Psychotropic medication use and risk of hormone-related cancers: the New York University Women’s Health Study

Ikuko Kato, Anne Zeleniuch-Jacquotte, Paolo G. Toniolo, Arslan Akhmedkhanov, Karen Koenig and Roy E. Shore

Abstract

Background The use of psychotropic medications may increase the risk of hormone-related cancers in females through increased gonadotropin secretion, but the data from epidemiologic studies are limited to evaluate the hypothesis.

Methods The association between the use of psychotropic medications and cancer incidence was studied in a prospective cohort study that involves 15,270 women who participated in mammographic screening. The relative risks (RR) and 95 per cent confidence intervals (CIs) for cancer associated with the use of psychotropic medications were estimated by the Cox’s proportional hazard model.

Results During an average of 7.3 years of follow-up, 1,130 incident cases of cancer were identified, including 566 breast, 67 endometrial and 47 ovarian cancers. The use of any type of psychotropic medication at baseline was associated with increased risks of breast [relative risk (RR) = 1.39, 95 per cent CI 1.11–1.74], endometrial (RR = 1.71; 95 per cent CI 0.93–3.14) and ovarian (RR = 1.48, 95 per cent CI 0.69–3.16) cancers, whereas no increase in risk was observed for other cancers (RR = 1.06). When the subjects were divided by menopausal status at baseline, premenopausal women tended to have higher risk of all hormone-related cancers (RR = 1.73, 95 per cent CI 1.27–2.35) than postmenopausal women (RR = 1.23, 95 per cent CI 0.94–1.62). The magnitude of the RR associated with the use of these medications did not change by length of follow-up. Analysis by type of medication did not find that the association was limited to specific types.

Conclusion The observed association needs to be confirmed in further studies based on more detailed medication history.

Keywords: breast cancer, ovarian cancer, endometrial cancer, psychotropic medication

Introduction

Among US women, cancers of the breast, endometrium and ovary account for more than 40 per cent of all newly diagnosed cancers and 24 per cent of all cancer deaths. As the growth and normal function of these organs are controlled by gonadotropin and female sex hormones, it has been postulated that these hormones have an important role in the development of cancers of these organs. In support of this hypothesis, epidemiologic studies have shown that reproductive histories, such as ages at menarche and menopause, parity and the use of female sex preparations, are associated with the risk of these cancers. Although each of these cancers has different risk profiles, as seen in the associations with oral contraceptives, clustering of these cancers within individuals and among families has long been recognized. Recent discovery of BRCA1 and BRCA2 genes, which are associated with familial breast and ovarian cancers, also suggests that these cancers have common genetic predisposition.

As the hypothalamic–pituitary system is the center of control of these hormones, chemical agents that have neuroendocrine action on the central nervous system may affect the levels of these hormones. Various classes of psychotropic medications have been found to modulate gonadotropin and prolactin secretion. Experimental studies have demonstrated that certain classes of these medications promote malignant growth including growth of breast tumours, in laboratory animals. However, these data are not consistent and some investigators claim a biphasic dose–response in tumour incidence, i.e. tumour promotion at lower concentrations and inhibition at higher concentrations. To date, the data from epidemiologic studies are limited to evaluate this hypothesis. To address this issue, we report here the observations.
Materials and methods

Study subjects were women who volunteered to participate in the New York University Women’s Health Study. Details concerning cohort eligibility and procedures of data collection and follow-up have been published previously. Briefly, the original study population consisted of 15,785 women who enrolled in the study between 1985 and 1991 in New York City (n = 14,275) or at a collaborating institution in Florida (n = 1,510). Women who in the preceding 6 months had neither used hormonal medications nor been pregnant were eligible for this study.

At enrollment, written informed consent was obtained; basic information on demographic, medical, anthropometric, reproductive and dietary data was collected through self-administered questionnaires; and 30 ml of nonfasting peripheral venous blood was drawn. The questionnaire asked about use of the following categories of medicines in the previous 4 weeks; blood pressure medications, analgesics, major tranquilizers (anti-psychotic and anti-manic agents), minor tranquilizers (sedatives, hypnotics and anti-anxiety agents), anti-depressants, anti-arthritis cortisone-type medications, female sex hormones, anti-convulsants, anti-parkinsonian agents and others. Information about dosage was not collected in a standardized way, and no data were available on the duration of usage. The questionnaires indicating the use of ‘other’ drugs were reviewed to identify and correct possible misclassification. Psychotropic medications analyzed here included major and minor tranquilizers, anti-depressants and anti-convulsants.

After the initial examination, the cohort was followed through mailed questionnaires to identify incident cases of cancer diagnosed before 1995 and to update some important epidemiologic risk factors. Telephone interviews were administered if subjects failed to respond to the mailed questionnaire. Medical records were obtained from hospitals and reviewed to confirm pathological diagnosis for self-reported cancer. Record linkages with state cancer registries in New York, New Jersey and Connecticut, and with the National Death Index supplemented the active follow-up. The result of capture-recapture analysis based on the cases among New York residents indicated 94 per cent completeness of follow-up.

A total of 515 subjects who had a history of any hormone-related cancer (breast, endometrium or ovary) before the date of their baseline examinations were excluded, leaving 15,270 subjects in the analysis. Each subject’s time at risk was computed as the time from her baseline examination to the date of the last response to a follow-up questionnaire, the diagnosis of cancer, death or 31 December 1994, whichever occurred first. If a woman developed more than one cancer during the follow-up period, only the first cancer was considered for the analysis. The relative risk (RR) and 95 per cent confidence intervals (CIs) for cancer associated with the use of psychotropic medications were estimated by the Cox’s proportional hazard model. Adjustment was made for age and other specific covariates for hormone-related cancers, i.e. Quetelet index [weight (kg)/height (m)²], age at menarche, menopausal status, parity and family history of breast cancer.

Results

As shown in Table 1, 1,782 (11.7 per cent) women reported using psychotropic medications of any kind in the 4 weeks preceding enrollment in the study. Minor tranquilizers were most common, followed by anti-depressants and major tranquilizers.

During an average of 7.3 years of follow-up, 1,130 incident cases of cancer were identified, including 566 breast, 67 endometrial and 47 ovarian cancers. The age-adjusted RRs associated with the use of any type of psychotropic medications at baseline are presented for all cancers as well as for specific sites of cancer. Whereas no increase in risk was observed for non-hormone-related cancers (RR = 1.06), there was a significant increase in risk of all hormone-related cancers combined (RR = 1.42; 95 per cent CI 1.16–1.75). The RR was 1.39 (95 per cent CI 1.11–1.74) for the breast, 1.71 (95 per cent CI 0.93–3.14) for the endometrium and 1.48 (95 per cent CI 0.69–3.16) for the ovary (Table 2).

Next, the RRs for all hormone-related cancers and breast cancer were calculated by type of medications, adjusted for other covariates in addition to age (Table 3). As expected, the results for all hormone-related cancers and those for breast cancer were very similar. The use of any type of psychotropic medications was associated with an increased risk, which was statistically significant for minor tranquilizers, major tranquilizers and anti-depressants.

If these medications work through changes in the secretion of gonadotropins and female sex hormones, the observed association may be more pronounced in premenopausal women who have functioning ovaries. To test this hypothesis, the multivariate RRs for all hormone-related cancers were calculated by menopausal status at baseline (Table 4). The RR associated

Table 1 Number and per cent of users of psychotropic medications in the cohort

<table>
<thead>
<tr>
<th>Type of psychotropic medications</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any medications</td>
<td>1782</td>
<td>11.7</td>
</tr>
<tr>
<td>Minor tranquilizers</td>
<td>1373</td>
<td>9.0</td>
</tr>
<tr>
<td>Major tranquilizers</td>
<td>92</td>
<td>0.6</td>
</tr>
<tr>
<td>Anti-depressants</td>
<td>269</td>
<td>1.8</td>
</tr>
<tr>
<td>Anti-convulsants</td>
<td>52</td>
<td>0.3</td>
</tr>
<tr>
<td>Number of cohort women</td>
<td>15270</td>
<td></td>
</tr>
</tbody>
</table>
with the use of all types of medications combined was 1.73 (95 per cent CI 1.27–2.35) for premenopausal women and 1.23 (95 per cent CI 0.94–1.62) for postmenopausal women. The difference in RRs was statistically significant (p = 0.02). Similar trends, i.e. higher RRs for premenopausal women, were observed for most types of medication and the difference for anti-depressants was also statistically significant (p < 0.01). When limited to breast cancer, the RRs associated with any type of psychotropic medications were 1.71 (95 per cent CI 1.22–2.39) for premenopausal women and 1.15 (95 per cent CI 0.85–1.57) for postmenopausal women, and those associated with anti-depressant use were 3.49 (95 per cent CI 1.90–6.10) and 0.69 (95 per cent CI 0.26–1.86), respectively. Both differences were also statistically significant (p = 0.02 and p < 0.01).

The use of psychotropic drugs may have been related to the anxiety for mammographic examination or symptoms from preclinical cancer that already existed at the time of the baseline examination. If so, the association should be stronger in the early follow-up period. When the RRs associated with the use of any type of psychotropic medications were calculated by follow-up time (up to 4 years versus 4 years or later), a similar increase in risk of total hormone-related cancers was observed for both early and late follow-up periods (RR = 1.40 and 1.45, respectively). A slightly higher (not significant) risk in the late follow-up period (RR = 1.52) was observed for breast cancer, compared with that in the early follow-up period (RR = 1.24).

### Discussion

The results of the present study indicate that use of psychotropic medications may increase the risk of hormone-related cancer in females by approximately 40 per cent. The stronger association for premenopausal women than for postmenopausal women supports the hypothesis that this effect may be through modifications of the secretion of gonadotropin (especially for ovarian cancer) and female sex hormones (especially estrogen for breast and endometrial cancers). Although an elevated RR was observed for most types of medications, it is not likely to be due to biased recall. Information was collected before cancer diagnosis and there was no association between the use of analgesics, the most common medications in this study population, and risk of these cancers (RR = 1.00). Also, the association is not likely to be due to the use of medications for symptoms caused by preclinical cancer, because it was similarly observed for early and late follow-up periods. However, the equally increased risk in both periods may not necessarily be reconciled with the biological plausibility. One would expect a higher risk in the later follow-up period, because people who started the medication just before their cohort enrollment may not have had a sufficient incubation time to develop cancer in the early follow-up period.

A few epidemiologic studies have directly examined the relationships between psychotropic medication use and risk of cancer. Among patients at Kaiser Permanente,18 overall cancer mortality was not associated with anti-depressant use, whereas risk of developing any type of cancer was 50–60 per cent higher for those using psychotropic medications in a prospective cohort in Washington County, Maryland.19 Two recent case–control studies on ovarian cancer showed an increased risk among women using anti-depressants, anti-anxiety agents or other psychotropic medications.20,21 These associations were

### Table 2

<table>
<thead>
<tr>
<th>Number of</th>
<th>Cases</th>
<th>Users</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone-dependent sites</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>566</td>
<td>90</td>
<td>1.39</td>
<td>1.11–1.74</td>
</tr>
<tr>
<td>Endometrium</td>
<td>67</td>
<td>13</td>
<td>1.71</td>
<td>0.93–3.14</td>
</tr>
<tr>
<td>Ovary</td>
<td>47</td>
<td>8</td>
<td>1.48</td>
<td>0.69–3.16</td>
</tr>
<tr>
<td>Subtotal</td>
<td>680</td>
<td>111</td>
<td>1.42</td>
<td>1.16–1.75</td>
</tr>
<tr>
<td>Other sites</td>
<td>450</td>
<td>58</td>
<td>1.06</td>
<td>0.80–1.39</td>
</tr>
<tr>
<td>All sites</td>
<td>1130</td>
<td>169</td>
<td>1.27</td>
<td>1.08–1.50</td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>Type of psychotropic medications</th>
<th>Breast cancer (n = 566)</th>
<th>All hormone-dependent cancer (n = 672)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of users</td>
<td>RR</td>
</tr>
<tr>
<td>Any medication</td>
<td>89</td>
<td>1.38</td>
</tr>
<tr>
<td>Minor tranquilizer</td>
<td>70</td>
<td>1.37</td>
</tr>
<tr>
<td>Major tranquilizer</td>
<td>6</td>
<td>2.00</td>
</tr>
<tr>
<td>Anti-depressants</td>
<td>16</td>
<td>1.75</td>
</tr>
<tr>
<td>Anti-convulsants</td>
<td>4</td>
<td>2.13</td>
</tr>
</tbody>
</table>

*Adjusted for Quetelet index, age at menarche, menopausal status, parity and family history of breast cancer in addition to age; 293 subjects with a missing value were excluded.
stronger for women who started medication premenopausally. A rare type of breast tumour among young women who had taken anti-convulsants for years was also reported.22

Studies among psychiatric patients have been inconsistent. Ettigi et al. found that breast cancer patients had more histories of admission to mental hospitals and of treatments with phenothiazine than control women,23 and Costa et al. found more breast cancer deaths than expected in a mental hospital in Romania.24 Others did not find any increased risk of breast cancer in psychiatric patients or in patients treated with phenothiazines.25–27 However, it should be noted that psychiatric patients may also differ from the general population in other risk profiles for hormone-related cancers, such as reproductive history.

A positive association between depression and cancer incidence was found in a prospective study of male workers of the Western Electric Company.28 In a separate community-based study, chronically depressed mood over a 6 year period, as measured by a psychiatric scale, was associated with increased total cancer incidence as well as increased risk of endometrial cancer.29 Non-significant increase in risk of breast cancer (RR = 1.96) among women with a psychiatric diagnosis of depression was also observed in a prospective study in Finland.31 On the other hand, there were no associations between total cancer mortality or morbidity and depression scales in other population-based studies.32–34 Neither diagnoses of depression nor depression scores were associated with subsequent risk of total cancer35 or breast cancer29 among participants in a health care program.

There are several biological mechanisms by which these medications may increase the risk of hormone-related cancers. First, certain types of sedatives, hypnotics and anti-anxiety agents, anti-depressants and anti-convulsants which act as inhibitors of dopamine or norepinephrine uptake, as well as some tranquilizers, such as chlorpromazine, are known to stimulate the secretion of gonadotropins or/and prolactin.9–12 In addition, tricyclics, phenothiazines, benzodiazepines and barbiturates can induce hepatic microsomal enzymes capable of enhancing estrogen metabolism,29 which would lead to increased gonadotropin secretion. Both estrogens and prolactin have been shown to increase the incidence of spontaneous and chemically induced mammary tumours in rodents.40,41 Raised endogenous estrogen levels and exogenous estrogen use have been associated with the risk of breast and endometrial cancer in humans.4,36 In addition, higher plasma prolactin levels were associated with breast cancer risk in a prospective study.42

Second, some anti-depressants, including both tricyclic and non-tricyclic agents, have been shown to bind to growth-regulatory intracellular histamine receptors. Evidence has been accumulating that intracellular histamine promotes normal and malignant cell proliferation.43,44 Brandes et al. reported that the incidence of chemically induced mammary tumours increased with anti-depressant treatment in rats.13 A similar tumour-promoting effect was observed for experimental colon cancer in rats14 as well as for a human tumour xenograft line in nude mice.15 However, results are conflicting,15,16 and an inhibitory effect at high concentrations has been reported.17

Third, underlying psychiatric conditions themselves may modulate the risk of these cancers. Individuals with depression often have impaired immune function, such as low mitogen-induced leukocyte proliferation and low peripheral natural killer cell count.45,46 This may be explained by an increased secretion of adrenal corticosterone, a potent immunosuppressor. In addition, people with psychiatric problems are more likely to engage in high-risk life styles, such as alcohol abuse.

There are several methodological limitations in the present study. First, the numbers of users of specific types of medications, except for minor tranquilizers, were small. Second, our baseline questionnaire was not originally designed to assess detailed medication histories, but was intended to screen out participants whose blood was not appropriate for certain laboratory assays.36 As a result, information about dosage was not collected in a standardized way and no data were available on the duration of usage, which prohibited dose–response analyses. In addition, the information was limited to the 4 weeks before cohort enrollment. Therefore, it is possible that some women were classified as users although they took

Table 4 Multivariate RR* and 95 per cent CIs for breast, endometrial and ovarian cancers by type of psychotropic medications and menopausal status at baseline

<table>
<thead>
<tr>
<th>Type of psychotropic medications</th>
<th>Postmenopausal (394 cases)</th>
<th>Premenopausal (278 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of users</td>
<td>RR</td>
</tr>
<tr>
<td>Any medication</td>
<td>61</td>
<td>1.23</td>
</tr>
<tr>
<td>Minor tranquilizer</td>
<td>53</td>
<td>1.36</td>
</tr>
<tr>
<td>Major tranquilizer</td>
<td>3</td>
<td>1.44</td>
</tr>
<tr>
<td>Anti-depressants</td>
<td>7</td>
<td>0.99</td>
</tr>
<tr>
<td>Anti-convulsants</td>
<td>1</td>
<td>0.74</td>
</tr>
</tbody>
</table>

*Adjusted for Quetelet index, age at menarche, menopausal status, parity and family history of breast cancer in addition to age; 293 subjects with a missing value were excluded.
medication for a short time, whereas long-time users who discontinued the medication at least 4 weeks before cohort enrollment would have been classified as non-users. Such misclassifications would be expected to distort the relative risks towards unity. Third, the numbers of cases with endometrial and ovarian cancers were not sufficient for separate analyses, despite the fact that these cancers have different risk profiles associated with certain exposures, such as oral contraceptives.

The results of the present study reflected mostly those of breast cancer. Finally, our study subjects were participants in breast cancer screening, which represents a self-selected, largely Caucasian population with high incidence of breast cancer. Therefore, caution should be exercised in generalizing the results of our study.

In conclusion, despite the limitations discussed above, a possible link between psychotropic medication use and risk of hormone-related cancers observed in this study warrants further investigations based on more detailed medication history and sufficient numbers of cases at each site.

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