

Cancer Incidence in Patients With Schizophrenia or Bipolar Disorder: A Nationwide Population-Based Study in Taiwan, 1997–2009

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Background: Both genetic and environmental factors have been reasoned for cancer development in schizophrenia patients. However, the influence of age of onset and duration of schizophrenia on cancer incidence has rarely been emphasized. Besides, bipolar disorder tends to resemble schizophrenia from the perspective of multiple rare mutations. Comparing pattern and risk of cancers between schizophrenia and bipolar patients is illuminating. **Methods:** This study used the Taiwan National Health Insurance Database. A total of 71 317 schizophrenia and 20 567 bipolar disorder patients from 1997 to 2009 were enrolled. Both cohorts were followed up for cancer during the same period by record linkage with the cancer certification in Taiwan. Age and gender standardized incidence ratios (SIRs) of overall and site-specific cancers were calculated. **Results:** The SIR for all cancers was 1.17 for the schizophrenia cohort. Increased cancer risk (SIR: 1.31, 95% CI: 1.17–1.48) was observed in females but not males. For the bipolar disorder cohort, the SIR for all cancers was 1.29, but the excess risk was found in males (SIR: 1.42, 95% CI: 1.14–1.77) and not females. Cancer risk decreases as the duration and age of onset of schizophrenia increases. If schizophrenia is diagnosed before 50, the SIRs for colorectal, breast, cervical, and uterine cancers increase but if diagnosed after 50, the SIRs for all cancers decrease except for breast cancer. In bipolar disorder, the SIRs for all site-specific cancers were insignificant. **Conclusions:** Among schizophrenia patients, overall cancer risk varies inversely with age at diagnosis and disease duration. Besides, gender-specific cancer risks differ between schizophrenia and bipolar disorder.

Key words: schizophrenia/bipolar disorder/cancer/standardized incidence ratio

Introduction

The hypothesis that schizophrenia patients have a decreased risk for cancer was first formulated in 1909.¹ Over the past 100 years, numerous reports demonstrated conflicting results regarding the relative risk for cancers among schizophrenia patients as opposed to general population.^{2–8} Both genetic and environmental factors have been reasoned for the disparities. The ethnic difference was first described in a multicenter collaborative registry of the World Health Organization (WHO), where an increased cancer incidence was found in the Japanese cohorts but a decreased cancer risk in the Danish and Caucasian cohorts.³ Notably, the increased cancer risk in the Japanese cohorts was mainly because the female population had elevated incidences of breast and uterine cancers. In an Israeli study, Grinshpoon et al⁶ also found increased incidences of female-specific cancers among the Jewish and Asian-African cohorts but no difference in overall cancer incidence.

Regarding environmental factors, heavy smoking was found prevalent among schizophrenia patients and might be associated with an increased risk of lung cancer. In the Finnish registry, schizophrenia patients were observed to have an increased incidence of lung cancer.⁴ In contrast, the WHO registry observed a decreased incidence of lung cancer among the Danish cohort, which was partly explained by the restriction of smoking in the facilities.³ Moreover, in many case-control studies, a decreased risk of lung cancer was obtained after adjusting for the smoking status.⁹ Other demographic factors might also affect the cancer risk for schizophrenia patients. For instance, in earlier researches before 1970, Malzberg¹⁰ showed excess cancer mortality in all younger patients, but a lower than expected cancer mortality in older males.³ Katz et al¹¹ uncovered an increase in cancer mortality among

short-stay psychiatric inpatients, as opposed to a reduced cancer mortality among those patients hospitalized for more than 10 years.³

Since early-onset cancers tend to have a genetic origin, whereas late-onset cancers are more lifestyle related, the first aim of this study was to clarify the influence of age of onset and duration of schizophrenia on cancer risk. We investigated the onset age- and disease duration-stratified cancer incidences in schizophrenia patients and estimated the standardized incidence ratios (SIRs) relative to the general population in Taiwan. The second aim was to compare the pattern and risk of cancers between schizophrenia and bipolar disorder patients. Although bipolar disorder is also a major psychiatric illness, its relationship with cancers has rarely been addressed. According to a recent genome-wide association study, common genetic variants were found in both schizophrenia and bipolar disorder, implying genetic similarities in the 2 conditions despite their distinct clinical features, disease courses, and prognoses.¹² While common genetic variants may also predispose to similar cancers, the SIRs for cancers should also be constructed in bipolar disorder patients and contrasted with those in schizophrenia patients.

Methods

Data Sources

We used a longitudinal health insurance database, National Health Insurance Research Database (NHIRD), provided by the Taiwan National Health Research Institute. Taiwan launched its compulsory social insurance program, National Health Insurance (NHI), to provide health care for all the island's residents in 1995. The annual coverage rate of the NHI program ranged from 96.1% to 99.6%, with more than 20 million Taiwanese residents enrolled since 1997.

In the Taiwan NHI system, the government defined a set of diseases, such as schizophrenia, mood disorders, and cancer, as "catastrophic illnesses" and provided regulations for the insured affected individuals to apply for a catastrophic illness certificate. Patients with catastrophic illness certification get free care for their illness or related conditions within the certificate's validity period.

The longitudinal health insurance database for people with catastrophic illnesses was used in this study. The database included all relevant information about the "catastrophic illness certificate" status, such as diagnosis, date of diagnosis, date of death, and outpatient/inpatient claimed data for the beneficiaries with catastrophic illnesses during the period 1995–2009.

Study Populations

Schizophrenia. Patients newly diagnosed with schizophrenia and simultaneously free of cancer were eligible

for enrollment in our cohort. To ensure the identification of new schizophrenia cases (ICD-9-CM code: 295), we skipped the first 2 years (1995–1996) of the longitudinal catastrophic illness database and selected individuals whose first ever issue of schizophrenia certificate occurred during 1997–2009. Accordingly, 74 466 first-ever issued schizophrenia catastrophic illness certificates were thus selected.

We excluded 18 patients who had missing data on date of birth, sex, or date of diagnosis and 471 patients with preexisting cancer. To further validate the diagnosis of schizophrenia, 2260 patients were excluded from the subsequent analysis because psychiatric diagnoses other than schizophrenia were documented in their medical records within a year (from 9 months prior to the issue date of schizophrenia certificate to 3 months afterward). In total, 71 317 schizophrenia patients were included. Among them, 28 839 were confirmed by their hospitalized data and coded as schizophrenia inpatients; 42 478 patients with no psychiatric hospitalized records within the 1 year time frame were coded as schizophrenia outpatients.

Bipolar Disorder. First, we identified 74 939 newly diagnosed patients with mood disorder (ICD-9-CM code: 296) who were issued catastrophic certificates each during 1997–2009. Seventeen patients with missing data on date of birth, sex, or date of diagnosis and 2349 patients with antecedent cancer were excluded. Because the code 296 contains both bipolar disorder and major depression, from the remaining 72 573 subjects, we further selected 20 567 patients with the diagnosis of bipolar disorder (ICD-9-CM codes: 296.0, 296.1, 296.4–296.8) within a year (from 9 months prior to the issue date of mood disorder certificate to 3 months afterward) based on their linkage inpatient and outpatient reimbursement data. Among the 20 567 initially cancer-free bipolar disorder patients, 9226 were confirmed by their hospitalization records and coded as inpatients; 11 341 patients with only outpatient bipolar disorder diagnosis were coded as outpatients.

The residual group consisting of 33 819 patients with major depression (ICD-9-CM codes: 296.2, 296.3), 3524 patients with dysthymic disorder (ICD-9-CM code: 300.4), and 14 663 patients with unspecified episodic mood disorder (ICD-9-CM code: 296.9), or other mental disorders were excluded from the study.

Cancer Status. The first-ever cancer status, including date of diagnosis and primary site, of the study subjects was also obtained by linkage to the catastrophic illness database. Cytological and/or other pathological reports or evidence supportive of malignancy would be required to apply for a catastrophic illness certificate for cancer. Benign tumors, in situ malignancies, Kaposi's sarcoma, and metastatic cancers were excluded from the cancer analysis. The ICD-9-CM codes for site-specific cancers

Table 1. Baseline Characteristics and Follow-Up Cancer Risk in Patients With Schizophrenia and Bipolar Disorder

	Number	Mean Age At Diagnosis	Mean Follow-Up Year	Number of Cancers Observed	SIR (95% CI)
Schizophrenia					
Total	71 317	37.0 ± 13.6	6.65	1129	1.17 (1.08–1.28)**
Sex					
Female	33 297	38.9 ± 14.2 ^a	6.56	654	1.31 (1.17–1.48)**
Male	38 020	35.4 ± 12.9	6.72	475	1.02 (0.90–1.16)
Type of care					
Inpatient	28 839	35.7 ± 13.1 ^b	6.95	421	1.18 (1.05–1.32)*
Outpatient	42 478	37.9 ± 13.9	6.44	708	1.17 (1.06–1.29)*
Bipolar disorder					
Total	20 567	38.5 ± 15.0	5.64	0367	1.29 (1.11–1.51)*
Sex					
Female	11 160	39.3 ± 14.7 ^a	5.54	173	1.17 (0.94–1.46)
Male	9407	37.5 ± 15.2	5.75	194	1.42 (1.14–1.77)*
Type of care					
Inpatient	9226	36.2 ± 14.2 ^b	6.42	162	1.31 (1.08–1.59)*
Outpatient	11 341	40.3 ± 15.0	5.00	205	1.28 (1.07–1.53)*

Note: SIR, standardized incidence ratio.

^a*P* value for gender difference <.001; ^b*P* value for type of care difference <.001; **P* value for SIR of cancer <.05; ***P* value for SIR of cancer <.001.

are 140–208. As an internal quality control measure for the validity of schizophrenia and bipolar disorder diagnosis, the cancer risks in patients with schizophrenia or bipolar disorder were also compared between outpatients and inpatients.

Background Cancer Incidence. We calculated background cancer incidence rates for general population from the cancer registry database, which was constructed under the regulations of the “Taiwan Cancer Control Act.” The regulation required that any medical facility in Taiwan comprising more than 50 beds is mandated to have a form of cancer registry and reporting including patient’s age, sex, date of birth, age at diagnosis, date of initial diagnosis, primary site of the cancer, histology, grading, and stage. The Taiwan Department of Health designated a cancer registry advisory board to assure the accuracy of the database. In our study, age- and gender-specific cancer incidence rates for each site for the general population were collected during the same period.

Because the data used in this study consist of deidentified secondary data released to the public for research purposes, the study was exempted from full review by the Institutional Review Board.

Statistical Analysis. The follow-up time for cancer, defined as person-years at risk, began with the issuance of schizophrenia catastrophic illness certificate and ended with issuance of a cancer catastrophic illness certificate,

death, or the end of the study period (December 31, 2009). We calculated expected number of cancers by multiplying the number of person-years accumulated in each stratum of age, sex, and follow-up time by the corresponding background specific rate. The SIR, calculated as the observed/expected number of cancer cases, was used as a measure of relative risk, with 95% CIs assuming a Poisson distribution of the observed number of cancers. Cox proportional hazards model was used to derive age-adjusted cancer hazard ratios (HRs) for patients with bipolar disorder relative to those with schizophrenia. The statistical analyses were performed in SAS 9.2.

Results

Table 1 shows baseline characteristics of schizophrenia and bipolar disorder patients. The mean and median ages at diagnosis were 37.0 and 35.0 years for schizophrenia, and 38.5 and 37.0 years for bipolar disorder, respectively. The median ages were fairly close to their means. The mean follow-up time in the bipolar disorder group, 5.64 years, was approximately 1 year less than that (6.65 y) of the schizophrenia cohort, reflecting the exclusion of “diagnosis-indefinite” bipolar disorder patients with a longer period of follow-up. The proportion of incident schizophrenia cases each year from 1997 to 2009 distributed fairly evenly (6.4%, 8.7%, 9.1%, 8.2%, 9.6%, 9.3%, 9.8%, 8.7%, 7.0%, 6.1%, 5.9%, 5.5%, and 5.7%), whereas that of bipolar disorder was notably variable with the lowest proportions occurring in the first 3 years (3.3%,

Table 2. Overall Cancer and SIR in Schizophrenia Patients According to Age at Diagnosis and Disease Chronicity by Gender

Category	All		Male		Female	
	Number of Cancers Observed	SIR (95% CI)	Number of Cancers Observed	SIR (95% CI)	Number of Cancers Observed	SIR (95% CI)
All patients	1129	1.17 (1.08–1.28) **	475	1.02 (0.90–1.16)	654	1.31 (1.17–1.48) **
Age at diagnosis						
0–19	12	2.18 (0.79–5.98)	10	3.01 (0.87–10.41)	2	0.91 (0.13–6.24)
20–29	69	1.85 (1.24–2.75)*	35	1.77 (1.02–3.07)*	34	1.94 (1.09–3.45)*
30–39	230	1.61 (1.31–1.99) **	112	1.53 (1.14–2.05)*	118	1.70 (1.27–2.30)**
40–49	332	1.32 (1.12–1.55)*	139	1.20 (0.94–1.53)	193	1.42 (1.14–1.76)*
50–59	254	1.13 (0.95–1.36)	91	0.92 (0.69–1.22)	163	1.31 (1.03–1.65)*
≥60	232	0.77 (0.65–0.91)*	88	0.58 (0.44–0.75) **	144	0.97 (0.77–1.22)
Years since diagnosis						
During year 1	143	22.9 (19.2–27.4) **	53	17.2 (12.9–22.8) **	90	28.5 (22.8–35.7) **
During year 2	111	6.79 (5.57–8.26) **	44	5.55 (4.07–7.56) **	67	7.95 (6.16–10.26) **
During years 3–5	366	3.07 (2.72–3.46) **	162	2.85 (2.39–3.41) **	204	3.27 (2.78–3.85) **
During years 6–10	413	0.83 (0.74–0.93)*	175	0.72 (0.61–0.86) **	238	0.93 (0.79–1.08)
After year 10	96	0.30 (0.24–0.37) **	41	0.27 (0.19–0.37) **	55	0.33 (0.25–0.44) **

Note: Abbreviation is explained in the first footnote to table 1.

P* value for SIR of cancer <.05; *P* value for SIR of cancer <.001.

4.2%, 6.1%, 7.0%, 8.4%, 9.5%, 10.4%, 10.0%, 9.2%, 8.7%, 8.3%, 7.7%, and 7.3%).

There were 33 297 women (46.7%) and 38 020 men (53.3%) in the schizophrenia population. The bipolar disorder population comprised 11 160 women (54.3%) and 9407 men (45.7%). For both cohorts, the mean age at diagnosis for females was a little older than that for males (38.9 vs 35.4 y in schizophrenia; 39.3 vs 37.5 y in bipolar disorder), and the mean follow-up time for females was similar to that for males (6.56 vs 6.72 y in schizophrenia; 5.54 vs 5.75 y in bipolar disorder) (table 1).

In total, 1129 overall cancers were observed among schizophrenia and 367 among bipolar disorder patients, yielding a SIR of 1.17 (95% CI: 1.08–1.28) and 1.29 (95% CI: 1.11–1.51), respectively, indicating an increased risk for cancers among both cohorts. Notably, there were 654 cancers observed in female schizophrenia patients, yielding a SIR of 1.31 (95% CI: 1.17–1.48) and 475 cancers observed in males, yielding a SIR with 1.02 (95% CI: 0.90–1.16), indicating that only female schizophrenia patients had an increased risk for cancers. Conversely, there were 194 cancers observed in male bipolar disorder patients, yielding a SIR of 1.42 (95% CI: 1.14–1.77) and 173 cancers in females, yielding a SIR with 1.17 (95% CI: 0.94–1.46), indicating that only male bipolar disorder patients had an increased risk for cancers. As an internal control, the baseline characteristics and the SIRs for all cancers were similar in both inpatients and outpatients with schizophrenia and bipolar disorder (1.18 vs 1.17 and 1.31 vs 1.28, respectively) except for a significantly longer mean follow-up years observed among bipolar disorder inpatients (6.42 vs 5.00 y) (table 1). Consequently,

we did not perform subsequent cancer risk analyses for bipolar disorder patients by age at diagnosis and disease duration due to the inhomogeneous distribution of follow-up years.

Table 2 compares the risk of overall cancers among male and female schizophrenia patients while taking age at diagnosis and chronicity of schizophrenia into consideration. When patients were stratified by age at diagnosis into the groups of 0–19, 20–29, 30–39, 40–49, 50–59, and ≥60, the overall cancer SIR was reduced gradually as the onset age of schizophrenia increased, and the SIR began to shift toward the protective end from age 50. As for duration of schizophrenia, 620 patients, 55.4% of the cancer cases, had a cancer by the fifth year from schizophrenia diagnosis, and the SIR for cancers dropped significantly from 22.9 (95% CI: 19.2–27.4) to 0.30 (95% CI: 0.24–0.37) as the duration extended from within 1 year to more than 10 years. The direction of SIR reversed after the fifth year from schizophrenia diagnosis.

Among female schizophrenia patients, the SIRs for all cancers went all the way down from age 20 to the oldest age at diagnosis groups. Only 2 cancer cases were found in female patients with schizophrenia before 20, making the SIR relatively unstable. On the other hand, if diagnosed after 60, the cancer risk in schizophrenia patients became less than that of general females. Among male patients, the SIR for all cancers decreased if schizophrenia was diagnosed later in life. If schizophrenia appeared beyond age 50, the risk of cancer was significantly less than the general population. The cancer risk was significantly reduced in elderly (≥60 y of age) male patients (SIR, 0.58; 95% CI: 0.44–0.75) but not females (SIR,

Table 3. Site-Specific Cancer and SIR in Schizophrenia Patients by Age Group at Diagnosis

Site (ICD9 code)	All		Age >50 y		Age <50 y	
	Number of Cancers Observed	SIR (95% CI)	Number of Cancers Observed	SIR (95% CI)	Number of Cancers Observed	SIR (95% CI)
Overall cancer (140–208)						
Oral cavity	128	1.13 (0.87–1.45)	30	0.77 (0.48–1.24)	98	1.31 (0.97–1.77)
Mouth and tongue (141, 144–145)	53	0.94 (0.53–1.66)	11	0.59 (0.28–1.24)	42	1.12 (0.72–1.74)
Pharynx (146–147)	47	1.30 (0.82–2.07)	8	0.86 (0.37–2.01)	33	1.47 (0.86–2.52)
Digestive						
All (150–159)	340	1.02 (0.88–1.19)	159	0.73 (0.60–0.90)*	181	1.57 (1.24–1.98) **
Stomach (151)	48	1.14 (0.75–1.72)	24	0.86 (0.50–1.48)	24	1.70 (0.88–3.27)
Colorectal (153–154)	108	0.98 (0.75–1.28)	54	0.72 (0.51–1.03)	54	1.53 (1.00–2.34)*
Liver (155)	124	0.92 (0.72–1.18)	56	0.66 (0.47–0.93)*	68	1.36 (0.94–1.96)
Respiratory						
All (160–165)	88	0.91 (0.68–1.22)	53	0.75 (0.53–1.07)	35	1.36 (0.82–2.27)
Lung (162)	78	0.93 (0.69–1.27)	51	0.80 (0.55–1.16)	27	1.36 (0.76–2.43)
Bone, skin, and breast						
All (170–175)	244	1.50 (1.23–1.83) **	100	1.46 (1.07–1.98)*	144	1.53 (1.18–1.99) **
Breast (174), female only	215	1.68 (1.35–2.09) **	88	1.75 (1.24–2.47)*	127	1.64 (1.24–2.17) **
Genitourinary						
All (179–189)	208	1.36 (1.10–1.67)*	101	1.13 (0.85–1.51)	107	1.67 (1.23–2.28) **
Cervix of uterus (180), female only	74	1.41 (0.99–2.02)	29	1.19 (0.69–2.04)	45	1.61 (1.00–2.58)*
Body of uterus (182), female only	39	2.15 (1.23–3.75)*	15	1.61 (0.71–3.65)	24	2.71 (1.25–5.86) **
Prostate (185), male only	10	0.64 (0.29–1.42)	10	0.66 (0.30–1.46)	0	NA
Bladder (188)	25	1.15 (0.65–2.05)	18	1.11 (0.57–2.18)	7	1.27 (0.42–3.89)
Kidney (189)	24	1.16 (0.64–2.08)	15	1.02 (0.50–2.10)	9	1.49 (0.53–4.16)
Other and unspecified						
All (190–199)	70	1.17 (0.83–1.65)	25	1.14 (0.64–2.02)	45	1.19 (0.77–1.83)
Brain (191)	15	1.44 (0.65–3.17)	4	1.15 (0.27–4.85)	11	1.58 (0.61–4.09)
Thyroid and other endocrine (193–194)	22	0.65 (0.38–1.11)	4	0.45 (0.14–2.48)	18	0.71 (0.39–1.31)
Haemopoietic						
All (200–208)	51	1.14 (0.76–1.71)	18	0.95 (0.50–1.82)	33	1.28 (0.76–2.14)
Lymphoma (200–203)	26	1.00 (0.58–1.71)	11	0.92 (0.41–2.09)	15	1.06 (0.51–2.19)
Leukemia (204–208)	25	1.35 (0.74–2.46)	7	1.01 (0.35–2.90)	18	1.54 (0.74–3.23)

Note: Abbreviation is explained in the first footnote to table 1.
 P* value for SIR of cancer <.05; *P* value for SIR of cancer <.001.

0.97; 95% CI: 0.77–1.22, *P* value for gender difference: .003). In female patients, the SIR for all cancers descended drastically from 28.5 (95% CI: 22.8–35.7) to 0.33 (95% CI: 0.25–0.44) as the chronicity of schizophrenia went from within 1 year to more than 10 years. Likewise, the all-cancer SIR in male patients declined from 17.2 (95% CI: 12.9–22.8) to 0.27 (95% CI: 0.19–0.37) when the disease course of schizophrenia elongated to be more than one decade. Generally speaking, after 5 years of schizophrenia diagnosis, the cancer risk appeared signifi-

cantly lower than that of the same-sex and similar age general population (table 2).

Table 3 demonstrates the SIRs for female-specific cancers such as breast (1.68; 95% CI: 1.35–2.09) and body of uterus (2.15; 95% CI: 1.23–3.75), showing that female schizophrenia patients had increased risks in these cancers. In those schizophrenia patients diagnosed before 50 years, the SIRs for colorectal (1.53; 95% CI: 1.00–2.34), breast (1.64; 95% CI: 1.24–2.17), cervix (1.61; 95% CI: 1.00–2.58), and uterine cancers (2.71; 95% CI:

1.25–5.86) were higher compared with general population. On the contrary, in patients with schizophrenia after 50, the SIRs for oral cavity, stomach, colorectal, liver, lung, and prostate cancers were lower than those of the general population, although only the SIR for hepatic cancer was significant (0.66; 95% CI: 0.47–0.93). However, for schizophrenia females diagnosed after 50, the SIR for breast cancer was still higher than that of their age-matched normal females (1.75; 95% CI: 1.24–2.47).

Table 4 shows a comparison of cancer risks between bipolar disorder and schizophrenia by gender and cancer site. In bipolar disorder, the SIRs for all site-specific cancers were insignificant. Among the sites, the SIR for prostate cancer was the highest (SIR: 2.22, 95% CI: 0.86–5.71, *P* value: .097). In females, bipolar disorder possessed a lower risk for most site-specific cancers than schizophrenia (HR: 0.95; 95% CI: 0.80–1.13) except for mouth and tongue (HR: 1.39; 95% CI: 0.14–13.56), gastric (HR: 1.65; 95% CI: 0.83–3.29), and colorectal cancers (HR: 1.69; 95% CI: 1.05–2.70). In males, bipolar disorder conferred a higher risk for all site-specific cancers than schizophrenia (HR: 1.61; 95% CI: 1.36–1.91), and the highest risk ratio was observed in prostate cancer (HR: 3.45; 95% CI: 1.52–7.79).

Discussion

This population-based study was by far the largest to examine the risk of cancer in those with schizophrenia or bipolar disorder.^{2–8,13} Schizophrenia patients were observed from 0 to 13 years with a mean follow-up time of 6.65 years. Though the follow-up time may seem short, it was sufficient enough to clarify whether those early-onset heredity-linked cancers may evolve from young schizophrenia patients. Regarding bipolar disorder, though the SIRs for individual cancer sites were not significant due to low statistical power, this large cohort with 115 998 person-years of follow-up still provides substantial evidence to determine the pattern and risk of cancer for patients with bipolar disorder.

As an innate limitation, age at diagnosis is merely a proxy variable for the actual age of onset in schizophrenia patients. The mean age at diagnosis for schizophrenia was higher than the typical onset age, leaving the disease chronicity somewhat underestimated. Nevertheless, due to the high utilization rate of NHI in Taiwan, we believe the time lag between the onset of schizophrenia symptoms and formal psychiatric diagnosis could be acceptable. Besides, the mean age at diagnosis in our schizophrenia cohort is similar to those of many large schizophrenia registries such as the Denmark registry⁸ 1969–1993 (the mean entry age: 38 y) and the Israel registry⁶ (the mean entry age: 35–40 y), reflecting a common time lag between the age of onset and age at diagnosis for schizophrenia in the real world. Furthermore, also compatible to the other schizophrenia registries, the mean age

of cancer occurrence in the schizophrenia patients was around 53 (data not shown).⁵

According to Jeste *et al.*,¹⁴ late-onset schizophrenia (onset after 45) and chronic schizophrenia (duration for more than 5 y) share similar genetic risks, clinical presentations, treatment responses, and clinical courses.¹⁵ In this regard, we observed decreased SIRs for overall cancers in both late-onset schizophrenia and chronic schizophrenia. Interestingly, a similar observation of decreased lung cancer risk among old-age schizophrenia patients has also been described by Dalton and colleagues.⁸ Henceforth, the construction of age-stratified cancer risk in schizophrenia patients may justify the conflicting results from previous studies.

Breier *et al.*¹⁶ divided the lifetime course of schizophrenia into 3 phases, which correspond well with the chronicity-related cancer risk reduction found in our study. The early deteriorating phase may cease by the fifth year from disease onset. In the middle stabilization phase, symptoms remain relatively unchanged for more than 10 years and may persist into the fifth decade. In the later improving phase, most patients are left with only minimal symptoms.¹⁶ In conjunction with our findings, the cancer risk peaked in the early deteriorating phase and gradually decreased as schizophrenia evolved into the later phases. This phenomenon should not result from concurrent cancers because schizophrenia patients with preexisting cancers were excluded. Brain inflammation associated with microglial activation has been proposed to be one of the potential causes of schizophrenia.^{17,18} The immunity-inflammation process in the pathogenesis of schizophrenia^{19,20} might account for the concurrent cancer risk. Dalton *et al.*⁸ attributed the increased cancer risk during the first follow-up year to emerging brain cancers among schizophrenia patients, but we could not make similar inferences because only fifteen brain cancers occurred (4 of them occurred during the first year).

Of the numerous carcinogens that a developing fetus can be exposed to, viruses may be linked to schizophrenia, in that viruses can stimulate harmful cytokines to devastate the neurodevelopmental process.^{19–21} From our report, in line with the immunity-inflammation hypothesis, schizophrenia patients were prone to virus-associated cancers (nasopharyngeal, cervical, and colorectal cancers) if diagnosed before 50 years.^{22,23} As the disease process in schizophrenia becomes protracted, the virus-related inflammation process could subside or at least stabilize, not further taxing the patients with additional cancer risk. Concerning genetic factors, schizophrenia is known for its high heritability, and enhanced cancer risks were found in schizophrenia patients with known chromosomal abnormalities.²⁴ Environmentally speaking, early-phase patients can be exposed to an escalating amount of noxious insults. Middle- and late-phase schizophrenia patients, however, are probably protected against cancers because of their biological characteristics

Table 4. Comparison of Cancer Risks Between Bipolar Disorder and Schizophrenia by Sex and Cancer Site

Site (ICD9 code)	Bipolar Disorder		Schizophrenia		Hazard Ratio (95% CI)
	Number of Cancers	SIR (95% CI)	Number of Cancers	SIR (95% CI)	
Overall cancer (140–208)					
Male	194	1.42 (1.14–1.77)*	475	1.02 (0.90–1.16)	1.61(1.36–1.91)**
Female	173	1.17 (0.94–1.46)	654	1.31 (1.17–1.48)**	0.95 (0.80–1.13)
Oral cavity (140–149)					
Male	36	1.54 (0.91–2.59)	109	1.12 (0.86–1.48)	1.63 (1.11–2.38)*
Female	4	0.83 (0.22–3.13)	19	1.13 (0.59–2.18)	0.75(0.25–2.21)
Mouth and Tongue (141, 144–145)					
Male	12	0.98 (0.44–2.17)	50	0.97 (0.66–1.43)	1.13 (0.60–2.13)
Female	1	0.73 (0.06–9.76)	3	0.65 (0.15–2.76)	1.39 (0.14–13.56)
Pharynx (146–147)					
Male	12	1.81 (0.70–4.68)	35	1.23 (0.75–2.02)	1.81(0.93–3.52)
Female	0		12	1.23 (0.75–2.02)	
Digestive (150–159)					
Male	81	1.31 (0.94–1.82)	206	1.01 (0.83–1.23)	1.55 (1.20–2.02)**
Female	55	1.36 (0.90–2.04)	134	1.03 (0.81–1.32)	1.45 (1.06–1.99)*
Stomach (151)					
Male	8	1.06 (0.39–2.87)	22	0.95 (0.53–1.70)	1.41(0.62–3.22)
Female	12	2.06 (0.76–5.56)	26	1.37(0.76–2.48)	1.65 (0.83–3.29)
Colorectal (153–154)					
Male	15	0.88 (0.44–1.76)	54	1.01 (0.69–1.47)	1.05 (0.59–1.88)
Female	26	1.49 (0.81–2.74)	54	0.96 (0.66–1.39)	1.69 (1.05–2.70)*
Liver (155)					
Male	39	1.40 (0.86–2.27)	93	0.97 (0.73–1.29)	1.71 (1.17–2.50)*
Female	8	0.65 (0.27–1.58)	31	0.80 (0.50–1.28)	0.91 (0.42–1.98)
Respiratory (160–165)					
Male	24	1.24 (0.68–2.27)	49	0.86 (0.59–1.27)	1.59 (0.96–2.63)
Female	10	0.81 (0.35–1.87)	39	0.99 (0.63–1.54)	0.86 (0.43–1.72)
Lung (162)					
Male	20	1.22 (0.62–2.35)	42	0.90 (0.59–1.36)	1.48 (0.85–2.56)
Female	8	0.70 (0.28–1.72)	36	0.98 (0.62–1.56)	0.73 (0.34–1.58)
Breast (174)					
Female	49	1.37 (0.89–2.11)	215	1.68 (1.35–2.09)**	0.87 (0.65–1.19)
Genitourinary (179–189)					
Male	28	1.88 (1.00–3.53)	41	0.4 (0.62–1.45)	2.05 (1.26–3.34)*
Female	34	1.06 (0.66–1.73)	167	1.52 (1.20–1.94)**	0.72 (0.50–1.04)
Cervix of uterus (180)					
Female	14	0.93 (0.45–1.93)	74	1.41 (0.99–2.02)	0.63 (0.37–1.15)
Body of uterus (182)					
Female	7	1.36 (0.44–4.27)	39	2.15 (1.23–3.75)*	0.70 (0.31–1.58)
Prostate (185)					
Male	14	2.22 (0.86–5.71)	10	0.64 (0.29–1.42)	3.45 (1.52–7.79)*
Bladder (188)					
Male	7	1.48 (0.46–4.75)	14	0.98 (0.47–2.04)	1.46 (0.58–3.64)
Female	3	1.28 (0.23–7.12)	11	1.50 (0.59–3.83)	0.91 (0.25–3.27)
Kidney (189)					
Male	4	1.34 (0.30–6.00)	14	1.46 (0.64–3.31)	1.11 (0.36–3.43)
Female	2	0.57 (0.10–3.23)	11	1.50 (0.59–3.83)	0.91 (0.25–3.27)
Other and unspecified (190–199)					
Male	7	1.25 (0.41–3.82)	26	1.21 (0.68–2.14)	1.12 (0.48–2.60)
Female	12	1.09 (0.48–2.47)	44	1.15 (0.74–1.77)	0.63 (0.14–2.88)
Brain (191)					
Male	1	0.69 (0.05–8.78)	5	0.84 (0.26–2.77)	1.04 (0.12–9.16)
Female	2	1.53 (0.17–13.97)	10	2.23 (0.73–6.78)	0.65 (0.14–2.97)
Thyroid and other endocrine (193–194)					
Male	0	NA	6	0.81 (0.28–2.39)	
Female	8	1.07 (0.39–2.91)	16	0.60 (0.32–1.12)	1.69 (0.72–3.97)
Haemopoietic (200–208)					
Male	10	1.56 (0.58–4.22)	28	1.15 (0.67–1.98)	1.54 (0.74–3.19)
Female	4	0.66 (0.19–2.35)	23	1.13 (0.62–2.06)	0.57 (0.20–1.64)

Note: Abbreviation is explained in the first footnote to table 1.
 *P value for SIR of cancer <.05; **P value for SIR of cancer <.001.

including wingless-related family of proteins (Wnt) pathway inactivation, dopamine effects, and enhanced natural killer cell activity.^{25,26} Besides, antipsychotic drugs have been hypothesized to account for the reduced cancer risk in schizophrenia patients in several studies.^{2-4,8} A cumulative high dose of phenothiazine has been shown to reduce risk for prostate cancer.²⁷ Dalton *et al*²⁸ recently reported long-term use of antipsychotics may decrease risks of rectal, colon, and prostate cancers. This anticarcinogenic effect in antipsychotics should also be considered for the decreased cancer risk among chronic schizophrenia patients.

In Taiwan, the risks for breast and uterine cancers were both higher in schizophrenia women than those in the general population. This finding was confirmed by Chou *et al*²⁹ who also tapped into the NHIRD in Taiwan. The increased cancer risks among female schizophrenia patients were also noted in other Asian populations. The increased risks could be related to low parity, obesity, human papillomavirus infection, and the prolactin-raising effect of antipsychotic medications in schizophrenia women.^{9,30} Catts *et al*⁹ have reasoned that antipsychotic-induced hyperprolactinemia is more commonly seen in Asians because of their slower metabolism of antipsychotics. The severity of hyperprolactinemia could partly explain the increased risk of female-specific cancers among Eastern schizophrenia patients.

Except for the female-specific cancers, the SIRs for most cancers in schizophrenia patients were reduced in late onset schizophrenia. Conversely, schizophrenia patients diagnosed before 40 had a significantly increased risk of oral cancers (data not shown). This finding could result from the high prevalence of cigarette smoking, betel chewing, and Epstein-Barr virus infection among the young schizophrenia patients in Taiwan.^{31,32} Among the environmental carcinogens for young patients, cytomegalovirus was reported to be associated with colorectal cancers, which were more frequently observed in our earlier-onset schizophrenia patients.^{33,34} Antipsychotic medications were also observed to be dose related to the level of fibroblast growth factor, which would further stimulate colorectal cancer growth in younger schizophrenia patients.^{35,36}

It is intriguing that the risk for liver-associated cancers was lower among late-onset schizophrenia patients relative to similar age general population. As major causes of hepatoma in Taiwan, chronic hepatitis B and hepatitis C infections were actually more prevalent in older psychotic patients than in general population.³⁷ Whether late-onset schizophrenia is associated with suppression of virus-related oncogenesis needs further investigation. For cancers that are highly smoking-related (such as lung cancers and bladder cancers), we did not see any risk pattern shift in either earlier-onset or later-onset schizophrenia. Understandably, because smoking information was unavailable, the schizophrenia effect on those cancers

could not be isolated. The risk for prostate cancers in schizophrenia did not differ from that in general population probably due to a rather short observation time.

For bipolar disorder, the SIRs for all site-specific cancers were insignificant. Two prior studies revealed inconsistent findings. In the United Kingdom, Hippius-Cox *et al*⁷ did not observe different risks between bipolar patients and controls. Nevertheless, BarChana *et al*¹³ found an enhanced risk for cancers among Israel-born Jewish patients. However, these reports are limited by the small sizes and thus may lack reliability. With the largest sample ever, we found an increased cancer risk in bipolar disorder males in Taiwan. Just as in female schizophrenia patients where the excess cancer risk was attributed to female-specific cancers, the excess cancer risk in bipolar disorder males was also associated with mainly male-specific cancers among our cohort. In this regard, schizophrenia and bipolar disorder are more different than alike despite the possibility of sharing common genetic variants. Prostate cancer has been related to androgen receptor.³⁸ In bipolar disorder females, hyperandrogenism was also found to be associated with valproate treatment, androgen receptor mutations, and polycystic ovarian syndrome.³⁹ Because evidence about androgen in bipolar disorder males is scarce, it is hard to conclude why the risk of prostate cancer was relatively high in Taiwanese with bipolar disorder. The interplay of androgen, androgen receptor, and valproate treatment is worth further approaching in different ethnical bipolar males.

A recent review has suggested that the disparity in cancer screening and medical care result in reduced cancer occurrence in patients with severe mental illness.⁴⁰ This medical inequality is unlikely considering the Taiwan NHI's excellent coverage rate. Evidently, the cancer incidence rates in our schizophrenia cohort are generally higher than those in the other schizophrenia registries, and overall cancer incidence in our bipolar disorder cohort is higher than that in the general population.

Finally, some limitations have to be addressed. First, we do not know whether schizophrenia with a longer duration (over 13 y) would confer a similarly lower cancer risk ratio. Using the NHIRD in Taiwan, Chou *et al*²⁹ selected schizophrenia patients obtaining the schizophrenia certificate from 1995 to 1999 and estimated their cancer incidence between 2000 and 2008. Their schizophrenia cohort mainly composed of those who were granted the certificate in 1995 and 1996. Because the NHI program was initiated in 1995, most of Chou's patients had actually been diagnosed way earlier than 1995 or 1996. Accordingly, the duration of schizophrenia in their sample is much longer than that in our sample. Because subjects in their study population had a decreased overall cancer risk (adjusted HR 0.71, 95% CI: 0.66–0.76), this finding further reinforced our overall cancer SIR estimate (0.62, 95% CI: 0.56–0.69) for the schizophrenia patients with durations longer than 5 years. Second, as an innate

limitation to NHIRD database, many demographic variables, major risk-factor variables, comorbid physical disorders, psychotropic medications, and cancer biomarkers could not be obtained in the first place so adjustment for those variables were not feasible. Third, recurrent or ongoing cases could have been diagnosed later in life, rendering age at diagnosis an unstable proxy for age of onset of schizophrenia. We intentionally excluded the schizophrenia patients within the first 2 years of issuance of catastrophic illness certificate because they comprised largely of recurrent or ongoing cases accumulated throughout the previous years. From 1997 onwards, only first-ever applicants for catastrophic illness of schizophrenia were included in the study, further minimizing the entrance of recurrent cases. Moreover, because new incident schizophrenia cases were evenly distributed each year, the contamination from delayed identification was tolerable if any. Finally, because the subtypes of schizophrenia and bipolar disorder were not adequately coded in NHIRD, we could not address the relationship between a specific cancer and a schizophrenia subtype.

In conclusion, compared with general population, the overall cancer risks were decreased in late-onset schizophrenia and chronic schizophrenia. Gender-specific cancer risks were different between schizophrenia and bipolar disorder in Taiwan.

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References

- Commissioners in Lunacy for England and Wales. *Annual Report*. London, UK: HMSO; 1909.
- Mortensen PB. The incidence of cancer in schizophrenic patients. *J Epidemiol Community Health*. 1989;43:43–47.
- Gulbinat W, Dupont A, Jablensky A, et al. Cancer incidence of schizophrenic patients. Results of record linkage studies in three countries. *Br J Psychiatry Suppl*. 1992;18:75–83.
- Lichtermann D, Ekelund J, Pukkala E, Tanskanen A, Lonnqvist J. Incidence of cancer among persons with schizophrenia and their relatives. *Arch Gen Psychiatry*. 2001; 58:573–578.
- Barak Y, Achiron A, Mandel M, Mirecki I, Aizenberg D. Reduced cancer incidence among patients with schizophrenia. *Cancer*. 2005;104:2817–2821.
- Grinshpoon A, Barchana M, Ponizovsky A, et al. Cancer in schizophrenia: is the risk higher or lower? *Schizophr Res*. 2005;73:333–341.
- Hippisley-Cox J, Vinogradova Y, Coupland C, Parker C. Risk of malignancy in patients with schizophrenia or bipolar disorder: nested case-control study. *Arch Gen Psychiatry*. 2007;64:1368–1376.
- Dalton SO, Mellekjaer L, Thomassen L, Mortensen PB, Johansen C. Risk for cancer in a cohort of patients hospitalized for schizophrenia in Denmark, 1969–1993. *Schizophr Res*. 2005;75:315–324.
- Catts VS, Catts SV, O'Toole BI, Frost AD. Cancer incidence in patients with schizophrenia and their first-degree relatives—a meta-analysis. *Acta Psychiatr Scand*. 2008;117:323–336.
- Malzberg B. Rates of discharge and rates of mortality among first admissions to the New York civil state hospitals. *Ment Hyg*. 1952;36:104–120.
- Katz J, Kunofsky S, Patton RE, Allaway NC. Cancer mortality among patients in New York mental hospitals. *Cancer*. 1967;20:2194–2199.
- Purcell SM, Wray NR, Stone JL, et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*. 2009;460:748–752.
- BarChana M, Levav I, Lipshitz I, et al. Enhanced cancer risk among patients with bipolar disorder. *J Affect Disord*. 2008;108:43–48.
- Jeste DV, Symonds LL, Harris MJ, Paulsen JS, Palmer BW, Heaton RK. Nondementia nonpraecox dementia praecox? Late-onset schizophrenia. *Am J Geriatr Psychiatry*. 1997; 5:302–317.
- Tran-Johnson TK, Krull AJ, Jeste DV. Late life schizophrenia and its treatment: pharmacologic issues in older schizophrenic patients. *Clin Geriatr Med*. 1992;8:401–410.
- Breier A, Schreiber JL, Dyer J, Pickar D. Course of illness and predictors of outcome in chronic schizophrenia: implications for pathophysiology. *Br J Psychiatry Suppl*. 1992;18:38–43.
- Steiner J, Bielau H, Brisch R, et al. Immunological aspects in the neurobiology of suicide: elevated microglial density in schizophrenia and depression is associated with suicide. *J Psychiatr Res*. 2008;42:151–157.
- van Berckel BN, Bossong MG, Boellaard R, et al. Microglia activation in recent-onset schizophrenia: a quantitative (R)-[11C]PK11195 positron emission tomography study. *Biol Psychiatry*. 2008;64:820–822.
- Hanson DR, Gottesman II. Theories of schizophrenia: a genetic-inflammatory-vascular synthesis. *BMC Med Genet*. 2005;6:7.
- Pert CB, Knight JG, Laing P, Markwell MA. Scenarios for a viral etiology of schizophrenia. *Schizophr Bull*. 1988;14:243–7.
- Duramad P, Tager IB, Holland NT. Cytokines and other immunological biomarkers in children's environmental health studies. *Toxicol Lett*. 2007;172:48–59.
- Hildesheim A, Apple RJ, Chen CJ, et al. Association of HLA class I and II alleles and extended haplotypes with nasopharyngeal carcinoma in Taiwan. *J Natl Cancer Inst*. 2002;94:1780–1789.
- Carrington M, Wang S, Martin MP, et al. Hierarchy of resistance to cervical neoplasia mediated by combinations of killer immunoglobulin-like receptor and human leukocyte antigen loci. *J Exp Med*. 2005;201:1069–1075.
- Demirhan O, Tastemir D. Chromosome aberrations in a schizophrenia population. *Schizophr Res*. 2003;65:1–7.

25. Catts VS, Catts SV. Apoptosis and schizophrenia: is the tumour suppressor gene, p53, a candidate susceptibility gene? *Schizophr Res.* 2000;41:405–415.
26. Cui DH, Jiang KD, Jiang SD, Xu YF, Yao H. The tumor suppressor adenomatous polyposis coli gene is associated with susceptibility to schizophrenia. *Mol Psychiatry.* 2005;10:669–677.
27. Mortensen PB. Neuroleptic medication and reduced risk of prostate cancer in schizophrenic patients. *Acta Psychiatr Scand.* 1992;85:390–393.
28. Dalton SO, Johansen C, Poulsen AH, et al. Cancer risk among users of neuroleptic medication: a population-based cohort study. *Br J Cancer.* 2006;95:934–939.
29. Chou FH, Tsai KY, Su CY, Lee CC. The incidence and relative risk factors for developing cancer among patients with schizophrenia: a nine-year follow-up study. *Schizophr Res.* 2011;129:97–103.
30. Tworoger SS, Hankinson SE. Prolactin and breast cancer risk. *Cancer Lett.* 2006;243:160–169.
31. Liao DL, Yang JY, Lee SM, Chen H, Tsai SJ. Smoking in chronic schizophrenic inpatients in taiwan. *Neuropsychobiology.* 2002;45:172–175.
32. Chien YC, Chen JY, Liu MY, et al. Serologic markers of Epstein-Barr virus infection and nasopharyngeal carcinoma in Taiwanese men. *N Engl J Med.* 2001;345:1877–1882.
33. Harkins L, Volk AL, Samanta M, et al. Specific localisation of human cytomegalovirus nucleic acids and proteins in human colorectal cancer. *Lancet.* 2002;360:1557–1563.
34. Guo JJ. Schizophrenia associated with increased risk of colon cancer but reduced risk of respiratory cancer. *Evid Based Ment Health.* 2008;11:93.
35. Sonvilla G, Allerstorfer S, Heinzle C, et al. Fibroblast growth factor receptor 3-IIIc mediates colorectal cancer growth and migration. *Br J Cancer.* 2010;102:1145–56.
36. Hashimoto K, Shimizu E, Komatsu N, et al. Increased levels of serum basic fibroblast growth factor in schizophrenia. *Psychiatry Res.* 2003;120:211–218.
37. Chang TT, Lin H, Yen YS, Wu HL. Hepatitis B and hepatitis C among institutionalized psychiatric patients in Taiwan. *J Med Virol.* 1993;40:170–173.
38. Massard C, Fizazi K. Targeting continued androgen receptor signaling in prostate cancer. *Clin Cancer Res.* 2011;17:3876–3883.
39. Joffe H, Cohen LS, Suppes T, et al. Valproate is associated with new-onset oligoamenorrhea with hyperandrogenism in women with bipolar disorder. *Biol Psychiatry.* 2006;59:1078–1086.
40. Howard LM, Barley EA, Davies E, et al. Cancer diagnosis in people with severe mental illness: practical and ethical issues. *Lancet Oncol.* 2010;11:797–804.