Cancer Risk Before Schizophrenia Diagnosis in Taiwan, 1995–2009

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The debate on whether schizophrenia precipitates or prevents cancers has lasted for over 1 century.1 Earlier researches almost focused upon the crude cancer risk after schizophrenia diagnosis. Inconsistent and even conflicting cancer incidence ratios were published. The inconsistency could be due to various sources of confounding. Until 1994, Mortensen was the first to take into account different smoking rates between schizophrenia patients and general population to attain smoking-adjusted cancer risks.2 Other lifestyle factors and psychotropic medications were also controlled for in the subsequent studies.3,4 Lichtermann even took a step further to conduct age, gender, and age-of-onset stratified analyses in both schizophrenia patients and their first-degree relatives.5 Despite all these efforts, the adjusted risk ratios were still at odds with one another and no conclusions could be made concerning how schizophrenia alters one’s cancer risks.

On this very topic, Ji et al provided 3 distinct indices using the Swedish schizophrenia registry: (1) smoking-adjusted cancer risk in schizophrenia patients, (2) cancer risk in their first-degree relatives, and (3) before-diagnosis cancer risk in schizophrenia patients.6 Among them, the first 2 indices were frequently reported in the literature. Because most of the factors related to schizophrenia process are impossible to be fully adjusted in registry data, the first-degree relatives of schizophrenia patients turn up as perfect proxies for investigation. The cancer risks for the disease-free relatives could be attributed to either shared genetic background or shared environmental background, but the risks are hardly related with the schizophrenia disease process itself. According to Ji et al, male schizophrenia patients have lower cancer risk than the general population (standardized incidence ratio [SIR]: 0.79, 95% CI: 0.75–0.82), but female patients have higher risk (SIR: 1.20, 95% CI: 1.15–1.24). Moreover, relative to the general Swedish population, the first-degree relatives are generally protected from cancer occurrence (Female SIR: 0.96, 95% CI: 0.94–0.98; Male SIR: 0.92, 95% CI: 0.89–0.96). In a recent meta-analysis, the pooled overall SIRs come fairly close (SIR for siblings: 0.89, 95% CI: 0.84–0.94; SIR for parents: 0.90, 95% CI: 0.88–0.93).7

The work of Ji et al indeed shed new light on “differential cancer risks” throughout schizophrenia development. They constructed not only “cancer risk after schizophrenia diagnosis” but also counter-intuitively, “cancer risk before schizophrenia diagnosis.” There are excellent reasons to do so. First, if schizophrenia and cancers are exclusively genetically linked, whichever condition is first identified should not alter the risk (as long as the observation period is adequately long). Second, cancer risk may distribute unevenly during different stages in schizophrenia. According to their results, the latter scenario is supported. The cancer-protection advantage disappears as patients go from psychiatrically undiagnosed state (SIR: 0.40, 95% CI: 0.38–0.43) to diagnosed state (SIR: 1.00, 95% CI: 0.97–1.03). In women, cancer protection before schizophrenia diagnosis (overall SIR before and after schizophrenia diagnosis: 0.94, 95% CI: 0.91–0.97) shifts into cancer proneness after schizophrenia diagnosis (SIR: 1.20, 95% CI: 1.15–1.24). In men, as schizophrenia manifests itself, the impact of cancer-protection also lessens (overall SIR before and after schizophrenia diagnosis: 0.63, 95% CI: 0.61–0.66; SIR after schizophrenia diagnosis: 0.79, 95% CI: 0.75–0.82).

To our best knowledge, Ji was one of the very few to estimate before-schizophrenia-diagnosis SIRs for cancers.8 Because evidence cumulated concerning cancer risks after schizophrenia diagnosis and those in first-degree relatives, it will be reassuring to establish results on cancer risks before schizophrenia diagnosis too. To obtain “cancer risk before schizophrenia diagnosis,” we used the National Health Insurance Research Database in Taiwan to identify 74 448 schizophrenia patients...
(39,669 men and 34,779 women) diagnosed between 1995 and 2009. The follow-up time for cancers was defined either by person-years until cancer identification before schizophrenia diagnosis or by person-years until schizophrenia diagnosis. The mean ages in 1995 were 30.92 for females and 27.54 for males; the mean follow-up time was 8.13 years for women and 7.95 years for men. A total of 471 patients with schizophrenia (337 women and 134 men) were identified with cancers by the end of 2009. The mean age for cancer identification was 45.6, and schizophrenia was diagnosed averagely 5.3 years later. We calculated expected number of cancers by multiplying the sum of at-risk person-years by the overall cancer rate in the corresponding population (from the cancer registry database associated with “Taiwan Cancer Control Act”). The standardized incidence ratios were calculated as the observed/expected number of cancer cases, with 95% confidence intervals assuming a Poisson distribution for the observed number of cancers. In summary, the before-schizophrenia SIR for cancers was 0.58 (95% CI: 0.52–0.65). The gender-specific SIR was 0.77 (95% CI: 0.67–0.88) in females and 0.36 (95% CI: 0.30–0.44) in males. As such, our results reinforce the findings by Ji et al that cancer risk is generally reduced before schizophrenia manifestation.

Based on our previous work concerning “cancer risk after schizophrenia diagnosis,” the overall SIR for cancers was 1.17 (95% CI: 1.08–1.28), female SIR 1.31 (95% CI: 1.17–1.48) and male SIR was 1.02 (95% CI: 0.90–1.16). Taken together with the before-schizophrenia cancer risks, the trend of “loss of cancer protection (as schizophrenia evolves)” was replicated. Furthermore, from our previous study, we also found the cancer risks appeared significantly lower than those of the general population after 5 years of schizophrenia diagnosis. That is, schizophrenia is generally cancer-protective in both the prodromal and chronic stages. In other words, schizophrenia solely increases cancer risk during the early deteriorating phase. The concurrent cancer risk is likely to be caused by the immunity-inflammation process that also contributes to schizophrenia itself.

For completion, our overall SIR before and after schizophrenia diagnosis was 1.14 (95% CI: 1.07–1.21); separately, 1.30 (95% CI: 1.19–1.41) in women, and 0.94 (95% CI: 0.85–1.04) in men. As far as “trend” is concerned, our findings are consistent with those from Ji et al although both the overall before-and-after-schizophrenia-diagnosis SIRs and the overall after-schizophrenia-diagnosis SIRs are consistently higher in our study.

In Swedish registry, schizophrenia men are protected from cancers, but schizophrenia women do not have the same benefit. In Taiwanese registry, schizophrenia women are at higher risk, whereas schizophrenia men are not apt for cancers. Interestingly, our findings are in line with the after-schizophrenia-diagnosis SIRs from some other Asian-based studies. Given no other plausible explanations, racial disparities are likely to account for the systemic difference. In short, Asian schizophrenia patients tend to possess relatively higher cancer risk profiles than Caucasians irrespective of gender. Catts reasoned that the racial disparity in cancer SIRs among schizophrenia patients might result from the disparity in background cancer incidence rates for general population. For instance, assuming cancer risk in schizophrenia patients is constant across countries, the cancer SIRs would be exaggerated in Asian countries wherein the background cancer incidence rates are usually lower than those of European countries.

In accordance with the after-schizophrenia-diagnosis SIR, Swedish female patients also have an increased cancer risk. Just as we did, Ji et al found female schizophrenia patients have increased risks specifically for female-specific cancers such as breast and endometrium cancers. Knowing the “cancer risk before schizophrenia diagnosis” appears to be lower in both Swedish and Taiwanese women, we are assured that some factors associated with the disease process of schizophrenia (for instance, antipsychotic-induced hyperprolactinemia) may have a universally promoting effect on female-specific cancers.

According to the 2 so far largest population-based studies, cancer risk in schizophrenia is not constant across the life span. To get a renewed in-depth outlook on the relationship between schizophrenia and cancers, we propose that cancer risk in schizophrenia should be framed as stage-specific risk rather than lifetime risk. In the meanwhile, more parallel comparisons should be made between international groups to elucidate risk transition trends and ethnic discrepancies. Finally, the before-after (schizophrenia diagnosis) comparisons may testify the environmental effects on specific cancers.

References

