Antidepressant medication use and breast cancer risk: a case-control study

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Background Animal and human studies have reported an association between antidepressant (AD) medication use and breast cancer risk. A population-based case-control study was designed specifically to examine this association among women in Ontario, Canada.

Methods The Ontario Cancer Registry (OCR) identified women diagnosed with primary breast cancer. Controls, randomly sampled from the female population of Ontario, were frequency matched by 5-year age groups. A mailed self-administered questionnaire included questions about lifetime use of AD and potential confounders. Multivariate logistic regression yielded odds ratio estimates.

Results ‘Ever’ use of AD was reported by 14% (441/3077) cases versus 12% (372/2994) controls. The age-adjusted odds ratio (AOR) for ‘ever’ use was 1.17, (95% CI: 1.01, 1.36). An increased risk was also observed for selective serotonin reuptake inhibitors = 1.33 (95% CI: 1.07, 1.66), Sertraline = 1.58 (95% CI: 1.03, 2.41), and Paroxetine = 1.55 (95% CI: 1.00, 2.40). None of the 30 variables assessed for confounding altered the risk estimate by more than 10%. Multivariate adjustment including all possible breast cancer risk factors yielded an unchanged, but not significant, point estimate (MVOR = 1.2, 95% CI: 0.96, 1.51). No relationship was observed for duration or timing of AD use.

Conclusions A modest association between ‘ever’ use of AD and breast cancer was found using the most parsimonious multivariate model. OR estimates did not change, but CI were widened and statistical significance lost, after adjustment for factors associated with breast cancer risk.

Keywords Antidepressant medication, breast cancer

There is epidemiological evidence that antidepressant (AD) medication use may be associated with an increased risk of breast cancer in women,1–5 although findings have been inconsistent, with three studies reporting no association6–8 and five other studies finding an increased risk of breast cancer in women taking tricyclic antidepressants (TCA) or selective serotonin reuptake inhibitors (SSRI).9–14 The preponderance of animal studies also indicate that certain antidepressants may promote tumours in experimental models.9–14 The widespread use of antidepressants15–17 and the rise in incidence of breast cancer18,19 have focused interest on whether AD use, a potentially modifiable factor, may be associated with breast cancer risk. We evaluated the association between the use of AD and risk of breast cancer using a population-based case-control study design.

Methods

Selection of cases and controls

Cases were selected based on the following criteria: (1) women diagnosed with breast cancer between June 1996 and May 1998, and reported, via pathology report, to the OCR as a first primary breast cancer, (2) aged 25–74 years at diagnosis, and (3) alive and resident of Ontario. The OCR is a population-based cancer registry and includes all cases of invasive cancer diagnosed among residents of Ontario. Physicians identified in
the pathology reports were sent a letter describing the study and were asked for permission to contact the patient, and to provide the patient address, telephone number, and vital status.

The random selection of controls was based on the following criteria: (1) females never diagnosed with cancer of the breast, (2) aged 25–74 years, and (3) alive and resident of Ontario. The population-based assessment rolls of the Ontario Ministry of Finance were used to identify eligible controls. These records are organized by geographical region, include all home owners and tenants, and list age, sex, telephone number, and address. There is evidence that 95% of cases can be located in these rolls, indicating a high degree of completeness (Holowaty EJ, personal communication). Controls were frequency-matched to cases within 5-year age groups.

Data collection
A mailed self-administered questionnaire included questions about past use of AD and other medications as well as information on many other known or potential risk factors for breast cancer. The questionnaire was 21 pages in length and extensively pre-tested and contained colour pill photographs of commonly prescribed AD, as well as non-steroidal anti-inflammatory drugs, antihistamines, benzodiazepines, hormones, and oral contraceptive preparations. In addition, subjects listed ‘others’ used that were not shown as a photograph. Subjects were asked to report details regarding use, such as the start and stop age for each medication taken. Subjects were also asked whether they had been diagnosed with various mental illnesses.

Follow-up procedures involved a reminder postcard sent to all women within 2 weeks of questionnaire mailing, and a telephone follow-up for non-responders. Telephone calls were also made after receipt of questionnaires to clarify information provided. Strategies for increasing response rate included a personalized cover letter and, for the controls, a $5-payment which was demonstrated to enhance the cumulative response rate.

Data analysis
Multivariate logistic regression analysis was performed using EGRET software. Exposure variables included ever/never use of any AD, duration of use, age at first and last use, and menopausal status at time of use. AD were also evaluated by class: SSRI, TCA, monoamine oxidase inhibitor (MAOI), and atypical. AD use prior to menopause was associated with a statistically significant increased breast cancer risk (AOR = 1.32, 95% CI: 1.05, 1.66) and no statistically significant increased risk, though the magnitude of association was modest (AOR = 1.17, 95% CI: 0.96, 1.36) and was not statistically significant in the multivariate analysis (MVOR = 1.2, 95% CI: 0.96, 1.51). No increased risk was observed with trends in duration of use, or time since first or last use. AD use prior to menopause was associated with a statistically significant increased breast cancer risk (MVOR = 1.28, 95% CI: 1.07, 1.54), but this was not observed among women who used AD only after menopause. MVOR point estimates did not differ significantly in any of the analyses, but did result in increased CI width and loss of statistical significance, due to increased standard error.

Table 3 shows the frequency distribution of cases and controls, AOR (age-adjusted odds ratio) and MVOR estimates and 95% CI for any regular AD use, duration of AD use, and time since first and last use. There was no confounding by any of the variables previously mentioned when using the 10% change in estimate criterion, so the most parsimonious model, adjustment for age only, is also presented. ‘Ever’ use of AD was associated with a statistically significant increased breast cancer risk, though the magnitude of association was modest (AOR = 1.17, 95% CI: 1.01, 1.36) and was not statistically significant in the multivariate analysis (MVOR = 1.2, 95% CI: 0.96, 1.51). No increased risk was observed with trends in duration of use, or time since first or last use. AD use prior to menopause was associated with a statistically significant increased breast cancer risk (AOR = 1.28, 95% CI: 1.07, 1.54), but this was not observed among women who used AD only after menopause. MVOR point estimates did not differ significantly in any of the analyses, but did result in increased CI width and loss of statistical significance, due to increased standard error.

Table 3 shows the frequency distribution of cases and controls, AOR, and MVOR for the four main classes of AD and for specific AD. The observed increase in risk was significant for SSRI in the AOR but not MVOR. In particular, sertraline and paroxetine were both associated with an increase in breast cancer risk (AOR = 1.58, 95% CI: 1.03, 2.41; MVOR = 1.45, 95% CI: 0.88, 2.40 and AOR = 1.55, 95% CI: 1.00, 2.40; MVOR = 1.6, 95% CI: 0.93, 2.77, respectively). In addition, SSRI used in the pre-menopausal period were associated with increased breast cancer risk (AOR = 1.32, 95% CI: 1.05, 1.66) (data not shown). No increased risk was observed for duration of use, or time since first or last use for any of the classes of AD; however, power was somewhat limited.

Discussion
The interpretation of the results of this study depend, in part, on the choice of statistical methods used to adjust for confounding. The MVOR results and the absence of a relationship with duration of exposure do not support the hypothesis that AD
may increase the risk of breast cancer. Significant increased breast cancer risks were observed, in the age-adjusted parsimonious model, for 'ever' use and with SSRI, in particular Paroxetine and Sertraline, although these were not statistically significant in the multivariate analyses. The point estimates for the two analyses, AOR and MVOR, however, are essentially the same, suggesting the absence of confounding.

Consistent with our findings, an association between certain AD and breast cancer risk was also reported in four other case-control studies. Kelly et al.,3 using a hospital-based case-control design, reported a 'borderline' increased risk of breast cancer associated with regular SSRI use (OR = 1.8, 95% CI: 1.0, 3.3) but did not find an overall association between 'ever' AD use and breast cancer. An elevated risk of breast cancer associated with the use of paroxetine and use of tricyclic medications for greater than 2 years was reported by Cotterchio et al.,1 although this case-control study had a limited sample size and CI were wide. To date, no other breast cancer study has evaluated paroxetine, a relatively new SSRI. Currently, more than 20% of women have ever used an SSRI; however, at the time this study was conducted, only 5% of controls reported using SSRI, which had been on the market for about 7 years. The possible association between the use of paroxetine and breast cancer risk observed in both the current study and one previous study warrants further investigation. Future studies should have adequate power to evaluate the individual and commonly used SSRI. Finally, Sharpe et al.5 reported that 'heavy exposure' to TCA for greater than 10 years was associated with elevated risk of breast cancer.

No association between use of AD and breast cancer was found by Wang et al.13 in a retrospective cohort study. AD use prior to or after the 2-year time frame of the study (1989–1991) was not assessed and this could have resulted in misclassification of subjects exposed to AD before or after the exposure period. In addition, no subjects were prescribed more recent SSRI as these were only recently available, so these medications

Table 1 Frequency distribution of cases and controls and age-adjusted odds ratio (AOR) estimates for selected variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n = 3133)</th>
<th>Controls (n = 3062)</th>
<th>AOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Highest level of education</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elementary</td>
<td>399 (13)</td>
<td>426 (14)</td>
<td>1.0</td>
</tr>
<tr>
<td>High School</td>
<td>1469 (47)</td>
<td>1386 (46)</td>
<td>1.18 (1.01, 1.38)</td>
</tr>
<tr>
<td>Post secondary</td>
<td>1246 (40)</td>
<td>1221 (40)</td>
<td>1.19 (1.00, 1.40)</td>
</tr>
<tr>
<td><strong>Cigarette smoking</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-smoker</td>
<td>1522 (49)</td>
<td>1578 (52)</td>
<td>1.0</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>1044 (34)</td>
<td>854 (28)</td>
<td>1.26 (1.13, 1.42)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>540 (17)</td>
<td>594 (20)</td>
<td>0.96 (0.84, 1.10)</td>
</tr>
<tr>
<td><strong>Ever diagnosed with depression</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2596 (86)</td>
<td>2577 (87)</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>417 (14)</td>
<td>382 (13)</td>
<td>1.08 (0.93, 1.26)</td>
</tr>
<tr>
<td><strong>Breast cancer in first-degree relative</strong></td>
<td>2433 (82)</td>
<td>2527 (89)</td>
<td>1.0</td>
</tr>
<tr>
<td>No</td>
<td>521 (18)</td>
<td>308 (11)</td>
<td>1.72 (1.48, 2.00)</td>
</tr>
<tr>
<td>Yes</td>
<td>1621 (55)</td>
<td>720 (25)</td>
<td>3.71 (3.32, 4.15)</td>
</tr>
<tr>
<td><strong>History benign breast cysts</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1312 (45)</td>
<td>2185 (75)</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>1621 (55)</td>
<td>720 (25)</td>
<td>3.71 (3.32, 4.15)</td>
</tr>
<tr>
<td><strong>Age at menarche</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤11</td>
<td>588 (19)</td>
<td>540 (18)</td>
<td>1.0</td>
</tr>
<tr>
<td>12</td>
<td>788 (26)</td>
<td>733 (24)</td>
<td>0.99 (0.85, 1.16)</td>
</tr>
<tr>
<td>13</td>
<td>907 (29)</td>
<td>880 (29)</td>
<td>0.94 (0.81, 1.09)</td>
</tr>
<tr>
<td>≥14</td>
<td>806 (26)</td>
<td>868 (29)</td>
<td>0.83 (0.71, 0.97)</td>
</tr>
<tr>
<td><strong>Parity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>461 (15)</td>
<td>377 (12)</td>
<td>1.0</td>
</tr>
<tr>
<td>1</td>
<td>398 (13)</td>
<td>357 (12)</td>
<td>0.94 (0.77, 1.16)</td>
</tr>
<tr>
<td>2–3</td>
<td>1725 (56)</td>
<td>1673 (55)</td>
<td>0.85 (0.72, 1.01)</td>
</tr>
<tr>
<td>≥4</td>
<td>520 (17)</td>
<td>629 (21)</td>
<td>0.64 (0.52, 0.77)</td>
</tr>
<tr>
<td><strong>Age at menopause</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45</td>
<td>612 (21)</td>
<td>647 (23)</td>
<td>1.0</td>
</tr>
<tr>
<td>45–49</td>
<td>550 (19)</td>
<td>531 (19)</td>
<td>1.09 (0.93, 1.28)</td>
</tr>
<tr>
<td>≥50</td>
<td>903 (31)</td>
<td>736 (26)</td>
<td>1.27 (1.09, 1.48)</td>
</tr>
<tr>
<td>Pre-menopausal</td>
<td>859 (29)</td>
<td>949 (33)</td>
<td>–</td>
</tr>
<tr>
<td><strong>Hormone treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-menopausal</td>
<td>859 (28)</td>
<td>949 (31)</td>
<td>n/a</td>
</tr>
<tr>
<td>No</td>
<td>1235 (40)</td>
<td>1128 (37)</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>996 (32)</td>
<td>946 (31)</td>
<td>0.96 (0.85, 1.09)</td>
</tr>
</tbody>
</table>

\* Numbers may not add to total due to missing values.  
\*a Mother, sister, or daughter.  
\*b Live births.  
\*d Last menstrual period.
were not assessed. Friedman et al.7 and Selby et al.8 also reported no association between use of AD and breast cancer risk but these studies were also completed prior to the availability of SSRI.

Our study involved a large sample of cases and controls selected from population-based sampling frames, and used a questionnaire specifically designed to obtain information about use of AD and other potential risk factors for breast cancer. Nevertheless, potential bias and confounding are concerns of all case-control studies, in light of which our results must be considered. Since both cases and controls were selected from population-based sampling frames, selection bias may have been limited. Response bias is a significant concern as the response rate for cases was 73% and for controls was 61%. Our dataset replicates the risk factor associations 'known' to be associated with breast cancer risk, suggesting that the case-control comparison is not on the face of it a biased one.

The potential for recall bias is a significant shortcoming of our study although efforts were made to reduce this; the research hypothesis was not stated in the questionnaire, the questionnaire

Table 2 Frequency distribution of cases and controls, age-adjusted odds ratio (AOR) and multivariate-adjusted odds ratio (MVOR) for antidepressant (AD) use and duration of use, time since first and last use

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>AOR</th>
<th>MVOR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Any regular AD use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never7</td>
<td>2636</td>
<td>(86)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Everd</td>
<td>441</td>
<td>(14)</td>
<td>1.17 (1.01, 1.36)</td>
<td>1.20 (0.96, 1.51)</td>
</tr>
<tr>
<td>Duration of AD use (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>70</td>
<td>(2)</td>
<td>1.13 (0.80, 1.60)</td>
<td>1.03 (0.66, 1.60)</td>
</tr>
<tr>
<td>1–3</td>
<td>75</td>
<td>(3)</td>
<td>1.10 (0.79, 1.54)</td>
<td>0.93 (0.61, 1.43)</td>
</tr>
<tr>
<td>3.5–8.5</td>
<td>50</td>
<td>(2)</td>
<td>0.84 (0.57, 1.22)</td>
<td>0.78 (0.49, 1.24)</td>
</tr>
<tr>
<td>9+</td>
<td>58</td>
<td>(2)</td>
<td>1.15 (0.78, 1.69)</td>
<td>1.14 (0.71, 1.83)</td>
</tr>
<tr>
<td>Time since last AD use (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1</td>
<td>185</td>
<td>(6)</td>
<td>1.06 (0.85, 1.31)</td>
<td>1.00 (0.74, 1.35)</td>
</tr>
<tr>
<td>2–7</td>
<td>44</td>
<td>(2)</td>
<td>1.12 (0.73, 1.72)</td>
<td>1.17 (0.70, 1.95)</td>
</tr>
<tr>
<td>8+</td>
<td>48</td>
<td>(2)</td>
<td>1.11 (0.73, 1.69)</td>
<td>0.95 (0.57, 1.59)</td>
</tr>
<tr>
<td>Time since first AD use (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>63</td>
<td>(2)</td>
<td>0.93 (0.66, 1.32)</td>
<td>0.97 (0.62, 1.50)</td>
</tr>
<tr>
<td>3–6</td>
<td>79</td>
<td>(3)</td>
<td>1.27 (0.91, 1.78)</td>
<td>1.15 (0.75, 1.75)</td>
</tr>
<tr>
<td>7–15</td>
<td>65</td>
<td>(2)</td>
<td>1.07 (0.75, 1.52)</td>
<td>0.99 (0.64, 1.54)</td>
</tr>
<tr>
<td>16+</td>
<td>70</td>
<td>(2)</td>
<td>1.04 (0.74, 1.46)</td>
<td>0.94 (0.61, 1.46)</td>
</tr>
</tbody>
</table>

a Adjusted for age, height, body mass index, age at menarche, parity, age at menopause, oral contraceptive use, alcohol consumption, family history of breast cancer, history of benign breast disease, clinical depression, anxiety.
b Numbers may not add to total due to missing values.

c Referent category for each variable.
d Defined as taken daily for at least 2 months started at least 12 months prior to diagnosis date for cases and referent date for controls.

Table 3 Frequency distribution of cases and controls, and age-adjusted odds ratios (AOR) and multivariate-adjusted odds ratio (MVOR) with 95% CI for ever use of the four main classes of antidepressants (AD) and specific AD

<table>
<thead>
<tr>
<th>AD Classb</th>
<th>Cases</th>
<th>Controls</th>
<th>AOR</th>
<th>MVOR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Never used any ADd</td>
<td>2636</td>
<td>(86)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>SSRIe</td>
<td>201</td>
<td>(7)</td>
<td>1.33 (1.07, 1.66)</td>
<td>1.32 (0.97, 1.80)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>56</td>
<td>(2)</td>
<td>1.58 (1.03, 2.41)</td>
<td>1.45 (0.88, 2.40)</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>51</td>
<td>(2)</td>
<td>1.55 (1.00, 2.40)</td>
<td>1.60 (0.93, 2.77)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>90</td>
<td>(3)</td>
<td>1.09 (0.81, 1.49)</td>
<td>1.05 (0.70, 1.57)</td>
</tr>
<tr>
<td>TCAf</td>
<td>208</td>
<td>(7)</td>
<td>1.12 (0.91, 1.37)</td>
<td>1.10 (0.83, 1.45)</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>135</td>
<td>(4)</td>
<td>1.10 (0.85, 1.42)</td>
<td>1.19 (0.85, 1.65)</td>
</tr>
<tr>
<td>Imipramine</td>
<td>25</td>
<td>(1)</td>
<td>0.88 (0.51, 1.51)</td>
<td>0.52 (0.26, 1.03)</td>
</tr>
<tr>
<td>Doxepin</td>
<td>29</td>
<td>(1)</td>
<td>1.21 (0.70, 2.10)</td>
<td>1.27 (0.65, 2.46)</td>
</tr>
<tr>
<td>MAOIG</td>
<td>9</td>
<td>(0.3)</td>
<td>0.87 (0.35, 2.14)</td>
<td>0.80 (0.27, 2.40)</td>
</tr>
<tr>
<td>Atypical</td>
<td>19</td>
<td>(0.6)</td>
<td>0.94 (0.5, 1.77)</td>
<td>1.04 (0.50, 2.16)</td>
</tr>
</tbody>
</table>

a Defined as taken daily for at least 2 months and started at least 12 months prior to diagnosis date.
b Number within each class do not add up to total, because only the most prevalent antidepressants are listed as individual drugs.
c Adjusted for age, height, body mass index, age at menarche, parity, age at menopause, oral contraceptive use, alcohol consumption, family history of breast cancer, history of benign breast disease, clinical depression, anxiety.
d Referent category for each variable.
e Selective serotonin reuptake inhibitors.
f Tricylic antidepressants.
g Monoamine oxidase inhibitor.
listed multiple medications of different types, and included photographs of anti-inflammatories, hormones and antihistamines, substantially de-emphasizing the focus on AD. As well, AD are currently not a widely suspected cause of breast cancer. Even in the absence of an obvious research hypothesis, cases may have made greater efforts to recall previous medication use or be more willing to disclose confidential information and this would tend to bias the results in favour of an association.

It is unlikely that general over-reporting of medication use by the cases occurred in our study, since we found that NSAID medication use was associated with a decreased breast cancer risk. In addition, in a study specifically designed to examine the issue of recall and misclassification, Cotterchio et al. compared self-reported AD use with AD use recorded in physicians’ records and found good agreement with physician records (kappa = 0.60, agreement = 80%; for use of specific AD agreement ranged from 82% to 100%) and more importantly no differential reporting of AD use by cases and controls.

Clinical depression or other factors could have resulted in confounding of the risk estimate. However, we found no confounding by any of the 30 variables assessed, including psychiatric history, such as depression or indication for use of AD. Furthermore, epidemiological evidence does not really support an association between depression and breast cancer risk. Multivariate adjustment of the OR for depression and their possible risk factors did not significantly change any of the point estimates when compared with the age-adjusted estimates, also consistent with a lack of confounding. The inclusion of variables that may not confound in the multivariate model increased the width of the CI but should not rule out attention to the more parsimonious age-adjusted model.

The absence of an association between trends in duration of AD use and increased risk of breast cancer is not consistent with a causal interpretation of the results. However, recall error due to the limitations of memory, particularly for dosage and AD use many years prior to participation in the study, rather than bias, may reduce the likelihood of detecting an association. It is also possible that any risk association is not linear.

Plausible biological mechanisms to explain the increased breast cancer risk associated with AD use may involve: increased prolactin levels, altered oestrogen metabolism, altered metabolism of carcinogens, and other modifications of cellular proliferation. The mechanism by which AD produce elevations in prolactin is uncertain, but there is evidence that serotoninergic agents stimulate prolactin release directly via postsynaptic 5-HT receptors in the hypothalamus or by inhibition of tubuloinfundibular dopaminergic neurons. Furthermore, the interaction between AD and cytochrome P450 enzymes may alter oestrogen metabolism or the bioactivation of carcinogens.

With the increasing prevalence of use of AD and the public health importance of breast cancer, even a small increased risk may be of significant public health concern as this is a potentially modifiable factor. The aetiology of breast cancer risk is not yet understood and the majority of the risk factors identified to date show only a modest increase in breast cancer risk. Since breast carcinogenesis is a complex multistage process it is likely that the effects of exposure to AD, if any, would be difficult to detect above the background of other exposures and susceptibilities. Case-control studies may be too crude a tool to detect subtle effects unless guided by improved understanding of potential biological mechanisms. Further research might be directed towards neuroendocrine consequences of AD, the effects on intermediate breast cancer endpoints such as benign proliferative breast disease or breast tissue density, and the completion of improved postmarketing surveillance studies and well-designed cohort studies.

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References

Animal studies indicate that neonatal exposure to antidepressants may induce or stimulate mammary tumour growth, and may enhance carcinogenesis in the colons of rats, and therefore might generally represent hazards for cancer in man. Hence the search for a role for antidepressants in breast cancer in human studies, for example, will no doubt continue. Meanwhile these studies may cause alarm. A paper from Ontario in this issue of the *International Journal of Epidemiology* continues this search—arguing for a small increase in risk—based on a large case-control study. The authors state that since

... breast carcinogenesis is a complex multistage process it is likely that the effects of exposure to antidepressants, if any, would be difficult to detect above the background of other exposure and susceptibilities.

Possibly, but maybe there really is no general causative association. Clearly it is not possible to be at all certain about this relationship, and certainly not to recommend any change in the use

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**Commentary: Antidepressants and breast cancer risk**

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