ORIGINAL ARTICLE

# Incidence of Cancer Among Persons With Schizophrenia and Their Relatives

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**Background:** It has repeatedly been reported that the risk for cancer in patients with schizophrenia is different from that of the general population, specifically a lower risk for lung cancer despite increased smoking. Confirmation of these associations could lead to hypotheses on shared risk or protective factors, either genetic or environmental.

**Methods:** From Finland's National Hospital Discharge and Disability Pension registers, Helsinki, we identified a cohort of 26 996 individuals born between 1940 and 1969 and treated for schizophrenia between 1969 and 1991. They were followed up for cancer from 1971 to 1996 by record linkage with the Finnish Cancer Registry, yielding 446 653 person-years at risk, and standardized incidence ratios (SIRs) were calculated. Likewise, 39 131 parents and 52 976 siblings of the patients with schizophrenia were followed up to explore familial genetic hypotheses on deviations in cancer risk.

**Results:** In patients with schizophrenia, an increased overall cancer risk was found (724 cases observed vs 619 expected; SIR, 1.17; 95% confidence interval [CI], 1.09-1.25). Half of the excess cases were attributable to lung cancer (SIR, 2.17; 95% CI, 1.78-2.60), and the strongest relative increase in risk was in pharyngeal cancer (SIR, 2.60; 95% CI, 1.25-4.77). Cancer incidence in siblings (SIR, 0.89; 95% CI, 0.83-0.94) and parents (SIR, 0.91; 95% CI, 0.89-0.93) was consistently lower than that in the general population.

**Conclusion:** Although specific lifestyle factors, particularly tobacco smoking and alcohol consumption, probably account for the increased cancer risk in patients with schizophrenia, the decreased risk in relatives would be compatible with a postulated genetic risk factor for schizophrenia offering selective advantage to unaffected relatives.

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NUMEROUS reports have suggested that the rates of physical illness differ between patients with schizophrenia and the general population. Although most evidence must be regarded as anecdotal,[1] some observations deserve further study, among them a decreased incidence of lung cancer,[2,3] which is counterintuitive given the increased rate and intensity of smoking among individuals with schizophrenia.[4] In genetic terms, the hypothesis is attractive that a schizophrenia vulnerability gene would simultaneously decrease the risk of lung cancer, despite heavy exposure to the strongest known environmental risk factor: tobacco smoke.

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Proportionate mortality studies of schizophrenia and cancer risk are biased in favor of lower cancer risk estimates because of the high rate of suicide associated with schizophrenia. On the other hand, patients with schizophrenia in permanent institutional care might have easier access to diagnostic screening measures or more regular postmortem examination than in the control population, thereby leading to an overestimate of cancer incidence. A well-designed, population-based, 3-center cohort study[5] found a decreased risk of lung cancer in patients with schizophrenia. A lower-than-expected incidence of cancers of the prostate, cervix, and corpus uteri and an increased incidence of female breast cancer was observed, but not consistently among the study centers.[5] We sought confirmation of these associations by record linkage in a yet larger and more homogeneous sample covering the entire population of Finland. Furthermore, we tried to identify and separate genetic effects from environmental ones by monitoring the nonpsychotic siblings and parents of patients with schizophrenia for cancer incidence. Although risk-enhancing behaviors associated with schizophrenia (eg, increased smoking) could still override a putative genetically based protection against cancer accompanying genetically transmitted schizophrenia vulnerability in patients, any associated selective advantage with respect to cancer risk should appear more clearly among their nonpsychotic relatives as a general decrease of cancer incidence compared with the general population.



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## SUBJECTS AND METHODS

### SUBJECTS

From the National Hospital Discharge Register and the National Disability Pension Register, Helsinki, Finland, we identified all individuals born between 1940 and 1969 who were hospitalized or received a disability pension for schizophrenia between 1969 and 1991, as described elsewhere.[6] Full operation of both registers started in 1968, and they cover Finland's total population of slightly more than 5 million. Register diagnoses were based on *ICD-8*[7] until 1987, after which *ICD-9*[8] codes were used (based on *DSM-III-R*[9] criteria for psychiatric diagnoses) until 1996. All diagnoses coded as 295 in *ICD-8* or *ICD-9* were accepted as cases to be followed up for cancer; this includes schizophrenia, schizophreniform disorder, and schizoaffective disorder, syndromes repeatedly shown to cosegregate in families on a common genetic basis (schizophrenia spectrum). Schizophrenia register diagnoses in Finland have been tested several times for reliability and specificity and were found to be directly applicable in epidemiological studies.[6]

By record linkage with the Central Population Register, Helsinki, via the unique personal identifiers assigned to all Finnish subjects on January 1, 1967 (or at birth, subsequently), we identified the parents and all siblings of the patients with schizophrenia. Cross-checks were made with the Central Population Register to obtain dates of emigration or death until December 31, 1996. Through the Finnish Cancer Registry, all patients with schizophrenia and their siblings and parents were followed up for cancer incidence up to December 31, 1996. The use of personal identifiers throughout the health care system leads to great precision of the record linkage procedure.[10] The Finnish population registration system is in principle complete, but some of the relatives who died in the 1970s may not have been linked to the index patient, and therefore the standardized incidence ratio (SIR) estimates in the first years of our follow-up tend to be slightly too low. This error, however, only marginally affects the overall SIRs among relatives. Permission for examining and linking the above registers was granted by the Ministry of Social Affairs and Health, Helsinki, Finland, and the institutional review board of the National Public Health Institute, Helsinki.

The 26996 subjects with schizophrenia were from 23083 families and were therefore expected to have 46166 parents. Primarily because of unknown paternity or maternity or both and, less commonly, because of parental divorce or death before 1960 (when the register was computerized), the data on 3795 fathers (16.4% of families) and 889 mothers (3.9%) could not be retrieved from the population register. Another 1071 fathers (4.6%) and 1280 mothers (5.5%) had died by 1971 (when the follow-up for cancer started) and were thus excluded. Instances of unidentified siblings should be much rarer because they would have had to die before the age of about 20 years to not appear in the register. However, as the same restrictions of ascertainment apply to the control population, resulting biases should be small.

### DIAGNOSIS AND REGISTRATION OF CANCER

All medical care in Finland is provided by a national health care system to which everybody has almost cost-free access. This results in extraordinarily complete, unbiased ascertainment of schizophrenia and cancer cases by the respective registers. Starting in 1961, the Finnish Cancer Registry has continuously received obligatory reports on all newly diagnosed cases of cancer from hospitals, practicing physicians, and hematologic and pathologic laboratories all over Finland, with about 90% of diagnoses based on histologic confirmation.[11] Death certificates mentioning cancer are automatically forwarded from Statistics Finland, Helsinki, to the Cancer Registry for review; fewer than 2% of all cancer cases came to the registry in this way alone. Ascertainment of cancer cases has been shown to be virtually complete.[12]

In Finland, medical or forensic autopsies are performed on average in 32% of all deaths and in 64% of deaths before the age of 65 years.[13] Forensic autopsy is obligatory in all cases of violent death, including suicide. Because about 40% of the excess mortality in schizophrenia is accounted for by unnatural causes,[14] the autopsy rate may be higher in patients with schizophrenia than that in the control population, resulting in a higher postmortem detection rate of clinically undiagnosed cancer in the former. However, this bias can be expected to be small because chance detection on autopsy of clinically unsuspected cancer should be rare, while the base rate of autopsies in the general population is exceptionally high in Finland, especially in cases of death under 65 years of age.

### STATISTICAL ANALYSES

Individual follow-up of patients, siblings, and parents for cancer started on January 1, 1971. For patients with a first diagnosis of schizophrenia (or spectrum disorders) in the Hospital Discharge Register or Disability Pension Register after this date, follow-up began from the date of first diagnosis. For all 3 groups, individual follow-up ceased on December 31, 1996, or on the date of emigration or date of death, whichever occurred earlier. Person-years were calculated by duration of follow-up (<2, 2-11, or >11 completed years of follow-up) and by 5-year age strata. Expected numbers of cancer cases (total and specific cancers as classified by primary site) in each stratum were obtained by multiplying the number of person-years at risk times the corresponding mean incidence rate of cancer in the general population of Finland during the same observation period. Standardized incidence ratios were calculated by dividing the number of observed cancer cases in each group by the expected number of cases. Calculation of 95% confidence intervals (CIs) of SIRs was based on the assumption that the numbers of observed cases followed a Poisson distribution.

## RESULTS

Altogether, 26996 patients with schizophrenia, 52976 of their nonschizophrenic siblings, and 39131 of their parents were eligible for follow-up (see **Table 1** for sex distribution). This corresponded to 446653, 1438143, and 905947 accumulated person-years at risk of cancer (or a mean 16.5, 27.1, and 23.2 years at risk), respectively. Of all the cases reported to the Finnish Cancer Registry, 1533 were benign lesions



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(mainly basal cell carcinomas of the skin) and thus excluded.

## CANCER INCIDENCE IN PATIENTS WITH SCHIZOPHRENIA

Among patients with schizophrenia, 724 cancers were diagnosed during follow-up, although 619 would have been expected from the incidence in the general population. The overall risk of cancer was significantly increased (SIR, 1.17; 95% CI, 1.09-1.25), more so in men than in women (**Table 2**). The largest increases were found for primary cancer of the lung (SIR, 2.17; 95% CI, 1.78-2.60) and pharynx (SIR, 2.60; 95% CI, 1.25-4.77). Significant increases were also seen for cancer of the gallbladder (SIR, 2.07; 95% CI, 1.03-3.70), the SIR being higher in men (SIR, 3.01; 95% CI, 0.98-7.01) than in women (SIR, 1.64; 95% CI, 0.60-3.57), and for cancer of the corpus uteri (SIR, 1.75; 95% CI, 1.19-2.48). Incidence of rectal cancer was decreased (SIR, 0.35; 95% CI, 0.13-0.75).

## CANCER INCIDENCE IN RELATIVES WITHOUT SCHIZOPHRENIA

Among nonschizophrenic siblings and parents of patients with schizophrenia, fewer cases of cancer emerged than were expected (siblings: 886 observed vs 999 expected; SIR, 0.89; 95% CI, 0.83-0.94; parents: 6165 vs 6755; SIR, 0.91; 95% CI, 0.89-0.93), similarly in both sexes (Table 2). Decreased incidence of lung cancer (SIR, 0.82; 95% CI, 0.68-0.97) and breast cancer (SIR, 0.77; 95% CI, 0.71-0.83) was seen in patients' mothers but not in other relatives. Cancer of the corpus uteri occurred less frequently than was expected in mothers (SIR, 0.81; 95% CI, 0.69-0.92) and in sisters (SIR, 0.38; 95% CI, 0.14-0.83). Prostate cancer in patients' fathers also occurred at a lower rate, although the 95% CI included unity (SIR, 0.97; 95% CI, 0.89-1.04). Incidence of colon cancer in parents was lower than was expected (291 observed vs 347 expected; SIR, 0.84; 95% CI, 0.75-0.93).

**Table 1. Number of Patients With Schizophrenia and Their Nonpsychotic Siblings and Parents Followed Up for Cancer Risk**

| | No. of Individuals | Years at Risk, Cumulative | Years at Risk, Mean |
|---|---|---|---|
| Patients | | | |
| Men | 15 578 | 253 057 | 16.2 |
| Women | 11 418 | 193 596 | 17.0 |
| **Total** | **26 996** | **446 653** | 16.5 |
| Siblings | | | |
| Men | 28 195 | 759 648 | 26.9 |
| Women | 24 781 | 678 495 | 27.4 |
| **Total** | **52 976** | **1 438 143** | 27.1 |
| Parents | | | |
| Men | 18 217 | 385 416 | 21.2 |
| Women | 20 914 | 520 531 | 24.9 |
| **Total** | **39 131** | **905 947** | 23.2 |

## COMMENT

In contrast to previous reports[5,15] of decreased or equal risk of cancer in patients with schizophrenia compared with controls, we found a moderately increased overall risk of cancer in these patients. To our knowledge, only these 2 published studies, a multicenter collaborative effort of the World Health Organization[5] and a more recent study in Denmark,[15] are directly comparable to ours in using population-based case registers of schizophrenia and of incident cancers to arrive at SIRs. Although 2 of the 3 study locations in the World Health Organization's collaborative study, Honolulu, Hawaii, and Nagasaki, Japan, also found cancer risks to be slightly increased in patients of Japanese descent with schizophrenia, a decreased overall cancer risk in both sexes emerged from the largest of the 3 study samples, the Danish (men: SIR, 0.67; 95% CI, 0.60-0.74; women: SIR, 0.92; 95% CI, 0.84-1.01).[5] The more recent record linkage study[15] from Denmark yielded the same result (SIR, 0.79; 95% CI, 0.66-0.94).

Lung cancer comprised the greatest discrepancy in total cancer rates between the present Finnish and the 2 Danish studies.[5,15] Incidence in patients with schizophrenia was strongly reduced in the first sample from Denmark (men: SIR, 0.38; 95% CI, 0.26-0.53; women: SIR, 0.33; 95% CI, 0.13-0.68),[5] but was 2-fold increased in Finland. Although formal data are lacking, it has been suggested that the decreased risk in Denmark might have resulted from tough restrictions on smoking on psychiatric wards.[16] Indeed, the second study[15] from Denmark on a more recent cohort not subjected to smoking control measures (72% of whom were smokers) showed a markedly higher relative lung cancer risk than the first study did (SIR, 0.78; 95% CI, 0.41-1.33). No restrictions on smoking in psychiatric care settings are imposed in Finland. This is therefore the first study, to our knowledge, to show in a population-based sample that schizophrenia is not paradoxically associated with decreased lung cancer risk, but rather with significantly increased risk, which corresponds well to what is expected from consistently and strongly increased prevalence and intensity of smoking in patients with schizophrenia.[4,17,18] In Finland, 61% of individuals with schizophrenia are regular smokers (70% of men and 50% of women; 36% smoke >20 and 25% smoke ≤20 cigarettes a day), while 3% smoke occasionally and 36% do not smoke at all.[19] Among 88 Finnish outpatients with chronic schizophrenia, 49 (56%) were smokers.[20] In the Finnish general population, 23% are regular smokers (27% of men and 19% of women), while 8% smoke occasionally.[21] Other conceivable reasons for a substantially reduced lung cancer risk in the older Danish cohort include a likely protective effect by longer exposure to phenothiazines, or systematic differences between the Danish and the Finnish populations with respect to genetic variants influencing cancer risk.

In conjunction with alcohol abuse and poor dental hygiene, smoking also increases the risk of cancers of the mouth and pharynx. Data on the prevalence of alcohol problems in Finnish patients with schizophrenia derive from an unselected cohort of all 12 058 live-births dur-



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**Table 2. Number of Cancers Observed and Expected in Probands, Siblings, and Parents, by Cancer Site***

| | Patients With Schizophrenia | | | Nonpsychotic Siblings | | | Nonpsychotic Parents | | |
|---|---|---|---|---|---|---|---|---|---|
| | Observed | Expected | SIR (95% CI) | Observed | Expected | SIR (95% CI) | Observed | Expected | SIR (95% CI) |
| All sites | 724 | 619 | 1.17 (1.09-1.25†) | 886 | 999 | 0.89 (0.83-0.94†) | 6165 | 6755 | 0.91 (0.89-0.93†) |
| Men | 317 | 254 | 1.25 (1.11-1.38†) | 370 | 437 | 0.85 (0.76-0.93†) | 3375 | 3626 | 0.93 (0.90-0.96†) |
| Women | 407 | 365 | 1.12 (1.01-1.22†) | 516 | 562 | 0.92 (0.84-0.99†) | 2790 | 3129 | 0.89 (0.86-0.92†) |
| Lungs | 106 | 48.8 | 2.17 (1.78-2.60†) | 51 | 55.5 | 0.92 (0.68-1.20) | 1066 | 1115 | 0.96 (0.90-1.01) |
| Larynx | 4 | 4.3 | 0.94 (0.26-2.39) | 8 | 5.5 | 1.47 (0.63-2.88) | 68 | 71.3 | 0.95 (0.74-1.20) |
| Esophagus | 5 | 4.5 | 1.10 (0.36-2.57) | 8 | 5.2 | 1.54 (0.66-3.02) | 79 | 86.2 | 0.92 (0.73-1.14) |
| Pharynx | 10 | 3.9 | 2.60 (1.25-4.77†) | 8 | 6.5 | 1.24 (0.53-2.43) | 25 | 33.8 | 0.74 (0.48-1.09) |
| Mouth and tongue | 22 | 14.6 | 1.51 (0.99-2.29) | 24 | 23.1 | 1.04 (0.70-1.55) | 176 | 156 | 1.13 (0.97-1.31) |
| Pancreas | 17 | 14.7 | 1.16 (0.67-1.84) | 11 | 16.3 | 0.67 (0.34-1.20) | 261 | 261 | 1.00 (0.88-1.12) |
| Liver | 8 | 5.2 | 1.55 (0.67-3.04) | 5 | 7.0 | 0.71 (0.23-1.65) | 66 | 87.5 | 0.75 (0.58-0.95†) |
| Gallbladder | 11 | 5.3 | 2.07 (1.03-3.70†) | 5 | 5.3 | 0.95 (0.31-2.21) | 102 | 95.4 | 1.07 (0.87-1.28) |
| Colon | 24 | 27.9 | 0.86 (0.55-1.27) | 35 | 41.1 | 0.85 (0.59-1.18) | 291 | 347 | 0.84 (0.75-0.93†) |
| Rectum | 6 | 17.3 | 0.35 (0.13-0.75†) | 19 | 21.6 | 0.88 (0.53-1.37) | 245 | 267 | 0.92 (0.81-1.03) |
| Breast (female) | 152 | 132 | 1.15 (0.98-1.34) | 210 | 198 | 1.06 (0.92-1.20) | 621 | 803 | 0.77 (0.71-0.83†) |
| Ovary | 31 | 25.5 | 1.22 (0.83-1.72) | 39 | 43.0 | 0.91 (0.64-1.23) | 138 | 186 | 0.74 (0.62-0.87†) |
| Cervix uteri | 14 | 10.7 | 1.31 (0.72-2.20) | 26 | 18.5 | 1.41 (0.92-2.06) | 100 | 84.8 | 1.18 (0.96-1.42) |
| Corpus uteri | 31 | 17.7 | 1.75 (1.19-2.48†) | 6 | 15.7 | 0.38 (0.14-0.83†) | 181 | 224 | 0.81 (0.69-0.92†) |
| Prostate | 7 | 14.3 | 0.49 (0.20-1.00) | 9 | 15.8 | 0.57 (0.26-1.08) | 591 | 612 | 0.97 (0.89-1.04) |
| Kidney | 26 | 19.9 | 1.30 (0.85-1.91) | 26 | 27.6 | 0.94 (0.62-1.38) | 220 | 226 | 0.97 (0.85-1.10) |
| Bladder, ureter, urethra | 17 | 14.4 | 1.18 (0.69-1.88) | 9 | 19.0 | 0.47 (0.22-0.90†) | 234 | 261 | 0.90 (0.79-1.01) |
| Central nervous system | 38 | 43.2 | 0.88 (0.62-1.20) | 80 | 95.7 | 0.84 (0.66-1.04) | 180 | 183 | 0.99 (0.85-1.13) |
| Lymph nodes | 30 | 20.3 | 1.48 (1.00-2.10) | 25 | 37.4 | 0.67 (0.43-0.98†) | 131 | 134 | 0.98 (0.82-1.15) |

**SIR indicates standardized incidence ratio; CI, confidence interval.*
*†The 95% CIs exclude unity.*

ing 1966 in the northern half of Finland. Among the 76 cases of schizophrenia identified in this birth cohort up to 1996, 25% tended to be heavy drinkers or have other alcohol use problems in daily life,[22] and 18% fulfilled *DSM-III-R*[9] criteria for alcohol abuse or dependence.[23] In accordance with expectations from increased exposure to tobacco and alcohol, the incidence of cancers of the oral cavity and pharynx was indeed doubled in our cohort.

The World Health Organization's 3-center study[5] found a significantly lower incidence of cancers of the prostate (relative risk, 0.38) and the cervix uteri (relative risk, 0.53) in the Danish schizophrenia subsample, and an increased incidence of female breast cancer in the Japanese subsample (relative risk, 3.23). Of these, only the deviation in prostate cancer risk could be confirmed in our Finnish sample (SIR, 0.49; 95% CI, 0.20-1.00). We observed cancers of the corpus uteri more often than was expected (SIR, 1.75; 95% CI, 1.19-2.48), consistent with a higher prevalence of risk factors to endometrial cancer[24-26] among women with schizophrenia, namely, fewer childbirths (low parity), higher body weight, and lower physical activity than are found in reference populations.[27-29]

It is reassuring to female patients with schizophrenia that the risk increase for breast cancer recently suggested by a case-control study,[30] albeit controversial for methodological reasons,[31-34] was not upheld in our population-based register linkage study. Neither neuroleptic treatment, previously thought to increase breast cancer risk by prolactin secretion, nor low parity or obesity seems to expose patients with schizophrenia to a markedly higher risk than that in the general population (but possibly to a higher relative risk than their mothers have; as suggested forthwith).

Cancer of the gallbladder was twice as common in patients with schizophrenia as it was in the general population. In epidemiological studies, gallstones have been suggested to be the main factor, increasing risk 4- to 5-fold; other risk factors include high parity, obesity, and a high-energy, high-fat diet.[35] Although high parity does not apply to women with schizophrenia, who tend to be less fertile than age-matched controls,[27] diet and high body weight (also medication-induced)[36,37] might explain this finding. To our knowledge, there are no studies on the incidence of gallstones and only a few[28,29] on body weight and dietary habits in schizophrenia, but one[29] did indeed show a higher dietary intake of fat in patients with schizophrenia. In Finland, the mean body mass index in women with schizophrenia has also been found to be higher than that in subjects from the general population (28.4 vs 24.6), although the difference was smaller in men (26.8 vs 25.6).[19] In our study, the rectum was the only cancer site for which incidence was strongly and significantly decreased in patients with schizophrenia (SIR, 0.35; 95% CI, 0.13-0.75). No risk difference from the general population was found for colon cancer, which is considered to have a similar (mainly dietary) origin.[38-41]

Although it appears from the aforementioned that the elevated incidence of cancer in patients with schizophrenia is largely due to increased risk behaviors in this group (especially tobacco smoking and alcohol abuse), this does not preclude the possibility that some genetic risk factor for schizophrenia vulnerability also confers lower liability to cancer, which is, however, overridden



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in manifest schizophrenia by the augmented risk behaviors mentioned. Although data were lacking to adjust individual cancer risk for duration and intensity of smoking (and for other environmental exposures) to determine whether the increase in incidence was smaller than, equal to, or larger than what would be expected owing to schizophrenia-associated risk behaviors, we had the unique opportunity to test this hypothesis because patients' siblings and parents who were unaffected by schizophrenia could be identified from the population register and followed up for cancer incidence in the same way as patients were. In both groups of relatives, we found a significantly decreased overall incidence of cancer in both sexes. We know of no other record linkage study on cancer in the relatives of patients with schizophrenia, but if replicable in independent cohorts, this finding would appear consistent with a hypothetical schizophrenia vulnerability gene that also leads to better cancer resistance in relatives. Its identity is speculative, but genes involved in the immune system might be candidates.[42-46] Alternatively, relatives' lifestyles may have contributed to their decreased cancer risk, and it is a limitation of our study design that we were unable to consider possible differences in risk behavior between the general population and first-degree relatives of patients with schizophrenia. It could be that being in close contact with a heavily smoking or drinking patient might deter relatives from substance abuse and thus protect them from associated cancers, but this seems unlikely given the limited effect of shared environment on the risk of alcohol or nicotine dependence, as has been documented by twin studies (<3.5% of variance explained),[47] and given the generally low age at onset of addiction[47] that would still allow for uninhibited decades of drug exposure at least in parents. However, any attempt to separate genetic factors from environmental exposure by "lifestyle" is somewhat artificial as it has been shown that genetic factors, the "nature of nurture," determine environmental exposure to a large degree. Smoking as the crucial risk behavior underlying lung cancer is probably intimately related to the neurobiology of schizophrenia.[4,17,18,48,49] From a clinical standpoint, our finding of a substantially increased risk of lung cancer and some other smoking related cancers in patients with schizophrenia should lead to intensified efforts in developing addiction treatment programs specifically suited to the needs of this vulnerable population.[18]

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