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ORIGINAL ARTICLE

Mortality from cancer in people with severe mental disorders in Emilia Romagna Region, Italy

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Abstract

Objective: To examine cancer-related mortality in patients with severe mental disorders (SMI) in the Emilia Romagna (ER) Region, Northern Italy, during the period 2008–2017 and compare it with the regional population.

Methods: We used the ER Regional Mental Health Registry identifying all patients aged ≥18 years who had received an ICD-9CM system diagnosis of SMI (i.e., schizophrenia or other functional psychosis, mania, or bipolar affective disorders) during a 10-year period (2008–2017). Information on deaths (date and causes of death) were retrieved through the Regional Cause of Death Registry. Comparisons were made with the deaths and cause of deaths of the regional population over the same period.

Results: Amongst 12,385 patients suffering from SMI (64.1% schizophrenia spectrum and 36.9% bipolar spectrum disorders), 24% (range 21%–29%) died of cancer. In comparison with the general regional population, the mortality for cancer was about 50% higher among patients with SMI, irrespective if affected by schizophrenia or bipolar disorders. As for the site-specific cancers, significant excesses were reported for stomach, central nervous system, respiratory, and pancreas cancer with a variability according to psychiatric diagnosis and gender.

Conclusions: Patients suffering from SMI had higher mortality risk than the regional population with some differences according to cancer type, gender, and psychiatric diagnosis. Proper cancer preventive and treatment interventions, including more effective risk modification strategies (e.g., smoking cessation, dietary habits) and screening for cancer, should be part of the agenda of all mental health departments in conjunction with other health care organizations, including psycho-oncology.

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KEYWORDS
bipolar disorders, cancer, mortality, oncology, psychiatry, psycho-oncology, schizophrenia

1 | INTRODUCTION

Over the last decades, a number of studies have brought attention to the problems of disparities and inequalities in the health of individuals affected by severe mental illness (SMI). Available data suggest an increased prevalence of physical illness which results in a life expectancy 15–20 years shorter among individuals with SMI than the general population.[1–8] Cancer has been indicated as one of the main culprits, not only because of its negative impact on quality of life and functioning, but also for the heavy toll it exerts on survival.[9]

Preliminary investigations on cancer-related mortality were carried out in the 1980s. They mostly suggested similar or slightly higher mortality rates in SMI populations than in the general population.[10–12] Whereas, more recent studies present a radically different scenario,[13] for example, in a large Swedish cohort study of 6,097,834 people followed for 7 years (2003–2009), patients with schizophrenia displayed a markedly premature mortality: the leading causes were ischemic heart disease and cancer, which appeared to be underdiagnosed.[14] In the United States, Olfson et al.[15] found that patients with schizophrenia had a standardized mortality ratio (SMR) (i.e., the ratio between the observed and the expected number of deaths) of 2.4 (95% CI, 2.4–2.5) for lung cancer, compared with the general population. In a further large Danish study on 56,152 women diagnosed with early-stage breast cancer, patients with psychotic disorders were less likely to be treated following proper cancer guidelines and this resulted in a significantly shorter survival than women with cancer but no SMI.[16] Similarly, patients with a diagnosis of schizophrenia[17–20] were less likely to receive stage-appropriate treatment for cancer, resulting in poorer outcomes across several other studies 17–21.[21] Such data have been recently summarized in a meta-analysis of 1,162,971 subjects, confirming that individuals with schizophrenia run a significantly higher risk of mortality from breast, colon, and lung cancer.[22]

Cancer-related morbidity and premature mortality seem to plague patients with bipolar-spectrum disorders not less than it does those with schizophrenia. Although this disorder is more prevalent than schizophrenia, less data are available showing a higher risk of developing cancer[23] and a higher SMR with respect to the general population.[24–26] With respect to this, in a 5-year-period study carried out in New Zealand among 8762 people with breast and 4022 with colorectal cancer, those affected by schizophrenia, schizoaffective, or bipolar disorders received diagnosis at a later stage and that contributed, after adjusting for several factors, a two and half times higher mortality for breast cancer and three times for colon cancer than people without SMI.[27]

A number of international studies on mortality in SMI are based on hospital-based registry, with the limit that data related to lifestyle and other variables evident in community-based studies cannot be examined. In Italy, since the closure of long-stay psychiatric hospitals, and the reorganization of mental health services with the development of community-based psychiatry,[28,29] studies examining the physical health care of people with SMI are important. In the few studies available on this subject, an increased risk of mortality for all causes was found both among outpatients and those who were admitted for the first time as inpatients in psychiatric units.[30] A higher mortality rate caused by several medical disorders was found in other studies carried out in Northern Italy on patients of community mental health.[31,32] More recently, Berardi et al., in a large 10-year retrospective cohort investigation of 137,351 patients, found an SMR of 1.99 with diseases of circulatory and respiratory systems, as well as neoplasms as the principal contributors to the mortality gap.[33]

Since no study, however, is available in Italy, specifically exploring cancer-related mortality in patients with SMI, the aim of the present work was to explore cancer mortality in a population with schizophrenia-spectrum versus bipolar-spectrum disorders from a well-defined community-based catchment area, over a period of 10 years and compare it with the general population.

2 | METHODS

2.1 | Study setting and sources of data

This study was carried out in the Emilia Romagna (ER) Region, an area in Northern Italy with about 4.5 million inhabitants and nine provinces (Bologna, as capital of the Region, Ferrara, Forli-Cesena, Modena, Parma, Piacenza, Ravenna, Reggio-Emilia, and Rimini). In the late 1960s, the ER Region was one of the first to experience the switch from asylum-based to community-based psychiatric care[34,35] ER Region rapidly implemented the new organization of mental health services following the 1978 Italian mental health law (13 May 1978, Law 180), within the general reform that instituted the National Health Service (23 December 1978, Law 833).

The Regional Mental Health Registry was used to identify participants and retrieve demographic data (age, gender, citizenship, and residency) together with psychiatric diagnosis and date of first admittance to the mental healthcare system. The Registry contains demographic and clinical information of all inpatients and outpatients referring to the Mental Health Departments (MHDs) of the Region as detailed in a previous study.[33] Demographic features, as well as diagnoses, are routinely recorded at the first clinical evaluation and then regularly updated by clinicians.

For the purpose of this study, we included patients aged 18 years or over who had received a diagnosis of severe mental

disorder, namely schizophrenia or other functional psychosis, mania, or bipolar affective disorders, from a psychiatric service within the MHDs of the ER Region in the period between 1 January 2008 and 31 December 2017. Residents outside the ER Region and patients who were registered with the MHDs before 2008 were excluded.

To ascertain the vital status, we linked the Mental Health Registry with the Regional Cause of Death Registry using an anonymous identity code. This code is provided to all health records of the residents by the regional authority. We defined a participant's death if the record of both registries match each other. The Regional Cause of Death Registry covers all the deaths in the Region and it contains anonymized information about sociodemographic characteristics, date, setting, circumstances, and initial cause of death. The cause of death derives from information recorded in the medical section of the death certificate by a certifier (attending physician, medical examiner, coroner), and it is classified according to the 10th revision of the International Classification of Disease (ICD-10) (Table S1) and coded according to the WHO rules. All information is collected following national protocols. Both registries undergo regular systematic quality checks. Change of residence to another region, as retrieved from the Regional Registry Office, indicated a lost to follow-up because of the impossibility to ascertain the life status of the patients. The regional population was used as the comparator group. The Regional Population Archive provided aggregated data on the age and gender composition of this population. (https://statistica.regione.emilia-romagna.it/servizi-online/statistica-self-service/popolazione).

The study was approved by the local Ethical Committee (N. 341/2019). All records in the Mental Health Registry were anonymized.

2.2 | Mental Health Registry and psychiatric diagnoses

The regional Mental Health Registry was used to identify study participants. The Mental Health Registry was implemented in the 1980s, but was completely operative in the whole regional catchment area only after the early 2000s. We decided to begin data collection from 2008 onwards (and therefore to consider a 10-year period). This date was chosen to ensure a bedding-in period of several years during which time any problems in the system should have been resolved. This excluded early data with possible weaknesses, and it ensured that the present study used more reliable and good quality data. Residents outside the ER Region, patients with an access to the MHD before 2008, and patients with intellectual disability, dementia, delirium, or other mental disorders following organic brain damage (ICD9-CM 290, 293, 294, 299.0, 299.01, 310, 317, 318, 319) were excluded. Demographic features, dates of visits, and treatment (i.e., pharmacological, psychological, rehabilitative) of all inpatients and outpatients who have accessed the MHDs in the region are routinely recorded at the first clinical evaluation and then constantly updated by clinicians; finally, all data are collected via an Information System at regional level.

The Registry contains information on psychiatric diagnoses collected by clinicians and defined according to the International Classification of Disease, 9th and 10th revisions, Clinical Modification (ICD-9 CM and ICD-10 CM) (ICD-9CM diagnosis). Because of the observational nature, the diagnoses in regional psychiatric services are clinically made (therefore not by using the structured Composite International Diagnostic Interview), with however the possibility for the service to discuss the cases, with the patients seen by the team rather than a single physician, according to the team-centered approach used in ER Region. Schizophrenia or other functional psychoses were defined as ICD-9 CM codes 295, 297, 298, excl. 298.0, 299 excl. 299.0, 299.00, 299.01 or ICD-10 F2; and mania and bipolar affective disorders by ICD-9 CM 296.0*, 296.1*, 296.4*, 296.5*, 296.6*, 296.7, 296.8* excl. 296.82 or ICD-10 F30, F31, F34.0.

2.3 | Statistical analyses

To describe the causes of death, we calculated the proportional mortality, namely the number of deaths within a population due to different causes during a time period over the total. In particular, we considered the proportional mortality for all neoplasms and site-specific malignant neoplasms in the study population, separately among patients with schizophrenia and other functional psychoses and among patients with mania and bipolar affective disorders and in the regional population.

To compare the risk of mortality between the regional and the study population, we computed the SMR. The SMR was calculated as the ratio of observed deaths in the study population divided by the number of expected deaths if the study population had the same gender, age (grouped in classes)-specific rates as the regional population, the standard. Rates of the standard population were obtained by using the above mentioned Regional Cause of Death Registry and the Population Archive. An SMR equal to 1 means that the observed deaths are equal to the expected, if it is greater than 1, it means that the observed deaths are higher than the expected and on the contrary, if it is lower than 1, it means that the observed deaths are smaller than the expected. SMRs with 95% confidence intervals (CI) were computed by gender (controlling for age class only), cancer and psychiatric diagnosis in case of more than 3 observed events. We considered the differences significant if the CI of the SMR excluded the value of one. The denominator was the person-years, calculated as the difference between 31 December 2017 or the date of leaving to another region or of death (if applicable), and the date of first access to a MHD.

3 | RESULTS

3.1 | Sample characteristics

The cohort consisted of 12,385 patients suffering from SMI, 7940 with schizophrenia and other functional psychoses (64.1%) and 4445

TABLE 1 Demographic characteristics of the study population at their first access to the Regional Mental Health Department

		Severe mental disorders		Schizophrenia and other functional psychosis		Mania and bipolar affective disorders	
		n	%	*n*	%	*n*	%
Total		12,385	100.0	7940	100.0	4445	100.00
Gender	Women	6524	52.68	3989	50.24	2535	57.03
	Men	5861	47.32	3951	49.76	1910	42.97
Age group. years	18–24	1443	11.65	1174	14.79	269	6.05
	25–44	4528	36.56	3066	38.61	1462	32.89
	45–64	4113	33.21	2255	28.40	1858	41.80
	65–74	1359	10.97	777	9.79	582	13.09
	75–84	728	5.88	505	6.36	223	5.02
	85+	214	1.73	163	2.05	51	1.15
Citizenship	Italian	10,659	86.06	6561	82.63	4098	92.19
	Non Italian	1726	13.94	1379	17.37	347	7.81
Residency	Urban[a]	4895	39.52	2961	37.29	1934	43.51
	Rural	7490	60.48	4979	62.71	2511	56.49

[a]All residents in municipalities with more than 60,000 inhabitants.

with mania and bipolar disorders (36.9%). Table 1 shows the main demographic characteristics of the population at the time of their first access to the MHD. The regional population contributed 37,292,694 person-years.

3.2 | Proportional mortality for cancer

During the study period there were 1095 deaths for cancer in the study population and 143,311 in the regional population. Among the study population with SMI, 23% of all deaths were due to cancer, a proportion inferior to that of the general population (29.6%; $p < 0.001$), in particular, among patients with schizophrenia spectrum disorders (21.2%, $p < 0.001$), while it was similar among patients with bipolar spectrum disorders (28.6%, $p = 0.725$). When the population was split by gender, the proportion of male patients with schizophrenia spectrum disorders or with bipolar spectrum disorders who died of cancer (21.242%, 18.5% and 26.5%, respectively) was lower than in the male general population (34.2%, $p < 0.001$). On the contrary, among females, the proportion of death by cancer in the SMI population was 25.5%, as in the female general population and the differences were not significant when considering the two subgroups of patients: 23.3% in patients with schizophrenia ($p = 0.339$) and 30.6% in patients with bipolar disorders ($p = 0.124$) (Table 2).

When examining the single cancer diagnoses, trachea, bronchial, and lung cancers were the most frequent cause of cancer death in the regional and in the whole study population. Trachea, bronchial, and lung cancer remained the leading cause of cancer death in female patients with SMI, whereas the leading cause of cancer death in the female regional population was breast cancer. In males, lung cancer was always the first cause, followed by cancers of the stomach in the study population and not by the cancer of the colon, rectum, and anus as in the general population.

Regarding the age of death, there was a higher proportion of deaths in the younger age class among patients with SMI than among the general population. More specifically death at the age 45–64 and 65–74 years was higher ($p < 0.001$ and $p = 0.009$) and the death at the age 75–84 or 85+ was lower ($p = 0.058$ and $p < 0.001$), irrespective of the psychiatric diagnosis (schizophrenia; bipolar disorders) than the general population (Table S2).

3.3 | Standardized mortality ratio for cancer

As reported in Table 3, the all-cause mortality was more than two times higher in patients with SMI than expected from the regional population (SMR 2.13, 95% CI 2.00–2.25). The mortality for cancer was about 50% higher than in the regional population (SMR 1.49, 95% CI 1.31–1.68). The same excess was registered in patients with schizophrenia and other functional psychosis (SMR 1.49, 95% CI 1.27–1.74) and in patients with mania and bipolar affective disorders (SMR 1.5, 95% CI 1.22–1.82). Males show higher excess of mortality than females when considering total mortality (SMR 2.35, 95% CI: 2.15–2.57 vs. 1.97, 95%. CI: 1.81–2.13), but not

TABLE 2 Number of deaths, all causes, all neoplasms, and site-specific neoplasms with % proportion over the total; regional and study population, whole sample and by gender

		Regional population		Severe mental disorders		Schizophrenia and other functional psychosis		Mania and bipolar affective disorders	
Site-specific neoplasms		*n*	%	*n*	%	*n*	%	*n*	%
Total deaths		484,102	100.00	1095	100	745	100	350	100
Total neoplasm		143,311	29.60	258	23.56	158	21.21	100	28.57
	Esophagus	1330	0.27	2	0.18	1	0.13	1	0.29
	Stomach	9149	1.89	18	1.64	10	1.34	8	2.29
	Colon, rectosigmoid, rectum, anus	15,043	3.11	25	2.28	14	1.88	11	3.14
	Liver, gallbladder, biliary tract	9144	1.89	16	1.46	10	1.34	6	1.71
	Pancreas	9834	2.03	17	1.55	13	1.74	4	1.14
	Larynx	996	0.21	1	0.09	0	0.00	1	0.29
	Trachea, bronchus and lung	28,492	5.89	52	4.75	28	3.76	24	6.86
	Melanoma	1413	0.29	1	0.09	0	0.00	1	0.29
	Breast	9610	1.99	22	2.01	12	1.61	10	2.86
	Ovary and other female genital organ	3087	0.64	1	0.09	1	0.13	0	0.00
	Uterus (cervix, corpus, unspecified)	2338	0.48	7	0.64	5	0.67	2	0.57
	Prostate	5694	1.18	7	0.64	5	0.67	2	0.57
	Kidney, pelvis, ureter and unspecified urinary organs	4420	0.91	9	0.82	6	0.81	3	0.86
	Bladder	4962	1.02	6	0.55	4	0.54	2	0.57
	Meninges, brain other parts of CNS	3497	0.72	9	0.82	2	0.27	7	2.00
	Lymphoid, hematopoietic and related lymphoid lymphopoietic, hematopoietic and related tissue	15,316	3.16	18	1.64	12	1.61	6	1.71
Females									
Total deaths		255,264	100.00	596	100.00	416	100.00	180	100.00
Total neoplasm		65,137	25.52	152	25.50	97	23.32	55	30.56
	Esophagus	374	0.15	1	0.17	1	0.24	0	0.00
	Stomach	3949	1.55	4	0.67	3	0.72	1	0.56
	Colon, rectosigmoid, rectum, anus	7095	2.78	15	2.52	8	1.92	7	3.89
	Liver, gallbladder, biliary tract	3738	1.46	9	1.51	4	0.96	5	2.78

(Continues)

TABLE 2 (Continued)

Site-specific neoplasms		Regional population		Severe mental disorders		Schizophrenia and other functional psychosis		Mania and bipolar affective disorders	
		n	%	*n*	%	*n*	%	*n*	%
	Pancreas	5108	2.00	12	2.01	11	2.64	1	0.56
	Larynx	129.00	0.05	0	0.00	0	0.00	0	0.00
	Trachea, bronchus and lung	8669	3.40	25	4.19	15	3.61	10	5.56
	Melanoma	572	0.22	1	0.17	0	0.00	1	0.56
	Breast	9518	3.73	22	3.69	12	2.88	10	5.56
	Ovary and other female genital organ	3087	1.21	1	0.17	1	0.24	0	0.00
	Uterus (cervix, corpus, unspecified)	2338	0.92	7	1.17	5	1.20	2	1.11
	Prostate	0	0.00	0	0.00	0	0.00	0	0.00
	Kidney, pelvis, ureter and unspecified urinary organs	1540	0.60	3	0.50	2	0.48	1	0.56
	Bladder	1268	0.50	3	0.50	1	0.24	2	1.11
	Meninges, brain other parts of CNS	1626	0.64	3	0.50	1	0.24	2	1.11
	Lymphoid, hematopoietic and related lymphoid lymphopoietic, hematopoietic and related tissue	7394	2.90	13	2.18	10	2.40	3	1.67
Males									
Total deaths		228,838	100.00	499	100.00	329	100.00	170	100.00
Total neoplasm		78,174	34.16	106	21.24	61	18.54	45	26.47
	Esophagus	956	0..42	1	0.20	0	0.00	1	0.59
	Stomach	5200	2.27	14	2.81	7	2.13	7	4.12
	Colon, rectosigmoid, rectum, anus	7948	3.47	10	2.00	6	1.82	4	2.35
	Liver, gallbladder, biliary tract	5406	2.36	7	1.40	6	1.82	1	0.59
	Pancreas	4726	2.07	5	1.00	2	0.61	3	1.76
	Larynx	867	0.38	1	0.20	0	0.00	1	0.59
	Trachea, bronchus and lung	19,823	8.66	27	5.41	13	3.95	14	8.24
	Melanoma	841	0.37	0	0.00	0	0.00	0	0.00
	Breast	92	0.04	0	0.00	0	0.00	0	0.00
	Ovary and other female genital organ	0	0.00	0	0.00	0	0.00	0	0.00
	Uterus (cervix, corpus, unspecified)	0	0.00	0	0.00	0	0.00	0	0.00

TABLE 2 (Continued)

Site-specific neoplasms	Regional population		Severe mental disorders		Schizophrenia and other functional psychosis		Mania and bipolar affective disorders	
	n	%	*n*	%	*n*	%	*n*	%
Prostate	5694	2.49	7	1.40	5	1.52	2	1.18
Kidney, pelvis, ureter and unspecified urinary organs	2880	1.26	6	1.20	4	1.22	2	1.18
Bladder	3694	1.61	3	0.60	3	0.91	0	0.00
Meninges, brain other parts of CNS	1871	0.82	6	1.20	1	0.30	5	2.94
Lymphoid, hematopoietic and related lymphoid lymphopoietic, hematopoietic and related tissue	7922	3.46	5	1.00	2	0.61	3	1.76

when considering only cancer related deaths, where females resulted to have higher SMR than males, although the difference was not significant.

An excess in mortality in comparison to the regional population was found for almost all site-specific neoplasms, even if the confidence interval of the estimates mostly included 1 except for some site-specific cancer (Table 3 and Figure 1).

Regarding the respiratory system, there was a significant excess in mortality for trachea, bronchus, and lung cancer in all and in female patients with SMI, in all patients with mania and bipolar affective disorders, and in females with schizophrenia and other functional psychosis (SMR range 1.52–1.85).

As for the gastrointestinal tract, stomach cancer mortality showed an excess in all and males patients with SMI and in males with mania and bipolar affective disorders (SMR range 1.71–3.34).

Cancer of the meninges and the brain was increased in all patients (in male patients with mania and bipolar affective disorders by more than three times), whereas mortality for pancreas cancer was increased only in females with schizophrenia (Figure 2).

4 | DISCUSSION AND CONCLUSIONS

This study examined cancer-related mortality in a well-defined representative population of individuals with SMI living in the community, over a period of 10 years. Our main finding was that cancer-related mortality was higher among patients with SMI, including schizophrenia spectrum and bipolar spectrum disorders, with respect to the general population.

More specifically, as a first result, we showed that the cause of death due to cancer regarded about 25% of deaths in patients with SMI, with a lower proportion amongst males with schizophrenia and higher among females with bipolar spectrum disorders. This is in line with other investigation showing that, as expected, the causes of death among people with SMI can be mainly related to direct complications of the psychiatric disorder itself (e.g., suicide) or indirect complications (e.g., cardiovascular and metabolic side-effects of drugs).[2,3]

Regarding the SMR, however, patients with SMI had a higher excess of cancer mortality in comparison with the general population. This was true both in the female and male populations and both for schizophrenia spectrum and bipolar spectrum disorders. The excess in mortality was significant for some kind of cancers, mainly the gastrointestinal tract (e.g., stomach and pancreas), respiratory system, and the central nervous system (CNS), although a variability according to gender and psychiatric diagnosis was registered.

The data confirm other investigations carried out in large population of patients with schizophrenia showing an increased risk of mortality for many forms of cancer, although not all the studies are in agreement with respect to the cancer site.[7]

TABLE 3 SMR for all causes, all neoplasms and for site-specific neoplasms, whole sample and by gender

		Severe mental disorders			Schizophrenia and other functional psychosis			Mania and bipolar affective disorders		
Site-specific neoplasms		**SMR**	**95% CI**		**SMR**	**95% CI**		**SMR**	**95% CI**	
Total deaths		2.13	2.00	2.25	2.22	2.06	2.38	1.96	1.76	2.17
Total neoplasm		1.49	1.31	1.68	1.49	1.27	1.74	1.50	1.22	1.82
	Esophagus	1.21	0.15	4.38						
	Stomach	1.71	1.01	2.70	1.53	0.73	2.81	2.01	0.87	3.95
	Colon, rectosigmoid, rectum, anus	1.42	0.92	2.09	1.28	0.70	2.14	1.65	0.82	2.95
	Liver, gallbladder, biliary tract	1.46	0.83	2.37	1.59	0.72	2.74	1.41	0.52	3.06
	Pancreas	1.37	0.80	2.20	1.72	0.91	2.93	0.83	0.22	2.13
	Larynx									
	Trachea, bronchus and lung	1.52	1.14	2.00	1.38	0.92	1.99	1.73	1.11	2.58
	Melanoma									
	Breast	1.51	0.95	2.29	1.34	0.69	2.34	1.79	0.86	3.29
	Ovary and other female genital organ									
	Uterus (cervix, corpus, unspecified)	1.96	0.79	4.03	2.28	0.74	5.31			
	Prostate	1.46	0.59	3.00	1.68	0.54	3.91			
	Kidney, pelvis, ureter and unspecified urinary organs	1.79	0.82	3.40	1.93	0.71	4.21			
	Bladder	1.20	0.44	2.62	1.29	0.35	3.30			
	Meninges, brain other parts of CNS	1.79	0.82	3.41				3.47	1.40	7.15
	Lymphoid, hematopoietic and related tissue	0.99	0.59	1.57	1.06	0.55	1.86	0.88	0.32	1.91
Females										
Total deaths		1.97	1.81	2.13	2.04	1.85	2.42	1.82	1.57	2.11
Total neoplasm		1.62	1.37	1.90	1.64	1.65	1.34	1.58	1.19	2.06
	Esophagus									
	Stomach	0.75	0.20	1.92						
	Colon, rectosigmoid, rectum, anus	1.55	0.87	2.55	1.29	0.56	2.54	2.01	0.81	4.15
	Liver, gallbladder, biliary tract	1.72	0.79	3.26	1.20	0.33	3.07	2.64	0.86	6.16
	Pancreas	1.64	0.85	2.86	2.38	1.19	4.26			
	Larynx									
	Trachea, bronchus and lung	1.85	1.20	2.73	1.82	1.02	3.01	1.19	0.91	3.50
	Melanoma									
	Breast	1.52	0.95	2.30	1.35	0.70	2.36	1.80	0.86	3.31
	Ovary and other female genital organ									
	Uterus (cervix, corpus, unspecified)	1.96	0.79	4.03	2.28	0.74	5.31			
	Prostate									
	Kidney, pelvis, ureter and unspecified urinary organs									
	Bladder									
	Meninges, brain other parts of CNS									
	Lymphoid, hematopoietic and related tissue	1.27	0.69	2.17	1.53	0.73	2.81	1.,27	0.69	2.17

TABLE 3 (Continued)

Site-specific neoplasms	Severe mental disorders			Schizophrenia and other functional psychosis			Mania and bipolar affective disorders		
	SMR	95% CI		SMR	95% CI		SMR	95% CI	
Males									
Total deaths	2.35	2.15	2.57	2.49	2.23	2.78	2.12	1.18	2.46
Total neoplasm	1.34	1.10	1.62	1.29	0.99	1.66	1.41	1.03	1.88
Esophagus									
Stomach	2.69	1.47	4.51	2.25	0.90	4.63	3.34	1.34	6.88
Colon, rectosigmoid, rectum, anus	1.26	0.60	2.31	1.26	0.46	2.74	1.25	0.34	3.20
Liver, gallbladder, biliary tract	1.22	0.49	2.51	1.78	0.65	3.88			
Pancreas	0.99	0.32	2.30						
Larynx									
Trachea, bronchus and lung	1.31	0.86	1.90	1.08	0.57	1.85	1.63	0.89	2.73
Melanoma									
Breast									
Ovary and other female genital organ									
Uterus (cervix, corpus, unspecified)									
Prostate	1.46	0.59	3.00	1.68	0.54	3.91			
Kidney, pelvis, ureter and unspecified urinary organs	2.05	0.75	4.46	2.28	0.62	5.84			
Bladder									
Meninges, brain other parts of CNS	2.54	0.93	5.52				5.18	1.68	12.00
Lymphoid, hematopoietic and related tissue	0.64	0.21	1.48						

Abbreviations: CI, confidence interval; SMR, standardized mortality ratio.

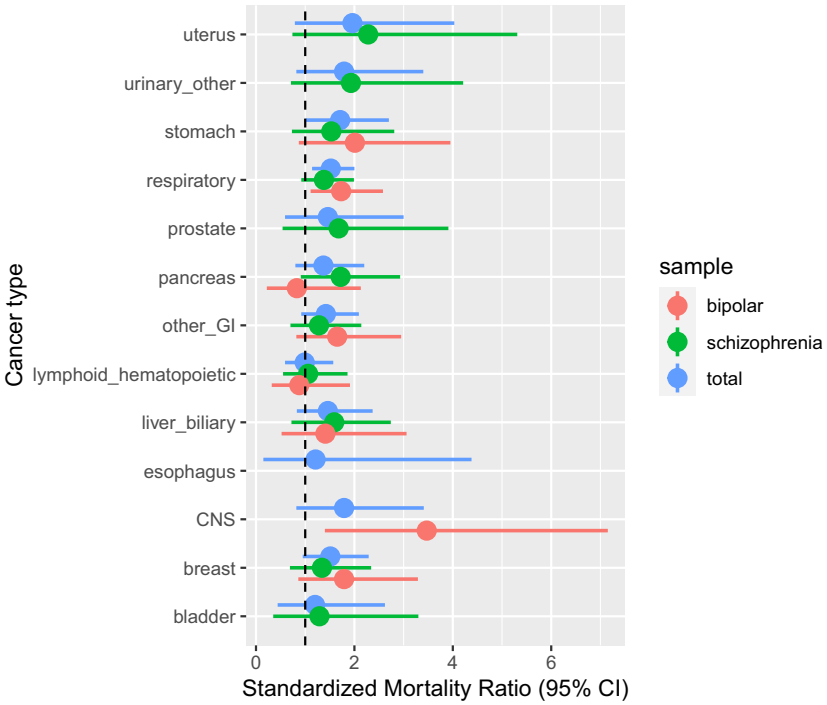

FIGURE 1 Standardized mortality ratio for different cancers by psychiatric diagnosis

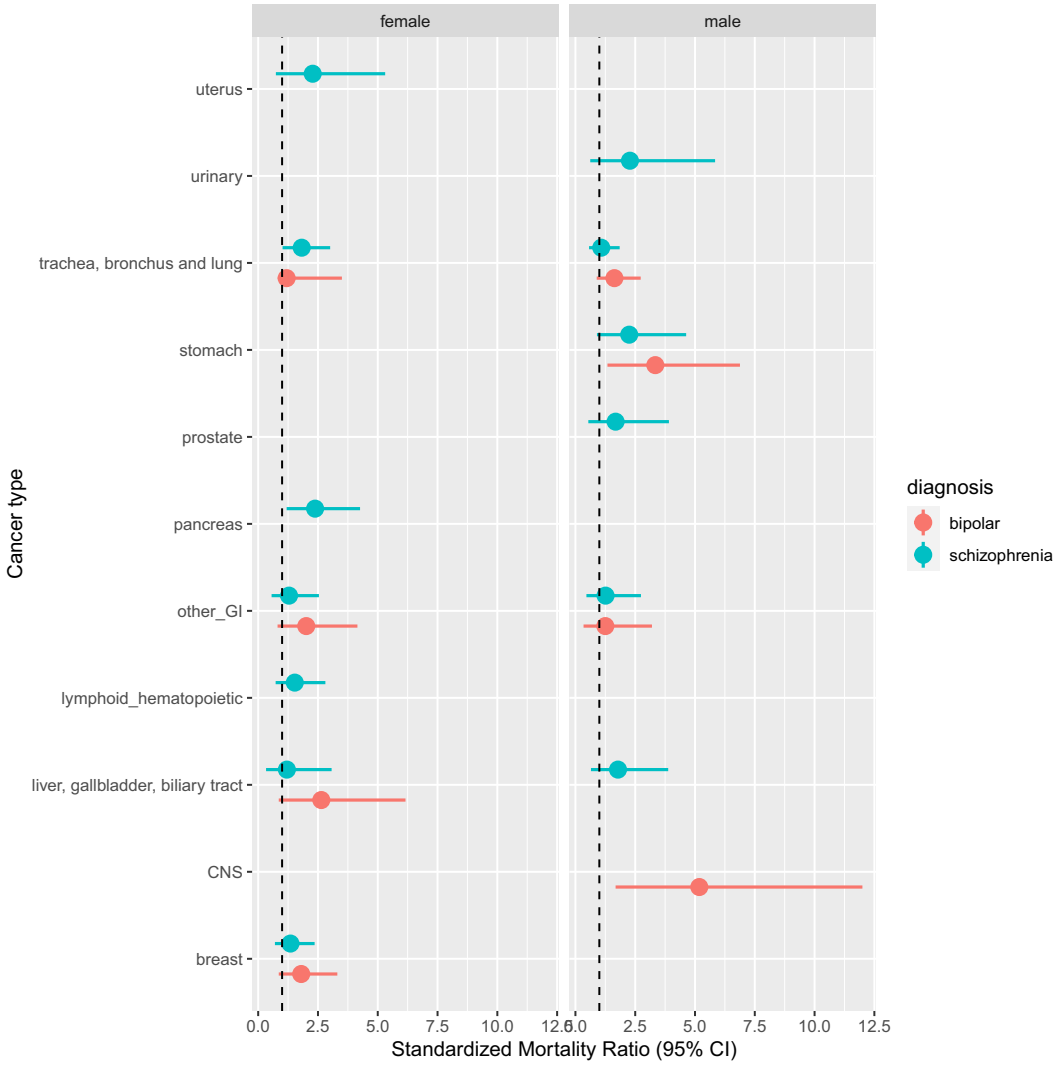

FIGURE 2 Standardized mortality ratio for different cancers by gender and psychiatric diagnosis

As far as bipolar spectrum disorders are concerned, we also found an increased risk for some types of cancer, in contrast with other studies that showed a similar trend with the general population.[36]

The explanation of why patients with SMI have a higher risk of mortality for cancer in comparison with the general population is not easy. Many factors have been postulated as possible causes of these findings in other studies. For example, a less likelihood to participate to cancer screening programs have been demonstrated both in patients with schizophrenia and bipolar disorders.[37,38] This can have determined a diagnosis of cancer in advanced stages because of less chances for patients to receive adequate screening programs,[39] as well as a lower likelihood to receive specialized interventions after diagnosis, including surgery, radiotherapy, or chemotherapy.[40,41]

In our study we noted a significant excess in mortality for some kind of tumors such as lung, stomach, and pancreas cancers that evidence proved to be more or less attributable to lifestyles risk factors like smoking, diet, or alcohol use. In fact, unhealthy lifestyles such as lacking of good nutrition[42] and physical activity,[43] as well as smoking[44,45] and alcohol abuse[46] are largely prevalent among people with mental disorders and might partly explain the elevated risk of dying from these types of cancer.

In contrast, it is less easy to explain the excess in mortality for brain tumors in patients with SMI. Although it is well known that psychotic symptoms can emerge in patients with brain tumors,[47] other studies showed a lower risk (e.g., glioma) in patients with SMI (e.g., schizophrenia).[48] Since we do not have information about the possible role of brain tumors in causing SMI in our sample, more research is necessary to explore this relationship.

We did not observe a significant difference in risk of mortality for the groups of neoplasms that included cancers such as breast, colorectum, and cervix cancer whose prognosis is related to screening attendance. Mortality for these cancers is higher than in the general population but the difference in not significant. This finding could be due to the small number of patients that limits the robustness of the

estimates. In addition, the lack of significant differences in mortality for these cancers could be ascribed to the attention devoted to screening activities in the ER Region. Some studies underlined that screening programs could be effective in reducing inequalities in survival after the diagnosis of some cancer, breast cancer in particular, at least where they are characterized by high coverage and by a free facilitated care pathway for screened positive subjects.[49]

In our study, we could not examine these specific issues and further research is needed to evaluate, as done in other studies, cancer-risk behavior of patients with SMI, their participation to cancer screening programs, and the quality and characteristics of cancer care.

In conclusion, the study in a large population of the Italian ER Region indicated a higher mortality among patients with SMI with respect to the general population. Importantly, our results are representative for the people with SMI in the Region, since most, if not the totality of them, are in fact taken care by the Regional Health Trust DMH, which includes a series of different mental health services (e.g., outpatient clinics, rehabilitation and day-care facilities, inpatient psychiatric units). Although the different organizational system do not allow to make correct comparison with studies carried put in other countries (e.g., United Kingdom, United States), examining the same field of mortality in SMI, our data confirm the problem of lower survival caused by cancer when patients have a severe psychiatric condition, such as schizophrenia or bipolar disorders.

5 | STUDY LIMITATIONS

The results of our study should be weighed considering various limitations, which warrant discussion. A first limitation is that we examined mortality of people of one of wealthiest Italian regions, with an advanced and efficient regional health system, and a policy of integration between primary care and mental health.[50] Therefore, our results cannot be generalized to the whole country. Also, our cohort was entirely composed of people resident in the region and this theoretically could have caused an underestimation of mortality since non-resident or homeless people may be prone to higher mortality. However, the proportion of persons excluded as not being resident is low (about 1% of the caseload). In spite of the fairly long time span of the study, for some site-specific cancers, the number of events was very small, leading to estimates with relatively large confidence interval requiring confirmation in larger studies.

6 | CLINICAL IMPLICATIONS

The most important clinical implication of the study is related to the need for more attention to this vulnerable segment of the population affected by SMI. Both community healthcare providers, such as primary care physicians, and mental health professionals should be aware of difficulties in the pathway to care. With respect to this, models of improving the healthcare system have been proposed, including the enhancement of cancer screening rate and early detection of cancer for patients with SMI. Activation of public health services, promotion of healthy behavior (e.g., smoking cessation programs and services, given the high rate of mortality for lung cancer) and healthy lifestyles (e.g., dietary habits, physical exercise) for this vulnerable population, via specific campaigns involving both mental health, psychosocial oncology and oncology departments, is mandatory.[51,52] Therefore, physical health related to cancer risk, diagnosis, and treatment should be an essential component of intervention in psychiatry, in order to favor the access to health services which, in turn, facilitates longer term benefits, such as reduced morbidity and mortality.[52,53]

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CONFLICT OF INTERESTS

All the authors declare that they have no conflict of interest related to the work described in their manuscript. LG received grants from Eisai and Angelini and royalties from Springer, Wiley, and Oxford University Press.

ETHICS STATEMENT

The study was approved by the local Ethical Committee (N. 341/2019). All records in the Mental Health Register were anonymized.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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