

# The incidence of cancer in schizophrenic patients

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**ABSTRACT** A cohort of 6168 schizophrenic patients was followed from 1957 to 1984 to determine the incidence of cancer in these patients. In the male schizophrenic patients the incidence of cancer was found to be significantly reduced in comparison with the general Danish population. This reduction was especially marked for cancer in the respiratory system, cancer of the prostate and cancer of the bladder. In the female patients the overall incidence of cancer did not differ from that of the general Danish population, but there was an increased risk of cancer of the digestive tract, especially cancer of the pancreas and a slight increase of the risk of breast cancer. In the female patients the risk of respiratory cancers and cancer of the female genital organs, especially cancer of the uterine cervix, was reduced.

These alterations of the incidence of cancer in schizophrenic patients cannot be ascribed to differences in diagnostic accuracy. As a possible explanation of these findings a reduced exposure to well known carcinogens such as cigarette smoke may be relevant. We speculate that exposure to neuroleptics such as phenothiazines and reserpine may also be part of the explanation for the findings.

The relationship between schizophrenia and cancer has been a subject of controversy among psychiatrists throughout most of this century. This controversy has been sustained by the lack of conclusive empirical evidence with respect to the occurrence of cancer in schizophrenic patients.<sup>1 2</sup>

It would be of much interest to demonstrate an altered occurrence of cancer in these patients, who are and have been subject to many special living conditions that might have modified the cancer risk. In this way schizophrenic patients form a subpopulation that offers the opportunity to study special risk factors, such as psychotropic drugs.

Most previous studies have been mortality studies, and a few of these have been based on study populations large enough to yield valid estimates of the mortality from cancer in schizophrenics.<sup>3-6</sup> Cancer mortality, however, is a mixed indicator of cancer occurrence that includes both the susceptibility of developing cancer and the ability to survive the disease. As the latter feature is heavily dependent on medical interventions, a more suitable measurement of cancer occurrence would be the incidence of cancer. The study of the incidence of one uncommon group of diseases, such as cancer, in a group of patients with another rare condition, such as schizophrenia, is, however, associated with many difficulties, because a large group of patients has to be followed for a long time to yield valid estimates of the incidence of cancer.

As a consequence of these difficulties it was decided in 1977 to start an international multicentre study of the incidence of cancer in schizophrenics, under the auspices of the Division of Mental Health, WHO, Geneva. It has so far only been possible to complete these studies in Japan and Denmark,<sup>7 8</sup> though preliminary results have been reported from the Oxford Centre in England.<sup>9</sup>

The present study represents an extended follow up of the original Danish study population.

## Methods

The study population consists of all persons who were inpatients in a Danish psychiatric hospital on a census day in 1957 with the diagnosis of schizophrenia.<sup>10</sup> Of the original 6178 patients, it was possible to re-identify all but 10. This was made possible by the many registers that are available in Denmark.<sup>11</sup>

A further eight persons had to be excluded, because they had developed cancer before the start of the observation period. Eight persons were excluded for computational reasons since they reached the age of 100 years at some time during the observation period. The final study population thus consisted of 6152 persons, 2956 males and 3196 females. By linkage of the names and the unique identification number of these persons to the Danish Cancer

Registry, using the methodology described by Jensen,<sup>12</sup> all patients who had received a cancer diagnosis during the period 26 September 1957 to 31 December 1984 were identified.

The cancer incidence was calculated by using the person-years method. The calculations were performed using the computer programme OVL P 6 developed by Juul.<sup>13</sup> This programme calculates the incidence rate ratio (IRR), ie, the observed number of cancer cases in the study population divided by the expected number of cases. The expected number of cases was calculated on the basis of the cancer incidence rate in the general Danish population, standardised for age. The calculations were performed separately for each of the periods 1957–62, 1963–67, 1968–72, 1973–77 and 1978–84, using as an external reference the Danish cancer incidence rates that have been published by the Danish Cancer Registry.<sup>14–17</sup> (The rates from 1981 were used as reference for the period 1978–84). The calculation was performed separately for males and females.

The Danish Cancer Registry has been in existence since 1943 and contains approximately 95–99% of all diagnosed cancer cases in Denmark.<sup>19</sup>

## Results

The number of cancer cases among schizophrenic patients and the IRR for the 13 main groups of tumours listed in the Danish Cancer Registry are shown in table 1. The male schizophrenic patients had a significantly reduced incidence of cancer (IRR = 0.76). This incidence reduction was especially marked for cancer in the respiratory system, in the male genital organs and in the urinary system. For the group "other and unspecified sites", which in this

population mainly consisted of sarcoma with no specified location, there was an increased risk.

In the female schizophrenic patients the overall cancer incidence rate did not differ from that in the general Danish population. There was, however, a slight increase in the incidence rate of tumours of the digestive tract, of metastases, and, as was the case in the males, of tumours in the group "other and unspecified sites". The incidence of respiratory cancers and tumours in the female genital organs was significantly reduced. There was a slight but non-significant increase in the risk of developing breast cancer.

In the total population of males and females the overall incidence rate of cancer was significantly reduced (IRR = 0.90). Most of this risk reduction can be ascribed to the reduced risk of developing respiratory cancers. The risk of developing breast cancer was slightly but significantly increased. The risk of developing tumours in the group "other and unspecified sites" was increased.

The material was further analysed by dividing the cases of cancer into subtypes. The result of this analysis is seen in table 2. Many of the incidence rates differed considerably from those in the general Danish population. However, these results should be interpreted with great caution because of the small numbers in each subgroup. In the male patients cancer of the larynx, lung, prostate, and bladder occurred with a reduced incidence. No subtype occurred with a significantly increased incidence in the male patients. There was, however, a slight non-significant increase in the incidence of cancer of the stomach and oesophagus, and of melanoma.

In the female patients cancer of the pancreas and non-Hodgkin lymphoma occurred with an increased

Table 1 Cancer incidence in 6152 schizophrenic patients 1957–1984; main groups.

Tumour site	Males		Females		Males + females	
	No of cases	IRR <sup>a</sup>	No of cases	IRR	No of cases	IRR
All sites	443	0.76†	585	1.06	1028	0.90†
Buccal cavity	11	0.65	4	0.55	15	0.62
Digestive tract	174	0.93	210	1.16*	384	1.05
Respiratory system	42	0.35‡	15	0.53†	57	0.38‡
Breast	2	1.85	125	1.19	127	1.19*
Female genital organs	–	–	70	0.74†	–	–
Male genital organs	44	0.57‡	–	–	–	–
Urinary system	47	0.72*	38	1.26	85	0.89
Skin	63	0.91	52	0.90	115	0.90
Other specified sites	14	0.83	19	1.05	33	0.95
Metastases	8	0.94	16	1.65*	24	1.32
Other and unspecified sites	12	2.59†	25	2.48‡	37	2.52‡
Lymphatic and haematopoietic system	32	0.88	28	0.96	60	0.92

<sup>a</sup> IRR = observed/expected no of cases standardised for sex and age.

\*p < 0.05; †p < 0.01; ‡p < 0.001

Table 2 Cancer incidence in 6152 schizophrenic patients 1957-1984; subtypes.

Tumour site	Males		Females		Males + females	
	No of cases	IRR	No of cases	IRR	No of cases	IRR
Lip	6	0.66	1	0.88	7	0.68
Oesophagus	9	1.18	6	1.21	15	1.19
Stomach	63	1.20	52	1.26	115	1.26*
Colon + rectum	71	0.81	99	1.07	170	0.94
Liver	7	0.82	8	1.11	15	0.95
Biliary tract	9	1.60	17	1.32	26	1.41
Pancreas	14	0.64	32	1.59†	46	1.10
Larynx	2	0.25*	2	1.76	4	0.43
Lung	36	0.34‡	7	0.29†	43	0.33‡
Lung, not primary	2	0.90	3	3.30*	5	1.60
Uterine cervix	-	-	20	0.68	-	-
Uterine corpus	-	-	22	0.78	-	-
Ovary	-	-	23	0.78	-	-
Prostate	40	0.56†	-	-	-	-
Testis	1	0.39	-	-	-	-
Kidney	16	0.87	21	1.46	37	1.13
Bladder	31	0.66*	17	1.08	48	0.78
Melanoma	6	1.17	8	1.12	14	1.14
Brain	7	0.69	15	1.50	22	1.45
Non-Hodgkin lymphoma	8	0.83	15	1.70*	23	1.24
Hodgkin's lymphoma	1	0.35	2	1.03	3	0.63
Malignant myeloma	7	1.01	4	0.67	11	0.85
Leukaemia	17	1.02	8	0.65	25	0.87

\* $p < 0.05$ ; † $p < 0.01$ ; ‡ $p < 0.001$ 

incidence. The incidence of lung cancer was significantly lowered.

When looking at the total population, cancer of the stomach occurred with an increased incidence and cancer of the lung occurred with a decreased incidence.

## Discussion

The finding of a reduced incidence of certain types of cancer in a special population such as schizophrenic patients immediately raises the question as to whether differences in diagnostic practices may account for the findings. This explanation finds support in the fact that several reports have been made of the frequent occurrence of unrecognised medical illnesses in psychiatric patients.<sup>20-24</sup> If this was the explanation of the findings in this study population, one would expect cancer to have been diagnosed by the unexpected finding of a tumour at autopsy to a greater extent than in the general Danish population. However, an investigation of 108 hospital records of schizophrenic cancer patients from this patient population showed that only one of these patients had had cancer diagnosed at autopsy. The autopsy rate in the schizophrenic patients (46.9%) did not differ significantly from that of the general Danish population (42.7%). Therefore it seems justified to believe that the procedure for diagnosing cancer in these schizophrenic patients has been at least as efficient as in the general Danish population, and it must be concluded that the findings in this study

represent real differences in cancer incidence rates.<sup>25</sup>

Of other possible explanations of these findings, an altered exposure to well known carcinogens must be considered. As the reduced incidence of cancer in these patients can be attributed especially to a reduced incidence of respiratory cancers, tobacco smoking in particular must be considered. It is well known that schizophrenic patients today are very heavy smokers.<sup>26</sup> However, the smoking habits that are relevant for the cancer incidence in this study population are those of the 50s and 60s. During this period smoking in this study population of schizophrenic patients was very limited, partly because of the limited amount of money these patients had at their disposal, and partly because of prohibition against smoking in Danish psychiatric hospitals. The money available for schizophrenic patients in this period would cover only about one pack of cigarettes a week at a maximum. Therefore, it seems justified to believe that the limitation of cigarette smoking in the 50s and early 60s has contributed to the lowered incidence of cancer that has now been found.

As regards the slight reduction in cancer of the uterine cervix, this may be explained by reduced sexual activity in the female schizophrenic patients.<sup>27</sup> Sexual activity is lowered partly because of the patients' mental disorder, and partly because of an often life long placement in a closed female ward in a psychiatric hospital. The low rate of pregnancies may also partly explain the increased risk of developing breast cancer.<sup>28</sup>

A point of considerable interest is whether

treatment with neuroleptics has modified the cancer incidence in these patients. A pilot study has been performed and published<sup>29</sup> in which male schizophrenic patients with cancer of the lung or cancer of the bladder and female schizophrenic patients with cancer of the breast or cancer of the uterine cervix were compared to age and sex matched controls from the same cohort of schizophrenic patients, using a logistic regression model. These were also compared with respect to exposure to risk factors such as occupation, duration of admission to a psychiatric hospital, and parity as to the various types of neuroleptics, including reserpine which found widespread use as a neuroleptic drug in schizophrenic patients in the period from 1954 to the mid 60s. It later lost its popularity as a neuroleptic because of its tendency to induce depression. Reserpine has been reported to increase the risk of developing cancer of the breast,<sup>30-32</sup> but other studies have not confirmed these findings.<sup>33-35</sup> In this population, however, where reserpine had often been given in dosages much higher than those generally used in the treatment of hypertension, its use was associated with a clear and significant increase in the risk of developing not only breast cancer, but also cancer of the uterine cervix. .

As a possible mechanism for the breast cancer inducing effect of reserpine, it has been suggested that it could be mediated through the ability of this agent to elevate serum prolactin levels.<sup>36</sup> However, other neuroleptics, for example the phenothiazines, also elevate serum prolactin levels without increasing the risk of breast cancer.<sup>37 39</sup> It thus seems that the cancer inducing effect of reserpine must be mediated through other mechanisms.

Reserpine was used more frequently in the female than in the male patients. This may be the explanation for the differences in the incidence of cancer of the pancreas between the male and the female patients, as a (non-significantly) increased risk of cancer of the pancreas has been described in association with reserpine use.<sup>30</sup>

Other neuroleptics such as the phenothiazines have been reported to inhibit tumour growth in animal experimental models.<sup>38 39</sup> In the Danish investigation<sup>29</sup> in this patient population neuroleptics other than reserpine were found to reduce the incidence of cancer of the lung, bladder, uterine cervix and breast. It thus seems that medication with psychotropic drugs may in part explain the differences in cancer incidence in this population of schizophrenic patients compared with the general Danish population. There is no obvious explanation for the increased incidence of cancer of the stomach. One possible explanation may be found in the fact that these patients generally come from a poor social

background, and an increased risk of cancer of the stomach associated with low social class has been reported.<sup>40</sup>

There is no obvious explanation for the reduced risk of cancer of the prostate or the increased risk of non-Hodgkin lymphoma in the female patients. A case-control study of the relation between cancer of the prostate and the use of neuroleptics is now being carried out by the author.

It can be concluded that the differences in cancer incidence found between schizophrenic patients and the general Danish population may be explained partly by reduced exposure to well known carcinogens such as tobacco smoking, and partly by the cancer reducing effect of some neuroleptic drugs and the risk increasing effect of reserpine. Therefore further studies to clarify the possible role of drugs, such as the phenothiazines, in the prophylaxis and treatment of cancer seem to be indicated.

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