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Cancer risk among parents and siblings of patients with schizophrenia

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Background A reduced risk of cancer has been noted among people with schizophrenia. Given that genetic causes have been proposed as an explanation of this finding, one would expect that the risk of cancer among first-degree relatives would be equally reduced.

Aims To investigate the risk of cancer among the biological parents and full siblings of people receiving in-patient care for schizophrenia.

Method Linkage analysis was conducted between national population, psychiatric and cancer databases. Standardised incidence ratios for all cancer sites were calculated by comparing the incident rates among first-degree relatives with national incidence rates.

Results A reduced cancer risk was found across all groups examined. Among parents, whose numbers were adequately large, the findings reached statistical significance. For index cases and siblings – a markedly younger population – only a trend was elicited.

Conclusions The genetic hypothesis – namely, the presence of a gene with the dual effect of reducing the cancer risk and disrupting neurodevelopment – is a plausible explanation for these findings.

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The reduced risk of cancer among patients with schizophrenia is a research puzzle (Jablensky & Lawrence, 2001). Indeed, this finding – which does not apply to other psychiatric disorders (Carney *et al*, 2004) – is totally unexpected, since people with schizophrenia have additional health risks, such as heavy smoking (Dalack *et al*, 1998), other unhealthy lifestyle habits (Brown *et al*, 1999) and often medical neglect (Cradock-O'Leary *et al*, 2002). Several recent studies (e.g. Barak *et al*, 2005; Grinshpoon *et al*, 2005), although not all (Goldacre *et al*, 2005), have replicated this puzzling result. Among the hypotheses proposed to explain the reduced risk is that the p53 gene generates, through apoptosis, the dual effect of disrupting neurodevelopment and reducing the risk of cancer (Catts & Catts, 2000; Park *et al*, 2004; Yang *et al*, 2004; Cui *et al*, 2005).

Confirmation of the genetic hypothesis would require that the first-degree relatives of patients with schizophrenia be found to have a similar reduced cancer risk, compared with suitable populations. The epidemiological evidence remains inconclusive: both a lower risk (Lichtermann *et al*, 2001) and no risk differential (Dalton *et al*, 2004) have been found. The Finnish study (Lichtermann *et al*, 2001) reported a lower risk among fathers, with a standardised incidence ratio (SIR) 0.93 (95% CI 0.90–0.96), and also among mothers (SIR=0.89, 95% CI 0.86–0.92), brothers (SIR=0.85, 95% CI 0.76–0.93) and sisters (SIR=0.92, 95% CI 0.84–0.99). Curiously, the cancer risk for patients with schizophrenia in that study was higher than the cancer risk for the general reference population (SIR=1.17, 95% CI 1.09–1.25). In contrast, when the Danish researchers compared the parents of patients with schizophrenia with the general population, they found not only no overall risk differential, but a 20% increased risk of lung cancer among the mothers (Dalton *et al*, 2004). These results were contested by Lichtermann (2005), who argued that the observation period in the Danish study did not cover the whole lifetime of the parents, and that there was insufficient empirical evidence in the published literature for the 'healthy parent' effect as an explanation for the reduced cancer risk found in the parents of patients with schizophrenia in his own study. In their reply, Dalton *et al* (2005) supported their thesis by reporting that they did find a reduced cancer risk in parents, but only when the comparison population included childless adults as in the Finnish study.

Like Denmark and Finland, Israel also has a continuously updated population register as well as registers for cancer cases and psychiatric hospital admissions. This has enabled us to replicate the attempt to confirm a reduced cancer risk among first-degree relatives, a project that continues our earlier study in which we found a lower risk of cancer in patients with schizophrenia (Grinshpoon *et al*, 2005).

METHODS

Identification of patients with schizophrenia

The following service procedures and policies facilitated the identification of people with schizophrenia for inclusion in our study

(a) primary care physicians usually refer patients with severe psychiatric disorders to specialist services;

(b) direct and relatively easy access to these services is also freely available on a drop-in basis (Levav & Grinshpoon, 2004);

(c) the Israel Defense Forces' medical examinations prior to recruitment (both genders) and during reserve duties (men only) serve as a universal screening procedure which is followed by a psychiatric assessment whenever deemed necessary;

(d) patients with psychosis are usually admitted to in-patient care;

(e) Israelis rarely seek hospitalisation for a schizophrenic disorder abroad.

This was confirmed in a community-based study of an Israel-born birth cohort, which found that all respondents identified with schizophrenia in the cohort were known to the in-patient psychiatric services (Levav *et al*, 1993).

We used the nation-wide psychiatric case register to identify patients with schizophrenia for our sample. This 50-year-old register is mandated by law to maintain a cumulative record of all psychiatric hospital admissions (Lichtenberg *et al*, 1999; Mental Health Services, Department of Information and Evaluation, 2004). The identity number used to record all patient movements is the same as that used by the national population register and the cancer register. The psychiatric case register also provided the patients' diagnoses upon admission and discharge as well as socio-demographic information. Diagnoses follow the ICD–10 (World Health Organization, 1992); those made prior to the introduction of ICD–10 have been updated. A test of the agreement between research diagnoses and those recorded in the register found a satisfactory match (Rabinowitz et *al*, 1994; Weiser *et al*, 2005). Although the recording of cases is complete for Jewish Israelis, this is not so for the Arab Israeli minority, particularly women, who use psychiatric in-patient services considerably less than Jewish Israelis (Mental Health Services, Department of Information and Evaluation, 2004). To avoid biasing the sample, the Arab Israeli minority was excluded.

Identification of cancer cases

The Israel National Cancer Registry (http://www.health.gov.il/icr was established in 1960 (Freedman *et al*, 2001). Reporting has been mandatory since 1982 for all medical facilities, public and private. The registry also collects data on cancer deaths from district health authorities and from the Ministry of the Interior's population register. As in the psychiatric case register, the information is organised using a personal identity number. Information completeness exceeds 95%. Continuous efforts are made to improve reporting and accuracy (Fishler *et al*, 2002). Multiple tests, as prescribed by the International Agency for Research on Cancer (Parkin *et al*, 2002), for example the percentage of cases with morphological verification, the mortality to incidence ratio and the percentage of cases ascertained by death certificate only, are conducted regularly to check data quality.

The number of residents with cancer who seek diagnosis and treatment abroad is probably small, since medical services in Israel are free and adequate. However, the exact number of those going abroad for care, as well as the number of Israelis living abroad who might have returned home to avail themselves of free medical care, is unknown. Neither figure is likely to be large.

Linkage procedure

The two case registers and the population register can be linked by means of the personal identity number. This identity number is supplemented automatically with the person's full name, gender, date of birth and place of origin and the father's first name, to ensure a reliable linkage. The process of identification and linkage comprised four steps. First, through the psychiatric case register, we identified a cohort of persons discharged from their last or only in-patient episode with a diagnosis of schizophrenic disorder (ICD–10 codes F20–29). To do this we made use of an existing database of family-linked files of individuals with schizophrenia. In this database (n=6132) almost all patients with schizophrenia (about 95%) were born in Israel in the years 1970–1988, either to immigrant or to native-born parents. The few who were born abroad were 5 years old or less on immigration. Second, we identified their biological parents (mothers n=5756; fathers n=5741) and their full siblings (brothers n=9445; sisters n=9846) using the population register's computerised family files. Third, we ran the files of both parents and siblings through the psychiatric case register to identify all patients discharged from their last or only in-patient episode with a diagnosis of schizophrenic disorder (F20–29), as noted above (fathers n=224; mothers n=393; brothers n=508; sisters n=354). Fourth, the files of index cases, parents and siblings were run through the cancer register to locate cancer cases. This four-stage process generated three sub-populations

(a) index cases with and without cancer;

(b) parents never hospitalised for schizophrenia, or hospitalised for schizophrenia at least once, with and without cancer;

(c) siblings never hospitalised, or hospitalised at least once for schizophrenia, with and without cancer (Table 1). Dates of death and emigration were obtained from the population registry.

The case registers (psychiatric and cancer) owned and maintained by the Ministry of Health are administered under strict legislatively defined procedures. To preserve confidentiality, linkages are made by methods that ensure researchers are not given files with the individual's real identity number. Internal review board approval to build the study family database was obtained from Butler Hospital, Providence, Rhode Island, USA.

Statistical analysis

The cancer incidence rates in the above three sub-populations were compared with the rates in the Jewish Israeli population using standardised incidence ratios (and their 95% confidence intervals), defined as the ratio of the observed to the expected number of cancer cases. The expected number of cases during the observation period was calculated by gender, area of origin (Africa–Asia, Europe–America or Israel) and age. Period-specific cancer incidence rates were used.

The person-years of exposure to cancer risk were defined as follows: index cases, from date of birth or date of immigration; parents, from date of immigration or from 1960, whichever was the later; and siblings, from date of birth or immigration or from 1960, whichever was the later (Table 2). The observation ended on death, diagnosis of cancer, emigration, or at the end of 2003.

Analysis by cancer site, gender and area of origin was conducted when the number of cancer outcomes in the sub-population was 10 or more. The test was performed for all index cases with a schizophrenic

Table 1 Cancer cases among patients with schizophrenia (index cases) and their first-degree relatives

	Group size *n*	Cancer cases *n*
Index cases		
Male	4073	28
Female	2059	14
Total	6132	42
Parents		
Male	5741	501
Female	5756	549
Total	11 497	1050
Siblings		
Male	9846	79
Female	9445	93
Total	19 291	172

Table 2 Exposure to cancer risk, calculated for age group and gender, for index cases and their first-degree relatives, excluding those diagnosed with schizophrenia

Age, years	Exposure to cancer risk, person-yearss					
	Parents		Siblings		Index cases	
	Male	Female	Male	Female	Male	Female
0–4	540	1495	43 364	42 533	20 048	10 168
5–9	2924	5398	44 321	43 545	20 346	10 284
10–14	8043	11 976	43 196	42 356	20 331	10 284
15–19	14 178	17 998	39 619	38 956	20 169	10 173
20–24	19 187	22 222	33 491	32 973	18 523	9122
25–29	23 166	24 960	25 348	25 243	13 424	6755
30–34	25 331	26 011	16 118	16 160	5544	2932
35–39	26 316	26 281	8529	8536		
40–44	26 609	25 757	3578	3420		
45–49	25 743	23 474	1070	887		
50–54	22 332	18 203	114	67		
55–59	15 900	10 723	13	12		
60–64	9243	4911	5	8		
65–69	4720	1915	8	6		
70–74	1767	456				
75+	650	96				
Total	226 648	221 876	258 774	254 701	118 385	59 717

Table 3 Standardised incidence ratios of cancer among index cases and first-degree relatives, compared with the general population, 1960–2004

	Cases		SIR (95% CI)
	Expected	Observed	
Index cases			
Male	31.96	28	0.88 (0.55–1.78)
Female	17.98	14	0.78 (0.37–1.19)
All parents			
Male	597.69	501	0.84 (0.76–0.91)
Asia–Africa	279.62	241	0.86 (0.75–0.97)
Europe–America	149.39	115	0.77 (0.63–0.91)
Israel	168.29	143	0.85 (0.71–0.99)
Female	634.85	549	0.86 (0.79–0.94)
Asia–Africa	255.40	228	0.89 (0.77–0.99)
Europe–America	140.99	119	0.84 (0.68–0.99)
Israel	238.01	197	0.83 (0.71–0.94)
Parents without schizophrenia			
Male	577.94	490	0.85 (0.77–0.92)
Female	592.00	515	0.87 (0.79–0.95)
All siblings			
Male	85.59	79	0.92 (0.69–1.13)
Female	111.95	93	0.83 (0.57–1.00)
Siblings without schizophrenia			
Male	83.09	77	0.93 (0.72–1.13)
Female	107.13	89	0.83 (0.66–1.00)

SIR, standardised incidence ratio.

disorder (F20–29), and separately for 'restricted' cases (F20, F22, F25) (e.g. paranoid schizophrenia) and 'extended cases' (F21, F23, F24, F28, F29) (e.g. acute schizophrenia-like psychotic disorder), assuming a differential weight for the imputed genetic component in the aetiology of each group of disorders.

Since we could not know who in the general population sample was a parent, in order to check the 'healthy parent' hypothesis (Dalton *et al*, 2004) we performed a sensitivity analysis restricted to women, taking into account that in the latest national census about 7.0% of all women aged 35 or over had no children. For all cancers, we assumed that childless women had increased relative risks of 1.0, 1.5 and 2.0 as compared with mothers. The corrected expected number of cases among mothers, E_c, was calculated as $E_c = E/(0.93+k0.07)$ where E is calculated using the official age group × gender × area of origin × period-specific cancer incidence rates, E_c is the corrected expected number of cases and k=1.0, 1.5 and 2.0. The standardised incidence ratio (SIR) and the corrected ratio (SIRc) and their 95% confidence intervals were calculated using Poisson regression, with E and E_c as the respective offset. All calculations were performed using SAS version 9.1.3 for Unix software.

RESULTS

Both parents, including those with schizophrenia, had reduced cancer risk: mothers, SIR=0.86 (95% CI 0.79–0.94); fathers, SIR=0.84 (95% CI 0.76–0.91). The cancer risk for parents after excluding those hospitalised with schizophrenia remained almost unchanged: mothers, SIR=0.87 (95% CI 0.79–0.95); fathers, SIR=0.85 (95% CI 0.77–0.92). Lower ratios were found for gender-concordant pairs of offspring and parent: female index case and mother, SIR=0.74 (95% CI 0.63–0.86); male index case and father SIR=0.81 (95% CI 0.73–0.90). For gender-discordant pairs, the ratios were: father of female index case, SIR=0.89 (95% CI 0.76–1.02); mother of male index case, SIR=0.93 (95% CI 0.84–2.02).

Standardised incidence ratios among parents by restricted or extended type of schizophrenia showed no statistically significant difference. By all areas of origin, mothers and fathers showed a statistically

Table 4 Standardised incidence ratios of cancer among mothers compared with estimates of reduced cancer risk in the general population after correcting for differential levels of relative risk of cancer among childless women, 1960–2004

	Cases, *n*		SIR (95% CI)
	Expected	Observed	
All mothers			
RR=1.0	634.85	549	0.86 (0.79–0.94)
RR=1.5	613.47	549	0.89 (0.82–0.97)
RR=2.0	593.40	549	0.93 (0.86–0.99
Mothers without schizophrenia			
RR=1.0	592.00	515	0.87 (0.79–0.95)
RR=1.5	572.50	515	0.90 (0.82–0.98)
RR=2.0	553.78	515	0.93 (0.86–0.99)

RR, relative risk; SIR, standardised incidence ratio.

significant risk reduction (Table 3). With regard to the four leading cancer sites among parents, two sites showed reduced risks: breast cancer, expected 239, observed 204, SIR=0.85 (95% CI 0.74–0.97); prostate cancer, expected 60, observed 46, SIR=0.77 (95% CI 0.55–0.99). For lung and colorectal cancers the ratios were lower than unity in both parents, but failed to reach statistical significance. Index cases and siblings had a non-significant risk reduction, probably because of their relatively younger age. Index cases: females, SIR=0.78 (95% CI 0.37–1.19), males, SIR=0.88 (95% CI 0.55–1.20). Siblings: brothers, SIR=0.92 (95% CI 0.72–1.13); sisters, SIR=0.83 (95% CI 0.66–1.00). The cancer risk among siblings, after excluding those with schizophrenia, remained almost unchanged: brothers, SIR=0.93 (95% CI 0.72–1.13); sisters, SIR=0.83 (95% CI 0.66–1.00) (Table 3).

The sensitivity analysis performed on mothers to check for the 'healthy parent' (mother) effect did not alter the findings; mothers of people with schizophrenia retained a significantly reduced cancer risk (Table 4).

DISCUSSION

The finding of a reduced risk for cancer was consistent across all groups, but particularly marked with respect to parents, and especially for gender-concordant parent–offspring pairs. For index cases and siblings, the risk differential did not reach statistical significance, most probably owing to lack of statistical power. In an earlier study of ours based on a much larger cohort (Grinshpoon *et al*, 2005), we did find a statistically significant reduced cancer risk for index cases. With respect to index cases, the problem in the study reported here might also be compounded by premature mortality (Goff *et al*, 2005).

With regard to specific cancer sites, the test in this study for breast cancer was the most adequate, since the relatively large sample size generated enough statistical power to demonstrate a statistically significant reduction. For other cancer sites, except for prostate cancer, the results were less definite.

This study has several methodological limitations and strengths. A first possible limitation was pointed out by Dalton *et al* (2004, 2005) – namely, that to control for the 'healthy parent' effect, parents of children without schizophrenia constitute a better reference group than the general population. We doubt, however, that their objection to the Finnish study (Lichtermann *et al*, 2001) for using the general population as a reference group is relevant in our case, because of our different demographic patterns. Whereas in Denmark the total fertility rate was 1.7 and only 24.0% of households had three or more members (Danmark Statistik, http://www.dst.dk), among Jewish Israelis, the respective figures reached 2.6 and 60% (Central Bureau of Statistics, http://www.cbs.gov.il). In 1997 the Israeli census found only 7.2% of women aged 35 and older to be childless, whereas in Denmark the proportion was nearly 18.0%. Moreover, our *ad hoc* and conservative sensitivity analysis (Lichtermann, 2005) generated no indication of the healthy parent (in our case, mother) effect.

A second factor that might undermine our conclusions is that whereas patients with schizophrenia are more frequently found in the low socio-economic groups (Dohrenwend *et al*, 1992), cancer in Israel is more frequent in the higher socio-economic groups (Israel National Cancer Registry, 1990; Israel Center for Disease Control, 1998). Curiously, socio-economic status as a confounding variable has seldom been discussed in the research literature. In our study, however, it may not constitute a problem since parents of patients with schizophrenia are not found in the lower socio-economic groups at a higher proportion than in the general population (Goldberg & Morrison, 1963; Byrne *et al*, 2004). Nor may socio-economic status be problematic with regard to the healthy siblings. Nevertheless, we checked for the socio-economic status effect by grouping our parents by ethnic origin. In Israel this is a reasonable proxy measure for socio-economic status, since Israelis born in Asia or Africa generally have a lower socio-economic status than their counterparts born in Europe or America (Schwartz *et al*, 1991). We found that parents of patients with schizophrenia had a decreased cancer risk, regardless of their continent of origin.

Third, our index cases were diagnosed by clinicians who, in the nature of their work, do not attempt to achieve a research-standard diagnosis. To increase validity we extended the period of observation by using the discharge diagnosis from the last or only in-patient episode. However, if our final sample included people diagnosed as having schizophrenia but who in fact had other disorders, these false-positive cases would only buttress our results. Fourth, our finding that more mothers than fathers had schizophrenia might suggest a sampling bias, because in the psychiatric case register we found considerably more men than women hospitalised with schizophrenia, for both index cases and siblings. Conceivably, there is a greater likelihood that women marry and have children before they require hospital treatment, given that their mean age at disease onset is higher than that of men. Fifth, although we did not have access to lifestyle issues highly associated with cancer, such as smoking, we doubt that health-promoting behaviour is any more frequent among parents of offspring with

schizophrenia than among parents in the reference population. Finally, early death among the parents of people with schizophrenia cannot be ruled out as a confounding factor. However, there is no evidence to suggest that early mortality is linked to cancer risk.

Our register-based study had two particular methodological strengths. Both databases provided us with fairly complete and accurate data; furthermore, we repeated the database linkage procedures to make sure that the matches were correct. Additionally, the differential cancer risk among ethnic groups in Israel and the closeness to the rates found in the USA for frequent cancer sites (Freedman *et al*, 2006) reduce the possible group-specificity of our results.

In sum, if the strengths of our study outweigh its limitations, we are confident that we detected a consistently lower risk of cancer among the parents of people with schizophrenia, and a trend among index cases and siblings. Several hypotheses have been proposed to explain these findings (Mortensen, 1994), among them, the dual role of a tumour suppressor gene such as *p53* (Catts & Catts, 2000; Ni *et al*, 2005). Tumour suppressor *p53* has been identified as the most frequently mutated gene in human cancer. The gene is usually activated following DNA damage or other types of cellular insult. Activated *p53* may block progression through the cell cycle or, alternatively, may lead to apoptosis, and in this way prevent the accumulation and transmission of genetic damage to daughter cells. In the specific context of neural development, it has been shown that *p53* fulfils an important role in the normal apoptosis-driven neurogenesis of various brain structures. In accordance with this notion, it has been postulated that increased *p53* levels in schizophrenia patients may increase cell death in potentially critical areas of the central nervous system. This hypothesis is consistent with the multiple structural defects in cerebral anatomy reported in schizophrenia. On the other hand, mutations in the *p53* gene (the most common cause for *p53* accumulation) may be associated with genomic instability in particular tissues and a greater probability of organ-specific neoplastic transformation. Taken together, these features suggest that *p53* might constitute a dual effector with important roles in the aetiology and development of schizophrenia and, concomitantly, in cancer protection or promotion (Catts & Catts, 2000; Park *et al*, 2004; Yang *et al*, 2004; Cui *et al*, 2005; Ni *et al*, 2005).

Although the genetic hypothesis has been challenged (Jablensky & Lawrence, 2001), based on our findings this hypothesis constitutes an attractive tentative explanation that deserves further research. An advantage of this line of research would be that by probing into the purported link between schizophrenia genes and cancer, we might learn something about schizophrenia by studying cancer (Kalkman, 2006).

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