Cancer Risk Among Future Schizophrenic Patients? A Biased Inference

Carsten Bøcker Pedersen^{*,1}, Thomas Munk Laursen¹, and Preben Bo Mortensen¹

¹Department of Economics and Business, National Centre for Register-Based Research, Aarhus University, Denmark

*To whom correspondence should be addressed; National Centre Register-Based Research, Aarhus University, Fuglesangs Allé 4, 8210 Aarhus V, Denmark; tel: +45 8716 5312, fax: +45 8716 4601, e-mail: cbp@ncrr.dk

The study by Ji et al¹ is based on the excellent Swedish population-based registers. Unfortunately, there are methodological flaws in the analyses of these excellent data. The main criticism is the estimation of the “risk” of cancer in persons who develop schizophrenia in the future.

In Ji et al, nonschizophrenic patients are those who die, emigrate from Sweden, or are alive and reside in Sweden without being diagnosed with schizophrenia within eg 20 years. Schizophrenic patients are those who survive, reside in Sweden, and are diagnosed with schizophrenia within the same time period. Persons with life-threatening cancers have poor survival and therefore a low chance of being attributed to the “future schizophrenic patient” group. Provided with the knowledge that the group of “future schizophrenia patients” cannot die from their cancer within the study period, it is not surprising that “future schizophrenic patients” have a decreased “risk” of cancer. To sum up, in their Table 2, they found that hypothetical persons who survive, do not emigrate from Sweden, and are registered with schizophrenia later during the study period have a decreased risk of any cancer compared with persons who are allowed to die and emigrate from Sweden during the study period (SIR=0.40) [before schizophrenia diagnosis], while persons who have developed schizophrenia have no decreased risk of any cancer (SIR=1.00) [after schizophrenia diagnosis]. No meaningful inferences can be drawn on the risk of cancer in a group of persons who are destined to survive long enough to be diagnosed with schizophrenia. A similar flaw was first described in the Stanford Heart Transplantation Program assigning patients to groups at time of transplantation instead of at time of enrolment for a new heart.²

In contrast, the inferences by Ji et al regarding the time period after being diagnosed with schizophrenia is appropriate. In this group of persons, the authors observed no overall increased risk of cancer in persons

with schizophrenia. In other words, the result in Ji et al is negative, in the sense that there is no overall association between schizophrenia and cancer.

Unfortunately, there are other flaws in the analyses of these excellent data that merits attention. The authors follow the total Swedish population from 1965 onwards until development of cancer, using information on first registered diagnoses with schizophrenia as a proxy for time of onset. This sort of analyses is based on the inherent assumption that for all persons followed they have information of the time of onset of both schizophrenia and cancer. For patients with both schizophrenia and cancer, the analyses, therefore, also assume knowledge of which disorder came first. Without this knowledge, it is not possible to provide meaningful inferences on the risk of cancer in patients with schizophrenia. The Swedish Hospital Discharge Register was first established in 1964 and from this year onwards, diagnoses from any contact to the Swedish psychiatric services were recorded. The first registered diagnoses can only be a meaningful proxy for time of onset if patients have the ability to be registered at time of onset. Due to the data collection procedure, a person born in eg 1920 cannot be registered with schizophrenia before 1964; inherent in their analyses of the data they are assuming that any diagnosis given after 1964 represents the patients’ first onset with schizophrenia,³ an obviously invalid assumption. As a consequence, it is not surprising that the authors demonstrated a higher age of onset with schizophrenia than reported in any previous study including true incident cases. The direction of the bias due to the reverse causality introduced cannot be evaluated.

We recommend that the authors limit their analyses to a population for which they have information on time of first admission with both schizophrenia and cancer. A reasonable definition of such a population could be persons who were born in Sweden 1955–1995, and

the analyses could then follow these persons forward in time. Also, within any observational study, one can divide persons into groups based on the persons' past experience and provide meaningful inferences. However, when a researcher retrospectively divides persons into groups based on future experiences, any inferences will be meaningless. Unfortunately, this was the case in the study by Ji et al.

Funding

This work was funded by the Stanley Medical Research Institute, Bethesda, Maryland, and by grants from The Lundbeck Foundation, Denmark. The funders had no involvement in any aspect of this work.

Acknowledgment

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

References

1. Ji J, Sundquist K, Ning Y, Kendler KS, Sundquist J, Chen X. Incidence of cancer in patients with schizophrenia and their first-degree relatives: a population-based study in Sweden. *Schizophr Bull* 2012; doi:10.1093/schbul/sbs065.
2. Gail MH. Does cardiac transplantation prolong life? A reassessment. *Ann Intern Med*. 1972;76:815–817.
3. Pedersen CB. No evidence of time trends in the urban-rural differences in schizophrenia risk among five million people born in Denmark from 1910 to 1986. *Psychol Med*. 2006;36:211–219.