Reduced Cancer Incidence among Patients with Schizophrenia

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BACKGROUND. The incidence of cancer in patients with schizophrenia has been conversely reported to be higher, lower, or similar to that in the general population. The effects of lifestyle factors such as excess smoking, exposure to neuroleptic medications, and genetic factors that may influence the incidence of cancer in this group are not clear. The current study was performed to evaluate the frequency of cancer in a large cohort of patients with schizophrenia and to determine the standardized incidence ratios (SIRs) of any malignancy in this group.

METHODS. Data regarding the design, setting, and participants of the current study were analyzed from a cohort of 3226 patients with schizophrenia who were enrolled in the computerized health registry of the Abarbanel Mental Health Center between1993–2003. The mean age of the patients at the time of the diagnosis of cancer was 49 $\pm$ 14.7 years, with the majority of patients (61%) being male. All patients with schizophrenia records in the database were combined with the records of the Israeli National Cancer Registry to identify pathologically confirmed cancer comorbidity. The cancer incidence rates among patients with schizophrenia were compared with the expected incidence in an age-matched and gender-matched general population sample for the same time interval.

RESULTS. Among 1247 female patients with schizophrenia, 22 (1.8%) developed breast cancer and 68 (5.5%) developed cancers of any type. Fifty-two of the 1979 male schizophrenic patients (2.6%) developed cancer. The SIRs were 0.58 (95% confidence interval [95% CI], 0.48–0.69) with a P value of < 0.05 for all cancers in the cohort, and 0.60 (95% CI, 0.37–0.90) for female breast cancer.

CONCLUSIONS. The results of the current study demonstrate a reduced risk of cancer in patients with schizophrenia. The mechanisms responsible for the lower risk need be investigated further. ***Cancer*** **2005;104:2817–21.**

KEYWORDS: cancer, incidence, schizophrenia, standardized incidence ratio.

The risk of cancer among patients with schizophrenia has been variously reported to be increased,[1] similar to that of the general population,[2,3] or decreased.[4,5] The majority of studies in the last decade have suggested that patients with schizophrenia are protected against cancer in general. The basis for this suggestion is several reports of a reduced mortality from cancer[6–8] and reports of a lower incidence of cancer among patients with schizophrenia compared with the general population.[5,9]

The effects of lifestyle habits and particularly heavy smoking[10,11] combined with less-than-optimal medical care [12,13] for this vulnerable section of the population suggest that the risk for cancer *should* be increased and that the diverse reports in the published literature may reflect a variety of methodological limitations. One of the variables that has not been consistently controlled for in previous studies and

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that is directly correlated with cancer frequency is age. Mortality is reported to be on average 10 years earlier for patients with schizophrenia compared with their comparison subjects in the general population.[14] The second and major variable that needs systematization among researchers is the diagnosis of both cancer and schizophrenia. The objective of the current study was to compute cancer frequency (standardized incidence ratios [SIR]) based on histologic diagnosis and corrected for age in a large cohort of patients with schizophrenia.

MATERIALS AND METHODS

In the current study, we linked data from the computerized database at the Abarbanel Mental Health Center in Bat-Yam, Israel with the National Cancer Registry of Israel. We compared cancer incidence rates in a large cohort of patients with schizophrenia with rates in the general Jewish population of Israel. All patients were of Jewish descent.

Setting

The Abarbanel Mental Health Center serves an urban catchment area of approximately 680,000 subjects. The center is affiliated with the Sackler School of Medicine of Tel-Aviv University. There are 550 inpatient beds and 60 day patients as well as a large outpatient clinic. The center is a tertiary psychiatric facility that is in contact with both secondary specialist clinics and primary care providers. In Israel, there are no private emergency psychiatric facilities and all acute psychiatric hospitalizations are regional and reported to the Ministry of Health.[15]

Subjects

All patients diagnosed with schizophrenia according to Diagnostic and Statistical Manual (of Mental Disorders) (DSM)-IV criteria who were followed at the Abarbanel Mental Health Center were included in the current analysis. The reporting of schizophrenia has been mandatory in Israel since 1949 by regulations of the Ministry of Health. The center's medical records database was only computerized in 1993. Only patient records that were registered in the computerized database were included in the current analysis.

All patient records in the Abarbanel Mental Health Center computerized database were combined with records from the Israeli National Cancer Registry within the Israeli Center for Disease Control (ICDC) to identify pathologically confirmed cases of cancer comorbidity.

We therefore identified all patients with schizophrenia with pathologically confirmed cancers diagnosed through December 31, 2003. Information was available regarding patient age, gender, ethnicity, age at onset of cancer, and type of cancer, if any. The Israeli Ministry of Health Ethical Committee approved the study.

The study cohort was linked to the Israel National Cancer Registry to identify cancer cases through December 2003. The Cancer Registry was established in 1960 and maintains data on all malignancies, including selected benign tumors (primarily of the central nervous system) in Israel. The Registry receives notification of all malignancies from hospital discharge reports, as well as from oncology and pathology departments throughout the country. Depending on the cancer site, cancer ascertainment during internal verifications is reported to be approximately 90–95% complete.[16] The records were linked by computer matching of patients' identification numbers and gender with the Cancer Registry data file. For all patient matches, the Cancer Registry provided a cancer diagnosis, coded according to the International Classification of Diseases-Ninth revision, along with the date of diagnosis.

Statistical Analysis

To compare cancer incidence rates in patients with schizophrenia with those of the general population, SIRs were based on the Jewish population of Israel. In the analysis, patients were at risk until the earliest date of cancer onset, death, or the end of follow-up (December 31, 2003).

It should be noted that the SIRs were computed for 5-year age groups and a single 10-year calendar period.

RESULTS

Of the 3226 records of patients with schizophrenia that were analyzed, 1247 patients (39%) were female and 1,979 patients (61%) male. The mean age for the group was 49 $\pm$14.7 years. Approximately 57% of the patients were Ashkenazi, 31% were Sephardic, and the remainder of the patients were of mixed origin. This ethnic composition is similar to that of the general Jewish Israeli population, which includes 62% Ashkenazi, 29% Sephardic, and 9% of other Jewish ethnic groups.[17]

Among the 1247 female patients with schizophrenia, 22 (1.8%) developed breast cancer and 68 (5.5%) developed a malignancy of any type. Fifty-two of the 1979 male patients with schizophrenia developed cancer (2.6%). The computed SIRs were 0.58 (95% confidence interval [95% CI], 0.48–0.69) with a P value of < 0.05 for all cancers in the cohort for all patients, and 0.61 (95% CI, 0.39–0.92) for female breast cancer (Table 1).

TABLE 1
Standardized Incidence Ratios and 95% Confidence Intervals by Tumor Site

Tumor site	Observed	Expected	SIR	Lower 95% CI	Upper 95% CI
Lip	4	2.89	1.38	0.37	3.54
Tongue	1	0.52	1.91	0.03	10.64
Nasopharynx	1	0.84	1.19	0.02	6.61
Esophagus	2	1.06	1.89	0.21	6.81
Stomach	3	8.57	0.35	0.07	1.02
Colon	9	13.66	0.66	0.30	1.25
Rectosigmoid junction	1	3.48	0.29	0.00	1.60
Rectum	1	5.37	0.19	0.00	1.04
Other biliary tract	1	0.85	1.17	0.02	6.51
Bronchus and lLung	9	13.94	0.65	0.29	1.23
Bones, joints and articular limbs	1	1.62	0.62	0.01	3.44
Hematopoietic	5	8.57	0.58	0.19	1.36
Skin	5	12.59	0.40	0.13	0.93
Breast	23	37.40	0.61	0.39	0.92
Vulva	1	0.45	2.23	0.03	12.38
Vagina	1	0.11	9.17	0.12	51.00
Cervix uteri	3	5.16	0.58	0.12	1.70
Corpus uteri	4	4.53	0.88	0.24	2.26
Uterus, NOS	2	0.57	3.50	0.39	12.63
Ovary	4	6.50	0.62	0.17	1.58
Prostate	2	6.53	0.31	0.03	1.11
Testis	1	2.13	0.47	0.01	2.62
Kidney	5	4.57	1.09	0.35	2.55
Renal pelvis	1	0.35	2.88	0.04	16.04
Ureter	1	0.19	5.34	0.07	29.70
Bladder	7	10.11	0.69	0.28	1.43
Eye and adnexa	1	0.60	1.67	0.02	9.32
Meninges	1	3.35	0.30	0.00	1.66
Brain	1	5.08	0.20	0.00	1.09
Thyroid gland	6	5.85	1.02	0.37	2.23
Other endocrine glands	1	1.14	0.88	0.01	4.90
Lymph nodes	7	11.31	0.62	0.25	1.28
Unknown primary site	5	8.16	0.61	0.20	1.43
All	120	208.26	0.58	0.48	0.69

SIR: standardized incidence ratio; 95% CI: 95% confidence interval; NOS: not otherwise specified.

Although the current study was based on very few cases, there was a significantly reduced risk of stomach and rectal cancer, as well as a reduced risk of prostate cancer.

DISCUSSION

The cooccurrence of cancer and schizophrenia has been the subject of many studies, with apparently conflicting results. The majority of the early studies were affected by methodological weaknesses. Several reports focused on cancer mortality. The weakness of measuring cancer mortality rather than incidence to index relative risk of cancer is that cancer mortality not only measures cancer incidence but also the survival of those who develop cancer.[6,8] Mortality from other causes may complicate the interpretation.[18] To our knowledge, only six published studies to date have used incidence data. Some of the better designed studies used register case ascertainment and controlled for age and gender.[19]

One of the earlier studies in this area was undertaken by the World Health Organization (WHO).[20] In brief, to overcome some of the methodological weaknesses identified in research in this field, the WHO designed a collaborative research in five settings worldwide in which both psychiatric and cancer registries cover the same population.[20] Two general findings were reported as a result of the WHO effort: 1) there is no evidence of any consistent general reduction or increase in the risk of cancer in patients with schizophrenia and 2) there is no apparent increase or decrease in the risk of certain malignancies that can be correlated with any sustained, long-term behavioral patterns and/or living conditions of schizophrenic patients.[9]

In the current study, we evaluated the hypothesis regarding cancer rates in a new setting and population as well as controlling for age and gender in an incidence study according to the suggestion by Catts and Catts.[19] In addition, the diagnosis of schizophrenia in the current study was rigorously established according to the DSM criteria following the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (Hebrew version) guidelines.[21] Therefore, our findings are to be compared with reports of similar design. There are three studies with which we need to compare our results: Dupont et al.,[4] Mortensen,[5] and the more recent study by Lichtermann et al..[1] In the first two studies, cancer incidence was reported to be reduced in a manner similar to that noted in the current study. It is important to note that when smoking was controlled for,[5] the results were even more robust. Conversely, Lichtermann et al.[1] reported on a higher overall cancer risk, with nearly half of the excess cases attributable to lung cancer, yet the incidence of breast cancer was unchanged. However, it should be noted that the current analysis focused on treated patients with schizophrenia and it is possible that those patients who never come to clinical attention have a worse medical outcome. In untreated patients with schizophrenia, the chance of neglecting serious physical illnesses, including cancer, because of a lack of appropriate medical care also should be considered. An additional factor that needs to be mentioned is the possibility of chance findings because of the small number of cancer cases noted in the current study.

The issue of breast cancer requires special emphasis. In the 1960s, several reports on the possible association between increased prolactin levels because of antipsychotic treatment and the risk of breast cancer were published.[22] Because these reports were inconclusive, Halbreich et al.[23] reviewed the mammograms, psychiatric history, and treatment of 275 female patients in a psychiatric state hospital and compared these with those of 928 women of a similar age at a general hospital radiology clinic. The incidence of breast cancer was found to be 9.5 times higher among the psychiatric patients compared with the general population. Conversely, in the current study, there was no higher incidence of breast cancer noted among female patients with schizophrenia. This is in keeping with the report by Lichtermann et al.,[1] as well as the findings of Dalton et al.,[24] in which the authors studied 7541 Danish women with schizophrenia and found that the overall relative risk for breast cancer adjusted for age, calendar period (in 5-year categories), age at first birth, and number of births was not found to be higher compared with the general population. However, the subject is controversial, as discussed by Halbreich et al.[22] The authors themselves noted that although this increased incidence may be attributed to antipsychotic-induced hyperprolactinemia, cigarette smoking, alcohol consumption, and other confounding factors such as reproductive factors also may play a role.

There are several possible explanations for the findings that cancer risk and incidence are reduced in patients with schizophrenia. The earlier hypothesis was put forward by Fox and Howell[25] and suggested that prolonged hospitalization wherein smoking is curtailed and diet controlled is a protective factor. The most recent theories focus on the possibility that increased apoptosis may account for the neurodevelopmental abnormalities as well as tumor resistance associated with schizophrenia. Park et al.[26] proposed that polymorphism of p53, a tumor suppressor gene central to the regulation of apoptosis and specifically found in patients with schizophrenia, may be associated with a reduced vulnerability to lung cancer. This hypothesis was recently supported by Yang et al.[27] in a large Chinese cohort.

Lichtermann et al.[1] demonstrated reduced cancer rates in first-degree relatives of patients with schizophrenia. This decreased risk in these relatives, the authors postulated, may be compatible with a genetic risk factor for schizophrenia that offers a selective advantage to unaffected relatives. Dalton et al.[28] also examined the hypothesis that a genetic protection against cancer might be manifested in the parents of children with schizophrenia. However, their study did not confirm the previously reported reduced risk for cancer observed in the parents of patients with schizophrenia and therefore does not support the concept of a genetic form of protection against cancer in the family members of patients with schizophrenia.

The mechanisms contributing to the reduced risk of cancer noted among patients with schizophrenia are to our knowledge still unknown, and their implications for public health merit further investigation.

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