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Incidence of Cancer in Patients With Schizophrenia and Their First-Degree Relatives: A Population-Based Study in Sweden

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Context: **Previous studies of the association between schizophrenia and cancer have produced conflicting results, probably because of the failure to control for confounding factors.** ***Objective:*** **To test if the possible association between schizophrenia and cancer is genetic by investigating the incidence of cancer in patients with schizophrenia and their relatives.** ***Design:*** **Retrospective cohort study with follow-up between 1965 and 2008. Estimated smoking rates were used to adjust the incidence rates of smoking-related cancers.** ***Participants:*** **The entire Swedish population.** ***Main outcome measures:*** **Risk of overall cancer and 34 site-/type-specific cancers.** ***Results:*** **A total of 59 233 patients in Sweden with schizophrenia were identified, of whom 6137 developed cancer during the study period, giving a decreased standardized incidence ratio (SIR) of 0.79 (95% CI 0.77–0.81). The decrease was more pronounced (SIR 0.40, 95% CI 0.38–0.43) before the first diagnosis of schizophrenia. The overall risk was significantly reduced among their unaffected parents (SIR 0.96, 95% CI 0.94–0.98) and siblings (SIR 0.92, 95% CI 0.89–0.96). Sex-stratified analyses indicated different incidence rates between males and females, with female patients having higher cancer risks than the general population.** ***Conclusions:*** **The significantly decreased incidences of cancers in patients diagnosed with schizophrenia and their unaffected relatives suggest that familiar/genetic factors contributing to schizophrenia may protect against the development of cancer, especially for those cancer sites observed in both settings. The increased risk of breast, cervical, and endometrial cancers after the first diagnosis of schizophrenia could be attributed to nongenetic factors such as antipsychotics administration, which may justify preventive medical screening.**

Key words: cancer/schizophrenia/national databases

Introduction

Schizophrenia is a serious mental disorder, with a lifetime prevalence of about 0.3%–0.7%.[1] Family and twin studies have established that both genetic and environmental factors impact significantly on risk of illness.[2–4] Patients with schizophrenia tend to have poor diets, be physically inactive,[1] and smoke heavily.[1,5] All these factors are associated with cancer development.[1,5] However, studies that have examined the association between schizophrenia and cancer have produced inconsistent results. Some studies have described an increased rate of cancer,[6,7] whereas others have shown no increase[8–10] or even a reduction in the incidence of cancer.[11,12] A possible explanation for the observed inconsistency could be the failure to control for some confounding factors (such as environmental and familial/genetic factors) because most of these studies used data from registries that lack information on these and other confounding factors. In addition, etiologies vary by type of cancers and treatment with antipsychotics could affect the subsequent development of some cancers but was seldom accounted for in earlier studies.[11]

Studies on unaffected parents and siblings of patients with schizophrenia could control for these confounding factors including potential exposure to antipsychotics and provide more valid data and new insights on the mechanism of altered risks.[10] One of the questions we were interesting in answering is whether there is a biological connection between schizophrenia and cancer. More specifically, we wanted to test the hypothesis that the source of correlation between risk for schizophrenia and cancer might arise in part from shared environmental and familial/genetic factors. One way to address this issue is to compare the risks of cancer in patients with schizophrenia and their unaffected relatives. In this study, we estimated the incidence rates for the overall and site-/type-specific cancers for patients diagnosed with

schizophrenia and their unaffected parents and siblings using Swedish nationwide registries. Because cigarette smoking is highly associated with schizophrenia and is a known risk factor for several types of cancers, estimated smoking rates in patients with schizophrenia and the general population were used to adjust the risks of lung and urinary bladder cancers. The present study is one of the largest on this subject, covering 59 233 patients with schizophrenia and allowing for separate analyses of patients by follow-up interval and diagnosis period.

Methods

We used the Swedish Hospital Discharge Register, which forms part of a research database maintained at the Center for Primary Health Care Research, Lund University, to identify individuals hospitalized with schizophrenia between 1965 and 2008. The Swedish Hospital Discharge Register was founded in 1964–1965 by the National Board of Health and Welfare and has had complete nationwide coverage since 1987. Patients with schizophrenia were identified according to the seventh (1965–1968; code 300), eighth (1969–1986; code 295), ninth (1987–1996; code 295), and tenth revisions of the International Classification of Diseases (ICD) (1997 onward; code F20). In Sweden, psychiatric care changed gradually during the study period, with outpatient treatment beginning to replace long-term inpatient care.[13] Therefore, we also included outpatients diagnosed with schizophrenia from 1997 onward to increase the number of cases. Our database only contains outpatient data for the period since 1997, which implies that some individuals with schizophrenia were missed. First diagnosis of schizophrenia was thus defined as first hospital (1965–2008) or outpatient clinic (1997–2008) diagnosis of schizophrenia during the study period. A total of 59 233 patients with schizophrenia were identified. Information on these patients was further linked to the Multi-Generation Register to identify their unaffected relatives, including parents and siblings. To obtain information on all incident cancers from the start of follow-up until December 31, 2008, information on the patients and their unaffected relatives was linked to the Swedish Cancer Registry. Founded in 1958 and maintained by the National Board of Health and Welfare, it has close to 100% coverage at the present time. Information on incident malignant tumors during the study period was obtained from the Cancer Registry using 4-digit ICD-7 codes (140–209). In Sweden, it is compulsory for clinicians and pathologists/cytologists to report all newly diagnosed cancers to the Cancer Registry.[14] The following ICD-7 codes were grouped: 161 (larynx) and 140–148 (lip, mouth, and pharynx), excluding 142 (salivary glands) as "upper aerodigestive tract" cancer; 200 and 202 as "non-Hodgkin lymphoma"; and 204–207 (leukemia), 208 (polycytemia vera), and 209 (myelofibrosis) as "leukemia." Rectal cancer was subdivided into cancers of the anus (squamous cell carcinoma, 154.1) and mucosal rectum (154.0). Lymphomas were classified as independent entities irrespective of their anatomic sites. Basal cell carcinoma of the skin is not registered in the Cancer Registry. A total of 34 cancer sites/types were included.

Additional linkages were extended to the Swedish National Population and Housing Census to obtain information on individual-level socioeconomic status, to the Cause of Death Register to identify date of death, and to the Emigration Registry to identify date of emigration. All linkages were performed by the use of the individual national identification number that is assigned to each person in Sweden for his/her lifetime. This number was replaced by a serial number in order to provide anonymity.

Person-years at risk were calculated from the date of birth, immigration or on January 1, 1965, whichever was the latest time, until diagnosis of cancer, death, emigration, or the end of the study period (December 31, 2008), whichever came first. The risk of cancer in patients with schizophrenia was further divided by the date of first diagnosis of schizophrenia, ie, the risk of cancer before or after the first diagnosis. For the risk of cancer after the first diagnosis of schizophrenia, the follow-up period was divided into 4 periods: <1 year, 1–4 years, 5–9 years, and ≥ 10 years. The same analyses were also conducted for males and females separately. Standardized incidence ratios (SIRs) were calculated as the ratio of the observed and expected numbers of cases.[15,16] The expected number of cases was calculated according to the incidence rates for all individuals without a diagnosis of schizophrenia, and the rates were standardized by 5-year-age group, gender, 5-year time period, socioeconomic status, residential area, and comorbidity.[17] Comorbidity was defined as first hospital diagnosis of obesity (278A [ICD-9] and E65-E68 [ICD-10]) or alcoholism (303 [ICD-9] and F10 [ICD-10]), and adjusting for these comorbidities could partly control the effects by alcohol drinking and obesity in patients with schizophrenia. Standardization for age at first childbirth and parity was also performed for cancers of the female reproductive system. Ninety-five percent confidence intervals (95% CI) for the SIRs were calculated assuming a Poisson distribution and were rounded to the nearest 2 decimals.[17]

Smoking is more prevalent among patients with schizophrenia than in the general population, especially after the diagnosis of schizophrenia.[18] However, we had no information on individual smoking behavior. To control for its confounding effect, we used the following formula to calculate adjusted expected numbers of cases for lung and urinary bladder cancers[19]:

$$\text{Smoking} - \text{adjusted expected number} = (a \times \text{RR} + b)/(c \times \text{RR} + d) \times \text{expected number}$$

where a and b, respectively, denote the prevalence of smoking and nonsmoking among patients with

schizophrenia; c and d, respectively, denote the corresponding prevalence among the general population; and RR denotes the relative risk of developing the specific cancer in smokers compared with nonsmokers. According to an International Agency for Research on Cancer summary, the RR for lung cancer is 10–20 and that for bladder cancer is 5 in individuals who smoke 20 cigarettes per day.[20] The prevalence of smoking has gradually decreased in Sweden, and we used 30% (the prevalence in the 1980s) as the reference.[21,22] The proportion of patients with schizophrenia who were smokers was assumed to be 70%.[18] The prevalence of chronic obstructive pulmonary disease (COPD), used as a proxy of tobacco smoking, was examined in patients with schizophrenia and the general population, to verify our assumption. We used the same formula to calculate adjusted expected numbers of cases for liver cancer to control for the effect of alcohol abuse. We assumed that the prevalence of alcohol abuse was 34% and 5%,[23,24] respectively, for patients with schizophrenia and the general population. The RR for liver cancer is 2 among individual with alcohol abuse. The percentage of T1c in prostate cancer, which represents tumors found in needle biopsies performed due to an elevated prostate-specific antigen level, was examined to see the screening effect. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC). The ethics committee at Lund University, Sweden, approved this study.

Results

A total of 59 233 subjects were diagnosed with schizophrenia in Sweden between 1965 and 2008 (table 1), with a total of 1 931 856 person-years at risk. Before the first diagnosis, a total of 1 073 118 person-years were observed, whereas 858 738 person-years were noted after the first diagnosis. More males were diagnosed with schizophrenia than females. The median age of first diagnosis was 38 for males and 47 for females.

A total of 6137 individuals with schizophrenia developed cancer during the study period (table 2), giving an overall SIR of 0.79 (95% CI 0.77–0.81) compared with the general population. The decrease in patients with schizophrenia was more pronounced before the first diagnosis (SIR 0.40, 95% CI 0.38–0.43), defined as first hospital (1965–2008) or outpatient clinic (1997–2008) diagnosis of schizophrenia during the study period. A total of 24 specific cancer sites showed decreased incidences before the first diagnosis of schizophrenia, whereas only 6 cancer sites showed decreased incidences after the first diagnosis. A significantly increased risk was noted for cancers of the liver, breast, cervix, and endometrium and cancer of unknown primary after the first diagnosis of schizophrenia. When calculated using smoking-adjusted expected numbers of cases, the SIRs for lung and urinary bladder cancers decreased to 0.49 and 0.42, respectively. Notably, cancer of the breast and endometrium had higher incidences in patients with schizophrenia.

Table 1. Patients Diagnosed With Schizophrenia in Hospitals and Outpatient Clinics in Sweden

	Male		Female	
	Number	%	Number	%
Age (y)				
<30	9640	29.9	4908	18.2
30–39	7477	23.2	5047	18.7
40–49	5260	16.3	4632	17.1
≥50	9827	30.5	12442	46.0
Time period				
1965–1974	6364	19.8	5693	21.1
1975–1984	10063	31.2	8677	32.1
1985–1994	7123	22.1	5995	22.2
1995–2008	8654	26.9	6664	24.7
All	32204	100.0	27029	100.0

We conducted separate analyses for male and female patients to examine if there is a difference in cancer risk between the sexes. When all cases were considered, as shown in table 3, both males (SIR 0.63, 95% CI 0.61–0.66) and females (SIR 0.94, 95% CI 0.91–0.97) had lower incidence rate as compared with the general population. However, when we considered only the cancer cases after the first schizophrenia diagnosis, there was a significant difference between males and females. While cancer risk remained lower than that in the general population for males, the risk for females was higher (SIR 1.20, 95% CI 1.15–1.24) (table 4). As noted above, risks for cancers of liver, lung, breast, and endometrium increased significantly. The only cancer with lower risk was skin cancer (squamous cell).

The overall risk was significantly reduced among their unaffected parents (SIR 0.96, 95% CI 0.94–0.98) and siblings (SIR 0.92, 95% CI 0.89–0.96) (table 5). Cancers of the breast, ovary, and skin (melanoma and squamous cell carcinoma) showed significantly reduced risks in the parents of patients with schizophrenia. The decrease was also noted in lung cancer, melanoma, and cancer of unknown primary in the siblings of patients with schizophrenia. In sex-stratified analyses, the fathers, mothers, brothers, and sisters all had lower overall SIRs than the general population (see online supplementary table 1).

The prevalence of COPD was the same (2.15%) among the relatives of patients with schizophrenia and the general population, which was lower than that in patients with schizophrenia (3.24%) (data not shown), suggesting that relatives of patients with schizophrenia had a smoking prevalence similar to that in the general population. The higher COPD prevalence in patients with schizophrenia included in this study confirmed that they had higher

Table 2. Population Adjusted Cancer Risk in Schizophrenic Patients Before and After Schizophrenia Diagnosis

	Before the First Diagnosis			After the First Diagnosis			All		
Cancer Site/Type	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
Upper aerodigestive tract	22	**0.31**	**0.19–0.47**	**87**	**0.61**	**0.49–0.76**	**109**	**0.51**	**0.42–0.61**
Salivary gland	2	**0.25**	**0.02–0.93**	10	0.86	0.41–1.59	12	0.60	0.31–1.05
Esophagus	2	**0.08**	**0.01–0.30**	47	0.88	0.65–1.18	49	**0.63**	**0.47–0.83**
Stomach	13	**0.10**	**0.05–0.18**	171	0.96	0.82–1.12	184	**0.59**	**0.51–0.69**
Small intestine	5	0.42	0.13–1.00	29	1.28	0.85–1.84	34	0.97	0.67–1.36
Colon	65	**0.38**	**0.29–0.48**	361	1.00	0.90–1.11	426	**0.78**	**0.71–0.86**
Rectum	33	**0.35**	**0.24–0.49**	167	**0.82**	**0.70–0.95**	200	**0.66**	**0.57–0.76**
Anus	2	0.44	0.04–1.62	20	1.60	0.97–2.47	22	1.25	0.78–1.90
Liver	6	**0.08**	**0.03–0.17**	182	**1.21**[a]	**1.04–1.40**	188	**0.81**	**0.70–0.94**
Pancreas	4	**0.05**	**0.01–0.14**	139	1.00	0.84–1.18	143	**0.67**	**0.56–0.79**
Nose	1	0.19	0.00–1.09	9	0.99	0.45–1.89	10	0.69	0.33–1.28
Lung	16	**0.09**	**0.05–0.14**	435	1.01[a]	0.92–1.11	451	**0.75**	**0.68–0.82**
Breast	283	**0.75**[b]	**0.66–0.84**	1042	**1.47**[b]	**1.38–1.56**	1325	**1.25**[b]	**1.18–1.31**
Cervix	49	**0.57**[b]	**0.43–0.76**	84	**1.39**[b]	**1.11–1.72**	133	0.85	0.71–1.01
Endometrium	83	0.99	0.79–1.23	228	**1.34**[b]	**1.17–1.53**	311	**1.35**[b]	**1.20–1.51**
Ovary	44	**0.48**	**0.35–0.65**	133	1.13	0.95–1.34	177	**0.85**	**0.73–0.98**
Other female genital	7	0.56	0.22–1.16	27	1.18	0.78–1.72	34	0.94	0.65–1.31
Prostate	39	**0.19**	**0.13–0.26**	373	**0.54**	**0.49–0.60**	412	**0.45**	**0.41–0.50**
Testis	21	0.84	0.52–1.29	28	1.27	0.84–1.83	49	0.94	0.69–1.24
Other male genital	4	0.81	0.21–2.09	12	1.24	0.64–2.17	16	1.06	0.60–1.72
Kidney	19	**0.23**	**0.14–0.37**	158	1.09	0.93–1.27	177	**0.78**	**0.67–0.91**
Urinary bladder	40	**0.42**	**0.30–0.57**	169	**0.73**[a]	**0.63–0.85**	209	**0.63**	**0.55–0.72**
Melanoma	42	**0.54**	**0.39–0.73**	119	**0.77**	**0.64–0.93**	161	**0.67**	**0.57–0.78**
Skin squamous cell	25	**0.39**	**0.25–0.58**	143	**0.78**	**0.66–0.92**	168	**0.63**	**0.54–0.73**
Nervous system	46	**0.44**	**0.32–0.58**	158	1.06	0.90–1.24	204	**0.80**	**0.69–0.92**
Thyroid gland	15	**0.50**	**0.28–0.83**	32	0.88	0.60–1.24	47	**0.69**	**0.51–0.92**
Endocrine glands	43	0.89	0.65–1.21	92	1.08	0.87–1.32	135	1.01	0.84–1.19
Bone	6	0.64	0.23–1.41	8	1.01	0.43–2.00	14	0.83	0.45–1.40
Connective tissue	7	**0.33**	**0.13–0.69**	37	1.17	0.83–1.62	44	0.82	0.60–1.10
Non-Hodgkin lymphoma	32	**0.36**	**0.25–0.51**	187	0.92	0.80–1.07	219	**0.75**	**0.65–0.85**
Hodgkin's disease	15	0.60	0.34–1.00	23	1.10	0.70–1.66	38	0.82	0.58–1.13
Myeloma	12	**0.38**	**0.20–0.67**	58	0.87	0.66–1.12	70	**0.71**	**0.55–0.89**
Leukemia	18	**0.30**	**0.18–0.48**	83	0.92	0.73–1.14	101	**0.67**	**0.55–0.82**
Cancer of unknown primary	9	**0.12**	**0.05–0.23**	210	**1.16**	**1.01–1.33**	219	**0.84**	**0.74–0.96**
All	1036	**0.40**	**0.38–0.43**	5101	1.00	0.97–1.03	6137	**0.79**	**0.77–0.81**

Note: O, observed number of cases; SIR, standardized incidence ratio; CI, confidence interval; Bold type, 95% CI does not include 1.00.
[a]Smoking-adjusted SIRs for lung cancer and urinary bladder cancer 0.49 and 0.42, respectively. Alcohol-adjusted SIR for liver cancer 0.94.
[b]Additionally adjusted for parity and age at first birth.

smoking rates, justifying adjustment for SIR calculation for smoking-related cancers. We also examined the proportion of T1c tumors in patients diagnosed with schizophrenia and prostate cancer. The proportion of T1c tumors was lower in patients with schizophrenia compared with the general population (26% vs 31%) (data not shown), confirming that patients with schizophrenia had lower rates of prostate cancer.

In an attempt to evaluate the effects of antipsychotic treatment, we further analyzed the risk of cancer by sex, follow-up time, and diagnosis period after the first diagnosis of schizophrenia (table 6). The overall risk for cancer in female patients increased significantly for all diagnostic periods and 3 of 4 follow-up periods. The most significant finding was for breast cancer, which had an increased risk irrespective of follow-up time and period after the first diagnosis. For male patients, the risk for prostate cancer decreased for most follow-up times and diagnostic periods. For both males and females, the incidence of cancers was higher than in the general population in the first year after receiving a schizophrenia diagnosis.

Conclusion and Discussion

In this population-based study, a total of 59 233 patients with schizophrenia were identified, and their risks of developing cancer were examined during 1965–2008. The major findings from this study are the following: First, the overall incidence of cancers was significantly lower than that in the general population for both patients with schizophrenia and their unaffected first-degree relatives after adjustment

Table 3. Cancer Risk in Patients With Schizophrenia by Gender

	Male			Female		
Cancer Site/Type	O	SIR	95% CI	O	SIR	95% CI
Upper aerodigestive tract	78	**0.48**	**0.38–0.60**	31	**0.58**	**0.39–0.83**
Salivary gland	5	0.47	0.15–1.11	7	0.73	0.29–1.51
Esophagus	30	**0.52**	**0.35–0.75**	19	0.92	0.55–1.43
Stomach	106	**0.56**	**0.46–0.68**	78	**0.63**	**0.50–0.79**
Small intestine	13	0.70	0.37–1.20	21	1.29	0.80–1.98
Colon	180	**0.71**	**0.61–0.83**	246	**0.83**	**0.73–0.94**
Rectum	100	**0.59**	**0.48–0.72**	100	**0.74**	**0.60–0.90**
Anus	7	1.21	0.48–2.51	15	1.27	0.71–2.09
Liver	78	**0.71**	**0.56–0.89**	110	0.91	0.75–1.09
Pancreas	76	**0.69**	**0.55–0.87**	67	**0.65**	**0.50–0.82**
Nose	8	0.91	0.39–1.81	2	0.35	0.03–1.28
Lung	270	**0.67**	**0.60–0.76**	181	0.91	0.78–1.05
Breast	10	1.62	0.77–3.00	1315	**1.24**	**1.17–1.31**
Cervix	0			133	0.84	0.71–1.00
Endometrium	0			311	**1.34**	**1.20–1.50**
Ovary	0			177	**0.85**	**0.73–0.98**
Other female genital	0			34	0.93	0.64–1.30
Prostate	412	**0.45**	**0.41–0.50**	0		
Testis	49	0.94	0.69–1.24	0		
Other male genital	16	1.05	0.60–1.72	0		
Kidney	116	0.89	0.73–1.06	61	**0.64**	**0.49–0.83**
Urinary bladder	148	**0.61**	**0.51–0.71**	61	**0.67**	**0.51–0.87**
Melanoma	72	**0.64**	**0.50–0.80**	89	**0.70**	**0.57–0.87**
Skin, squamous cell	90	**0.59**	**0.47–0.73**	78	**0.66**	**0.52–0.83**
Nervous system	107	0.86	0.71–1.04	97	**0.74**	**0.60–0.91**
Thyroid gland	11	**0.54**	**0.27–0.97**	36	0.75	0.52–1.03
Endocrine glands	37	0.86	0.60–1.18	98	1.07	0.87–1.31
Bone	7	0.67	0.27–1.40	7	1.08	0.43–2.23
Connective tissue	23	0.79	0.50–1.18	21	0.85	0.53–1.31
Non-Hodgkin lymphoma	124	**0.74**	**0.62–0.89**	95	**0.74**	**0.60–0.91**
Hodgkin's disease	27	0.94	0.62–1.37	11	0.62	0.31–1.11
Myeloma	36	**0.69**	**0.48–0.96**	34	**0.71**	**0.49–0.99**
Leukemia	61	**0.75**	**0.58–0.97**	40	**0.57**	**0.41–0.77**
Cancer of unknown primary	98	0.83	0.67–1.01	121	0.85	0.71–1.02
All	2405	**0.63**	**0.61–0.66**	3732	**0.94**	**0.91–0.97**

Note: Abbreviations are explained in the first footnote to table 2.

for confounding factors, suggesting that some of the etiologic factors predisposing to schizophrenia are protective against the development of cancer. Second, 24 of 34 cancer sites/categories investigated in this study had significantly lower incidence rates before the first diagnosis of schizophrenia. The other 10 cancer sites/categories also showed the same tendency of lower risk although the results did not reach statistical significance. These results imply that schizophrenia is associated with decreased risk of cancer. Third, we observed significant differences in cancer risk for male and female patients after the first schizophrenia diagnosis. The overall cancer risk remained lower than in the general population for the males, but the risk for the females increased significantly.

Our conclusion of a possible genetic connection between schizophrenia and cancer is based on several findings. The first is the overall cancer incidence rates of patients with schizophrenia, their parents, and siblings. All these groups had significantly lower SIRs compared with the general population. Second, specific to melanoma, the SIRs in patients with schizophrenia, their parents, and full siblings were all consistent with the interpretation of a genetic contribution. Our result for melanoma is also consistent with the results of a few previous studies.[9,19] The third line of supporting evidence is the SIRs for the patients before first schizophrenia diagnosis. All 34 cancer sites/categories included in this study had SIRs less than one; 24 of them were statistically significant. These observations are unlikely to be random events. In other words, genetic factors contributing to the development of schizophrenia may protect against the development of several cancers. In the literature, there is evidence supporting this notion. Some tumor suppressor genes, including those encoding p53 and APC (adenomatous polyposis coli), have been shown to be associated with susceptibility to schizophrenia.[25,26]

Table 4. Cancer Risk After the Diagnosis of Schizophrenia by Gender

	Male			Female		
Cancer Site/Type	O	SIR	95% CI	O	SIR	95% CI
Upper aerodigestive tract	63	**0.59**	**0.45–0.75**	24	0.68	0.43–1.01
Salivary gland	4	0.59	0.15–1.53	6	1.11	0.40–2.42
Esophagus	28	0.71	0.47–1.03	19	1.38	0.83–2.15
Stomach	99	0.87	0.71–1.06	72	1.03	0.81–1.30
Small intestine	11	0.85	0.42–1.52	18	**1.75**	**1.03–2.77**
Colon	157	0.89	0.76–1.04	204	1.04	0.90–1.19
Rectum	84	**0.70**	**0.56–0.87**	83	0.93	0.74–1.15
Anus	7	1.55	0.61–3.20	13	1.53	0.81–2.62
Liver	74	0.99	0.78–1.24	108	**1.40**	**1.14–1.69**
Pancreas	72	1.00	0.78–1.26	67	1.00	0.77–1.27
Nose	7	1.23	0.49–2.55	2	0.57	0.05–2.10
Lung	260	0.93	0.82–1.05	175	**1.22**	**1.05–1.41**
Breast	8	1.84	0.78–3.63	1034	**1.52**	**1.43–1.61**
Cervix	0			84	1.18	0.94–1.46
Endometrium	0			228	**1.55**	**1.35–1.76**
Ovary	0			133	1.13	0.94–1.34
Other female genital	0			27	1.13	0.75–1.65
Prostate	373	**0.53**	**0.48–0.59**	0		
Testis	28	1.03	0.68–1.48	0		
Other male genital	12	1.18	0.61–2.07	0		
Kidney	102	1.18	0.96–1.43	56	0.97	0.73–1.26
Urinary bladder	120	**0.68**	**0.57–0.82**	49	0.81	0.60–1.07
Melanoma	54	**0.67**	**0.50–0.87**	65	0.80	0.61–1.02
Skin, squamous cell	78	**0.67**	**0.53–0.84**	65	**0.73**	**0.57–0.94**
Nervous system	83	1.11	0.89–1.38	75	0.99	0.78–1.24
Thyroid gland	7	0.57	0.22–1.17	25	0.96	0.62–1.42
Endocrine glands	29	1.02	0.69–1.47	63	1.09	0.84–1.39
Bone	3	0.65	0.12–1.92	5	1.74	0.55–4.09
Connective tissue	20	1.10	0.67–1.70	17	1.17	0.68–1.87
Non-Hodgkin lymphoma	104	0.88	0.72–1.07	83	0.95	0.75–1.17
Hodgkin's disease	17	1.25	0.73–2.01	6	0.76	0.27–1.66
Myeloma	30	0.82	0.55–1.17	28	0.89	0.59–1.29
Leukemia	50	1.02	0.76–1.35	33	0.79	0.54–1.11
Cancer of unknown primary	96	1.13	0.92–1.38	114	1.15	0.95–1.38
All	2088	**0.79**	**0.75–0.82**	3013	**1.20**	**1.15–1.24**

Note: Abbreviations are explained in the first footnote to table 2.

A recent study that explored susceptibility genes for schizophrenia using the SZGene database found that more than 140 schizophrenia-associated genes were mutated in cancer according to information from the Cancer Gene Census database.[27] However, we cannot completely exclude the possibility that shared environmental factors between patients with schizophrenia and their first-degree relatives contribute to the reduced SIRs. Diagnostic overshadowing may partly explain the decreased incidence of cancer after the first diagnosis because clinicians may neglect the physical complaints of patients with schizophrenia and not fully examine the presenting symptoms, leading to a delayed diagnosis of cancer and/or lower detection rates.[28] However, because the risk for the parents and siblings is similarly reduced even if some diagnostic overshadowing occurs, it is not very likely to be a major factor that would alter the conclusion. Another possible interpretation is that the first-degree relatives of patients with schizophrenia may share a personality predisposition that may reduce their propensity to seek medical help, therefore, leading to reduced incidences in these groups. However, we were unable to assess the possible effects of a premorbid personality in this study. Two large-scale studies have involved first-degree relatives of patients with schizophrenia,[7,29,30] and the results of these studies were inconsistent. In the study by Lichtermann et al,[29] the parents of patients with schizophrenia were compared with the general population, and the authors found that the risks for the parents were reduced, which is consistent with our observations. In the study by Dalton et al,[30] the authors used married couples with no child diagnosed with schizophrenia as controls and included only cancer cases diagnosed after the birth of the first child. They concluded that there was no difference in risk of cancer in the parents of patients with schizophrenia. This difference in risk may be due to the use of different control groups. Ultimately,

Table 5. Cancer Risk in Unaffected Relatives of Schizophrenia Patients

	Parents			Siblings		
Cancer Site/Type	O	SIR	95% CI	O	SIR	95% CI
Upper aerodigestive tract	267	0.94	0.83–1.06	60	0.80	0.61–1.03
Salivary gland	26	0.93	0.60–1.36	12	1.27	0.65–2.23
Esophagus	91	0.81	0.65–1.00	30	1.34	0.90–1.91
Stomach	465	0.96	0.87–1.05	54	0.93	0.70–1.22
Small intestine	66	1.18	0.91–1.50	10	0.72	0.34–1.32
Colon	917	0.98	0.91–1.04	160	0.95	0.81–1.11
Rectum	527	1.00	0.91–1.09	93	0.90	0.72–1.10
Anus	31	1.22	0.83–1.73	5	0.56	0.18–1.31
Liver	353	1.01	0.91–1.12	39	0.77	0.55–1.06
Pancreas	334	0.96	0.86–1.07	54	0.96	0.72–1.26
Nose	16	0.78	0.44–1.26	3	0.58	0.11–1.70
Lung	931	0.97	0.91–1.04	168	**0.79**	**0.68–0.92**
Breast	1498	**0.94**	**0.90–0.99**	612	0.94	0.86–1.01
Cervix	239	**1.23**	**1.08–1.40**	90	1.02	0.82–1.25
Endometrium	353	0.92	0.83–1.02	104	1.11	0.90–1.34
Uterus	0			1	0.71	0.00–4.09
Ovary	254	**0.81**	**0.71–0.91**	93	0.98	0.79–1.20
Other female genital	60	1.12	0.85–1.44	18	1.54	0.91–2.44
Prostate	1871	1.00	0.96–1.05	341	0.91	0.81–1.01
Testis	19	0.72	0.43–1.13	47	0.94	0.69–1.25
Other male genital	19	0.83	0.50–1.30	4	0.58	0.15–1.50
Kidney	356	0.99	0.89–1.09	84	1.09	0.87–1.35
Urinary bladder	566	0.95	0.87–1.03	93	0.85	0.69–1.05
Melanoma	311	**0.85**	**0.76–0.95**	172	**0.86**	**0.73–0.99**
Skin, squamous cell	411	**0.82**	**0.74–0.90**	66	0.94	0.66–1.24
Nervous system	338	1.00	0.90–1.12	178	1.03	0.88–1.19
Thyroid gland	88	1.00	0.80–1.24	41	0.92	0.66–1.24
Endocrine glands	208	1.06	0.92–1.22	86	1.13	0.90–1.39
Bone	21	1.28	0.79–1.95	15	1.11	0.62–1.84
Connective tissue	66	0.87	0.67–1.11	22	0.77	0.48–1.17
Non-Hodgkin lymphoma	447	0.92	0.84–1.01	119	0.87	0.72–1.04
Hodgkin's disease	44	0.90	0.65–1.20	34	1.04	0.72–1.46
Myeloma	175	1.01	0.87–1.17	29	0.91	0.61–1.31
Leukimia	194	0.90	0.78–1.04	62	0.81	0.62–1.04
Cancer of unknown primary	415	0.99	0.90–1.09	59	**0.71**	**0.54–0.91**
All	11977	**0.96**	**0.94–0.98**	3058	**0.92**	**0.89–0.96**

Note: Abbreviations are explained in the first footnote to table 2.

other genetically informed studies may be necessary to clarify these effects.

Our observations that there is a difference in cancer risk between males and females and that female patients have increased cancer risk after schizophrenia diagnosis are intriguing. When individuals are diagnosed with schizophrenia, they would be treated with antipsychotic medicine. The increased incidences for cancers of small intestine, liver, lung, breast, cervix, and endometrium after the first diagnosis of schizophrenia suggest that antipsychotics have a significant impact on the development of these cancers, and these effects may be exerted through sex hormone–linked pathways. It has been known that antipsychotic treatment, including the second generation of antipsychotics, could lead to an elevation of prolactin,[31,32] which is a risk factor for breast, cervix, and endometrial cancers. However, the mechanisms of the elevated risks for cancers of liver, small intestine, and lung are not clear. The distinct difference between males and females suggest that there may be an interaction between antipsychotics and female hormones, and this interaction may promote the development of these cancers. A recent study also found that there is a difference in the general cancer risk between male and female patients with schizophrenia,[33] and breast cancer was significantly higher than in that the general population. This is consistent with our findings. There is evidence that some risk factors of schizophrenia may be sex-specific, and sex may have a role in the development of these cancers. The convergence of sex linkage may provide some insights for further studies to identify risk genes involved in both schizophrenia and cancer.

A general limitation with the present study is that first diagnosis of schizophrenia was defined as first hospital (1965–2008) or outpatient clinic (1997–2008) diagnosis of schizophrenia during the study period. This means

Table 6. Risk of Gender-Specific Cancers in Patients Diagnosed With Schizophrenia by Follow-Up Time and Diagnosis Period

Cancer Site	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
Women												
Follow-up time	<1 y			1–4 y			5–9 y			≥10 y		
Breast	82	**2.50**	**1.99–3.10**	155	**1.28**	**1.09–1.50**	183	**1.35**	**1.16–1.56**	622	**1.49**	**1.38–1.61**
Cervix	7	1.63	0.65–3.38	21	1.40	0.86–2.14	20	1.45	0.88–2.24	36	1.26	0.88–1.74
Endometrium	22	**2.77**	**1.73–4.20**	29	1.00	0.67–1.44	35	1.12	0.78–1.56	142	**1.39**	**1.17–1.63**
All	284	**2.30**	**2.04–2.59**	465	1.03	0.94–1.13	574	**1.16**	**1.07–1.26**	1690	**1.17**	**1.11–1.22**
Diagnosis period	1965–1974			1975–1984			1985–1994			1995–2008		
Breast	352	**1.55**	**1.39–1.72**	451	**1.52**	**1.39–1.67**	169	**1.30**	**1.11–1.52**	70	**1.33**	**1.04–1.68**
Cervix	23	1.06	0.67–1.60	37	**1.48**	**1.04–2.04**	17	1.57	0.92–2.53	7	1.64	0.65–3.40
Endometrium	88	**1.49**	**1.19–1.84**	93	**1.29**	**1.04–1.58**	33	1.17	0.81–1.65	14	1.23	0.67–2.06
All	1041	**1.23**	**1.16–1.31**	1292	**1.21**	**1.14–1.28**	483	**1.12**	**1.02–1.22**	197	**1.16**	**1.00–1.33**
Men												
Follow-up time	<1 y			1–4 y			5–9 y			≥10 y		
Prostate	35	1.41	0.98–1.96	43	**0.48**	**0.35–0.65**	59	**0.60**	**0.45–0.77**	236	**0.58**	**0.50–0.65**
All	216	**1.81**	**1.58–2.07**	310	0.72	0.64–0.80	364	0.76	0.68–0.84	1198	0.74	0.69–0.78
Diagnosis period	1965–1974			1975–1984			1985–1994			1995–2008		
Prostate	146	**0.65**	**0.55–0.77**	141	**0.53**	**0.44–0.62**	61	**0.65**	**0.50–0.83**	25	0.68	0.44–1.01
All	759	0.77	0.72–0.83	865	0.76	0.71–0.81	346	0.88	0.79–0.98	118	0.81	0.67–0.97

Note: Abbreviations are explained in the first footnote to table 2.

that we were unable to collect all individuals with schizophrenia in the Swedish population and that age at diagnosis does not entirely represent age at onset. However, as schizophrenia is a chronic disease, we believe that few individuals were not treated as outpatients at least once between 1997 and 2008. In addition, our aim was to examine the cancer risk among patients with schizophrenia and their relatives, and any bias due to missing data is therefore most likely to be nondifferential. In this study, the mean age of first diagnosis is considerably older than most other studies, especially for the female patients. This is probably because we used the hospital discharge registry to obtain the age of diagnosis. It seems that in Sweden, as in other Nordic countries, the conceptualization of schizophrenia has historically been more influenced by Kraepelin and the more narrow view of this illness; these factors have generally resulted in a conservative diagnostic approach.[34] This older age of first diagnosis should, however, have a minimal effect on our results. An older age of first diagnosis would result in higher cancer incidences before the diagnosis of schizophrenia. This would inflate the incidence, leading to an over-estimation of the SIRs before diagnosis. For the same reason, the SIRs after diagnosis would be under-estimated. However, we observed SIRs of less than 1 for all cancer sites/types before diagnosis and SIRs greater than 1 for the female patients after diagnosis. These go into the opposite direction of the expected effects of a delayed age of first diagnosis. Therefore, our conclusions are probably basically correct.

The diagnosis of schizophrenia is normally associated with weight gain, high levels of smoking and drinking, poor diet, and less physical exercise. All these factors are known to increase the incidence of cancer, and they may contribute to an increased cancer incidence in patients with schizophrenia. Previous studies have consistently shown that the prevalence of smoking in patients with schizophrenia is very high.[35–38] A recent meta-analysis of 42 studies from 20 countries demonstrates a weighted average OR for smoking of 5.9 compared with the general population, and heavy smoking is strongly related to schizophrenia.[18] The increased risk of liver cancer after the first diagnosis of schizophrenia may be due to the higher levels of alcohol consumption in patients with schizophrenia compared with the general population because there is a high comorbidity between schizophrenia and alcohol abuse,[39] and alcohol use is a risk factor for liver cancer.[40]

Strengths of the present study include the large number of patients from a national population and the completeness of the follow-up of patients and their relatives. The inclusion of data from the first relatives along with that of patients with schizophrenia allowed us to infer a possible genetic connection between schizophrenia and cancer. The use of a nationwide database of the entire population avoided selection bias. One limitation of this study is, however, the lack of information on individual risk factors such as smoking habits, alcohol consumption, medication, and other treatment. However, we tried to control for their confounding effects by adjusting for a diagnosis of alcoholism and obesity as well as our estimation of smoking rates.

In summary, in one of the largest studies on cancer in patients with schizophrenia to date, we found that the overall cancer incidence rates among patients with schizophrenia and their first-degree relatives are

significantly lower than that of the general population. These findings suggest that genetic factors contributing to the development of schizophrenia may protect against the development of some cancers. The implication of shared genetic factors in schizophrenia and cancer warrants further investigation on this topic and provides a new avenue to study both conditions. We also observed a sex difference in the incidence rates, with decreased risk for prostate cancer and increased risks for cancers of breast, cervix, endometrium, and liver after the first diagnosis of schizophrenia. These findings suggest that gender plays a role in both cancer and schizophrenia. This may have significant implications in the surveillance of patients with schizophrenia. More attention should be directed to the screening of some cancers in patients with schizophrenia and the effects of antipsychotics on the development of these cancers.

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Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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