



Letter to the Editor

Cancer risk in people with bipolar disorder: Perspectives for future study



Dear Editor,

Bipolar disorder (BD) is a mental disorder that causes extreme swings in mood, energy, and the ability to perform day to day tasks. Besides suicide, BD is associated with decreased life expectancy, which has been attributed to comorbidities including malignancy (Crump et al., 2013). There are several explanations for the association between BD and subsequent cancer incidence: an unhealthy lifestyles associated with increased risk of cancer; adverse effects of prolonged psychotropic medication use; alterations in immune pathways and subsequent inflammatory responses, predisposing individuals to immune-related diseases such as cancer; and social deprivation with lack of access to preventative care (Weinstein et al., 2016).

Epidemiologic findings on the cancer incidence in people with BD are inconsistent. They were limited by small numbers of people with BD or cancer, the use of cross sectional designs without longitudinal data, or inclusion of people with other mental illnesses such as schizophrenia. This study aimed to summarize the results of studies on the risk of cancer in people with BD and to suggest a direction for further research.

We searched the Pubmed, Embase, and Cochrane Library databases from inception to January 28, 2019, without language restrictions. We used search keywords related to BD (bipolar disorder or manic-depressive illness), cancer (malignant or cancer or carcinoma or neoplasm or tumor), and outcomes (risk or incidence or ratio). Citations were primarily screened by the title and abstract level, and the reference lists of relevant articles were reviewed to identify additional papers not captured in the database searches.

Primary studies investigating cancer occurrence among people with BD were eligible for inclusion. Additional eligible criteria were that each study had to report the risk of developing cancer (e.g., not cancer-related mortality) and provide measures of association (hazard ratio or incidence ratio) and precision (confidence interval). To ensure causal inference, we excluded literatures with a cross-sectional nature in which the order of occurrence of cancer and BD was unknown. In the case of multiple publications from the same database, we chose the most relevant publication. The meta-analysis protocol followed the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.

We extracted information from each study (i.e., first author, year of publication, country, study design and population, fully adjusted estimates for association, and adjusted variables); some estimates had to be recalculated (e.g., pooling the estimates of overall cancer, smoking-related cancer, or sex-specific cancer). We calculated pooled hazard ratio from the estimates reported in the individual studies. We assessed heterogeneity using Higgins I^2 , and used the DerSimonian and Laird random-effects model if $I^2 > 50\%$. Publication bias was assessed using the Begg's rank correlation test. Stata version 9.2 (StataCorp, College Station, TX, USA) was used for all statistical analyses.

Six studies were included in the final analysis (as shown in Table 1).

People with BD did not have an increased overall risk of cancer or a gender-associated increased overall risk of cancer. However, the cancer-specific analysis found people with BD had a 31% higher risk of breast cancer. No publication bias was found.

The pooled analysis revealed that people with BD did not have an increased hazard for overall cancer incidence. Our findings suggested that increased cancer-screening vigilance would not be needed for people with BD; providing equitable access to screening services would have greater benefits. Attendance at cancer screening in people with psychotic disorders is known to be much lower (Weinstein et al., 2016). In addition, the results of a Swedish national cohort study indicated that chronic disease mortality of people with BD is similar to that of the general population when time of diagnosis is similar (Crump et al., 2013).

It remains possible that some cancers were undiagnosed in people with BD, possibly because diagnostic overshadowing resulted in the physical symptoms wrongly considered as manifestations of the mental illness (Weinstein et al., 2016). This misclassification would tend to bias the hazard downward. Although people with mental illness tend to live more unhealthy lifestyles compared with the general population, we found few studies that examined lifestyle factors in relation to cancer risk in people with BD. The non-adjustment for those deleterious behaviors might exaggerate the differences and bias the results. Future observational studies should include the critical covariates such as health-related habits (e.g., smoking, alcohol, obesity, and physical activity) and medical services utilization.

Methodologies to isolate drug effects from disease effects should also be used. Lithium's effect on cancer development in people with BD remains inconclusive (Martinsson et al., 2016). Therefore, a well-designed pharmacoepidemiologic study is needed to reliably assess this drug and elucidate the dose-dependent response.

The case and sample sizes used in individual studies may have been too low for sufficient power to detect associations between breast cancer risk and BD. The published results for three of the four studies were not statistically significant, but our analysis found statistical significance and no heterogeneity. The potential mechanisms are not well-substantiated. One mechanism is elevated prolactin levels subsequent to the use of psychotropic medications in people with BD. Prolactin is a hormone required for growth and differentiation of mammary gland cells; it might be associated with the increased incidence of estrogen-dependent tumors. Synergism between prolactin and estrogen occurs in proliferating breast cancer cells *in vitro* (Rasmussen et al., 2010), and administration of prolactin in mice increases mammary tumor risk (Halbreich et al., 2003). If a future study with more detailed data (e.g., family history, gynecologic history) finds significant associations between BD and breast cancer, active screening for breast cancers in people with BD should be integrated into clinical practice.

In conclusion, except for breast cancer screening, current evidence does not support more rigorous cancer screening of people with BD.

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Table 1
Characteristics of studies included in the meta-analysis.

First author (year)	Country	Design	No. of BD	Stratified by	O-HR (95% CI)	Covariates other than age and sex
Kahan et al. (2018)	Israel	Retrospective	3304	Sex	1.05 (0.86–1.27)	–
Mclay et al. (2017)	Canada	Retrospective	520	–	0.58 (0.29–1.14)	Admission year, postal code
Martinsson et al. (2016)	Sweden	Retrospective	5442	Sex/Cancer	1.03 (0.93–1.15)	–
Osborn et al. (2013)	UK	Retrospective	4948	Cancer	0.99 (0.80–1.21)	Follow up time, deprivation, smoking, obesity
Lin et al. (2013)	Taiwan	Retrospective	20,567	Sex/Cancer	1.29 (1.11–1.51)	Follow up time
McGinty et al. (2012)	USA	Retrospective	1002	Sex/Cancer	2.60 (2.00–3.20)	–

UK, United Kingdom; USA, United States of America; BD, bipolar disorder; O–HR, hazard ratio for overall cancer; CI, confidence interval.

Research using a prospective data source with more detailed information and basic elucidation of the causal pathways between BD and breast cancer are needed to confirm or refute our findings.

Conflict of interest

None.

Disclosure

None.

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