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Cancer in schizophrenia: is the risk higher or lower?

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Abstract

Studies exploring the relationship between schizophrenia and cancer have shown conflicting results. Our study explores this association in three Jewish–Israeli population groups defined by their continent/place of birth (Israel, Europe–America, and Africa–Asia). The identification of the patients was made through the linkage of the nationwide psychiatric and cancer registries. The incidence of cancer in patients diagnosed with schizophrenia was compared with the incidence in the general population. The results showed that the cancer standardized incidence ratios (SIRs) for all sites were significantly lower among men and women with schizophrenia, 0.86 [95% confidence interval (CI) 0.80–0.93] and 0.91 (95% CI 0.85–0.97), respectively. This reduced overall risk was clearest for those born in Europe–America, both men (SIR 0.85, 95% CI 0.74–0.97) and women (SIR 0.86, 95% CI 0.77–0.94). Among women diagnosed with schizophrenia, the SIR was statistically higher for cancer in the breast among those born in Asia–Africa (1.37, 95% CI 1.12–1.63) and in the corpus uteri among the Israel-born (2.75, 95% CI 1.69–3.81) than among their counterparts in the general population. Lung cancer was significantly higher in men born in Asia–Africa diagnosed with schizophrenia than in the respective comparison population group (1.58, 95% CI 1.13–2.2).

Our findings, and those of the literature, justify conducting a multinational study that includes identification of cancer-related risk factors among patients with schizophrenia and their families, and information on the use of psychotropic medications. This effort may clarify an epidemiological puzzle that remains outstanding.

Keywords: Schizophrenia; Cancer; Epidemiology; Comorbidity

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1. Introduction

Numerous studies have found that persons diagnosed with schizophrenia have a reduced risk to develop cancer (Gulbinat et al., 1992; Mortensen, 1994; Lawrence et al., 2000; Cohen et al., 2002; Oksbjerg Dalton et al., 2003). This association is puzzling since it is contrary to the presence of risk factors noted in this population; for example, persons with schizophrenia smoke heavily (Dalack et al., 1998); rarely engage in physical exercise (Brown et al., 1999); and may neglect other health-related behaviors, such as eating a balanced diet (Scottish Schizophrenia Research Group, 2000) or abusing alcohol. The low breast cancer risk found in some studies (Oksbjerg Dalton et al., 2003) is inconsistent with the elevated prolactin levels caused by antipsychotic medications that have been hypothesized to raise such a risk (Halbreich et al., 1996) Admittedly, exceptions to the negative findings do exist, particularly for selected cancer sites (Mortensen, 1994), including for breast cancer (for a recent review, see Mortensen, 2002).

Several explanations have been raised in an attempt to solve this "epidemiological puzzle that dates decades" (Jablensky and Lawrence, 2001). Health service factors may bias the diagnosis of cancer among persons with schizophrenia, and primary care physicians (PCPs) may tend to easily dismiss their complaints (Goldman, 1999; Cradock-O'Leary et al., 2002; Folsom et al., 2002). Mortensen (1994) imputed to neuroleptic medication the lower risk of prostrate cancer among persons with schizophrenia. Genetic explanations have also been raised to account for this reduced risk (e.g., Park et al., 2004 have explained the lower incidence of lung cancer among persons with schizophrenia as resulting from the role of a protective gene). Earlier, Lichterman et al. (2001) also raised such an explanation to account for the results obtained in their well-conceived study. These authors used an epidemiological strategy to explore the cancer incidence among siblings and parents of persons with schizophrenia, and found it to be consistently lower than in the general population. Paradoxically, however, the patients with schizophrenia had an increased overall risk, standardized incidence ratio (SIR) of 1.17 [95% confidence interval (CI) 1.09–1.25]. However, most recently, Oksbjerg Dalton et al. (2004) failed to confirm Lichterman et al.'s lower parental risk. Thus, the "epidemiological puzzle" alluded to earlier extends to the parents of persons with schizophrenia as well. To us, these conflicting research findings (Table 1) fully justify an additional inquiry.

This study capitalizes on the existence in Israel of a comprehensive psychiatric database and a cancer registry. These two countrywide resources provide complete and reliable data that can generate the required number of persons-years for an adequate test (Baldwin, 1979). In addition, the country population is ethnically mixed, which allows to explore the risk in groups with varied incidences of cancer.

2. Objective

The objective of the present study was to establish the association between schizophrenic disorders and cancer for aggregated and specific sites in three gender-mixed Jewish population groups defined by their continent/place of birth (Israel, Europe–America, and Africa–Asia) by using a record linkage design.

3. Methods

3.1. Identification of patients with schizophrenia

Israel offers a high supply of health and psychiatric services through a national health insurance program. The system enables PCPs to refer persons with a suspected psychiatric disorder to specialized services that are located countrywide and that are free of charge (Levav and Grinshpoon, 2004). Direct access to mental health services is possible as well for those who wish to circumvent the PCP. For Jewish–Israelis, the medical examinations conducted by the Israel Defense Forces (IDF) for new recruits (both genders) and for the reserves (only men) constitute an additional universal filter. Not surprisingly, a community-based epidemiological study found that almost all Israel-born persons with schizophrenia were known to the mental health services (Levav et al., 1993).

The psychiatric database, which uses a single identification number, cumulatively records all admissions and discharges to all psychiatric inpatient

Table 1
Summary of studies exploring the association of schizophrenia with cancer, 1992–2003

Study	Year	Country	Schizophrenia (*n*)	Cancer (*n*)	Person-years of risk	Data source		Risk of cancer
						Schizophrenia	Cancer	
This study	2004	Israel	26,518	1435	144,888	Psychiatric Case Register	Cancer Register	Male SIR=0.85 (0.78–0.92) Female SIR=0.90 (0.84–0.96)
Oksbjerg Dalton et al.	2003	Denmark	7541 women	74	74,699	Central Psychiatric Register	Cancer Register	Adjusted OR=0.91 (0.71–1.12) (breast cancer)
Cohen et al.	2002	USA	235	130	NR	1986 National Mortality Followback Survey	Hospital records or death certificates	Adjusted OR=0.59 (0.38–0.93)
Lichtermann et al.	2001	Finland	26,996	794	446,653	National Hospital Discharge and Disability Pension Register	Cancer Register	SIR=1.17 (1.09–1.25)
Lawrence et al.	2000	Australia	172,932[a]	496	NR	Linked database (contacts with mental health services)	Cancer Register	Male RR=0.83 (0.70–0.98) Female RR=1.13 (0.99–1.28)
Mortensen	1994	Denmark	9156		70,000	Central Psychiatric Register	Cancer Register	Male SIR=0.76 Female SIR=1.06
Gulbinat et al.	1992	Denmark	6152	792	NR	Central Psychiatric Register	Danish Cancer Register	Male SIR=0.67 (0.60–0.74) Female SIR=0.92 (0.84–1.0)
		USA, Honolulu	6977	59	NR	Hawaii State Psychiatric Case Register	NR	Male SIR=1.21 (0.49–2.49) Female SIR=1.73 (1.03–2.74)
		Japan, Nagasaki	3107	44	NR	All psychiatric institutions and Nagasaki Mental Health Center	Medical Association Tumor Statistical Committee	Male SIR=1.43 (0.85–2.26) Female SIR=1.67 (1.17–2.44)

Adjusted OR=adjusted odds ratio (95% CI); RR=rate ratio; SIR=standardized incidence rate; NR=not reported.
[a] Total number of patients in contact with mental health services in Western Australia in 1966–1995.

facilities in the country. It has existed since the 1950s, and the reporting is mandated by law (Lichtenberg et al., 1999; Ministry of Health, 2003). Since hospitalization for a schizophrenic disorder is rarely sought abroad, the enumeration of all persons with schizophrenia is assumed to be almost complete. While this is the case for Jewish–Israelis, the Arab–Israeli minority, particularly women, uses the psychiatric inpatient services less (Ministry of Health, 2003). To avoid a biased sample, the Arab–Israelis were not included in this study.

This psychiatric case register includes diagnoses upon admission and discharge and socio-demographic information. Diagnoses are recorded according to ICD-10; those made prior to the last WHO classification have been updated.

3.2. Identification of cancer cases

Israel possesses a cancer registry established in 1960 (Freedman et al., 2001). Reporting to this database has been mandatory since 1982 and covers all public and private medical facilities in the country. The registry also collects data on cancer deaths from district health authorities and the population register of the Ministry of Interior. Data on every resident in this registry are organized according to personal identification number, as in the psychiatric one. In addition to the demographic information, all available data on the disease are similarly recorded, as follows: date and place of diagnosis, detailed tumor location (using the ICD-03 codes; World Health Organization, 1976), histopathology, stage at times of diagnosis, tumor size, lymphatic nodes compromised, and treatments provided. The completeness of the cancer registry is over 95%; efforts to improve both reporting and accuracy have continued through further evaluations and training of personnel in all cancer institutes (Fishler et al., 2002).

The number of Israeli residents who would have been diagnosed as suffering from cancer and who sought diagnosis and treatment abroad is likely limited, as medical services in Israel are adequate and free of charge, including for those in the terminal stages. However, the exact numbers are not known.

Importantly for our inquiry, both case records can be linked by means of the personal identification number.

3.3. Subjects

All Jewish–Israelis between the ages of 15 and 45 years who were admitted to any facility, both psychiatric hospitals and psychiatric wards of general hospitals, during the years 1962–2001 and whose diagnoses met the ICD-10 F20 category were included in the study cohort. To enhance the reliability of the clinical diagnosis of schizophrenia, the discharge diagnosis of the last hospitalization was used. These index cases were subsequently searched through the cancer registry to identify those diagnosed with cancer before and at any time after the hospitalization for schizophrenia.

The heterogeneity of the Israeli population, which comprises local-born and immigrants from 70 countries, enables to check the direction of the association between cancer and schizophrenia among various ethnic groups, since the risk of cancer in these groups varies (e.g., the aggregate rate is higher among immigrants from Europe–America than among those from Asia–Africa; Israel Center for Disease Control, 1998; Barchana et al., 2001). This difference exists for selected cancer sites as well (Israel Center for Disease Control, 1998; Steinitz et al., 1989; Israel National Cancer Registry, 1990–2000; Barchana et al., 2002). Subjects were aggregated into three population groups according to their respective place of origin: Israel, Europe–America, and Africa–Asia. Although all groups were investigated, special attention was given to the Israel-born, for several reasons: the date of first hospitalization is always known, having occurred in Israel; all men have been screened by the IDF; and their health behavior is more homogeneous than that of the immigrant groups.

3.4. Statistical analysis

The age-adjusted incidence rates of cancer among the cohort diagnosed with schizophrenia and aged 15–45 years at the time of the first hospitalization were compared with the age-adjusted incidence rates in the general population. For this population, the numerator was based on cases identified in the cancer registry, while the denominator was based on data provided by census publications (Central Bureau of Statistics, 1962–2001).

Since the first hospitalization for schizophrenia and the date of first entry in the cancer registry differed, we calculated the number of person-years to enable the analysis. Cases were censored upon death, diagnosis of a malignant tumor, emigration from Israel, or the last date for entry of cases with schizophrenia into the cohort, December 31, 2001. Person-years were calculated for men and women, for the entire population, and by place of birth. Persons with a cancer diagnosis prior to the hospitalization for schizophrenia (n=108) were not included.

The expected number of incident cases of cancer for the entire patient group with schizophrenia and for each population group and by gender was calculated. The observed and expected numbers of cancer cases for each stratum were compared, and the 95% CI of the SIR was determined. The analysis by cancer site, gender, and place of origin was conducted when the sample size of a stratum was 10 or greater.

4. Results

Of the 33,372 persons with schizophrenia evaluated between the years 1962 and 2001, 1504 had developed cancer. Table 2 shows the person-years accrued during the 40 years of observation by gender, age group, and place of birth.

Table 2
Person years by age, gender, and place of origin

Age (years)	Place of origin					
	Asia–Africa		Europe–America		Israel	
	Male	Female	Male	Female	Male	Female
15–19	1045	762	1272	815	8110	5809
20–24	4450	2832	4629	2795	23,368	15,073
29–29	8176	5757	7805	4884	30,573	19,851
30–34	11,748	8906	9754	7501	29,882	21,349
35–39	14,165	11,622	11,247	10,133	25,510	19,889
40–44	15,036	13,310	11,937	12,474	19,093	16,109
45–49	13,686	12,905	10,840	12,264	11,684	10,541
50–54	10,726	10,477	8277	10,272	5819	5583
55–59	7365	7546	5602	7821	3262	3395
60–64	4636	5013	4046	6129	1990	2169
65–69	2486	2810	2526	4169	1014	1178
70–74	1073	1193	1336	2407	473	615
75+	420	483	820	1478	227	437
Total	95,012	83,616	80,092	83,141	161,005	121,998

Table 3 shows the SIR values for all sites and selected cancer sites during the period of observation by gender and place of birth. Overall, the SIR values were lower for both men and women with schizophrenia, 0.86 (95% CI 0.80–0.93) and 0.91 (95% CI 0.85–0.97), respectively, than in the comparison (general) population. In three sites, the SIR was statistically lower than 1.0 (women: melanoma, 0.47; men: prostate, 0.53 and brain, 0.56), suggesting a lower risk among those with schizophrenia. In three sites, the SIR was higher than 1.0 (men: lung, 1.38; women: corpus uteri, 1.64 and breast, a marginal 1.11), suggesting an increased risk.

For all cancer sites combined, the lower risk was clearest for persons with schizophrenia born in Europe–America, both men (SIR 0.85, 95% CI 0.74–0.97) and women (0.86, 95% CI 0.77–0.94). In two sites, the SIR values were significantly higher among the Asia–Africa-born: breast cancer among women, 1.37 (95% CI 1.12–1.63), and lung cancer in men, 1.58 (95% CI 1.13–2.2). Cancer of the corpus uteri was higher in Israel-born women (2.75, 95% CI 1.69–3.81).

5. Discussion

Our findings were mixed. The SIR for aggregated sites for the combined ethnic groups of patients with schizophrenia was below 1 for both men and women, suggesting a reduced cancer risk. In contrast, the risk of cancer was higher in persons with schizophrenia than in the general population in the following specific sites: lung in men, and corpus uteri and breast in women.

The check among the Israel-born, where nearly all persons with schizophrenia are under care (Levav et al., 1993), showed a lower risk for all sites, but the SIR did not reach statistical significance. For specific sites, the SRI values almost mimicked the finding in all population groups, except for cancer in the corpus uteri where the SIR did not reach statistical significance.

Our findings differ from some of previous studies but agree with others (Table 1). Lichterman et al. (2001) found a higher overall risk among probands with schizophrenia in Finland, while others (e.g., Gulbinat et al., 1992) found a lower risk in Denmark. With regard to specific sites, cancer of

Table 3
SIR of cancer in persons with schizophrenia by localization, place of birth, and gender

Localization	Place of birth	Gender	Cases		SIR	95% CI	
			Expected	Observed		Lower	Upper
Lung	Asia–Africa	M	30.48	48	1.58	1.13	2.02
		F	4.07	6	1.48	0.29	2.66
	Europe–America	M	27.41	32	1.17	0.76	1.57
		F	12.05	9	0.75	0.26	1.24
	Israel	M	13.78	23	1.67	0.99	2.35
		F	4.51	8	1.77	0.54	3.00
	Total	M	74.62	103	1.38*	1.11	1.65
		F	27.13	23	0.85	0.50	1.19
Melanoma	Asia–Africa	M	1.85	5	2.71	0.33	5.08
		F	0.62	1	1.62	0.00	4.79
	Europe–America	M	9.11	14	1.54	0.73	2.34
		F	11.87	9	0.76	0.26	1.25
	Israel	M	19.89	14	0.70	0.34	1.07
		F	17.19	8	0.47	0.14	0.79
	Total	M	38.59	33	0.86	0.56	1.15
		F	37.95	18	0.47*	0.26	0.69
Brain	Asia–Africa	M	9.64	8	0.83	0.25	1.41
		F	9.33	12	1.29	0.56	2.01
	Europe–America	M	7.39	7	0.95	0.25	1.65
		F	11.81	15	1.27	0.63	1.91
	Israel	M	4.35	5	1.15	0.14	2.16
		F	4.78	5	1.05	0.13	1.96
	Total	M	35.49	20	0.56*	0.32	0.81
		F	33.99	32	0.94	0.62	1.27
Breast	Asia–Africa	F	80.09	110	1.37	1.12	1.63
	Europe–America		140.58	152	1.08	0.91	1.25
	Israel		104.37	108	1.03	0.84	1.23
	Total		333.34	370	1.11†	1.00	1.22
Corpus uteri	Asia–Africa	F	6.20	13	2.10	0.96	3.24
	Europe–America		19.40	26	1.34	0.83	1.86
	Israel		9.44	26	2.75*	1.69	3.81
	Total		39.56	65	1.64*	1.24	2.04
Prostate	Asia–Africa	M	15.23	12	0.79	0.34	1.23
	Europe–America		15.74	9	0.57	0.20	0.95
	Israel		5.60	3	0.54	0.00	1.14
	Total		45.16	24	0.53*	0.32	0.74
All sites	Asia–Africa	M	217.58	205	0.94	0.81	1.07
		F	245.06	248	1.01	0.89	1.14
	Europe–America	M	252.65	216	0.85*	0.74	0.97
		F	429.77	368	0.86*	0.77	0.94
	Israel	M	207.35	181	0.87	0.75	1.00
		F	301.72	286	0.95	0.84	1.06
	Total	M	696.26	602	0.86*	0.80	0.93
		F	992.98	902	0.91*	0.85	0.97

* Significant.
† Marginal significance.

the lung and uteri was found to have a higher risk by Lichterman et al. (2001); we made similar findings. Breast cancer was found to have a lower risk by Oksbjerg Dalton et al. (2003), whereas the risk was higher in Israel, especially among immigrants from Europe–America.

This epidemiological puzzle remains unsolved (Mortensen, 2002), in both persons with schizophrenia as well as among their parents (see the different findings with regard to the latter in the two studies published thus far, both conducted in Scandinavian countries; e.g. lower risk in the study of Lichterman et al., 2001 but none in the one by Oksbjerg Dalton et al., 2004).

The higher risk for lung cancer that we found is consistent with the high rate of smokers among persons with schizophrenia (Srinivasan and Thara, 2002). The increased risk for breast cancer and tumors of the corpus uteri, also found in Hawaiians of Japanese origin although not among Caucasians (Gulbinat et al., 1992), may result from hormonal factors (i.e., higher prolactinemia following the long-term intake of neuroleptics; Halbreich et al., 1996). The low risk of melanoma is conceivably related to the tendency of these patients to remain indoors and avoid intense exposure to the intense sun radiation in Israel, and to the antiproliferative effect of some antipsychotic medication (Nordenberg et al., 1999; Gil-Ad et al., 2004).

For some authors, the lower risk of cancer would stem from a selective genetic advantage (Lichterman et al., 2001; Park et al., 2004). Jablensky and Lawrence (2001) argued, after a sober critical analysis of the literature, that it is premature to conclude this. The latest report by Oksbjerg Dalton et al. (2004) would support these critics. The genetic factor, singly or in interaction, if it indeed were present, could explain the low risk in cancer sites where lifestyles and health-related behavior may not play a salient role. This putative genetic factor does not seem to render protection in all ethnic groups nor in both genders based on this study in Israel.

Our inquiry had methodological strengths and weaknesses. As noted in Methods, our cancer and psychiatric registries likely cover almost all of the Jewish population affected by the two disorders, as a result of the organization of the health services in the country and the relative favorable attitudes of the population with regards to them. The visits to the PCP are frequent (e.g., the average yearly visits among the insured in the largest health service organization reach almost 8.0.; H. Munitz, personal communication, 2004). Only a few people may seek diagnosis and care abroad.

Furthermore, the bias in missing cancer incident cases due to underdetection by physicians among individuals with psychiatric disorders is decreased as the registry also includes data from death certificates. Lastly, the diagnostic reliability of cancer is satisfactory, particularly in recent years wherein most of our index population entered the period of risk.

The enumeration of persons with schizophrenia based on hospitalizations may be nearly complete, since ambulatory services were less developed during the period covered, when the tendency to admit persons with severe disorders to psychiatric inpatient services was standard clinical practice. As for the clinical diagnosis of schizophrenia, it has been shown to be satisfactory (Goodman et al., 1984; Rabinowitz et al., 1994). In addition, we attempted to enhance the robustness of the diagnosis by using a conservative criterion. The long period of observation, four decades, enabled us to accrue a number of person-years larger than the 100,000 years recommended by Baldwin (1979) and Jablensky and Lawrence (2001) for an adequate analysis.

There were some methodological and substantive limitations to our studies. Methodologically, we did not obtain a research diagnosis of schizophrenia, nor did we check whether some persons diagnosed with schizophrenia might have been affected by a brain tumor, primary or secondary, which could have mimicked schizophrenia-like psychopathology. In addition, we limited our comparison group based on the general population to the 15- to 45-year-old range (i.e., the age of risk for schizophrenia). Thus, cancer patients who have died within this age range did not enter into our cohort and, hence, potential persons with schizophrenia may have been eliminated from the numerator. This, in turn, could result in a low diagnosis of schizophrenia among people with cancer than to a low incidence of cancer among people with schizophrenia. However, it is unlikely that our results were affected given the extremely low cancer mortality rates in the target age group of the general population, 30/100,000 (Israel Center for Disease Control, 1998).

Substantively, we did not explore the pharmacological history of patients with schizophrenia. Recall here that the possible protective effect of antipsychotic medication has been raised as an explanation for the lower risk of cancer in persons with schizophrenia (Mortensen, 2002).

6. Conclusion

Although the results showed an overall reduced risk for cancer among persons with schizophrenia, we found as well that the risks by specific tumor sites vary markedly. In view of these contrasting results and those obtained by other investigators, what is now required is a multinational study with sufficient statistical power. This inquiry should explore risk factors for cancer in probands and families, including information on the use of psychotropic medication. This may advance the clarification of an intriguing subject that has yet to reach closure.

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