Cancer Risk in Parents of Patients With Schizophrenia

TO THE EDITOR: Reassuring as it is to see that a recent record linkage study from Denmark by Susanne Oksbjerg Dalton, M.D., Ph.D., et al. (1) accurately replicated our previous finding of a reduced incidence of cancer in the parents of patients with schizophrenia in Finland compared with the general population (2), I was surprised to recognize that this difference vanished when parents whose children were free of schizophrenia were chosen as the comparison group instead. Thus, the authors made a point that our common finding with the general population as the reference group should be invalid, and they claimed a "healthy parenthood effect" as the critical source of bias. However, when testing our genetic hypothesis, they should have considered parents exposed to cancer risk throughout their lifetime. I am not sure whether their method of having follow-up for cancer in parents starts only at the birth of the first child or, alternatively, at the birth (or age at disease onset) of the first child with schizophrenia might have biased their finding of equal cancer risk (e.g., given that some studies find schizophrenia risk to depend on birth order, e.g., Kemppainen et al. [3]). Also, the "healthy parenthood effect" they introduced from a Danish study that found parents of children with cancer at no higher incidence than the general population (4) did not receive general support from several other population studies in parents of individuals with cancer at a younger age (5–7), and it seems counterintuitive at least since a significant proportion of cancer at a younger age is known to occur on a genetic basis. In fact, the only other retrievable large population study that compared cancer risk between the relatives of patients with cancer and the relatives of otherwise deceased persons from Utah (instead of the general population) still found familial cancer risk increased (8). Therefore, I doubt the general validity of the "healthy parenthood effect." It would have been useful to see whether cancer risk in the Danish comparison group of parous individuals with no child affected by schizophrenia was indeed lower than in the general population, including parous and nonparous individuals. Unfortunately, the lack of resources does not currently permit me to replicate, in turn, selection of a parous comparison group from the Finnish population register and analyses similar to those of the Danish study. Meanwhile, I commend the colleagues from Denmark for drawing benefit from the excellent epidemiological material available in Nordic countries, and I hope that other appropriate registers (e.g., Hemminki et al. [9]) will contribute.

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Dr. Dalton and Colleagues Reply

TO THE EDITOR: We introduced the healthy parenthood effect as a proposed explanation for the observed change in results according to which comparison group was used in our study of cancer risk in the parents of schizophrenic offspring. We compared the cancer rates in the parents of schizophrenic offspring (exposed group) to those of other parents, which we consider to be the most correct, and found no difference in cancer risk. When we included persons who had not had any children and used the general population rates of cancer as the comparison, a method similar to that of Dr. Lichtermann and colleagues, we also observed a reduced risk of several forms of cancer, in line with the findings of our Finnish colleagues. It is unlikely that our results were biased by the choice of start of follow-up because we followed up from the time of birth of the schizophrenic offspring in the exposed group in both analyses. We do not think that the results published by our Finnish colleagues are specific to the parents of schizophrenic patients but more generally to being parents. The healthy parenthood effect denotes selective processes that lead to the forming or initiation of a family and, second, to the maintenance of a relatively regular and healthy lifestyle when living a family life. This would probably mean that parents, compared to all adults, smoke less, drink less, exercise more, and so forth. The results that we highlight from the literature in our article as supporting the notion of a healthy parenthood effect include mainly cancer forms with a large environmental component. To the best of our knowledge, there have been no studies of the risk of cancer in parents in general and, as Dr. Lichtermann points out, most studies of cancer risk in cancer families will reflect the high-risk nature and report the higher risk of some forms of cancer with a large familial component. However, the study by Westergaard et al. (1996)—apart from reporting a high risk of testicular cancer in the fathers and brothers of testicular cancer patients—did indeed also find a reduced risk of overall cancer, a reduction mainly carried by reduced lung cancer and gastrointestinal cancer risk. The differences in cancer risk based on whether the exposed group is compared to only other parents or the total population in Denmark must somehow be connected to

parental status, making the healthy parenthood effect a plausible explanation.

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Irritability and Depression

TO THE EDITOR: Manics are irritable. Some depressives are irritable. Ergo, some depressives are bipolar. Not necessarily true. This topic was discussed in a recent article by Giovanni B. Cassano, M.D., et al. (1).

DSM-III and DSM-IV turned diagnoses into symptom checklists. This may increase the reliability of diagnosis, but it does not follow that the symptom necessarily is associated with the diagnosis. Many diagnoses are associated with irritability or distractibility, and even more are associated with impaired concentration or insomnia. These symptoms may occur in mania, but they are so nonspecific that they cannot be said to imply mania.

Much of medicine used to be like psychiatry, i.e., without definitive diagnostic tests. Imagine diagnosing a myocardial infarction without ECGs or enzymes; a constellation of symptoms, including chest pain, diaphoresis, dizziness, irregular heartbeat, etc., suggest a myocardial infarction, but none of these symptoms alone would indicate a myocardial infarction. All occur much more frequently in other conditions.

An unfortunate (and unintended) legacy of DSM-III and DSM-IV is the attribution of diagnostic significance to nonspecific symptoms that are only diagnostically meaningful when they are part of a constellation of symptoms or a syndrome. This has led to agitated, irritable depressives being called bipolar (often "mixed") and to the overdiagnosis of bipolar disorder (analogous to the overdiagnosis of schizophrenia prior to 1970).

Undeniably, some apparent unipolar depressives will turn out to be bipolar. However, the majority of unipolar depressives will never become manic or hypomanic, even with antidepressants, and the presence of irritability, agitation, and other nonspecific symptoms associated with mania does not make these patients even a little bit bipolar.

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Dr. Cassano Replies

TO THE EDITOR: In our recent article on the mood spectrum, we showed that in patients with carefully diagnosed recurrent unipolar depression, there is variability in the lifetime experience of manic-hypomanic symptoms and that increased scores on this manic-hypomanic component of our measure of mood spectrum were associated with a higher likelihood of suicidality and paranoia.

It is undeniable, as Dr. Mattes asserts, that the presence of irritability does not necessarily imply mania. Indeed, our conclusions were not based on individual symptoms but on a dimension that includes 60 items, of which only three could be construed to assess irritability. Therefore, although irritability is frequent, it is not the most prominent aspect of the manic-hypomanic component, which includes a range of mood, energy, and cognitive features.

Regarding the attribution of diagnostic significance to "nonspecific symptoms," our intention was not to purport that unipolar patients who have a high number of manic-hypomanic features should be relabeled "bipolar." Still, the linear relationship found between the depressive and the manic-hypomanic components in patients with both unipolar and bipolar disorder when we used a dimensional approach suggests continuity between these disorders. Moreover, we found an association between the manic-hypomanic component and suicidality and paranoia both in unipolar *and* bipolar patients. In our view, this finding has important clinical implications. The question of whether this dimensional spectrum approach will eventually lead to the identification of a distinct phenotype of unipolar patients presenting similarities with bipolar patients is still open. We are currently conducting a clinical trial that we hope will shed some light on this issue.

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Sertraline for Recurrent Major Depression

TO THE EDITOR: Jean-Pierre Lépine, M.D., and his colleagues (1) evaluated the efficacy of sertraline for the prophylactic treatment of recurrent depressive disorder. We read this double-blind, randomized study with great interest and wish to raise some concerns about the methodological issues.

The use of placebo arms in randomized, controlled trials remains a controversial issue. It has been criticized on ethical grounds. In this context, the Declaration of Helsinki demands that individual patients in a study "be assured of the best proven diagnostic and therapeutic method," even in a control group (2). This statement clearly discards the use of a placebo as a control when a "proven" treatment exists.

In this trial, the way the authors tried to establish that sertraline is more effective than placebo is misleading. Even if sertraline is worse than an existing treatment, it may still be "effective" in that it is better than no treatment (placebo). In this regard, Hill (3) pointed out that the essential medical question at issue is how the new treatment compares with the old one, not whether the new treatment is better than nothing. Similarly, Cochrane (4) stated that no new treatment should be introduced into medicine unless it has been shown in randomized, controlled trials to be superior to existing treatments or equivalent to existing treatment but cheaper or safer.

As there are drugs with proven efficacy for recurrent depressive disorders, such as lithium, we are keen to know why the authors did not try to compare the efficacy of sertraline with existing drugs. It appears that the authors were keen to reflect a drug-specific effect rather than demonstrating its relative efficacy. As readers, we would like to know why the authors carried out such a long placebo phase (2 months). The