ORIGINAL ARTICLE

Risk of Malignancy in Patients With Schizophrenia or Bipolar Disorder

Nested Case-Control Study

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Context: There is conflicting evidence on whether people with schizophrenia have a different risk of cancer from that of the general population.

Objective: To determine the risk of 6 common cancers in patients with schizophrenia or bipolar disorder.

Design: Population-based, nested, case-control study.

Setting: A total of 454 practices contributing to the QRESEARCH general practice database.

Participants: We analyzed 40 441 incident cases of 6 cancers (breast, colon, rectal, gastroesophageal, prostate, and respiratory) and up to 5 controls per case matched by single year of age, sex, general practice, and calendar time.

Main Outcome Measures: Odds ratios (ORs) for cancer risk associated with schizophrenia and bipolar disorder, adjusting for smoking, body mass index, socioeconomic status, comorbidities, and prescribed medications, including antipsychotics.

Results: For breast cancer, we identified 10 535/50 074 cases/controls; colon cancer, 5108/24 458; rectal cancer, 3248/15 552; gastroesophageal cancer, 3854/18 477; prostate cancer, 10 190/48 748; and respiratory cancer, 7506/35 981. After adjustment, patients with schizophrenia had a 190% increased colon cancer risk (adjusted OR, 2.90; 95% confidence interval [CI], 1.85-4.57), a marginal increased breast cancer risk (adjusted OR, 1.52; 95% CI, 1.10-2.11), and a 47% decreased respiratory cancer risk (adjusted OR, 0.53, 95% CI, 0.34-0.85). Patients with schizophrenia taking antipsychotics had a 308% increased colon cancer risk (adjusted OR, 4.08; 95% CI, 2.43-6.84). Patients with bipolar disorder had cancer risks similar to patients with neither condition after adjustment.

Conclusions: Patients with schizophrenia have a significantly higher risk of colon cancer and a lower risk of respiratory cancer compared with patients without schizophrenia after adjustment for confounders. In contrast, the risks of cancer in patients with and without bipolar disorder are similar, suggesting that residual confounding is unlikely to explain the findings. The increased risk of colon cancer is particularly marked in patients with schizophrenia who take antipsychotic medications.

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FOR ALMOST 100 YEARS, THERE has been speculation that patients with schizophrenia have lower cancer risks than the general population. In 1909, this possibility was raised by the Board of Control of the Commissioners in Lunacy for England and Wales,[1] but a century later the evidence is still far from clear. Whereas some studies have suggested a lower cancer incidence or mortality rate in people with schizophrenia,[2-7] others have found either an increased cancer incidence[8] or mortality[9] associated with schizophrenia or nonsignificant effects.[10,11] Existing studies have been limited by size, use of biased populations (such as hospital-based cohorts), and lack of ability to control for potential confounding effects. Failure to adjust for these factors is extremely important given that patients with mental health problems have a higher prevalence of common risk factors, including smoking, alcohol consumption, and obesity[12,13]; they are also less likely to report physical symptoms or to adhere to treatment regimens.[14,15]

Considerable uncertainty therefore exists regarding the risk of common cancers in patients with schizophrenia. This is important with respect to designing screening programs as well as etiology. For example, there are theories that schizophrenia itself has a possible protective effect, including a tumor suppressor gene or enhanced natural killer cell activ-

ity.[16,17] Alternatively, medication used in the treatment of schizophrenia may have an antipsychotic effect via the inhibition of enzymes involved in mutation.[18]

Therefore, we undertook a study to compare the risks of 6 common cancers between patients with and without schizophrenia using a very large population-based research database called QRESEARCH, which enabled us to adjust for many potential confounding variables. In addition, we compared cancer risks in patients with bipolar disorder, who have similar lifestyle characteristics as patients with schizophrenia but who are likely to differ with respect to use of medication and any inherent physical correlates of the disease.

METHODS

STUDY POPULATION AND SAMPLE

The full QRESEARCH database (http://www.qresearch.org/) currently contains the anonymized primary care clinical records of more than 10 million people registered at any time in the past 16 years with 525 general practices in the United Kingdom. Consent to provide data is sought from practices using the Egton Medical Information Services (EMIS) medical records system, and detailed analyses have shown that participating practices are somewhat larger than nonparticipating practices but in all other respects are very similar.[19] The database derives from a representative sample of 6% of all the general practices throughout England, Wales, Scotland, and Northern Ireland. The database includes patients' medical records before their registration with any of these practices. The computer system at each participating practice automatically uploads data every 24 hours, ensuring that the most recent information is available. The database has been subjected to detailed analyses of age-sex distributions, birth rates, death rates, consultation rates, prevalence rates, and mortality rates, showing good correspondence with other sources[20] and good levels of completeness and consistency.[21]

We obtained ethical approval from the Trent Multicenter Research Ethics Committee. We used version 7 of the QRESEARCH database, which contained data until August 1, 2005, and included general practices that had used their current computer system for at least 12 months. We identified an open cohort of patients registered with these practices during the 10-year study period (January 1, 1995, to July 1, 2005). For each of 6 common cancers (breast, colon, rectal, gastroesophageal, prostate, and respiratory), we assembled a separate set of individually matched cases and controls from this cohort. Cases all involved patients aged 25 to 100 years with a first-ever record of the index cancer during the study period, including those where the diagnosis was recorded post mortem. We used incidence density sampling to identify up to 5 controls for each incident case matched by single year of age, calendar time, sex, and practice. All the controls were alive and registered with the practice at the date their matched case was first recorded to have the relevant cancer; this was the index date for each case and its controls. Patients were excluded from the study if they had any cancer diagnosis in their record before the first diagnosis of the index cancer (for cases) or the equivalent date (for controls).

We included only patients with at least 12 months of computerized medical record data before their index date to ensure that prescribing data were complete. We excluded breast cancer cases with a record of mastectomy or tamoxifen use more than 12 months before their first record of cancer because these treatments could indicate that they were not incident cases at the time of cancer diagnosis. We also excluded controls with any prior record of mastectomy or tamoxifen use because they could be breast cancer cases without a formal diagnosis in their record.

DATA

We extracted demographic information, including year of birth, sex, and Townsend score (a measure of socioeconomic status). We also extracted each patient's most recent body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) and smoking status before their index date. Cancer cases and controls were coded as having schizophrenia or bipolar disorder if there was a recorded diagnosis at least 12 months before their index date. We included data on 4 comorbid physical conditions before the index date (ischemic heart disease, diabetes mellitus, hypertension, and rheumatoid arthritis).

We assessed exposure to medications on the basis of at least 1 prescription before the index date. To avoid bias due to reverse causality, we excluded medication used in the 12 months immediately preceding the index date. We included medications for which there was previous evidence of positive or negative association with malignancy, including nonsteroidal antiinflammatory drugs, cyclooxygenase 2 inhibitors, aspirin, statins, hormone therapy, oral contraceptives, antidepressants (selective serotonin reuptake inhibitors and tricyclic antidepressants), and antipsychotic medications (conventional antipsychotics, atypical antipsychotics, and lithium).

STATISTICAL METHODS

For each cancer, we undertook multiple conditional logistic regression to estimate odds ratios (ORs) associated with schizophrenia and bipolar disorder. We adjusted the models for the possible confounding effects of smoking (current smoker, not current smoker, or not recorded), BMI ($<$25, 25-29, $\geq$30, or not recorded), Townsend score (in fifths), comorbidities (binary), and medications (binary) as well as the other serious mental health condition. We adjusted for use of hormone therapy and oral contraceptives in the breast, colon, and rectal cancer models. All cases and controls were included in the analyses by treating "missing" as a category for the smoking, BMI, and socioeconomic variables. The analyses were repeated on the subset of cases and controls with full data on all variables.

To further examine the relationship between cancer risk and use of antipsychotic medications, we calculated ORs for each cancer for patients with schizophrenia with and without recorded use of antipsychotic medications compared with patients with neither mental health problem. All analyses were conducted using a software program (Stata version 9.1; StataCorp, College Station, Texas).

RESULTS

A total of 454 QRESEARCH practices met the inclusion criteria for this analysis. The total study population consisted of 4 040 494 patients, giving rise to 18 772 868 person-years of observation. We identified 47 924 incident cases of the 6 cancers, of which 7483 met the exclusion criteria, leaving 40 441 cases for analysis. For breast cancer, 740 cases with mastectomy or tamoxifen use more than 12 months previously were excluded, as were 416 controls with any prior record of mastectomy or tamoxifen use. Almost 92% of the respiratory cancer cases were

Table 1. Prevalence of Schizophrenia and Bipolar Disorder in Cases and Controls by Cancer Type

	Cancer					
	Breast	Colon	Rectal	Gastro-esophageal	Prostate	Respiratory
Cancer cases, No. (%)						
Schizophrenia only	47 (0.45)	31 (0.61)	8 (0.25)	12 (0.31)	12 (0.12)	20 (0.27)
Bipolar disorder only	42 (0.40)	12 (0.23)	6 (0.18)	7 (0.18)	15 (0.15)	32 (0.43)
Both conditions	2 (0.02)	1 (0.02)	0	2 (0.05)	1 (0.01)	3 (0.04)
Neither condition	10 444 (99.14)	5064 (99.14)	3234 (99.57)	3833 (99.46)	10 162 (99.73)	7451 (99.27)
Total	**10 535**	**5108**	**3248**	**3854**	**10 190**	**7506**
Cancer controls, No. (%)						
Schizophrenia only	143 (0.29)	48 (0.20)	48 (0.31)	48 (0.26)	108 (0.22)	139 (0.39)
Bipolar disorder only	154 (0.31)	55 (0.22)	30 (0.19)	36 (0.19)	85 (0.17)	94 (0.26)
Both conditions	10 (0.02)	3 (0.01)	2 (0.01)	5 (0.03)	8 (0.02)	9 (0.03)
Neither condition	49 767 (99.39)	24 352 (99.57)	15 472 (99.49)	18 388 (99.52)	48 547 (99.59)	35 739 (99.33)
Total	**50 074**	**24 458**	**15 552**	**18 477**	**48 748**	**35 981**

Table 2. Characteristics of Cases and Controls by Cancer Type

	Breast Cancer		Colon Cancer		Rectal Cancer	
Characteristic	Cases (n = 10 535)	Controls (n = 50 074)	Cases (n = 5108)	Controls (n = 24 458)	Cases (n = 3248)	Controls (n = 15 552)
Sex, No. (%)						
M	10 (0.1)	46 (0.1)	2669 (52.3)	12 758 (52.2)	2013 (62.0)	9617 (61.8)
F	10 525 (99.9)	50 028 (99.9)	2439 (47.7)	11 700 (47.8)	1235 (38.0)	5935 (38.2)
Age, median (interquartile range), y	61 (51 to 72)	61 (51 to 72)	72 (64 to 79)	72 (64 to 79)	71 (62 to 78)	71 (62 to 78)
Townsend score recorded, No. (%)	10 335 (98.1)	48 578 (97.0)	4959 (97.1)	23 557 (96.3)	3150 (97.0)	14 980 (96.3)
Townsend score, median (interquartile range)	−1.61 (−3.24 to 1.25)	−1.48 (−3.22 to 1.33)	−1.27 (−3.07 to 1.53)	−1.41 (−3.17 to 1.50)	−1.06 (−3.01 to 1.83)	−1.21 (−3.06 to 1.81)
Smoking status recorded, No. (%)	8960 (85.0)	40 784 (81.4)	4258 (83.4)	19 261 (78.8)	2653 (81.7)	12 217 (78.6)
Smokers, No. (%)	2073 (19.7)	9641 (19.3)	803 (15.7)	3911 (16.0)	664 (20.4)	2727 (17.5)
BMI recorded, No. (%)	8147 (77.3)	37 071 (74.0)	3831 (75.0)	17 196 (70.3)	2359 (72.6)	10 834 (69.7)
BMI, median (interquartile range)	25.5 (22.8 to 29.0)	25.4 (22.7 to 29.1)	26.1 (23.5 to 29.0)	26.0 (23.5 to 29.0)	26.1 (23.5 to 28.9)	26.1 (23.6 to 29.0)
Months of previous data, median (interquartile range)	61 (37 to 95)	61 (37 to 94)	66 (40 to 102)	67 (40 to 102)	68 (39 to 102)	69 (39 to 102)
Comorbidities, No. (%)						
Diabetes mellitus	431 (4.1)	2028 (4.1)	424 (8.3)	1553 (6.3)	254 (7.8)	1021 (6.6)
Ischemic heart disease	546 (5.2)	2793 (5.6)	683 (13.4)	3092 (12.6)	404 (12.4)	2057 (13.2)
Rheumatoid arthritis	131 (1.2)	745 (1.5)	40 (0.8)	339 (1.4)	39 (1.2)	213 (1.4)
Hypertension	2292 (21.8)	10 520 (21.0)	1452 (28.4)	6877 (28.1)	927 (28.5)	4080 (26.2)
Use of medications, No. (%)						
NSAIDs	1273 (12.1)	5832 (11.6)	562 (11.0)	2916 (11.9)	362 (11.1)	1934 (12.4)
Aspirin	1270 (12.1)	5830 (11.6)	1139 (22.3)	5295 (21.6)	667 (20.5)	3342 (21.5)
Cyclooxygenase 2 inhibitors	591 (5.6)	2442 (4.9)	240 (4.7)	1075 (4.4)	111 (3.4)	681 (4.4)
Statins	573 (5.4)	2855 (5.7)	454 (8.9)	2149 (8.8)	271 (8.3)	1339 (8.6)
Hormone therapy	2458 (23.3)	9940 (19.9)	283 (5.5)	1363 (5.6)	140 (4.3)	765 (4.9)
Oral contraceptives	626 (5.9)	2573 (5.1)	35 (0.7)	151 (0.6)	24 (0.7)	104 (0.7)
Antidepressant SSRIs	1219 (11.6)	5736 (11.5)	374 (7.3)	1747 (7.1)	195 (6.0)	1095 (7.0)
Antidepressant TCAs	1855 (17.6)	8344 (16.7)	682 (13.4)	3196 (13.1)	367 (11.3)	2034 (13.1)
Antipsychotics	1478 (14.0)	6643 (13.3)	639 (12.5)	2962 (12.1)	334 (10.3)	1806 (11.6)

(continued)

lung cancer (6894 of 7506). **Table 1** gives the number of cases and controls for each cancer and the prevalence of schizophrenia and bipolar disorder in each group. Nine cases and 37 controls had diagnoses of both schizophrenia and bipolar disorder. **Table 2** summarizes the characteristics of cases and controls for each cancer, and **Table 3** compares patients with and without schizophrenia or bipolar disorder, showing that the groups with mental health problems were somewhat younger and more likely to smoke and had lower rates of some comorbidities than the group with neither mental health problem.

Table 4 gives the ORs for each cancer associated with schizophrenia and bipolar disorder, unadjusted and adjusted for socioeconomic status, smoking, BMI, comorbidities, and use of medications. The adjusted analysis (also shown in the **Figure**) shows that people with schizo-

Table 2. Characteristics of Cases and Controls by Cancer Type (cont)

Characteristic	Gastroesophageal Cancer		Prostate Cancer		Respiratory Cancer	
	Cases (n = 3854)	Controls (n = 18 477)	Cases (n = 10 190)	Controls (n = 48 748)	Cases (n = 7506)	Controls (n = 35 981)
Sex, No. (%)						
M	2503 (64.9)	11 966 (64.8)	10 190 (100)	48 748 (100)	4843 (64.5)	23 156 (64.4)
F	1351 (35.1)	6511 (35.2)	0	0	2663 (35.5)	12 825 (35.6)
Age, median (interquartile range), y	72 (64 to 79)	72 (64 to 79)	73 (67 to 79)	73 (67 to 79)	71 (63 to 78)	71 (63 to 77)
Townsend score recorded, No. (%)	3743 (97.1)	17 850 (96.6)	9989 (98.0)	47 222 (96.9)	7305 (97.3)	34 729 (96.5)
Townsend score, median (interquartile range)	–1.05 (–3.01 to 2.05)	–1.34 (–3.14 to 1.76)	–1.80 (–3.38 to 0.99)	–1.60 (–3.26 to 1.19)	–0.01 (–2.48 to 3.03)	–0.92 (–2.92 to 2.26)
Smoking status recorded, No. (%)	3251 (84.4)	14 674 (79.4)	8727 (85.6)	38 499 (79.0)	6528 (87.0)	28 965 (80.5)
Smokers, No. (%)	1007 (26.1)	3230 (17.5)	1612 (15.8)	8149 (16.7)	3554 (47.3)	6747 (18.8)
BMI recorded, No. (%)	2884 (74.8)	13 008 (70.4)	7893 (77.5)	34 342 (70.4)	5637 (75.1)	25 820 (71.8)
BMI, median (interquartile range)	25.5 (22.9 to 28.6)	26.0 (23.5 to 28.9)	26.0 (23.9 to 28.4)	26.1 (23.8 to 28.7)	25.0 (22.4 to 28.1)	26.1 (23.6 to 29.0)
Months of previous data, median (interquartile range)	69 (42 to 103)	69 (42 to 102)	71 (42 to 107)	72 (42 to 106)	66 (39 to 100)	65 (39 to 99)
Comorbidities, No. (%)						
Diabetes mellitus	340 (8.8)	1240 (6.7)	750 (7.4)	3835 (7.9)	534 (7.1)	2499 (6.9)
Ischemic heart disease	561 (14.6)	2585 (14.0)	1714 (16.8)	8076 (16.6)	1161 (15.5)	5115 (14.2)
Rheumatoid arthritis	40 (1.0)	264 (1.4)	92 (0.9)	460 (0.9)	143 (1.9)	477 (1.3)
Hypertension	1058 (27.5)	4960 (26.8)	2966 (29.1)	13 094 (26.9)	1898 (25.3)	9953 (27.7)
Use of medications, No. (%)						
NSAIDs	476 (12.4)	2195 (11.9)	1273 (12.5)	5535 (11.4)	880 (11.7)	4120 (11.5)
Aspirin	919 (23.8)	4160 (22.5)	2730 (26.8)	12 510 (25.7)	1980 (26.4)	8204 (22.8)
Cyclooxygenase 2 inhibitors	174 (4.5)	788 (4.3)	472 (4.6)	1935 (4.0)	390 (5.2)	1785 (5.0)
Statins	344 (8.9)	1584 (8.6)	1159 (11.4)	5121 (10.5)	787 (10.5)	3709 (10.3)
Hormone therapy	136 (3.5)	663 (3.6)	0	0	433 (5.8)	1862 (5.2)
Oral contraceptives	24 (0.6)	128 (0.7)	0	0	33 (0.4)	167 (0.5)
Antidepressant SSRIs	257 (6.7)	1220 (6.6)	561 (5.5)	2554 (5.2)	703 (9.4)	2674 (7.4)
Antidepressant TCAs	541 (14.0)	2271 (12.3)	1028 (10.1)	4605 (9.4)	1261 (16.8)	4613 (12.8)
Antipsychotics	486 (12.6)	2196 (11.9)	988 (9.7)	4678 (9.6)	940 (12.5)	4236 (11.8)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

phrenia had significantly higher risks of breast cancer (adjusted OR, 1.52; 95% confidence interval [CI], 1.10-2.11) and colon cancer (adjusted OR, 2.90; 95% CI, 1.85-4.57) and a significantly lower risk of respiratory cancer (adjusted OR, 0.53; 95% CI, 0.34-0.85). There were no significant differences in their risks of rectal, gastroesophageal, or prostate cancer. Patients with bipolar disorder had ORs closer to unity for each cancer, and there were no statistically significant associations after adjustment for confounders.

Restricting the respiratory cancer analysis to lung cancer cases and their controls made little difference to the observed reduction in risk for people with schizophrenia (adjusted OR, 0.59; 95% CI, 0.37-0.95). Restricting the analysis for each cancer to patients with full data on all confounding variables made no substantial difference to the adjusted ORs for colon, rectal, gastroesophageal, or prostate cancer. For breast and respiratory cancers, the adjusted ORs were closer to unity and the CIs were wider (breast: OR, 1.28; 95% CI, 0.84-1.96; respiratory: OR, 0.67; 95% CI, 0.39-1.15).

Overall, 489 of the 710 patients with schizophrenia (68.9%) had 1 or more prescriptions for antipsychotic medications at least 12 months before their index date. **Table 5** shows separate ORs for each cancer for patients with schizophrenia who had or had not been prescribed antipsychotic medications compared with patients with neither mental health condition, first unadjusted and then adjusted as described in the "Statistical Methods" subsection of the "Methods" section. The 52.2% increase in breast cancer risk found for patients with schizophrenia overall (after adjustment) was not substantially different in the subgroups with and without antipsychotic medication use (55.0% and 42.6%, respectively). The almost 3-fold increased risk of colon cancer in patients with schizophrenia overall was stronger (>4-fold) in the subgroup of patients with schizophrenia also prescribed antipsychotic medications. The overall 46.5% reduced risk of respiratory cancer in patients with schizophrenia was most marked (85.8%) in the subgroup not taking antipsychotics. In view of the small numbers in some of the subgroup analyses, particularly for rectal and gastroesophageal cancers, caution is needed in interpreting these ORs.

COMMENT

This is a very large population-based study to determine the risks of 6 common cancers (breast, colon, rectal, gastroesophageal, prostate, and respiratory) in patients with schizophrenia or bipolar disorder. The key finding

Table 3. Characteristics of Patients With and Without Schizophrenia or Bipolar Disorder

Characteristic	Patients With Schizophrenia[a]		Patients With Bipolar Disorder[a]		Patients With Neither Condition	
	Cases (n = 139)	Controls (n = 571)	Cases (n = 123)	Controls (n = 491)	Cases (n = 40 188)	Controls (n = 192 265)
Sex, No. (%)						
M	56 (40.3)	289 (50.6)	50 (40.7)	212 (43.2)	22 125 (55.1)	105 808 (55.0)
F	83 (59.7)	282 (49.4)	73 (59.3)	279 (56.8)	18 063 (44.9)	86 457 (45.0)
Age, median (interquartile range), y	67 (58 to 74)	68 (59 to 75)	67 (60 to 75)	69 (60 to 76)	70 (61 to 78)	70 (61 to 78)
Townsend score recorded, No. (%)	135 (97.1)	554 (97.0)	121 (98.4)	461 (93.9)	39 242 (97.6)	185 937 (96.7)
Townsend score, median (interquartile range)	1.16 (–1.98 to 4.02)	1.26 (–1.81 to 4.35)	–0.56 (–2.53 to 3.60)	–0.55 (–2.84 to 2.68)	–1.28 (–3.10 to 1.68)	–1.38 (–3.16 to 1.55)
Smoking status recorded, No. (%)	120 (86.3)	436 (76.4)	107 (87.0)	418 (85.1)	34 159 (85.0)	153 574 (79.9)
Smokers, No. (%)	59 (42.4)	185 (32.4)	56 (45.5)	135 (27.5)	9603 (23.9)	34 101 (17.7)
BMI recorded, No. (%)	103 (74.1)	372 (65.1)	99 (80.5)	379 (77.2)	30 558 (76.0)	137 545 (71.5)
BMI, median (interquartile range)	26.5 (23.3 to 30.8)	26.0 (23.0 to 29.9)	25.1 (22.1 to 29.1)	26.3 (23.1 to 29.8)	25.7 (23.1 to 28.7)	25.9 (23.4 to 28.9)
Months of previous data, median (interquartile range)	60 (40 to 93)	58 (35 to 88)	61 (37 to 96)	59 (35 to 98)	67 (39 to 101)	67 (39 to 101)
Comorbidities, No. (%)						
Diabetes mellitus	9 (6.5)	47 (8.2)	10 (8.1)	45 (9.2)	2715 (6.8)	12 089 (6.3)
Ischemic heart disease	10 (7.2)	47 (8.2)	15 (12.2)	79 (16.1)	5045 (12.6)	23 598 (12.3)
Rheumatoid arthritis	3 (2.2)	2 (0.4)	1 (0.8)	6 (1.2)	481 (1.2)	2490 (1.3)
Hypertension	26 (18.7)	94 (16.5)	28 (22.8)	90 (18.3)	10 543 (26.2)	49 300 (25.6)
Use of medications, No. (%)						
NSAIDs	17 (12.2)	25 (4.4)	15 (12.2)	58 (11.8)	4795 (11.9)	22 452 (11.7)
Aspirin	23 (16.5)	97 (17.0)	29 (23.6)	107 (21.8)	8655 (21.5)	39 144 (20.4)
Cyclooxygenase 2 inhibitors	5 (3.6)	15 (2.6)	12 (9.8)	23 (4.7)	1961 (4.9)	8671 (4.5)
Statins	7 (5.0)	31 (5.4)	12 (9.8)	41 (8.4)	3570 (8.9)	16 688 (8.7)
Hormone therapy	11 (7.9)	22 (3.9)	24 (19.5)	72 (14.7)	3419 (8.5)	14 511 (7.5)
Oral contraceptives	0	2 (0.4)	1 (0.8)	6 (1.2)	744 (1.9)	3120 (1.6)
Antidepressant SSRIs	29 (20.9)	100 (17.5)	57 (46.3)	151 (30.8)	3226 (8.0)	14 783 (7.7)
Antidepressant TCAs	39 (28.1)	114 (20.0)	54 (43.9)	241 (49.1)	5645 (14.0)	24 725 (12.9)
Antipsychotics	110 (79.1)	379 (66.4)	65 (52.8)	253 (51.5)	4698 (11.7)	21 918 (11.4)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

[a] Forty-six patients had both schizophrenia and bipolar disorder and are included in both groups.

in patients with schizophrenia was a 3-fold increased risk of colon cancer, which was more than 4-fold in patients also prescribed antipsychotic medications, despite adjustment for the potential confounding effects of socioeconomic status, smoking, obesity, comorbidity, and concurrent use of other medications. This is a novel and unexpected finding that needs further investigation. We also found a 52.2% increased risk of breast cancer, and a 46.5% decreased risk of respiratory cancer (predominantly lung cancer) after adjustment for the same variables. Patients with bipolar disorder had similar cancer risks as people without either mental health condition after adjustment for the potential confounding variables.

COLON AND RECTAL CANCERS

The most important finding in this study is a marked increased risk of colon cancer in patients with schizophrenia. This is a novel finding and one that is in contrast with previous studies,[4,8,22] which have tended to suggest no difference in risk of colon cancer in patients with schizophrenia. The previous UK study by Goldacre et al[22] found a nonsignificant rate ratio of 0.72. Their study differed from this one in a variety of ways, being based on records of hospital admissions rather than on the primary care records of the whole population, the reference cohort being drawn from patients admitted to the hospital for other conditions, and rates being standardized by age and sex but no adjustment being made for potential confounding variables. The finding of an almost 3-fold increased risk of colon cancer persisted whether or not the results were adjusted for known risk factors, including obesity[23] and socioeconomic status,[24] and for use of hormone therapy or oral contraceptives, which might reduce risk.[25] We did not adjust for diet, exercise, or alcohol consumption,[26] and these factors tend not to be reliably recorded in electronic medical records. We found that the increase in colon cancer was greatest in patients with schizophrenia prescribed antipsychotic agents. This is in contrast to a recent study[27] that reported a reduction in risk associated with these drugs,

Table 4. Odds Ratios for Risk of Each Cancer Associated With Schizophrenia and Bipolar Disorder[a]

	Participants, No. (%)		Odds Ratio (95% CI)[b]	
	Cases	Controls	Unadjusted	Adjusted
Breast cancer	n = 10 535	n = 50 074		
Neither mental health problem	10 444 (99.14)	49 767 (99.39)	1 [Reference]	1 [Reference]
Schizophrenia	49 (0.47)	153 (0.31)	1.50 (1.08-2.07)	1.52 (1.10-2.11)
Bipolar disorder	44 (0.42)	164 (0.33)	1.25 (0.89-1.76)	1.21 (0.86-1.71)
Colon cancer	n = 5108	n = 24 458		
Neither mental health problem	5064 (99.14)	24 352 (99.57)	1 [Reference]	1 [Reference]
Schizophrenia	32 (0.63)	51 (0.21)	2.85 (1.82-4.45)	2.90 (1.85-4.57)
Bipolar disorder	13 (0.25)	58 (0.24)	0.97 (0.52-1.79)	0.95 (0.51-1.76)
Rectal cancer	n = 3248	n = 15 552		
Neither mental health problem	3234 (99.57)	15 472 (99.49)	1 [Reference]	1 [Reference]
Schizophrenia	8 (0.25)	50 (0.32)	0.77 (0.36-1.63)	0.78 (0.36-1.66)
Bipolar disorder	6 (0.18)	32 (0.21)	0.91 (0.37-2.24)	0.99 (0.40-2.43)
Gastroesophageal cancer	n = 3854	n = 18 477		
Neither mental health problem	3833 (99.46)	18 388 (99.52)	1 [Reference]	1 [Reference]
Schizophrenia	14 (0.36)	53 (0.29)	1.25 (0.69-2.27)	1.06 (0.58-1.93)
Bipolar disorder	9 (0.23)	41 (0.22)	1.05 (0.50-2.17)	0.98 (0.47-2.05)
Prostate cancer	n = 10 190	n = 48 748		
Neither mental health problem	10 162 (99.73)	48 547 (99.59)	1 [Reference]	1 [Reference]
Schizophrenia	13 (0.13)	116 (0.24)	0.54 (0.30-0.95)	0.59 (0.33-1.05)
Bipolar disorder	16 (0.16)	93 (0.19)	0.86 (0.50-1.47)	0.87 (0.51-1.49)
Respiratory cancer	n = 7506	n = 35 981		
Neither mental health problem	7451 (99.27)	35 739 (99.33)	1 [Reference]	1 [Reference]
Schizophrenia	23 (0.31)	148 (0.41)	0.71 (0.46-1.11)	0.53 (0.34-0.85)
Bipolar disorder	35 (0.47)	103 (0.29)	1.68 (1.13-2.48)	1.21 (0.79-1.85)

Abbreviation: CI, confidence interval.
[a] Mental health categories do not sum to overall totals because 46 patients had both schizophrenia and bipolar disorder and are included in both groups.
[b] All models are adjusted for smoking, obesity, socioeconomic status, diabetes mellitus, hypertension, ischemic heart disease, rheumatoid arthritis, and use of nonsteroidal anti-inflammatory drugs, cyclooxygenase 2 inhibitors, aspirin, statins, selective serotonin reuptake inhibitors, tricyclic antidepressants, and antipsychotics. In addition, the breast, colon, and rectal cancer models are adjusted for use of hormone therapy and oral contraceptives.

although this was found in a wider population, of whom only 6% had schizophrenia.

For rectal cancer, which has few established risk factors, we found no significant increase or decrease in risk for patients with severe mental illness, in contrast to other studies,[4,8,22] which demonstrate a decrease in risk, but our numbers in these subgroups were small.

BREAST CANCER

We found a marginal 52.2% increase in risk of breast cancer in women with schizophrenia. This is consistent with some[4,28,29] but not all studies, which have generally found no difference[5,8,22,30] or a reduction in risk.[2] There have been suggestions that an increase in risk of breast cancer could be mediated by a prolactin-releasing effect of neuroleptic medications,[31] but a recent study did not confirm this,[27] and we found only a marginal association with medication. We adjusted for some risk factors that could confound the relationship between schizophrenia and cancer risk, including obesity[32] and use of oral contraceptives or hormone therapy.[33,34] However, we did not adjust for the observed lower parity in women with schizophrenia,[4] which tends to be associated with an increased risk of breast cancer. In other words, it is possible that the marginal increased risk of breast cancer demonstrated in this study is due to residual confounding by lower parity rather than a true increase in risk.

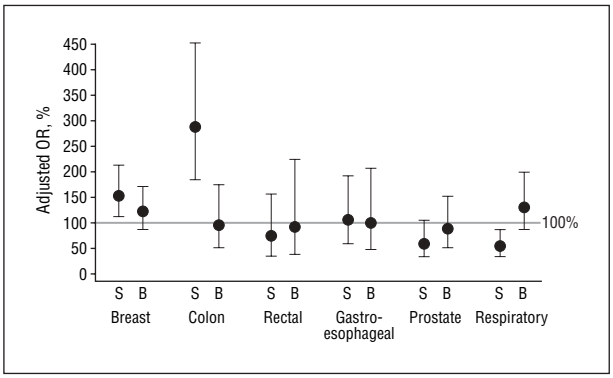

Figure. Adjusted odds ratios (ORs) for each cancer for patients with schizophrenia (S) and bipolar disorder (B) compared with patients without mental health problems. Error bars represent 95% confidence intervals.

RESPIRATORY CANCER

Some previous studies have reported a higher incidence or mortality due to respiratory cancer,[6,8,10] but others report a lower risk consistent with the present findings[4,7] or a nonsignificant difference.[5,22] Smoking is a major risk factor for lung cancer and is more prevalent in people with schizophrenia,[12] making it a potential source of substantial confounding in these studies; it was adjusted for in the present analysis. The largely institutionalized life of many people with schizophrenia could protect them

Table 5. Odds Ratios for Risk of Each Cancer in Patients With Schizophrenia With and Without Antipsychotic Medication Use

	Participants, No. (%)		Odds Ratio (95% CI)	
	Cases	Controls	Unadjusted	Adjusted[a]
Breast cancer	n = 10 535	n = 50 074		
Neither mental health problem	10 444 (99.14)	49 767 (99.39)	1 [Reference]	1 [Reference]
Schizophrenia without medication	9 (0.09)	31 (0.06)	1.34 (0.64-2.83)	1.43 (0.68-3.01)
Schizophrenia with medication	40 (0.38)	122 (0.24)	1.51 (1.05-2.16)	1.55 (1.08-2.23)
Colon cancer	n = 5108	n = 24 458		
Neither mental health problem	5064 (99.14)	24 352 (99.57)	1 [Reference]	1 [Reference]
Schizophrenia without medication	4 (0.08)	19 (0.08)	0.92 (0.31-2.74)	0.97 (0.32-2.91)
Schizophrenia with medication	28 (0.55)	32 (0.13)	4.07 (2.43-6.82)	4.08 (2.43-6.84)
Rectal cancer	n = 3248	n = 15 552		
Neither mental health problem	3234 (99.57)	15 472 (99.49)	1 [Reference]	1 [Reference]
Schizophrenia without medication	0	20 (0.13)	NA	NA
Schizophrenia with medication	8 (0.25)	30 (0.19)	1.29 (0.59-2.81)	1.26 (0.58-2.78)
Gastroesophageal cancer	n = 3854	n = 18 477		
Neither mental health problem	3833 (99.46)	18 388 (99.52)	1 [Reference]	1 [Reference]
Schizophrenia without medication	7 (0.18)	24 (0.13)	1.34 (0.57-3.14)	1.07 (0.45-2.53)
Schizophrenia with medication	7 (0.18)	29 (0.16)	1.19 (0.52-2.74)	1.07 (0.46-2.49)
Prostate cancer	n = 10 190	n = 48 748		
Neither mental health problem	10 162 (99.73)	48 547 (99.59)	1 [Reference]	1 [Reference]
Schizophrenia without medication	7 (0.07)	47 (0.10)	0.69 (0.31-1.54)	0.75 (0.34-1.68)
Schizophrenia with medication	6 (0.06)	69 (0.14)	0.43 (0.18-0.98)	0.47 (0.20-1.08)
Respiratory cancer	n = 7506	n = 35 981		
Neither mental health problem	7451 (99.27)	35 739 (99.33)	1 [Reference]	1 [Reference]
Schizophrenia without medication	2 (0.03)	51 (0.14)	0.18 (0.04-0.76)	0.14 (0.03-0.60)
Schizophrenia with medication	21 (0.28)	97 (0.27)	0.98 (0.61-1.58)	0.72 (0.44-1.18)

Abbreviations: CI, confidence interval; NA, not applicable.
[a] All models are adjusted for smoking, obesity, socioeconomic status, diabetes mellitus, hypertension, ischemic heart disease, rheumatoid arthritis, bipolar disorder, and use of nonsteroidal anti-inflammatory drugs, cyclooxygenase 2 inhibitors, aspirin, statins, selective serotonin reuptake inhibitors, and tricyclic antidepressants. In addition, the breast, colon, and rectal cancer models are adjusted for use of hormone therapy and oral contraceptives.

from some environmental risks, and antipsychotic drugs have been suggested as being protective, but in this sample the reduction in risk was greatest in patients not taking antipsychotic medications. The authors of a recent study[27] that found an increased risk of lung cancer associated with antipsychotic medication suggested residual confounding by smoking. Again, we found that patients with bipolar disorder did not share the reduced risk associated with schizophrenia.

GASTROESOPHAGEAL CANCER

We found no significant difference in risk of gastroesophageal cancer in people with schizophrenia, which is consistent with 2 previous studies.[2,8] Other studies have reported a higher risk of cancer of the esophagus after adjusting for age and sex[4,22] and reduced mortality from gastric cancer.[35] In the present study, adjustment for potential confounders, including socioeconomic status,[24] moved the OR closer to unity, but we did not adjust for alcohol consumption, which is a strong risk factor for cancers of the upper digestive tract.[36]

PROSTATE CANCER

The adjusted analysis suggests a 40.7% lower risk of prostate cancer in people with schizophrenia, but in view of the small numbers in these subgroups, this was not a statistically significant reduction. The magnitude of the association is consistent with that of previous studies, which have shown an approximately 50% lower risk.[4,6-8] Little is known about risk factors for prostate cancer, but a protective effect of neuroleptic medications, particularly phenothiazines, has been suggested[27,37]; our subgroup analysis is consistent with this but is based on numbers too small to reach a firm conclusion. Alternatively, the lower risk could represent an ascertainment bias if patients with schizophrenia are less likely to have screening for prostate cancer.

STRENGTHS AND LIMITATIONS OF THIS STUDY

Aggregated general practice databases, such as QRESEARCH, have previously been used successfully to evaluate risk factors for diseases in the population.[38-41] The use of routine clinical records and a nested case-control design gave this study a large and representative population-based sample, matched cancer cases and controls, no response or recall bias, and a comparison group with another mental health condition (bipolar disorder). Recording of clinical diagnoses was shown to have good levels of accuracy and completeness in general practice in the United Kingdom, including malignancy and psychiatric illness, where the diagnosis is recorded after specialist investigations and consultations.[42,43] The quality of the electronic medical record is thought to be highest in practices that contribute to primary care data-

bases.[44] Advantages of this study in contrast to previous work are that we adjusted for confounders such as smoking, BMI, and socioeconomic status and for commonly used medications, including antipsychotics. Information on alcohol consumption, diet, exercise, and reproductive history is less reliably recorded and was not included. However, in people with bipolar disorder, who would be expected to share some of the increased risk attributable to these lifestyle factors, we did not find the associations with cancer observed in patients with schizophrenia. Even with almost 19 million person-years of observation, the small number of patients with mental health problems in some subgroups limited the size of the effect that could be detected.

It is possible that some cancers were undiagnosed in people with schizophrenia or bipolar disorder, perhaps owing to underreporting of physical problems or lack of participation in screening programs. However, such a misclassification of outcomes would tend to bias the OR downward rather than generating spuriously positive findings, such as the increased risk of colon cancer in patients with schizophrenia. By excluding diagnoses of schizophrenia or bipolar disorder made in the 12 months preceding the diagnosis of cancer, we minimized the possibility that apparent psychiatric symptoms were a manifestation of the cancer.

IMPLICATIONS FOR RESEARCH AND CLINICAL PRACTICE

The possible association between schizophrenia and increased risk of colon and breast cancers is of practical and theoretical importance not only in terms of the organization of services (such as screening) but also in the understanding of the etiology of disease. Given the study design, it is not possible to eliminate the possibility of residual confounding by such factors as alcohol consumption, diet, and reproductive history. However, in people with bipolar disorder, who would be expected to share some of the increased risk attributable to lifestyle, we did not find higher rates of breast or colon cancer.

In particular, the increased risk of colon cancer demonstrated in this study, which was greatest for those taking antipsychotic medications, is a novel and unexpected finding. The magnitude of the risk and the degree of statistical significance does not rule out a chance finding, although it does make it unlikely. The finding of a lower risk of respiratory cancer, particularly in those who were not taking antipsychotic drugs, argues for an intrinsic protection associated with schizophrenia rather than the previously suggested effect of medication. Further research is needed to confirm or refute these findings using an independent data source with a more detailed analysis of individual drugs, including a comparison of the older class of antipsychotics with the newer atypical agents.

The higher rate of some common cancers in people with schizophrenia emphasizes the need for proactive monitoring of their physical health, which has previously been highlighted.[45] Factors such as obesity, smoking, and high alcohol consumption are more prevalent in this group[12,13] and increase the risk not only of cancer but of many other conditions, including diabetes mellitus and cardiac disease. Antipsychotic medications differ in the extent to which they increase the risk of obesity and other conditions.[46,47] If there is an inherently higher risk of some cancers in people with schizophrenia, it is particularly important to minimize any additional risks associated with lifestyle or prescribed medications.

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