAPD had a higher incidence of cancer overall, compared to those without NAPD (IRR = 1.15, 95% CI: 1.11 – 1.20), adjusting for all other covariates; exclusion of female-specific cancers did not

significantly alter the estimate. In contrast, there was no difference in cancer incidence for males with versus without NAPD adjusting for all covariates, but removal of male-specific cancers produced an estimate indicating higher incidence of the remaining cancers (IRR = 1.14, 95% CI: 1.08 – 1.20).

3.3 Stage at Diagnosis

The frequencies and percentages for each stage at diagnosis are presented in Table 3, along with results of the proportional odds model of stage at diagnosis and the logistic regression model of missing stage at diagnosis. People with NAPD had 23% greater odds (OR = 1.23, 95% CI: 1.13 – 1.34) of being diagnosed with a more advanced stage of cancer relative to the comparison group. Our post-hoc analysis suggested that people with NAPD also had 24% greater odds (OR = 1.24; 95% CI: 1.17 to 1.32) of missing data for stage at diagnosis relative to those in the comparison group.

4 Discussion

In the present study, we identified higher incidence of cancer in people with NAPD relative to the general population, with substantial variation by cancer site and effect modification by sex. Our findings are strengthened using population-based health administrative data in a country with universal healthcare, which allows for a large, representative sample and a longer follow up period. Furthermore, this study represents one of few longitudinal studies to examine both cancer incidence and stage at diagnosis among people with psychotic disorders within the same cohort.

While prior meta-analyses have produced conflicting findings as to whether people with psychotic disorders have higher rates of cancer – with one finding lower rates,[2] and another showing no difference[3] – it is noteworthy that they found heterogeneity in both the direction and magnitude of effect by cancer site. It is possible that the small but significantly elevated risk of cancer overall that we observed among people with NAPD was driven by higher rates of more common cancers in this population, such as lung, breast, and colorectal cancers. Similar to previous studies, we found that females with NAPD had

significantly higher incidence of cancer compared to those without NAPD,[5] which was not driven by higher incidence of female-specific cancers. In contrast, we found no difference in cancer incidence between males with and without NAPD.[5] After excluding prostate cancer, males with NAPD had higher risk of cancer overall, which has also been observed in earlier studies.[5]

Initially, it was hypothesized that people with psychotic disorders have lower incidence of cancer, with one theory positing that genetic polymorphisms associated with schizophrenia, reduced the risk of developing cancer.[3] This is supported by a meta-analysis demonstrating a lower risk of all cancers in close relatives of people with schizophrenia, despite finding no difference in cancer risk for people with schizophrenia.[3] While opponents have argued that there are many unknown factors influencing cancer risk in this population,[16] it is possible that the protective effects conferred by genetics are overcome by lifestyle factors among people with psychotic disorders.[17] These factors would explain the lower incidence of cancer in relatives of people with schizophrenia, but a similar incidence of cancer among people with schizophrenia, relative to the general population.

First, adjustment for higher rates of smoking among people with psychotic disorders[1] has been shown to attenuate the relative risk of lung and bladder cancer in people with psychotic disorders.[3] Second, poor eating habits and sedentary lifestyles are more common in people with psychotic disorders, and contribute to higher rates of obesity and metabolic syndromes, such as diabetes.[1] These cardiometabolic conditions have demonstrated associations with various cancers, including breast, colorectal, and esophageal,[18] and can further be exacerbated by antipsychotic medications.[19] Downregulation of insulin growth factors and low testosterone in diabetes also contribute to lower prostate cancer risk,[20] which may cause the lower risk observed among males with psychotic disorders.[3] Fourth, hyperprolactinemia resulting from antipsychotic medications may be responsible for higher rates of breast and uterine cancer among females with psychotic disorders, and lower rates of prostate cancer among males with psychotic disorders.[21–23] Lastly, people with schizophrenia spectrum disorders have higher

odds of hepatitis infection–due to a combination of poor screening adherence, low vaccination rates, risky sexual behaviour, and injection drug use[24]–which may contribute to higher incidence of hepatocellular carcinoma.[25]

We observed higher odds of advanced stage at diagnosis in people with NAPD, which is consistent with the findings of prior meta-analyses of people with serious mental illnesses in countries with universal healthcare.[6] This finding may be indicative of a diagnostic delay due to disparities in access to healthcare services, stigma, or differences in healthcare-seeking behaviour.[6,26] Previous studies have shown that people with schizophrenia are less likely to participate in screening for breast, cervical, prostate, and colorectal cancer.[27–29] Furthermore, people with psychotic disorders have higher prevalence of many chronic health conditions, which may be dismissed or misattributed to the psychiatric diagnosis, known as diagnostic overshadowing,[30] and thereby reduce the likelihood of receiving specialized services for these conditions.[31] Therefore, it is possible that dismissal or misattribution of symptoms in relation to malignancy may contribute to delayed diagnosis and treatment of cancer.

In Canada, organized screening programs for cervical and colorectal cancer screening – allowing for early detection and removal of pre-cancerous lesions – have translated into dramatic reductions in incidence of and mortality from these cancers over time,[32,33] On the other hand, breast and prostate cancer screening initiatives have had a more modest impact, and may have even led to over-diagnosis and unnecessary treatment in some instances.[34] As such, low uptake of screening among people with psychotic disorders may explain the higher incidence of cervical and colorectal cancers, while underestimating the incidence of prostate and breast cancers, relative to the trends in the general population.[35]

A large proportion of people who developed cancer in this study had an unknown stage at diagnosis, which likely reflects poor recording of staging information in provincial health administrative databases, which has been identified previously.[36] Nonetheless, we found that people with NAPD had higher odds of unknown stage at diagnosis, which has been shown in prior studies.[7] This finding

demonstrates that patients with psychotic disorders may be less likely to receive adequate cancer staging, due to either lack of access or uptake, which may limit the availability of information pertinent to cancer prognosis. It is important to note that these differences persist in studies conducted in Canada, which has a universal healthcare system,[7] which suggests that cost is only one of many factors influencing quality of care for marginalized populations, such as people with psychotic disorders.

4.1 Study Limitations

The present study was limited by the data available in the ICES databases, and so we could not adjust for important confounding variables, such as obesity, smoking, and antipsychotic medications.[1,3] The case definition used to identify people with NAPD has high sensitivity, which may have misclassified some our cohort as having NAPD, although we expect this misclassification to be nondifferential.[10] This case definition did not include people with affective psychoses, and thus our findings may not be generalizable to people with those diagnoses, including bipolar disorder with psychotic features and major depressive disorder with psychotic features. Furthermore, the exposed group included people with a first diagnosis of NAPD; therefore, information on specific, future diagnoses was not included.

Our cohort had a large proportion of missing data for stage at diagnosis, which may limit the generalizability of our findings if people differ systematically according to availability of staging data; we found that people with NAPD were more likely to have missing stage data. As well, our cohort was relatively young, given that we followed people from the time of first diagnosis of NAPD. This feature is reflected in the relatively low rates of myeloma and laryngeal cancer in our cohort, both of which are generally diagnosed in older adults,[37,38] and so our conclusions may be limited to those cancers which commonly occur in younger people. Furthermore, the low rates of myeloma and laryngeal cancer, as well as Hodgkin's lymphoma, reduce the precision of our estimates for those cancers.

4.2 Clinical Implications

The elevated incidence of cancer at several sites among people with non-affective psychotic disorders should underline the importance of collaboration across disciplines and provision of cohesive psychiatric care to meet the specialized needs of patients with psychotic disorders.[26,39,40] In addition, the greater odds of having more advanced stage cancer at diagnosis among people with psychotic disorders is indicative of a diagnostic delay and differences in accessing healthcare. The development of cancer treatment guidelines among people with NAPD and programs which target education, screening, and early diagnosis among individuals with psychotic disorders may facilitate better health outcomes.[40]

4.3 Conclusions

This retrospective cohort study identified a small but significant elevation in incidence of cancer among people with NAPD relative to the general population. However, both the direction and magnitude of effect varied significantly by cancer site, and there was evidence of effect modification by sex. We also found the people with NAPD had more advanced stage at diagnosis, which may be indicative of diagnostic delay. Future research should examine a wider array of confounding factors involved in cancer incidence and stage at diagnosis, as well as potential mediating effects of antipsychotic medications and cardiometabolic comorbidities. Moreover, efforts should be made to improve education surrounding cancer prevention, screening, diagnosis, and treatment targeted to people with psychotic disorders.

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As a prescribed entity under Ontario's Personal Health Information Protection Act (PHIPA), ICES is authorized to collect and use health care data for the purposes of health system monitoring, evaluation, and decision support. Secure access to these data is governed by policies and procedures that are approved by the Information and Privacy Commissioner of Ontario. The dataset from this study will be held securely in coded form at ICES and an analyst will have full access to study data. While data sharing agreements prohibit ICES from making the dataset publicly available, access can be granted to those who meet pre-specified criteria for confidential access. The full dataset creation plan is available upon request.

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7 Tables and Figures

Table 1. Validated algorithm for identifying cases of non-affective psychotic disorders in ICES databases[10]

Database	Qualifying Event
Discharge Abstract Database (DAD)	≥ 1 primary discharge diagnosis of schizophrenia, schizoaffective disorder, schizophreniform, or psychosis not otherwise specified (ICD-9 codes 295.x or 298.x; ICD-10 codes F20, F25, or F29)
OR	
Ontario Health Insurance Plan (OHIP) Database	≥ 2 OHIP billings within 24 months with a diagnostic code (DXCODE) for schizophrenia, schizoaffective disorder, schizophreniform, or psychosis not otherwise specified (ICD-9 codes 295.x or 298.x; ICD-10 codes F20, F25, or F29)

ICD = International Classification of Diseases

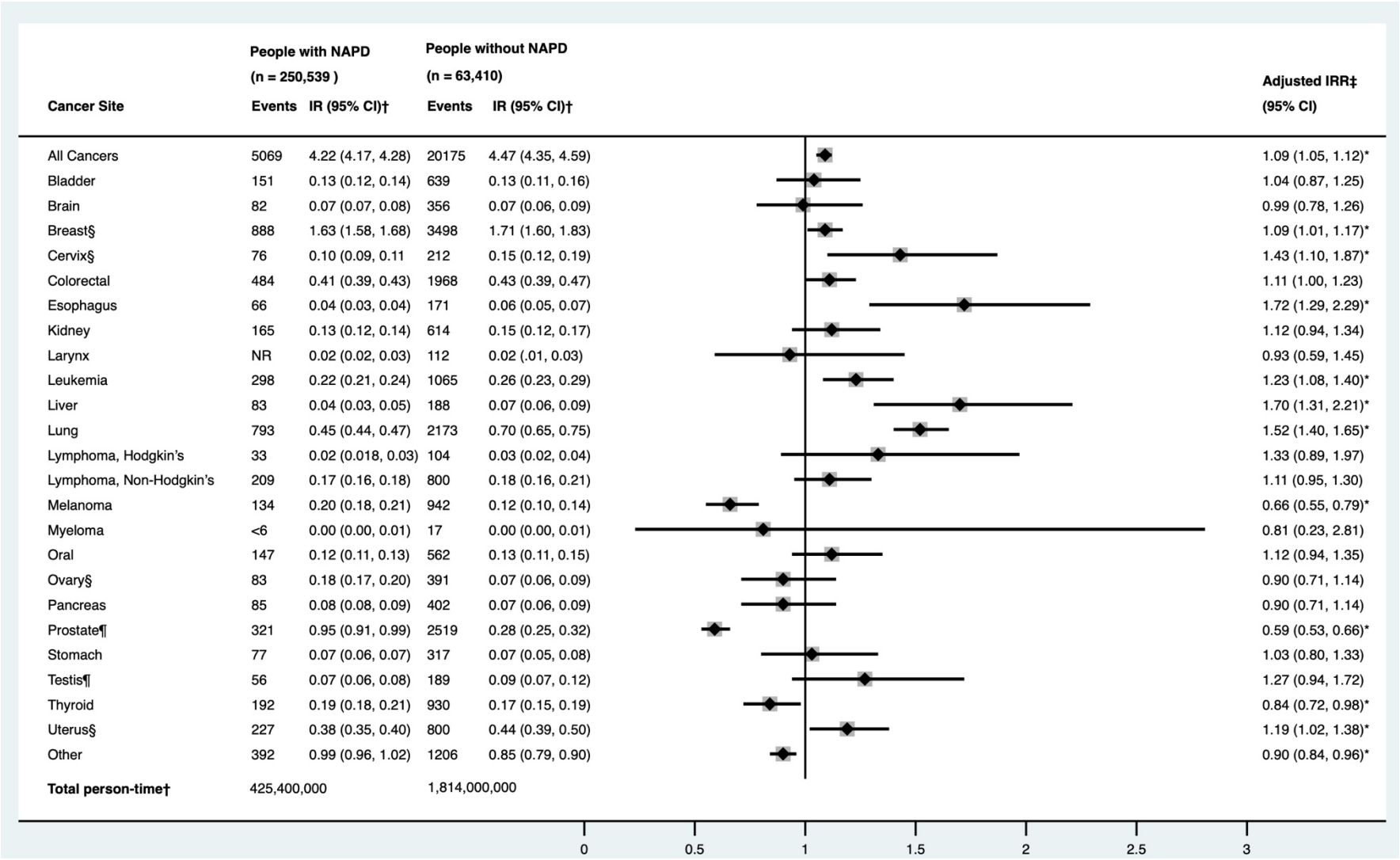
Table 2. Descriptive characteristics of the study cohort, by diagnosis of non-affective psychotic disorder

Characteristic		People with NAPD n (%) (N = 63,410)	People without NAPD n (%) (N = 250,539)	Standardized Difference (%)
Age (years)	**Mean (SD)**	36.0 (11.9)	36.01 (11.9)	0.1
	15 – 20	6,090 (9.6)	24,010 (9.6)	0.1
	20 – 29	14,686 (23.2)	58,210 (23.2)	0.2
	30 – 39	17,183 (27.1)	67,628 (27.0)	0.2
	40 – 49	15,382 (24.3)	60,766 (24.25)	0.0
	50 – 59	10,069 (15.9)	39,925 (15.94)	0.2
Sex	Female	28,394 (44.8)	112,030 (44.7)	0.1
	Male	35,016 (55.2)	138,509 (55.3)	0.1
Neighbourhood-level income quintile	1 (lowest)	19,818 (31.3)	49,954 (19.9)	26.1*
	2	14,065 (22.2)	49,889 (19.9)	5.6
	3	11,133 (17.6)	49,918 (19.9)	6.1
	4	9,793 (15.4)	50,033 (20.0)	11.9*
	5 (highest)	8,601 (13.6)	50,745 (20.3)	17.9*
Rurality of residence	Urban	57,186 (90.2)	218,776 (87.3)	9.1
	Rural	6,224 (9.8)	31,763 (12.7)	9.1
Access to family physician	Yes	56,326 (88.8)	209,218 (83.5)	17.3*
	No	7,084 (11.2)	41,321 (16.5)	14.7*
Psychiatric diagnosis	Schizophrenia spectrum disorder	38,004 (59.9)	--	--
	Psychosis not otherwise specified	25,406 (40.1)	--	--

NAPD = non-affective psychotic disorder, SD = standard deviation

* Significant between-group difference

Figure 1: Incidence of cancer by site, and results of Poisson regression models of all-site and site-specific cancer incidence



CI = confidence interval, IR = incidence rate, IRR = incidence rate ratio, NAPD = non-affective psychotic disorder
†events per 1000 person-years
‡ adjusted for age, sex, neighbourhood-level income, rurality of residence, and access to family physician
§ female only, ¶ male only, *statistically significant ($p<0.05$)

Table 3. Stage at diagnosis for people diagnosed with cancer, and results of proportional odds models of stage at diagnosis and logistic regression model of missing stage at diagnosis

Stage	People with NAPD n (%) (n = 5,069)	People without NAPD n (%) (n = 20,175)
I (early)	688 (13.6)	3,285 (16.3)
II	531 (10.5)	2,733 (13.6)
III	424 (8.4)	1,823 (9.0)
IV (late)	565 (11.2)	1,974 (9.8)
Missing	2,861 (56.4)	10,360 (51.4)
	OR (95% CI) **Crude**	**OR (95% CI)** **Adjusted**[†]
Higher stage at diagnosis[‡]	1.23 (1.13, 1.34)	1.16 (1.06, 1.27)
Missing stage at diagnosis	1.24 (1.17, 1.32)	1.23 (1.15, 1.32)

CI = confidence interval, NAPD = non-affective psychotic disorder, OR = odds ratio

[†] adjusted for age, sex, neighbourhood-level income, rurality of residence, access to family physician, and cancer site

[‡] excluding people with data missing for stage at diagnosis