Cancer comortality patterns in schizophrenia and psychotic disorders: a new methodological approach for unique databases

VLADETA AJDACIC-GROSS,^{1,2} ALOIS TSCHOPP,² MATTHIAS BOPP,² FELIX GUTZWILLER²
& WULF RÖSSLER^{1,3}

1 Research Unit for Clinical and Social Psychiatry, Psychiatric University Hospital, Zurich, Switzerland

2 Institute of Social and Preventive Medicine, University of Zurich, Switzerland

3 Collegium Helveticum, Joint Research Institute of the University of Zurich and the Swiss Federal Institute of Technology, Zurich, Switzerland

Key words

schizophrenia, psychosis,
cancer, mortality, bootstrapping

Correspondence

Vladeta Ajdacic-Gross, Research
Unit for Clinical and Social
Psychiatry, Psychiatric University
Hospital, Militärstrasse 8/PO
Box 1930, CH-8021 Zurich,
Switzerland.
Telephone (+41) 44 2967433
Fax (+41) 44 2967449
Email: vajdacic@dgsp.uzh.ch

Received 8 February 2012;
revised 8 June 2012;
accepted 12 July 2012

Abstract

The aim of this study was to determine the pattern of cancer comortality in deaths registered with schizophrenia and psychotic disorders. It focused on the question of whether the proportions of different types of cancer diverge when they are co-registered with schizophrenia/psychotic disorders or with other causes of death in mortality statistics. We developed an analysis approach applicable to common mortality statistics data when no linkage with morbidity databases or other registers is possible. The analysis covered Swiss mortality data from a 39-year period (1969–2007) and was confined to the most frequent cancers. We applied a two-step case-control analysis with bootstrapping (1000 repetitions). The cases were defined by the cancer-schizophrenia registrations for each specific cancer, whereas the controls were matched from the remaining cases (matching criteria: sex, age, region, subperiod). Cancers with deviant standardized mortality ratios (SMRs) included stomach cancer (1.6; 2.2 after reweighting), lung cancer (0.8; 0.5 after reweighting) and breast cancer (1.6; 1.5 after reweighting). The comortality pattern of cancers in schizophrenia and psychotic disorders diverges from the pattern found in other co-registered causes of death. The relatively low frequency of lung cancers is particularly paradoxical in view of the smoking habits of schizophrenia patients. Copyright © 2014 John Wiley & Sons, Ltd.

Introduction

In general, the research results on the co-occurrence of cancer and schizophrenia have been extraordinarily conflicting. The overall incidence of cancer (Bushe and Hodgson, 2010) but also the incidence of specific cancers such as breast

cancer (Bushe *et al.*, 2009) was reported as being higher, the same, or lower, depending on the population and, above all, the methodology of the study. This made some authors believe that “a single definitive study of schizophrenia and cancer is unfeasible” (Bushe and Hodgson, 2010).

In this study we introduced a new methodological approach. The study explored the comortality patterns of the most frequent cancers in deaths with schizophrenia/other psychoses co-registration in mortality statistics. It examined whether the proportions of the most frequent cancers co-registered with schizophrenia and other psychoses differ from the corresponding proportions found in overall cancer mortality. While other studies in this field have either followed a cohort of patients and controls over a long-time period or relied on linkage of mortality and morbidity data bases, this study used a bootstrapping approach applicable to a unique large data base such as mortality data.

Analysing comortality is not a straightforward task. The proportions of specific causes of death, for example, specific cancers, typically differ by sex and age when different (sub)samples are compared. Moreover, the pattern(s) is (are) influenced by biasing factors such as the regional registration and co-registration practices. However, there are also more implicit factors that may interfere and introduce bias:

- the registration priority of psychiatric or other chronic diseases;
- the probability that a chronic or psychiatric disease is known or obvious to the physician filling in the death certificate, which depends on the characteristics of the respective disease (or group of diseases);
- the co-registration practice in specific cancers or within specific subspecialties in oncology: this depends on the affinity between the cancer and the chronic or psychiatric disease (for example, the probability of psychiatric disorders being co-registered is greater in brain cancers than in intestinal cancers).

In this study we introduced a two-step analysis design, thereby applying in each step a case-control approach within a bootstrapping procedure. The case-control approach served to account for the demographic and biasing factors, which may be supposed to influence the co-registration of cancer and schizophrenia/other psychoses in the mortality statistics. In the first step, we assessed preliminary co-registration patterns and adjusted them for the most obvious biasing factors. In the second step we weighted the figures in order to account for the co-registration practice in specific cancers. Bootstrapping served in each of these two steps to determine the parameters of interest.

The analysis covered Swiss mortality data from a 39-year period (1969 – 2007). The comparisons were confined to the most frequent types of cancer.

Data and methods

Legally regulated, formalized death registration has existed in Switzerland since 1876, with deaths being certified by a physician. Data from individual records is available in computerized form starting from 1969. Switzerland used the ICD-8 (International Classification of Diseases, 8th revision) coding system until 1994 and then switched to ICD-10 coding in 1995. Since 1995 the maximum number of registered causes of death has also been increased from three to four, thus changing the probabilities for the co-occurrence of diseases.

The analyses were restricted to records with malignant neoplasms as the underlying cause of death (ICD-8 140-209, ICD-10 C00-C97) with at least one additional or concomitant cause of death (labelled in the following as the “overall cancer sample”). The latter restriction was introduced to account for the heterogeneous lethality of cancers. If a psychiatric disease was listed in these records, it thus necessarily appeared in one of the additional cause of death categories.

In the first step of the analysis we extracted records from the overall cancer sample with a specific psychiatric disease registered as one of the additional causes of death. We matched them 1:1 with randomly selected controls from the overall cancer sample along the following criteria:

- sex
- age (five-year age groups)
- region (German part versus French and Italian part of Switzerland)
- period (1969 – 1981, 1982 – 1994, 1995 – 2007)

Other variables such as marital status, religious affiliation or autopsy status were not considered relevant enough within the given context and were not included in the criteria. In sum, the first step of the analysis provided the preliminary proportions of specific cancers from both the case and control subsets and delivered preliminary parameters.

In the second step of the procedure we calculated weighting coefficients in order to account for the registration practice specific for each cancer type. It is plausible that the probability of co-registering brain diseases may vary mainly due to the focus of the oncology subspecialty. We derived the weighting coefficients by comparing the co-registration frequency of psychiatric diseases (ICD-8 290-319, ICD-10 F00-F99) within a specific cancer as opposed to the overall cancer sample. The former delivered the cases and the latter the controls for this calculation. Both were drawn randomly from the

specific cancer sample and the overall cancer sample, respectively. The basis for drawing these cases and controls was the sample profile adapted from the first step of the analysis and, of course, the same matching criteria as mentioned earlier. The weighting coefficients were used to correct the co-occurrence frequencies from the first step of analysis.

In order to receive stable figures we applied bootstrapping, that is, we performed 1000 runs of the two-step procedure. Bootstrapping returned, in this instance, 1000 values for the parameters of interest, which, for the sake of simplicity, can be handled by univariate statistics.

Our parameter of interest was, apart from the standardized mortality ratio (SMR), the chi-square used when comparing a sample frequency with a population frequency. The mean and confidence intervals of the chi-squares were assessed using univariate statistics and the empirical 0.01 limits. Moreover, we assumed consistent SMRs both in the preliminary calculation and after correction. SMRs derive from comparing observed mortality with the expected mortality. A SMR is defined as a quotient: number of observed deaths (or rates)/number of expected deaths (or rates).

Results

In the period 1969–2007, 608,865 cases with malignant neoplasms were registered in the Swiss mortality statistics, with 580,570 (95.4%) reporting cancer as a main cause of death, and 398,246 cases (65.4%) reporting an additional cause of death. For schizophrenia and other psychotic disorders, there were 17,014 registered cases in the period 1969–2007, with 1063 (6.2%) of them registered as the main cause of death. The combination “cancer as the main cause of death and schizophrenia or other psychotic disorders as additional cause of death” was registered in 1738 cases.

Table 1 displays the frequencies, the overall SMRs and the bootstrapping results of the specific cancers co-registered with schizophrenia/psychotic disorders. Given the selection criteria (0.01-significance level both in the preliminary calculation and after correction, consistent SMRs), cancers of the stomach (SMR = 1.61 and 2.20 after correction) and breast (SMR = 1.56 and 1.5) show an increased risk relative to other cancers, whereas lung cancer shows a decrease (SMR = 0.81 and 0.51).

Discussion

The most popular research question in this field has been whether people with schizophrenia and other psychoses have a higher overall risk of cancer than the rest of the

population (Hodgson *et al.*, 2010). This study focused on a more specific issue, the comortality of different cancers in schizophrenia/psychosis versus the comortality in other causes of death. It introduced a new methodological approach in order to compare the proportions of specific cancers within a target condition (schizophrenia/psychosis) with their proportions in the reference condition (i.e. overall cancer mortality) within a unique database. The results showed that stomach cancer and breast cancer were co-registered with schizophrenia and psychotic disorders more frequently than expected, whereas lung cancer was co-registered less frequently than expected. In detail, the risk increase in breast cancer was 50–56%, and the risk decrease in lung cancer was 19–39%, depending on whether a correction factor was adopted in the analysis. In contrast to other studies, we also found an increase of risk in stomach cancers (61–120%), but no increase in colon cancers.

The results identified in our study are in line with the results from other studies with respect to breast and lung cancer. Despite some heterogeneous results, major reviews (Bushe *et al.*, 2009; Bushe and Hodgson, 2010; Catts *et al.*, 2008) have indicated an increased risk of breast cancer, whereas a decreased risk of lung cancer was concluded, in particular when adjustment for smoking was introduced.

The list of putative causal factors determining either an increase or a decrease in cancer risk in schizophrenia/psychosis entails smoking, substance misuse, exercise, diet, treatment effects, hyperprolactinaemia, obesity, birth order, and other obstetric factors (Hodgson *et al.*, 2010). The most paradoxical and challenging finding is the low risk in lung cancer, given that patients display distinctly high smoking prevalence rates (Catts *et al.*, 2008). The risk excess in breast cancer may be partly explained by the higher proportion of nulliparous women in patients with schizophrenia/psychosis (Oksbjerg Dalton *et al.*, 2003).

Methodological issues

Our study has two major methodological differences with regard to other studies in this field. Firstly, we introduced an approach which is applicable to a unique large data base such as mortality data, whereas other studies have either followed a cohort of patients and controls over a long time period, or relied on a linkage of mortality and morbidity databases. Secondly, the methodology used in this study does not allow for comparisons of rates, either overall cancer rates or rates of specific cancers, with the rates in the population. This is the price of analysing a unique database.

Table 1. Bootstrapping results for the most frequent cancers in schizophrenia/psychotic disorders

Malignant neoplasms	ICD-8	ICD-10	N	Baseline				With correction			
				SMR	Chi ² boot-strapped	Chi ² ICI-uCI	SMR	Chi ² boot-strapped	Chi ² ICI-uCI	SMR	Chi ² boot-strapped
Lip, oral cavity, pharynx	140-9	C00-14	27	0.71	4.03	3.72-4.35	0.33	18.05	17.43-18.70		
Stomach	151	C15	156	1.61	34.29	32.78-35.8	2.20	147.77	137.22-158.31		
Intestines, colon, rectum	152-4	C17-21	176	0.88	3.67	3.32-4.02	1.23	24.92	21.01-28.85		
Liver	155	C22	35	0.76	3.49	3.18-3.80	0.94	1.96	1.68-2.23		
Pancreas	157	C25	69	0.77	5.19	4.80-5.58	1.25	12.32	10.23-14.41		
Trachea, bronchus, lung	162	C33-4	228	0.81	9.58	9.01-10.14	0.51	73.76	71.15-76.37		
Melanoma	172	C43	22	1.15	1.42	1.17-1.68	1.64	9.98	8.74-11.22		
Breast	174	C50	281	1.56	42.13	40.62-43.6	1.50	51.84	44.06-59.62		
Cervix uteri, uterus	180-2	C53-5	72	1.06	1.16	0.97-1.35	1.19	8.63	6.92-10.35		
Ovary	183	C56	68	1.06	1.22	1.01-1.44	1.85	66.54	57.60-75.49		
Prostate	185	C61	88	1.04	1.05	0.89-1.20	2.32	216.80	188.30-245.30		
Bladder	188	C67	49	1.04	1.11	0.93-1.29	0.96	2.05	1.76-2.34		
Brain	191	C71	30	0.81	2.26	2.03-2.50	1.12	2.27	2.22-3.17		
Lymphomas	200-2	C81-5	40	0.63	9.43	8.93-9.93	1.19	7.84	6.63-9.05		
Leukemias	204-9	C91-5	40	0.52	18.33	17.66-19.00	1.26	12.31	10.33-14.30		

There are several methodological issues which should be considered in order to disentangle the conflicting results of earlier studies and which have also consequences within the context of this study. The first and most natural observation is that the frequencies do matter. Large databases are preferable, although some studies used relatively small patient samples (Barak *et al.*, 2008). Beyond this commonplace, there is a more subtle configuration of methodological differences:

- Opposite results in lung and breast cancer (risk increase in lung cancer, risk decrease in breast cancer) or insignificant results may be found in prospective studies which start with schizophrenia/psychosis samples and limit the age range either by a predefined range of birth years and/or the duration of the follow-up (Goldacre *et al.*, 2005; Lichtermann *et al.*, 2001; Oksbjerg Dalton *et al.*, 2003).
- However, similar results were reported by studies which are based on large samples (Dalton *et al.*, 2005), optionally start with a cancer sample (Hippisley-Cox *et al.*, 2007), and in any case cover a long period or a large number of person-years, respectively.

As a consequence of different samples and follow-up durations the two groups differ most markedly regarding the age profiles that underlie the co-occurrence or comorbidity of cancer and schizophrenia/psychosis. Opposite results occur in “younger samples”, while similar results occur in “older samples”.

Similar conclusions have been drawn by Bushe *et al.* (2009) in their review on breast cancer incidence in schizophrenia. Studies with large cohorts (>100,000 persons/person-years) tend to report greater incidence rates of breast cancer in women with schizophrenia. Furthermore, age plays an important role: the higher the age of the subjects, the higher are the rates of breast cancer.

Limitations

The methodological approach of this study deals with the proportions of cancers when comparing two subsamples from the mortality statistics (e.g. a sample with schizophrenia/psychosis co-registrations versus a sample with co-registrations of other causes of death or no co-registrations).

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Since this approach is limited to the comparison of the proportions, it provides no information about the rates. Thus, conclusions about cancer rates in schizophrenia as compared with cancer rates in the general population are not justified.

The further limitations of this study are those of register data. In particular, mortality data entails only the most important demographic information besides the causes of death, but, for example, no information about medical and pharmacological treatment. The information about the main cause of death and additional causes relies on distinct registration priorities for the diseases of interest. While cancers have a high priority and are typically entered as main causes of death in the mortality statistics, mental disorders are typically registered as additional causes and are underreported. We would expect that patients with severe forms of schizophrenia/psychosis are less underreported than patients with less severe forms.

Pragmatically, the selection of matching criteria for the case-control analysis is limited by the variables available in the mortality statistics. Lacking matching criteria, which might have improved the analysis, would have included more detailed information, particularly about schizophrenia and other psychoses (for example, source of the diagnosis, comorbidity with other mental disorders, pharmacological treatment).

Another type of limitation is associated with the long-term window included in this study, which entails a change in classification systems (ICD-8 to ICD-10), but also more subtle changes in diagnostic habits and registration practices. Eventually, their biasing effect was only partly absorbed by the actual matching criteria.

Acknowledgements

This study was supported by the Swiss National Science Foundation (grant #32-042345.94/1). The data was extracted from the Swiss mortality records with authorization granted by the Swiss Federal Statistical Office in Neuchâtel, Switzerland.

Declaration of interest statement

The authors have no competing interests.

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