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Research report

Enhanced cancer risk among patients with bipolar disorder

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Abstract

Background: In contrast to numerous epidemiological studies that explored the risk for cancer among persons with schizophrenic psychoses, analogous studies conducted on people with bipolar disorder are rarer, despite some commonalities in biological, treatment-related variables and unhealthy lifestyles. This study investigates the risk for cancer among psychiatric inpatients diagnosed with bipolar disorder.
Methods: Linkage analysis was conducted based on the psychiatric and the cancer national databases. Standardized incidence ratios (SIR) for both aggregated sites and for breast cancer were calculated by comparing the incidence rates among hospitalized patients with bipolar disorder with the incidence rates in the Jewish–Israeli general population.
Results: An enhanced cancer risk was found for bipolar disorder in both genders: men, SIR 1.59 (95% CI 1.01–2.17); women, SIR 1.75 (95% CI 1.31–2.18). The risk for breast cancer was higher, but not significantly, than in the general female population, SIR 1.70 (95% CI 0.99–2.41).
Limitations: Our sample was derived from psychiatric inpatients, thus it is likely that the bipolar disorder cases had greater severity. Putative factors such as diet, smoking and medications were not investigated.
Conclusions: Our study showed an enhanced risk for cancer among patients with bipolar disorder. Clinicians might note this risk for timely diagnosis and treatment.

Keywords: Bipolar disorder; Cancer; Epidemiology; Israel

1. Introduction

Several epidemiological studies have focused on the association of schizophrenic disorders and the risk for cancer among patients (Goldacre et al., 2005; Grinshpoon et al., 2005) and their first-degree relatives (Dalton

Abbreviations: PCR, Psychiatric Case Register; INCR, Israel National Cancer Registry; CI, Confidence Interval; ICD, International Classification of Diseases.

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et al., 2004; Levav et al., 2007; Lichtermann et al., 2004). In contrast, there is limited recent research on a similar association for bipolar disorder (Høyer et al., 2000; Krishnan, 2005; Laursen et al., 2007; Weeke and Vaeth, 1986), and this despite some of their commonalities regarding biological factors (Craddock et al., 2006; Owen et al., 2007), treatment-related variables, e.g., medication and episodes of hospitalizations, and unhealthy behavior (Laursen et al., 2007). Of late, Carney and Jones (2006) appropriately noted the superficial attention given to the risk for cancer in those patients. The exceptions are the very few studies conducted in Australia (Lawrence et al., 2000); the UK (Osborn et al., 2007); the USA (Carney et al., 2004); and in two Scandinavian countries (Høyer et al., 2000; Laursen et al., 2007; Osby et al., 2001). Lawrence et al. (2000) found a lower non-significant statistical cancer mortality risk for ICD-9 "affective psychosis" (incident) rate ratios: men, 0.91 (95% CI 0.76–1.07) and women, 1.06 (95% CI 0.94–1.19). Osborn et al. (2007) found no increased risk for mortality from cancer in patients with "severe mental illnesses", identified in a large general practice database. Carney et al. (2004), who based their study on mental health claims in an insured population, found that "mood disorders" were not-statistically significant more common in the sample of women who later developed cancer than in women who did not. The overall conclusions derived from those three studies are partially affected by their heterogeneous methods, e.g. different data sources, broad diagnostic definitions and various diagnostic labels. The three Scandinavian linkage studies are based on the psychiatric case and population registries available in those countries. The earlier Danish study (Høyer et al., 2000) found that bipolar disorders had a non-statistical difference compared with unipolar depression, 1.08 (95% CI 0.93–1.24). Also the more recent Danish study by Laursen et al. (2007) found a non-significant statistical risk, 1.03 (95 CI% 0.92–1.15). The results of the Swedish study (Osby et al., 2001) differed slightly, the authors found a minimally higher risk for cancer among women but not for men, standardized mortality rates, 1.2 (95% CI 1.1–1.4) and 1.1 (95% CI 0.9–1.3), respectively. Since these studies were based on mortality statistics, which depend not only on morbidity but on survival, no firm conclusions could be drawn.

The scarcity of research inquiries and their non-conclusive results contrast with the presence of several factors among inpatients with bipolar disorder that might affect the risk for cancer, e.g., diet, smoking, and medications (Carney et al., 2004; Carney and Jones, 2006; Craddock et al., 2006; Krishnan, 2005; Laursen et al., 2007; Lawrence et al., 2000; Osborn et al., 2007; Owen et al., 2007). This relative research vacuum justifies a new inquiry in which some of the above methodological limitations are addressed.

2. Methods

To explore the risk of cancer among patients with bipolar disorder we linked two nation-wide databases, the Psychiatric Case Registry, which records all admissions to and discharges from inpatient psychiatric settings, and the Cancer Registry, that records both morbidity and mortality information.

2.1. Identification of inpatients with bipolar disorder

The Psychiatric Case Register (PCR) was used to identify Israel-born Jewish patients first admitted during the years 1980–2005 with a diagnosis of bipolar disorder (ICD-10 F31) and manic (non-organic) state (ICD-10 F30) during their last hospitalization. The 50-year old PCR is mandated by law to maintain a cumulative record of all hospitalizations (Lichtenberg et al., 1999; Mental Health Services, 2004). Diagnoses are based on the ICD-10; those made prior to its use have been updated. A test of the agreement between research diagnoses and those recorded in the PCR found a satisfactory match (Rabinowitz et al., 2000; Weiser et al., 2005). To enhance the reliability we adopted the diagnosis last entered into the PCR. In addition to the diagnoses, the PCR also provided socio-demographic information. Importantly for linkage purposes, the identity number used to record all patient movements is the same one used by the Israel National Cancer Registry (INCR). While the PCR's recording of cases tends to be complete for Israel-born Jewish patients, this is not the case for the Arab–Israeli minority, particularly women, whose use of psychiatric inpatient services is limited (Mental Health Services, 2004). To avoid biasing the sample, the Arab–Israeli minority was excluded.

2.2. Identification of cancer cases

The INCR was established in 1960. Reporting of incident cancer cases – morbidity data – has been mandatory since 1982 for all public and private medical facilities. The INCR also collects data on cancer deaths – mortality statistics – from the appropriate governmental agencies. As in the PCR, the information is organized using a personal identity number. Information completeness exceeds 95%. Importantly, continuous efforts are made to improve reporting and accuracy (Fishler et al.,

2002; Israel Center for Disease Control, 1998; Israel National Caner Registry, 2006). Multiple quality data tests, as recommended by the International Agency for Research on Cancer (Parkin et al., 2002), are conducted regularly (for example, the percentage of cases with morphological verification, the mortality to incidence ratio, or the percentage of cases ascertained by death certificate only). The INCR stores information on cancer cases diagnosed both in Israel and abroad; most of the latter are new immigrants.

2.3. Linkage procedure

The two case registers were linked by means of the personal identity number. To assure reliable linkage, the identity number was supplemented with the person's gender, date of birth and place of origin, and the father's first name. No family name was recorded.

Both registries, that are owned and maintained by the Ministry of Health, are administered under strict legislative procedures. To preserve confidentiality, the researchers are not given the files with the subjects' names. Ethical approval for the study was obtained from the Helsinki Committee of the Tirat Hacarmel Mental Health Center.

2.4. Analyses

The cancer incidence rates in the above two diagnostic groups taken together (manic and bipolar disorders F30 and F31) were compared with the rates in the Israel-born Jewish population using standardized incidence ratios (SIR) and the respective 95% confidence intervals. A SIR is defined as the ratio of the observed to the expected number of cancer cases. The expected number of cases during the observation period was calculated by gender and age. Period-specific age and gender cancer incidence rates, including those diagnosed upon death, were used (Fishler et al., 2002). The person–years of exposure to cancer risk were defined for the index cases as follows, from date of birth to death, diagnosis of cancer, emigration, or the end of year 2005.

The cancer incidence rate of manic and bipolar disorders was contrasted with that for schizophrenia (F20) using similar procedures. Analyses were performed using SAS 9.13 software for Unix.

Table 1
Cancer cases among patients with manic (ICD-10 F30) and bipolar (ICD-10 F31) disorders (ICD-10 F25) by sex

Disorders	*N*	Cancer cases
Manic, ICD-10 F30		
Male	145	4
Female	108	8
Total	253	12
Bipolar, ICD-10 F31		
Male	862	25
Female	1006	53
Total	1868	78

Table 2
Cancer SIRs among patients with manic (ICD-10 F30) and bipolar disorder (ICD-10 F31) compared to the general population by sex, 1980–2005

Subjects	Cases		SIR	95% CI	
	Expected	Observed		Lower	Upper
Males	18.20	29	1.59	1.01	2.17
Females	34.95	61	1.75	1.31	2.18

3. Results

Samples. A total of 2121 patients were identified according to the following diagnostic categories: manic disorder, 253 (men, 145; women, 108); and bipolar disorder, 1868 (men, 852; women, 1006) (see Table 1). The total numbers of person–years generated were men, 9957 and women, 12056. Eighty percent of all patients had their last admission after 1996, when the psychiatric services were more accurate in their diagnoses. Two or more admissions were recorded for 35.6% of patients with manic disorder and 67.5% for bipolar disorder.

Cancer risk. The risk for cancer among the manic and bipolar disorder diagnostic groups combined was statistically significantly higher for both genders: men, SIR 1.59 (95% CI 1.01–2.17), and women, SIR 1.75 (95% CI 1.31–2.18) (see Table 2).

There were 22 cases available to examine the risk for breast cancer among women. For the manic and bipolar disorder diagnostic groups combined, the risk was higher than in the general female population, but it did not reach statistical significance, SIR 1.70 (95% CI 0.99–2.41).

The risk for cancer among patients with bipolar disorder was significantly higher for both men and women than among individuals with schizophrenia of the same origin (Israel-born Jews who were admitted during the same years, 1980–2005), men, SIR 1.97 (95% CI 1.26–2.69) and women, SIR 2.24 (95% CI 1.68–2.80).

4. Discussion

We found a clear enhanced risk for cancer among patients with bipolar disorder. The risk was also higher for breast cancer, although the results did not reach statistical significance — likely, due to the small number

of cases. No other cancer site had sufficient number of cases to be examined independently.

This study has several limitations: 1. Like in our previous published studies (cf. Grinshpoon et al., 2005) we did not use research diagnoses. However, we relied on the discharge diagnoses made during the single or the last hospitalization, when more than one admission was recorded. Obviously, multiple inpatient admissions allowed for a longer period of observation. This also assured that the diagnosis was made during more recent times, when psychiatrists become more diagnostic-sensitive following the introduction of lithium and other mood stabilizers as standard secondary preventive interventions. Also, several recent reliability checks conducted on the Psychiatric Case Register (Rabinowitz et al., 2000; Weiser et al., 2005) showed good concordance between research and clinical diagnosis. However, if the final sample included some persons diagnosed with schizophrenia that might have a lower cancer risk (Grinshpoon et al., 2005), these false positive cases would only buttress the results. 2. The bipolar cases this study collected might not represent all people who had the disorder during the study period, but rather include patients who suffered from a more severe episode that required inpatient care. The criteria applied for inclusion, restricted to Israel-born Jews, might have reduced selectivity factors since this population group uses psychiatric services more often than other groups, and, in the case of men, is under the medical surveillance of the Army. The following psychiatric service procedures facilitated the recruitment of persons with bipolar disorder: a) Primary care physicians usually refer patients with severe psychiatric disorders to specialty services; b) In addition, easy access to these services is also freely available on a drop-in basis (Levav and Grinshpoon, 2004); c) The Israel Defense Forces' medical examinations prior to recruitment (both genders) and during reserve duties (men only), serve as a universal screening procedure which is followed by a psychiatric assessment whenever deemed necessary; d) Often, patients with major psychiatric disorders are admitted to inpatient care; and e) Israelis rarely seek hospitalization abroad. 3. We did not collect enough cases to enable us to identify specific risks by cancer site; and 4. Being dependant on computerized records we did not obtain relevant information on healthy lifestyle-related behaviors and medications. We, therefore, lack the necessary information to account for the findings.

We believe that this study has several strengths: 1. The study relied on both, morbidity and mortality information, and thus it was less dependant on treatment issues and survival than the mortality-based studies (cf. Weeke and Vaeth, 1986); 2. Our upgraded computerized facilities reduced the risk of linkage errors. Both databases provided fairly complete and accurate data, and we repeated the database linkage procedures to make sure that the matches were correct; and 3. Being national registries there was less of a chance to miss cases. These methodological improvements might explain the differences in results from the studies reviewed in the introduction.

As the Jewish population in Israel is ethnically heterogeneous, genetic and environmental factors are unlikely to play a role in explaining the differences with previous studies. The comparison with inpatients with schizophrenia, showing a markedly increased risk compared to another diagnostic group, permitted confirmation of the results and suggested that these findings cannot just be explained as just a result of selection bias due to hospitalization.

In conclusion, what did we learn? Contrary to previous studies on schizophrenia (e.g., Dalton et al., 2004; Goldacre et al., 2005; Grinshpoon et al., 2005; Levav et al., 2007; Lichtermann et al., 2004) and most of those exploring the risk of cancer among persons with bipolar disorder (see Introduction) we found higher SIRs among men and especially among women. Having identified the enhanced risk, the next obvious step is to account for the putative factors to design preventive measures. Candidate factors are related to health behavior and medication. For example, studies have shown that bipolar disorder is associated with obesity (McIntyre et al., 2006), the metabolic syndrome (Cowey and Hardy, 2006; Taylor and MacQueen, 2006), high rate of smoking (Waxmonsky et al., 2005), and poor health-related behavior (Kilian et al., 2006). In addition, mood stabilizers, anticonvulsants, and antipsychotic medications, which are commonly used to treat bipolar disorder, have been linked to weight gain and the development of adverse metabolic changes (Newcomer, 2006). Molecular targets of mood stabilizers involve glycogen synthase kinase-3 (GSK-3) for lithium (Noble et al., 2005), and histone deacetylase (HDAC), for valproate, both drugs are known to attenuate apoptotic activity (Hrzenjak et al., 2006). Also lithium and valproate activate cell survival factors and induction of trophic proteins, including brain-derived neurotrophic factor, heat-shock protein (HSP), and Bcl-2 (Chuang, 2005). Thus the chronic exposure to mood stabilizers possessing putative antiapoptotic (Senatorov et al., 2004), cytoprotective (Lai et al., 2006) and cell proliferation promoting activities, in the presence of heavy smoking behavior and metabolic abnormalities (Waxmonsky et al., 2005), as well as possible susceptibility gene variants relevant to cancer, such as PALB2 (partner and

localizer of BRCA2) (Wellcome Trust Case Control Consortium, 2007), and epigenetic mechanisms (van Vliet et al., 2007), may contribute to the increased risk for cancer in persons with bipolar disorder.

This inquiry was limited to build a case for study; therefore, none of the above-cited factors, including comorbid physical illnesses and drug treatment were explored here. What we have clearly shown is that it is incumbent upon the medical and psychiatric services to be on the alert, particularly since there is a tendency to overlook physical disorders in patients affected by severe mental disorders (Cradock-O'Leary et al., 2002).

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Conflict of interest

None of the authors have conflicts associated with this study.

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