

Lessons from end-of-life care among schizophrenia patients with cancer: a population-based cohort study from the French national hospital database

Running title: End-of-life care among patients with schizophrenia and cancer

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Abstract

Background. Patients with schizophrenia (SZ) are a vulnerable, underserved and undertreated population which has been neglected in health disparities work. We have little understanding of the end of life (EOL) care in patients with a diagnosis of SZ and cancer. The objective of the study was to determine whether EOL care delivered to SZ patients with cancer (cases) differed from those delivered to patients without diagnosis of mental illness (controls).

Methods. A population-based cohort study of all patients ≥ 15 years who died in hospital in France (2013-2016) and had a diagnosis of advanced cancer was undertaken (n=398,913). Within this cohort, cases and controls were selected and the following key outcomes were compared: access to palliative care and indicators of high-intensity EOL care. Multivariable generalized linear models were performed with adjustment for social deprivation, year of death, duration between cancer diagnosis and death, metastases, comorbidity and hospital category.

Findings. The study included 2481 SZ patients and 222,477 controls. SZ patients were more likely to receive palliative care (adjusted Odds Ratio 1.61 [1.45;1.80], $p < 0.0001$) and less high-intensity EOL care (*e.g.*, chemotherapy 0.53 [0.46;0.62], $p < 0.0001$; surgery 0.71 [0.63,0.80], $p < 0.0001$) than controls. The SZ patients were also more likely to die younger, had a shorter duration between cancer diagnosis and death, more thoracic cancers and comorbidities.

Interpretation. The differences between SZ patients and controls suggest the existence of disparities in health and health care. These findings underscore the need for a better understanding of health inequalities to propose effective interventions in this vulnerable population.

Keywords. High intensity end-of-life care, palliative care, cancer, schizophrenia, health services research.

Research in context

Evidence before this study. Three databases (Medline, Web of Science and Google Scholar) were explored using the following paradigm based on the Mesh search words of Medline: “end-of-life” AND “cancer” AND “schizophrenia” between inception and March 2019. Previous works on end of life (EOL) in schizophrenia (SZ) patients with cancer are rare and reported contradictory findings. Few qualitative studies alerted on the risk of SZ patients for receiving poor quality EOL care, but their small sample sizes question the generalizability of findings. The only three quantitative studies on this issue are based on relatively dated data (before 2012 for the most recent study) with alternatively a lack of palliative care, similar or better EOL care and similar access to palliative care with more frequent invasive treatments but less chemotherapy and examinations. There are no recent quantitative studies exploring EOL care in SZ patients with cancer. Nationwide observational studies are necessary to provide objective and recent data on EOL care patients with SZ and then to provide a basis for improving their EOL.

Added value of this study. This study was carried out on recent data at a national level with more than 200,000 death of cancer at hospital between 2013 and 2016. This study provided new data on EOL on a large population of patients with SZ and cancer (n=2481). Compared with the patients without diagnosis of mental illness, the SZ patients died 8 years earlier, had a higher level of comorbidities, more thoracic cancer, less metastases, a shorter duration from cancer diagnosis to death and more specialty center care. They were also less deprived. After matching and adjustment, they were found to have more palliative care and less high-intensity EOL care.

Implications of all the available evidence. Patients with SZ may benefit from a better EOL care (*i.e.*, more palliative care and less high-intensity care) than their controls. The meaning of this finding may be discussed, resulting from either patients’ and families’ wishes or difficulties in offering early and relevant cancer care to SZ patients. Several striking characteristics of the SZ patients in this work (*e.g.*, earlier age of death, higher level of comorbidities, shorter duration from cancer diagnosis to death) suggest the existence of disparities in health and health care. Caring for an individual with SZ and cancer requires

knowledge and expertise in both oncologic and psychiatric issues, and may call for better education training of health care professionals and care coordination/integration.

Introduction

Cancer is a leading cause of death worldwide. With earlier detection of cancer and significant progress in treatments and supportive care in recent years, the survival and quality of life of cancer patients have improved greatly. However, not all cancer patients benefit equally from these advances. Racial minorities, low socio-economic status, lack of medical insurance, residence in remote areas, elderly age, and mental illnesses are all factors that may affect cancer treatment, survival, and care quality ¹. Among mental illnesses, patients with schizophrenia (SZ) are one of the most vulnerable, underserved and undertreated population ^{2,3} which has been neglected in health disparities work and cancer health services research ⁴. SZ is associated with a marked decrease in life expectancy, approximately 14 years on average, essentially due to accidents, suicide and physical illnesses including cancer. Compared to patients without diagnosis of mental illness, SZ patients suffers from an increased delay in diagnoses and lower rates of adapted care due to both physician- (stigma, diagnostic overshadowing) ^{5,6} and patient- (insight into illness, help seeking) related factors, observations that are being reported around the world. SZ patients have been specifically reported to have a 1.5- to 4-fold higher cancer mortality ^{4,7-9} and lower rates of cancer screening exams ¹⁰. While most of the studies have focused on the debate over an increased or decreased risk of cancer incidence in SZ, only a few have explored end-of-life (EOL) care in patients with a diagnosis of SZ and cancer.

Palliative care is an approach that improves the quality of life of patients and their families who are coping with problems associated with life-threatening illness ¹¹. Such improvement is made through prevention, assessment, and treatment of pain and other symptoms and the provision of psychological, emotional, and spiritual support. Palliative care is patient and family centered and emphasizes patient autonomy and advance planning for care ¹². Patients become eligible for palliative care delivered by a hospice organization at the point they are expected to have less than six months of remaining life. Cure of the terminal illness is no longer being pursued. Most previous works on EOL and cancer were performed in population without diagnosis of mental illness with two major concerns about poor-quality EOL care ¹²⁻¹⁵: (i) lack of referral or late referral to palliative care unit; (ii) high-intensity EOL care (Hi-EOL) resulting in high rates of emergency department (ED) visits, intensive care unit (ICU) stays, overuse of chemotherapy and all potentially life-prolonging interventions near death. In addition to well-known barriers to optimal EOL care (*e.g.*,

inadequate advance care planning, lack of communication between professionals and patients or their natural caregivers, poor health literacy, uncertainty about imminence of death)^{14,16,17}, some barriers may specifically affect patients with SZ such as stigma and common stereotypes regarding mental illnesses and the personal factors of the patients such as persecutory delusion and attribution bias, memory and attention impairments, avolia/lack of motivation, hostility, impaired autonomy, social withdrawal and increased isolation/poor social support in the end of life^{3,5}. EOL care is optimized when patients and their families participate in determining goals of care, yet half of SZ patients have impairments in decision-making capacity and when incapacitated, frequently lack surrogate decision makers¹⁸.

Previous works on EOL in SZ patients with cancer are rare and reported contradictory findings. Few qualitative studies alerted on the risk of SZ patients for receiving poor quality EOL care, but their small sample sizes question the generalizability of findings¹⁹. The only three previous quantitative studies are based on relatively dated data (before 2012 for the most recent study) with alternatively a lack of palliative care²⁰, similar or better EOL care¹⁸ and similar access to palliative care with more frequent invasive treatments but less chemotherapy and examinations²¹. There are no recent quantitative studies exploring EOL care in SZ patients with cancer. Nationwide observational studies are necessary to provide objective and recent data on EOL care patients with SZ and then to provide a basis for improving their EOL.

The objective of this study was to determine whether the EOL care delivered to SZ patients with cancer differed from those delivered to patients without diagnosis of mental illness.

Methods

Study design and data source

This is a population-based cohort study of all patients aged ≥ 15 years who died from cancer in the hospital in France between January 1, 2013, and December 31, 2016. The study was based on the French national hospital database (Programme de Médicalisation des Systèmes d'Information (PMSI)), in which administrative and medical information is systematically collected for acute (PMSI-MCO) and psychiatric (PMSI-PSY) care. This information is anonymized and can be reused for research purposes¹⁵. The PMSI is based on diagnosis-related groups, and all diagnoses are coded according to the International Classification of Diseases, Tenth Revision (ICD-10). The selection process, inclusion and exclusion criteria are presented in the **Figure 1**.

From this selection, we defined 3 populations:

- 1) Cases: The SZ patients were patients with a SZ diagnosis according to the specific ICD codes (F20*, F22*, F25*) in the PMSI-MCO database and/or in the PMSI-PSY database.
- 2) Controls: The patients without diagnosis of mental illness were patients from the PMSI-MCO database without psychiatric conditions according to the specific ICD codes (chapter F*) and without admission in psychiatry (PMSI-PSY).
- 3) Matched controls: Cases and controls were matched using a 1:4 ratio according to 3 criteria: age at death (+/- 2 years), sex and primary cancer localization (15 modalities).

Outcome measures

The different outcomes are based on previously defined criteria^{12,17} and are presented in **Table 1**.

Appendix Table A1 lists the specific codes used for each outcome.

Collected data

Six sociodemographic, clinical or hospital characteristics were collected due to their potential impact on the EOL care of patients.

- Social deprivation assessed by an index validated on French data and based on the postal code of the domicile²². The FDep09 index involves four socioeconomic ecological variables: percentage of high-school graduates, median household income, percentage of blue-collar workers and the unemployment rate. The FDep09 index was categorized according to quartiles, from the least (Q1) to the most deprived area (Q4).

- year of death (as the EOL practice may have evolved throughout time as mentioned in the rationale);
- duration from cancer diagnosis to death;
- comorbidities assessed using the Charlson modified Comorbidity Index²³ (computed from ICD-10 codes recorded as primary or secondary diagnoses over the course of the last 3 months of life, excluding dementia and the 2 items referring to cancer, *i.e.*, metastatic solid tumor and malignancy);
- metastasis (ICD-10 codes C78 and C79) (as a metastasis diagnosis may accelerate palliative care admission);
- hospital category (at last hospitalization before death).

Statistical analysis

The analyses were conducted in 2 steps.

First, comparisons between cases and controls (unmatched populations) were performed for sociodemographic, clinical and hospital data: Chi-square tests or Student's t tests according to the nature of the variable (step 1).

Second, comparisons between cases and matched-controls were performed using univariate conditional logistic regressions for binary outcome measures and univariate generalized mixed models with log-normal distribution for quantitative outcomes. Then, we performed as many multivariate analyses as outcomes to analyze the association between the groups (cases/ matched-controls) and each outcome. Six confounding factors were included in the models: social deprivation (4 categories/quartiles from the most favored (Q1) to the most deprived area (Q4)), year of death (4 categories: 2013 to 2016), duration between cancer diagnosis and death (days), metastases (yes/no), Charlson modified comorbidity index (3 categories: 0, 1 or 2, ≥ 3 comorbidities) and hospital category (2 categories: specialty for cancer vs. nonspecialty centers). These analyses were performed with a multivariable generalized linear model with the matched cluster as a random intercept using the PROC GLIMMIX in SAS (step 2). For quantitative data, the response distribution was lognormal and the identify link function was used. For binary data, the response distribution was binomial and the logit link function was used. To assess goodness-of-fit of the models, we reported the ratio between the Pearson Chi-square statistic and its degrees of freedom. Multiple comparison corrections (false discovery rate) were performed.

The statistical analysis was performed with SAS 9.4 (SAS Institute). Statistical significance was defined as $p < 0.05$.

Role of the funding source

This work was funded by AP-HM (Assistance Publique des Hôpitaux de Marseille) and Aix-Marseille University. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Overall, 3,361,043 patients with cancer were identified in France between 2013 and 2016. Among them, 398,913 deaths (11.9%) were identified during this period, and 224,958 (6.7%) were finally included in this study after removing dementia and psychiatric diagnoses other than schizophrenia (Flow chart **Figure 1**). A total of 2481 patients were defined as SZ patients (cases) and compared to 222,477 patients without diagnosis of mental illness (controls) (step 1). A total of 2,474 SZ patients were then matched with their 9,896 controls (7 SZ patients were excluded in the matching process due to the absence of matched controls) (step 2).

1) Comparison between cases and controls

Compared to controls, SZ patients were found (**Table 2**):

- to die younger and to be less deprived. No statistically significant difference was found with respect to sex;
- to have a shorter duration from cancer diagnosis to death;
- to have more thoracic, central nervous system, respiratory system and less digestive and male genitalia cancers;
- to have a more frequent comorbidities, including more peripheral vascular disease, hemiplegia or paraplegia, mild liver disease, HIV/AIDS, chronic pulmonary disease and less congestive heart failure;
- to have more specialty center care for the last hospitalization.

2) Comparison between cases and matched controls

In addition to the abovementioned differences, SZ patients were found to have lower metastases than their matched controls in the univariate analyses (**Table 3**).

In the multivariate analysis, SZ patients were found (**Table 4**)

- to have more frequent palliative care unit admissions in the last 31 days of life and in the last 3 days of life and a longer length of palliative care follow-up before death;
- to have less chemotherapy, surgery, imaging, endoscopy and blood transfusion ;
- to be less likely to be admitted to an air extraction chamber, to an acute care unit with longer LOS and to have fewer deaths in the ICU/ED.

All the Pearson Chi-Square/DF values were lower than 1, except for the duration between cancer diagnosis and death which was greater than 1 but in an acceptable range (1.47). **Appendix Table A2** lists the Pearson Chi-Square/DF values for each model.

Discussion

The present findings may be summarized as follows: between 2013 and 2016, 2481 patients with SZ and cancer died in French hospital care. Compared with patients without diagnosis of mental illness, the SZ patients died 8 years earlier, had a higher level of comorbidities, more thoracic cancer, less metastases, a shorter duration from cancer diagnosis to death and more specialty center care. They were also less deprived. After matching and adjustment, they were found to have more palliative care and less Hi-EOL care.

Our study cannot determine with certainty why there is a discrepancy in EOL outcomes for SZ vs. control patients. However, as described in recent works ³, the differences found in our work between SZ patients and controls suggest the existence of disparities in health and health care.

SZ patients were found to die 8 years younger from cancer than controls, which is consistent with higher level of comorbidities found in the present results and in previous studies suggesting a reduced life expectancy in SZ patients due to somatic causes and comorbidities ²⁴. These frequent and multiple somatic comorbidities may negatively influence the prognosis of cancer: modifications and complexity of cancer treatment, the

necessity of close collaboration with primary care providers which may be insufficient in advanced psychiatric disease, and poorer survival. Models of integrated care for people with severe mental disorders and somatic comorbidities should be further developed in France, before cancer occurrence and during cancer care.

In our study, SZ patients died more frequently of tobacco-related cancers, whereas schizophrenia was not associated with an increased risk of lung cancer incidence in the general population²⁵. This suggests that tobacco-related cancers may be more lethal in this specific population, which had been already found in a previous French cohort study in the 1990s⁸. SZ patients may have delayed cancer diagnosis and may present with a more severe form of cancer⁴, as suggested by the shorter duration from cancer diagnosis to death. Barriers to lung cancer care has been also reported for SZ patients⁴. SZ has been extensively associated with high rates of hard tobacco smoking. Thirty-percent of the French general population is currently identified as engaging in daily tobacco smoking vs. 52% of SZ outpatients who have high rates of severe nicotine dependence²⁶; furthermore, more than two-thirds of excess deaths due to natural causes in SZ patients are due to smoking-related diseases²⁷. A higher lifetime tobacco smoking dose-effect as well as failing to quit smoking after a cancer diagnosis may increase thoracic cancer mortality in this population. Smoking cessation programs and cancer screening should be reinforced to prevent thoracic cancer and to improve cancer prognosis.

SZ patients were found to have lower rates of metastases compared to their matched controls, suggesting a difference in cancer stages at first contact with oncology team. An early identification of cancers in SZ patients seems unlikely in light of our experience and the literature²⁸. More likely, patients may benefit less from complementary explorations than the controls, as suggested by their lower rates of imaging exams in the last month of life. Another hypothesis may be that SZ patients may be more likely to die from their primary local cancer before the development of metastases due to a lack or delayed treatment initiation. If this hypothesis was confirmed, a better cancer screening for SZ patients based on specific and targeted approaches is necessary.

Patients with SZ were preferentially found in specialized centers, suggesting a lack of contact with secondary (*i.e.*, non-specialty centers) and primary care (*i.e.*, family physician) previously described in France²⁹.

Unexpectedly, patients with SZ were less deprived than controls while severe mental disorders have been extensively associated with low socio-economic level. Deprived patients with SZ may be more prone to die earlier from other causes of mortality including cardiovascular diseases, addictions and unnatural causes of deaths (including trauma and self-attempt). Social deprived SZ patients who die from cancer may also have a lower access to EOL care compared to the most favored ones. A lack of social support in the elderly with SZ (*e.g.*, due to parents' aging and divorce) may be more pronounced in deprived populations, leading to a rupture with the healthcare system, lack of cancer diagnosis and cancer care, adherence issues and lost to follow-up/deaths outside the hospital ³⁰.

SZ patients did not benefit from the same care as their matched controls in our study. SZ patients had more palliative care, which was not expected according to the results of previous studies ¹⁸⁻²¹. This result appears to be coherent with the lesser amount of high-intensity care provided to SZ patients: less chemotherapy, surgery, imaging, endoscopy, fewer blood transfusions. Less chemotherapy and imaging were previously reported in a study based on the Taiwanese national database ²¹. In contrast, this same study found that more surgery was performed in SZ patients than in patients without diagnosis of mental illness ²¹. Three levels of explanations can be proposed ⁴.

On the provider level, treating physicians may be more prone to switch to palliative care in patients with severe mental illness, given that providing treatments with a high risk of toxicity and with strict administration protocols may be more difficult in patients with lower treatment adherence and cognitive impairment. This explanation may also be a reason for the lower rates of chemotherapy in our sample. SZ patients also appear to experience a higher rate of postoperative complications, including respiratory failure, sepsis, deep venous thrombosis, pulmonary embolism, paralytic ileus, stroke, and postoperative delirium ³¹, which may explain the lower rate of surgery considering the unfavorable benefit-risk balance. SZ Individuals may be excluded from making decisions about their EOL care in part due to provider concerns about their emotional fragility and competence ³². These results may also reflect mental illness stigma and diagnostic overshadowing (*i.e.*, inadequate or delayed treatment on account of the misattribution of their physical symptoms to their mental illness) described in previous works ^{5,6}.

On the patient level, the lower rates of high-intensity care may be due to SZ patients' hostility toward treatment, which may be associated with a higher risk of violence (hostility/paranoid delusion, psychomotor agitation)⁴. A previous study has also found that SZ patients may more frequently document do not resuscitate orders than patients without diagnosis of mental illness¹⁸.

On the health system level, palliative care units have been designed to manage complicated situations (including lack of social support/isolation, homelessness and impaired autonomy that may interfere with each step of cancer care)^{4,33}, which may explain the longer length of follow-up in SZ patients in palliative care units in our study.

Limitations. These results should be taken with caution as only deaths were analyzed in the present study. Another study should determine the cancer mortality rates in SZ patients compared to matched controls and should explore the whole cancer care of SZ patients. Data on psychiatric symptomatology and psychotropic drugs were not available in the database and have not been explored. Our work only describes advanced cancer patients who died in hospitals, which may restrict the generalizability of our findings to less advanced cancer and patients who died at home. However, only 3% of patients died at home and 13% died in nursing homes in 2013 in France³⁴. It should be mentioned that people receiving hospital palliative care died more frequently in the hospital compared to people not receiving such care; however, our patients were matched to their controls according to their age at death, sex and primary cancer localization, and the results were adjusted for social deprivation, year of death, duration between cancer diagnosis and death, metastases, Charlson modified comorbidity index and hospital category, which strengthens our results.

Strengths. The strength of this study is the analysis of a 4-year national database of more than 200,000 deaths from cancer in France. It is the largest epidemiological study performed in the field of EOL in SZ patients to date. We used a dedicated method of patient selection, which has been validated by the French National Institute for Cancer (INCA).

Conclusion

Patients with SZ may benefit from a better EOL care (*i.e.*, more palliative care and less high-intensity care) than their controls. The meaning of this finding may be discussed, resulting from either patients' and families' wishes or difficulties in offering early and relevant cancer

care to SZ patients that may lead providers to orientate them more quickly toward palliative care units. Several striking characteristics of the SZ patients raise questions about their quality of care. Caring for an individual with SZ and cancer requires knowledge and expertise in both oncologic and psychiatric issues, and may call for better education training of health care professionals and care coordination/integration. These findings underscore the need for a better understanding of health inequalities to propose effective interventions in this vulnerable population.

Declaration of interest

We declare no competing interest.

Authors' contribution.

GF and LB wrote the first draft of the manuscript. VP and VO carried out the selection process and the statistical analyses. All authors have reviewed the final manuscript.

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