Original Article

Cancer Mortality in Patients With Schizophrenia

An 11-year Prospective Cohort Study

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BACKGROUND: Schizophrenia has been associated with a rate of premature mortality that is 2 to 3 times higher than that in the general population. Although the role of cancer in this excess mortality remains unclear, previous incidence or mortality studies found contradictory results. **METHODS:** In 1993, a large prospective study was initiated in a cohort of 3470 patients with schizophrenia to examine cancer-related mortality and predictors. Standardized mortality ratios (SMRs) were calculated, adjusting for age and sex relative to a representative sample of the French general population. **RESULTS:** During the 11-year follow-up, 476 (14%) patients died; the mortality rate was thus nearly 4-fold higher than in the general population. Cancer was the second most frequent cause of mortality (n = 74), with a global SMR of 1.5 (95% confidence interval [95% CI], 1.2-1.9). For all cancers, the SMRs were 1.4 (not significant) for men and 1.9 (95% CI, 1.4-2.8) for women. For men, lung cancer was the most frequent localization (n = 23; 50%), with an SMR of 2.2 (95% CI, 1.6-3.3). For women, breast cancer was the most frequent localization (n = 11; 39%), with an SMR of 2.8 (95% CI, 1.6-4.9). In comparison with patients who did not die of cancer, there were 2 significant baseline predictors of death by lung cancer in the final logistic regression model: duration of smoking and age >38 years. **CONCLUSIONS:** The results of the current study demonstrated an increased risk of mortality by cancer in patients with schizophrenia, especially for women from breast cancer and for men from lung cancer. **Cancer 2009;115:3555–62. © 2009 American Cancer Society.**

KEY WORDS: cancer, mortality, schizophrenia, standardized mortality ratio.

Schizophrenia is a psychotic disorder affecting approximately 1% of the general population and involving severely impaired thinking, emotions, and behavior. Since the introduction of the chlorpromazine in 1952, antipsychotic drugs have greatly improved the treatment of schizophrenia symptoms. Nevertheless, schizophrenia is a not curable illness, with a chronic course characterized by recurrences and remissions. Although some individuals with schizophrenia regain their premorbid functioning, most experience evidences functional disability, with social and relational repercussions.[1]

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Schizophrenia is associated with a higher rate of premature mortality than observed in the general population; excess mortality is 2 to 3 times higher and the life expectancy is 20% shorter.[2-6] Moreover, the mortality gap between the general population and patients with schizophrenia has widened in recent decades.[6] Suicide, which is the main cause of this excess mortality, is nevertheless not sufficient to explain this excess.[7] In addition, schizophrenic patients suffer higher rates of somatic illnesses, in particular metabolic syndrome and cardiovascular diseases.[8,9]

Epidemiologic data regarding cancer prevalence in patients with schizophrenia are somewhat contradictory. In early studies, the incidence of cancer among patients with schizophrenia was found to be lower than in the general population.[10-12] Several explanations of this finding have been proposed, including a putative protective effect of some drugs[13] and protective genetic factors.[14,15]

Subsequent incidence and mortality studies report contradictory results, with higher,[5,14,16] equivalent,[17-19] or lower[7,20] rates of cancer among schizophrenic patients than the general population, depending on the study. For instance, in their meta-analysis based on 37 studies that investigated mortality in schizophrenia in comparison with the general population, Saha et al[6] found a median standardized mortality ratio (SMR) >1 (SMR = 1.37), but 1 of the lowest median SMRs in comparison with other causes of death. Moreover, studies of cancer in people with schizophrenia are methodologically heterogeneous and the majority were retrospectively designed.

Nevertheless, it would be valuable to determine more precisely the prevalence of cancer in patients with schizophrenia to improve prevention and early detection, thereby reducing the subsequent excess mortality. Therefore, in 1993, we initiated a large prospective epidemiologic study in a cohort of patients with schizophrenia to examine cancer-related mortality and predictors. One of our aims was to identify predictors of death by cancer.

MATERIALS AND METHODS

Setting

All French public departments of adult psychiatry (n = 829) were invited to participate in the study. A total of 122 (14.7%) departments throughout the French territory agreed to participate and recruit patients. Patient inclusion began in January 1993 and lasted 3 months; all schizophrenic patients attending participating departments either as inpatients or as outpatients during this period were considered for inclusion in the study.[21] Because of the yearly basis of assessment of patient deaths, it was necessary to restrict the inclusion period to 3 months, permitting a single yearly contact with the public psychiatric departments participating in this study.

Subjects

Male and female patients, ages 18 to 64 years at the time of inclusion, were required to fulfill the criteria of the International Classification of Diseases, 10th edition (ICD-10), for schizophrenia.[22] To ensure a more homogeneous population, patients with schizoaffective disorders were not included. Moreover, to allow more relevant comparisons with the general population control group, in particular regarding primary care access, we did not include patients hospitalized for prolonged periods (>1 year). The study was approved by the local research ethics committee. All participants received detailed information regarding the study and provided written consent.

A total of 3470 patients were included, with a mean number of patients, by site, of 28.4 (range, 3–116 patients). Foreign patients born outside France were excluded from the analysis because it was not possible to contact the town hall at their place of birth to validate the cause of death (n = 36).

Assessments

Data collected at inclusion using a standardized questionnaire were the following: demographics; physical health status (height, weight, and body mass index [BMI]were collected, taking into account the frequency of weight gain and obesity in patients with schizophrenia); smoking status (if smoking, number of cigarettes smoked per day and since when); and alcohol use, as determined from the 4-item CAGE questionnaire,[23] which has been validated for schizophrenic subjects[24] (the CAGE questionnaire includes 4 items: 1) "Have you ever felt you should cut down on your drinking?" 2) "Have people annoyed you by criticizing your drinking?" 3) "Have you ever felt bad or guilty about your drinking?" and 4) "Have you ever had a drink first thing in the morning to steady your nerves or

to get rid of a hangover?"); illicit drug use during the previous 12 months (if yes, which drug[s]); age at first hospitalization for schizophrenia; subtype of schizophrenia (according to ICD-10 criteria); antipsychotic medication at inclusion (name and dosage of drugs); and degree of mental suffering as assessed by the psychiatrist according to a 4-point scale (absent, moderate, great, and extreme). Baseline demographic and clinical characteristics of these schizophrenic patients have been presented in a previous article addressing mortality by suicide in this cohort.[21] Among the 3434 patients, 64% were men and the mean age ± the standard deviation was 39.3 ± 11.3 years.

Participating psychiatric departments were contacted on a yearly basis to ascertain whether the patients had died. The end date of follow-up was December 31, 2003. For patients known to have died, the town clerk of the town of birth was contacted to confirm the death. For patients lost to follow-up, the town halls of their places of birth were contacted to retrieve the life status and causes of death. Consequently, there were no missing data relating to mortality over the 11-year follow-up period. The date and cause of death were retrieved from the national death certificate where appropriate. The ninth edition of the ICD (ICD-9)[25] was used to code and input the causes of death into the database. We systematically asked the investigators about circumstances and causes of patients' deaths; as a consequence, we recoded some cases with undetermined causes of death (according to the national death certificate), if the cause was known by the investigator. This was the case, over the 11 years of follow-up, for a total of 42 cases initially classified as undetermined causes of death. SMRs were calculated on this basis and adjusted for age and sex relative to the general population.

Statistical Analysis

Sex-specific cancer mortality rates were compared with equivalent rates for a representative sample of the French general population from a survey by INSEE-CREDES (ICS) in 1991.[26] SMRs were calculated for female subjects, male subjects, and all subjects to determine the frequency of death caused by cancer in the study population compared with that in the general population.

Baseline variables were analyzed by Kaplan-Meier survival analysis for overall cancers and more specifically, for lung and breast cancers. The age cutoff value (38 years) was the median of the ages at inclusion of the 3434 patients included.

In a second step, variables selected by univariate analysis were used to investigate potential risk factors with hazards ratios generated by Cox proportional hazards regression.[27] For these models, the specific candidate predictor variables considered were as follows: sex, age, BMI, smoking status, smoking duration, number of cigarettes smoked per day, alcohol use (as determined by the CAGE questionaire), duration of illness, hospitalization in a physical health unit within the 6 months before inclusion, and antipsychotic treatments. For the multivariate analyses, among these variables, we only considered those presenting a univariate P value $<.2$. The multivariate models were generated for all cancers, lung cancer, and breast cancer, using a backward stepwise procedure. For all cancers and lung cancer, analyses were performed on both male and female patients, whereas for breast cancer, we limited the analysis to female patients. Explanatory variables were retained in the final model if the P value was $<.1$.[28]

Statistical computations were performed using SAS (version 8.0) software (SAS Institute Inc, Cary, NC)

RESULTS

During the 11-year follow-up, 476 (13.9%) patients died: 143 (4.2%) patients died of suicide, 74 (2.2%) of cancer, 70 (2.0%) of cardiovascular disease, 86 (2.5%) of other natural causes, 56 (1.6%) of unknown causes, and 47 (1.4%) of accidental or nonsuicidal poisoning. The rate of death was significantly higher in the schizophrenic group than in the general population, with an SMR for all causes of death of 3.6 (95% confidence interval [95% CI], 3.3-3.9) for men and of 4.3 (95% CI, 3.7-5.1) for women. Cancer, with 74 deaths, was the second most common cause of death after suicide, with 46 deaths due to cancer in men and 28 in women.

The respective SMR for cancer overall and the different localizations of cancer are presented in Table 1. For all cancers, the mortality rate was significantly higher for schizophrenic patients than for the general population in the whole sample and in women, but not in men. Lung cancer was the most frequent localization in schizophrenic men (n = 23; 50.0%). Mortality rates due to cancer in

Table 1. Standardized Mortality Ratios and 95% Confidence Intervals According to Tumor Location

Parameter	Total (n=74)				Men (n=46)				Women (n=28)			
	Expected	Observed	SMR	95% CI	Expected	Observed	SMR	95% CI	Expected	Observed	SMR	95% CI
All cancer	48.7	74	1.5	1.2-1.9	34.0	46	1.4	NS	14.7	28	1.9	1.4-2.8
Lung	12.6	26	2.1	1.5-3.0	10.6	23	2.2	1.6-3.3	2.0	3	1.5	NS
Breast	4.0	11	2.8	1.6-4.9	–	–	–	–	4.0	11	2.8	1.6-4.9
Colon	2.3	5	2.2	NS	1.5	1	0.7	NS	0.8	4	5.0	2.1-12.0
ENT	0.9	4	4.4	1.9-11.0	0.8	4	5.0	2.1-12.0	0.1	0	–	–
Stomach	1.3	3	2.3	NS	1.0	1	1.0	–	0.3	2	6.7	2.0-22.0
Pancreas	2.1	3	1.4	NS	1.5	2	1.3	NS	0.6	1	1.7	NS
Brain	1.4	3	2.1	NS	1.0	2	2.0	NS	0.4	1	2.5	NS
Lymph	1.2	2	1.7	NS	0.5	2	2.5	NS	0.4	0	–	–
Other digestive	0.3	2	6.7	2.0-22.0	0.2	2	10.0	3.3-30.6	0.1	0	–	–
Bladder	0.8	2	2.5	NS	0.7	2	2.9	NS	0.1	0	–	–
Uterus	0.8	2	2.5	NS	–	–	–	–	0.8	2	2.5	NS
Ovary	0.9	2	2.2	NS	–	–	–	–	0.9	2	2.2	NS
Testicle	0.1	1	10.0	2.1-49.0	0.1	1	10.0	2.1-49.0	–	–	–	–
Blood	1.6	1	0.6	NS	1.0	1	1.0	–	0.6	0	–	–
Prostate	0.7	1	1.4	NS	0.7	1	1.4	NS	–	–	–	–
Liver	2.2	1	0.5	NS	1.9	1	0.5	NS	0.3	0	–	–
Skin	0.6	1	1.7	NS	0.4	0	–	–	0.2	1	5.0	NS
Not determined	8.6	4	0.5	NS	6.4	3	0.5	NS	2.2	1	0.5	NS

SMR indicates standardized mortality ratio; 95% CI, 95% confidence interval; NS, not significant; ENT, ear, nose, and throat.

schizophrenic men were significantly higher than those in the general male population for lung, ear-nose-throat (ENT), testicle, and 'other digestive' localizations. Breast cancer was the most frequent localization in schizophrenic women (n = 11; 39.2%), and mortality rates due to cancer were higher for schizophrenic women than for the general population of women for breast, colon, and stomach.

We compared the baseline demographic and clinical characteristics of schizophrenic patients who died from cancer with those of the rest of the cohort (Table 2). Univariate analysis involving survival analyses found that the baseline variables that were significantly correlated with overall cancer mortality in schizophrenic patients were as follows: age >38 years at the time of inclusion ($P = .0001$), being a smoker ($P = .047$), duration of smoking of >5 years ($P = .016$), benzamide prescription ($P = .02$), hospitalization in a nonpsychiatric unit within the 6 months before inclusion ($P = .09$), disease duration of >10 years at inclusion ($P = .0005$), and 1 positive response in the CAGE questionnaire ($P = .039$). For lung cancer, baseline variables significantly associated with mortality were as follows: being a man ($P = .007$), age >38 years at inclusion ($P = .0002$), disease duration of >10 years ($P = .013$), being a smoker ($P = .0002$), smoking >10 cigarettes per day ($P < .0001$), duration of smoking of >5 years ($P < .0001$), and 1 positive response in the CAGE questionnaire ($P = .001$). For breast cancer, baseline variables significantly associated with mortality were as follows: age >38 years at inclusion ($P = .005$) and smoking >10 cigarettes per day ($P = .02$).

Baseline characteristics selected by univariate analysis were analyzed with the Cox proportional hazards regression models for lung cancer and for breast cancer, respectively (Table 3). The multivariate model identified 2 baseline variables as significant independent risk factors for lung cancer mortality in schizophrenic patients: age at inclusion ($P = .04$) and number of years of tobacco consumption ($P < .0001$). It identified only 1 baseline variable as a significant independent risk factor for breast cancer mortality in schizophrenic patients: age at inclusion ($P = .0004$).

DISCUSSION

At the end of the 11-year follow-up, the mortality rate in our sample of patients with schizophrenia, including all

Table 2. All Cancer, Lung Cancer, and Breast Cancer: Survival Analysis (Log-rank Test)

	All Cancer (n=74)		Lung Cancer (n=26)		Breast Cancer (n=11)	
Characteristic	No. (%)	*P*	No. (%)	*P*	No. (%)	*P*
Sex						
Male	46 (62.2)	.85	23 (88.5)	.007	0 (0)	—
Female	28 (37.8)		3 (11.5)		11 (100)	
Age at inclusion, y						
≤38	10 (13.5)	<.0001	4 (15.4)	.0002	1 (9)	.005
>38	64 (86.5)		22 (84.6)		10 (91)	
BMI						
≤24	39 (53.4)	.50	17 (65.4)	.11	4 (36.4)	.38
>24	34 (46.6)		9 (34.6)		7 (63.6)	
Smoking						
Smoker	50 (67.5)	.047	24 (92.3)	.0002	5 (45.4)	.47
No smoker	24 (32.5)		2 (7.7)		6 (54.6)	
Smoking duration, y						
≤5	27 (36.5)	.02	3 (11.5)	<.0001	7 (63.6)	.40
>5	46 (62.1)		23 (88.5)		4 (36.4)	
Cigarettes per d						
≤10	35 (47.3)	.11	4 (15.4)	<.0001	10 (91)	.02
>10	39 (52.7)		22 (84.6)		1 (9)	
Duration of disease, y						
≤10	22 (29.7)	.0005	7 (27)	.01	3 (27.3)	.11
>10	50 (67.5)		19 (73)		8 (72.7)	
CAGE						
At least 1 item positive	22 (27.7)	.039	12(46.15)	.0011	2 (18.2)	.84
No item positive	52 (70.3)		14 (53.85)		9 (81.8)	
Hospitalization in a physical health unit in the 6 mo before inclusion						
Hospitalization	12 (16.2)	.009	4 (15)	.15	0	.32
No hospitalization	62 (83.8)		22 (85)		11 (100)	
Antipsychotics						
≤2	69 (93.2)	.90	22 (85)	.07	11 (100)	.37
>2	5 (6.7)		4 (15)		0	
Benzamides						
Yes	3 (4)	.02	24 (92.3)	.40	0	.20
No	71 (96)		2 (7.7)		11 (100)	
Phenothiazines						
Yes	44 (40.5)	.92	19 (73)	.14	6 (54.6)	.76
No	30 (59.5)		7 (27)		5 (45.4)	

BMI indicates body mass index.

causes of death (natural causes, accidental causes, and suicide), was nearly 4-times higher than that in the general population. Measured as numbers of cases, cancer was the second most common cause of death in our sample of schizophrenic patients, after suicide, and before cardiovascular disease. The SMR for the risk of death by cancers overall was 1.5-times higher than that for the general population. This SMR is similar to the SMR of 1.4 reported by Saha et al in a meta-analysis of 37 studies.[6]

However, the SMR of death due to all cancers was significantly higher for women but not for men. This is in accordance with most previous mortality studies. In the study by Mortensen and Juel,[16] cancer mortality was significantly lower in male schizophrenic patients than in the

Table 3. Results of the Backward Stepwise Logistic Regression (Proportional Hazards Model) for All Cancer, Lung Cancer, and Breast Cancer

Predictive Variable	Hazards Ratio (95% CI)	*P*
All cancer		
Smoking	2.59 (1.55–4.32)	.0003
Age at inclusion (>38 y)	1.09 (1.0–1.11)	<.0001
Hospitalization in a physical health unit in the 6 mo before inclusion	1.78 (0.93–3.40)	.08
Treatment with benzamides	0.37 (0.12–1.17)	.09
Lung cancer		
Age at inclusion (>38 y)	2.77 (1.06–7.18)	.04
Duration of smoking, y	1.07 (1.04–1.11)	<.0001
BMI (>24)	2.29 (1.01–5.16)	.05
One positive CAGE response	2.20 (0.99–4.87)	.05
Breast cancer		
Age at inclusion (>38 y)	1.09 (1.04-1.15)	.0004

95% CI indicates 95% confidence interval; BMI, body mass index.

general male population (SMR, 0.85; 95% CI, 0.76-0.94), whereas it was significantly higher in female patients than in the general female population (SMR, 1.17; 95% CI, 1.06-1.28). Osby et al[17] also found that the SMR of death due to all cancers was only significantly increased in women (SMR, 1.3; 95% CI, 1.1-1.5). The same tendency, although not significant, was found by Saku et al[18] in a sample of 2268 patients with schizophrenia, with SMRs of death due to all cancers of 0.8 and 1.4 for male and female patients, respectively. This is also consistent with the results of the meta-analysis by Brown,[7] who found a significantly lower SMR in schizophrenic males (SMR, 0.9; 95% CI, 0.78-0.93) and nonsignificantly higher SMR (1.1) in females. In view of the sex distribution of cancer locations, this over-mortality due to cancer in schizophrenic women may suggest that breast cancer in schizophrenic women may be more often misdiagnosed and/or worse treated than lung cancer in schizophrenic men. Two explanations can be proposed: first, some symptoms of lung cancer, such as cough, may be more easily detected than signs of breast cancer by medical staff or family, allowing earlier treatment thereby improving outcome; second, lung cancers affecting schizophrenic patients may more often be histologic types with less severe prognosis and a more favorable course. No data are available for assessing this possibility.

The risk of death due to lung cancer in male patients with schizophrenia in our sample was significantly higher than that in the general population (SMR, 2.2; 95% CI, 1.6-3.3). Conversely, Mortensen[12] and Mayfield et al[23] found a lower rate of death due lung cancer in their sample of schizophrenic patients. Osby et al[17] also found a lower than reference SMR in males for lung cancer, although the difference was not statistically significant (SMR, 0.73; 95% CI, 0.4-1.3). Possibly, these findings are consequences of both a protective effect of the hospital environment (schizophrenic patients had less opportunity to smoke) and some neuroleptic drugs having a protective effect against lung cancer. Smoking has been restricted in Danish and Swedish hospitals for longer than in France, and this may at least partly explain the difference in mortality rate due to lung cancer between our study and that of Mortensen and Juel[16] In our study, the proportion of patients who were smokers was significantly higher than in the general population (56.3 vs 33.0%, respectively; $P < .001$). This agrees with the recent meta-analysis by Catts et al[19] who found that the incidence of lung cancer in patients with schizophrenia was significantly higher (standardized incidence ratio [SIR], 1.31; 95% CI, 1.01-1.71) than in the general population, but that it was not after adjusting for smoking prevalence (SIR, 0.69); this suggests that smoking is the main factor explaining the high prevalence of lung cancer in schizophrenia patients.

Our multivariate analysis identified only 2 baseline variables that were significant independent risk factors for lung cancer in schizophrenia patients: age and number of years of tobacco consumption. This result suggests that the risk factors for lung cancer associated with schizophrenia are the same as those in the general population. We did not find any specific protective factor for lung cancer in schizophrenia; in particular, antipsychotics did not appear to be a protective factor against death due to cancer at this location. Mortensen suggested that neuroleptic treatment reduced the risk of developing cancer.[29,30] However, at least 2 arguments oppose this possibility: first, the reduced cancer incidence was apparent before the patients' first hospital admission when they were unlikely to have had substantial exposure to antipsychotic medication[20]; and second, a recent in vitro study showed that antipsychotic medications at therapeutic doses do not have antitumor effects.[31]

In female schizophrenic patients, the risk of death due to breast cancer was significantly higher than in the general population. One possibility, as suggested above, is

a delay in diagnosis due to a less attention by the patient to her somatic symptoms, such as alarm symptoms of breast pathology, and the difficulty for schizophrenic patients to benefit from optimum treatment; compliance to treatment may also be worse among such patients than in the general population. In a meta-analysis of incidence studies, Catts et al found that the breast cancer rate was significantly higher in female patients (SIR, 1.12; 95% CI, 1.02-1.23).[19] One explanation put forward by these authors was that nonsmoking risk factors are more prevalent in female patients. For example, nulliparity, obesity, poor diet, and hyperprolactinemia related to antipsychotic medication exposure are all more prevalent in female patients and potentially increase the risk of breast cancer. This agrees with the finding of univariate analyses that benzamide prescription at inclusion was a risk factor for death due to cancer, hyperprolactinemia being frequently associated with these neuroleptics. Nevertheless, in the multivariate analysis, we identified only 1 baseline variable that was a significant independent risk factor for breast cancer: age.

In male schizophrenic patients, the mortality rate due to ENT, testicle, and digestive system cancers was significantly higher than in the general population, but these results have to be interpreted with caution because of small numbers of cases for these 3 cancers. Similarly, in women with schizophrenia, the SMRs were significantly high for stomach and colon cancers, but again very small numbers of patients were involved.

The main strength of our study is its prospective design, with a period of follow-up of 11 years. This appears to be the optimal approach to assessing mortality and its causes. Nevertheless, to our knowledge, few prospective studies of mortality due to cancer in schizophrenic patients have been published to date. Another strength is the substantial sample size, with >3400 schizophrenic patients initially included in the study. In addition, to improve the validity of the causes of death data, we systematically asked each investigator about the circumstances in which patients had died. Consequently, we recoded the cause of death for some cases that had been coded as undetermined on the national death certificate.

The major limitation of our study is applicable to all mortality studies: mortality rates are not direct reflections of cancer incidence because unobserved delays in diagnosis and differences in ease of access to optimal treatment can differ between groups and affect the mortality rates. The second limitation is the absence of histologic data, limiting the interpretation of higher mortality rates associated with cancers at some locations. The third limitation concerns the impact of antipsychotic drugs, and more precisely the absence of prospective assessment of treatment changes during the follow-up period. Another limitation is that all potential explanatory factors were not exhaustively assessed at baseline. Indeed, various social factors can contribute to explaining the higher cancer mortality rate in schizophrenic patients than in the general population. The continuing cultural stigma associated with schizophrenia can lead to barriers to access to medical care for these patients and may also contribute to diagnostic or treatment delays.

In conclusion, the results of the current study confirm that more schizophrenic women but not men die of cancer than would be expected by reference to the general population. Lung cancer is the most frequent cause of death by cancer in men and breast cancer in women. Further studies should be conducted and the histologic type of the cancers investigated. Our results also emphasize the importance of detecting somatic disease in schizophrenic patients. It appears essential for psychiatrists to be attentive to the medical care of schizophrenic patients and to evaluate their compliance to therapy for somatic disease.

Conflict of Interest Disclosures

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