American Journal of Epidemiology
Vol. 151, No. 10
Printed in U.S.A.


## ORIGINAL CONTRIBUTIONS

# Antidepressant Medication Use and Breast Cancer Risk

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Experimental and epidemiologic studies suggest that antidepressant medication use may be associated with breast cancer risk. This hypothesis was investigated using a population-based case-control study; cases diagnosed in 1995–1996 were identified using the Ontario Cancer Registry, and controls were randomly sampled from an Ontario Ministry of Finance database. Data were collected using a self-administered questionnaire, and multivariate logistic regression was used to estimate odds ratios and 95% confidence intervals. Adjusted odds ratio estimates ranged from 0.7 to 0.8 and were not statistically significant for "ever" use of antidepressants, tricyclics, and selective serotonin reuptake inhibitors. Compared with no antidepressant use, use of tricyclic antidepressants for greater than 2 years' duration was associated with an elevated risk of breast cancer (odds ratio (OR) = 2.1, 95% confidence interval (CI): 0.9, 5.0). Of the six most commonly reported antidepressant medications, only paroxetine use was associated with an increase in breast cancer risk (OR = 7.2, 95% CI: 0.9, 58.3). Results from this study do not support the hypothesis that "ever" use of any antidepressant medications is associated with breast cancer risk. Use of tricyclic medications for greater than 2 years, however, may be associated with a twofold elevation, and use of paroxetine may be associated with a substantial increase in breast cancer risk. *Am J Epidemiol* 2000;151:951–7.

antidepressive agents; breast neoplasms; case-control studies; pharmacoepidemiology; risk factors

Breast cancer is a primary cancer concern among women in North America today. Approximately 30 percent of all newly diagnosed female cancers are breast cancers, and 19 percent of all female cancer-related deaths are due to breast cancer (1). Age-adjusted breast cancer incidence rates in North America increased by 20–25 percent between the early 1970s and the early 1990s (1, 2). However, after decades of research into etiologic factors, little is known about the primary prevention of breast cancer, and established risk factors account for less than half of all breast cancer cases (3).

Antidepressant medications are being used with increasing frequency, especially among women (4). This, coupled with animal and human data that indicate antidepressant medications may increase the risk of breast cancers (5–8), suggests there is cause for concern regarding the use of antidepressant medications. Despite the animal data suggesting that antidepressants may promote mammary tumors (5, 9), only sparse epidemiologic data exist regarding the relation between antidepressant medication use and the risk of breast cancer (7, 8, 10). Findings from the only two studies to evaluate lifetime antidepressant medication use and breast cancer risk are not consistent. A large case-control drug surveillance study conducted in the United States between 1977 and 1996 recently reported an elevated breast cancer risk associated with "ever" use of selective serotonin uptake inhibitor (SSRI) antidepressants (odds ratio (OR) = 1.6); however, no association with breast cancer risk was found for "ever" use of both tricyclic and other antidepressant medications (8). Another case-control study conducted in the 1970s reported an adjusted odds ratio estimate of 2.84 ($p < 0.04$) associated with antidepressant use; however, this increased risk was in relation to tricyclic and monoamine oxidase inhibitor antidepressants, since the now popular SSRIs (e.g., Prozac; Eli Lilly and Company, Indianapolis, Indiana) were not available prior to the 1980s and hence were not assessed (7).

Our study evaluated the association between the use of various antidepressant medications and breast cancer risk using a population-based case-control study design.

Received for publication March 16, 1999, and accepted for publication August 5, 1999.

Abbreviations: AOR, age-adjusted odds ratio estimate; CI, confidence interval; MVOR, multivariate odds ratio estimate; OR, odds ratio estimate; SSRI, selective serotonin reuptake inhibitor.

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## MATERIALS AND METHODS

### Case and control definition and ascertainment

This study was conducted within the National Enhanced Cancer Surveillance Study (11). Cases were an age-stratified (<50 and ≥50 years of age) random sample of women aged 25–74 years, diagnosed with primary breast cancer during 1995 and 1996 (pathology report confirmed) and recorded in the population-based Ontario Cancer Registry. As the 1-year survival for breast cancer is 90 percent (12), surrogate respondents were not used.

Population controls, aged 25–74 years, were randomly sampled from the property assessment rolls of the Ontario Ministry of Finance; this database includes all home owners and tenants and lists age, sex, and address. Female controls were randomly selected and 1:1 frequency matched, within 5-year age groups, to the breast cancer cases.

### Data collection

Data were collected through mailed, self-administered, structured questionnaires that included information on 1) sociodemographic data; 2) duration, dosage, timing, and type of antidepressant medications used; and 3) potential confounders. Subjects were asked "have you ever taken antidepressants for at least 2 weeks at any time in your life?" (a list of 11 antidepressants was given to provide examples). If subjects responded "yes," then the questionnaire indicated they should fill in a chart with the name and dates started and stopped for each time period antidepressants were taken. Within 2 weeks of questionnaire mailing a follow-up postcard was sent to all women, within 4 weeks of questionnaire mailing a second questionnaire was sent out to those who had not yet responded, and after 6 weeks follow-up telephone calls were made to those who did not respond. A third questionnaire was sent to anyone requesting it. Returned questionnaires were reviewed for comprehensibility, and subjects were telephoned if questionnaires were not filled out completely.

### Data analysis

Descriptive statistics were calculated for all study variables stratified by case-control status, and logistic regression was used to calculate age-adjusted odds ratio estimates and 95 percent confidence intervals. Potential confounders were categorized based on categorizations previously demonstrated to be associated with breast cancer risk in the literature or defined as tertiles/quartiles/median based on the distribution in the controls. Risk factors identified in the literature and study variables found to be associated with both disease status ($p < 0.30$) and antidepressant use in controls ($p < 0.30$), using chi-square analysis of $2 \times K$ tables and Pearson's chi-square $p$ values, were considered to be potential confounders and were included in the model-building multivariate phase of analysis. The likelihood ratio test statistic was computed for each of the 36 study variables (potential confounders) based on the reduction in residual deviance after the addition of the study variable of interest to a prior fitted model containing only age group. Statistical analysis was performed using SAS (13) and EGRET software (14).

Associations between the risk of breast cancer and antidepressant medication use were initially examined by computing crude odds ratio estimates and approximate 95 percent confidence intervals (15) for ever versus never use. Because age was frequency matched in the design phase, this variable was included in all models. Further analysis included age-adjusted odds ratio estimates for 1) each class of antidepressant medication and 2) specific antidepressants. In addition, the relation between the risk of breast cancer and tertiles of duration of antidepressant use was evaluated (with no antidepressant use as the referent group). Similarly, the time since first use and the time since last use of antidepressant medications were examined.

Multivariate logistic regression analysis was performed to obtain adjusted odds ratio estimates for various types and aspects of antidepressant medication use while simultaneously adjusting for confounders (15). For each analysis, potential confounding variables (as defined above) were evaluated based on the 10 percent change in odds ratio estimate methods (16). Variables resulting in such a change in the age-adjusted odds ratio estimate were included in the corresponding final multivariate model. The possibility of interactions between antidepressant medication use and other variables was assessed by the statistical significance of the likelihood ratio test statistic ($p < 0.05$) after the addition of the product term(s) to the model (17).

Women who reported antidepressant medication *only* in the 6-month period prior to their breast cancer diagnosis date (or following diagnosis) and women who took antidepressants for less than 2 weeks' duration were considered to be nonusers for all analysis.

The response rate was 83 percent for breast cancer cases and 67 percent for female controls. If "unable to locate subject" were excluded from the denominator, the response rate was 86 percent and 80 percent for cases and controls, respectively.

## SULTS

he distribution of cases and controls was similar education, alcohol intake, clinical depression, age menarche, and ever use of estrogen replacement rapy/hormone replacement therapy (data not own). A significantly higher proportion of cases orted a family history of breast cancer, having had ign proliferative breast disease, and consuming a ater amount of dietary fat compared with controls. slightly greater proportion of cases reported using l contraceptives, age at first pregnancy ≥25, age at nopause ≥45, and a lower proportion of cases orted having been pregnant ≥4 times.

Table 1 shows the frequency distribution, age-justed and multivariate-adjusted odds ratio estimates, d 95 percent confidence intervals for any antidepres-nt medication use and for each class of antidepressant edications. Antidepressant medication use, adjusted ly for age, was weakly associated with breast cancer sk (age-adjusted odds ratio estimate (AOR) = 1.2, 95 rcent confidence interval (CI): 0.8, 1.7). However, is association did not remain when adjusted for con-unders. Tricyclic antidepressant medication use, djusted only for age, was weakly associated with reast cancer risk (AOR = 1.2, 95 percent CI: 0.8, 1.8); owever, no association was found between tricyclics nd breast cancer risk in the multivariate model. Both ne crude and adjusted odds ratio estimates for the asso-iation between SSRI antidepressant medication use nd breast cancer risk were slightly decreased, though ot statistically significant (multivariate odds ratio esti-nate (MVOR) = 0.7, 95 percent CI: 0.3, 1.5). There vas little difference in the distribution of reported nonoamine oxidase inhibitor or atypical antidepressant nedication use between cases and controls; however, he number of women reporting use of these medica-ions was extremely small.

Table 2 shows the age-adjusted and multivariate-adjusted odds ratio estimates associated with tertiles of duration of any antidepressant medication use, tricyclic, and SSRI medication use. The duration of antidepressant medication use for ≥25 months was associated with an increased risk of breast cancer when only age was adjusted for (AOR = 1.6, 95 percent CI: 0.9, 2.8); however, the multivariate odds ratio estimate approached unity (MVOR = 1.1, 95 percent CI: 0.5, 2.4). Both the age-adjusted and multivariate-adjusted odds ratio estimates for ≥25 months of tricyclic antidepressant medication use were associated with an increased risk of breast cancer (AOR = 2.5, 95 percent CI: 1.2, 5.1; MVOR = 2.1, 95 percent CI: 0.9, 5.0). The duration of SSRI medication use for greater than 2 years is not associated with an increased risk of breast cancer (MVOR = 0.7, 95 percent CI: 0.2, 2.2). No associations or patterns were found between time since first and last use of antidepressant medications and breast cancer risk (data not shown).

The frequency distribution of cases and controls and the age-adjusted and multivariate-adjusted odds ratio estimates for use of specific antidepressant medications are presented in table 3. Because of small numbers, the precision of the odds ratio estimates is poor. Paroxetine medication was associated with an increased breast cancer risk after controlling for clinical depression (MVOR = 7.2, 95 percent CI: 0.9, 58.3). This estimate is of borderline statistical significance; however, the odds ratio estimate adjusted only for age is statistically significant (AOR = 9.1, 95 percent CI: 1.2, 72.5). There was no association between reported use of amitriptyline or fluoxetine medication and breast cancer risk, after adjusting for confounders in the multivariate model. The multivariate odds ratio estimate for imipramine medication use suggested no association with breast cancer risk; however, the odds ratio estimate adjusted only for age suggested that

**TABLE 1. Age-adjusted and multivariate-adjusted odds ratio estimates and 95% confidence interval, for any antidepressant use and each class of antidepressant medication use, Ontario, Canada, 1995–1996**

| Variable | Cases | | Controls | | AOR* | 95% CI* | MVOR* | 95% CI |
|---|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | | | | |
| No antidepressant use (referent) | 629 | 89.7 | 641 | 91.3 | 1.0 | | 1.0 | |
| Any antidepressant use | 72 | 10.3 | 61 | 8.7 | 1.2 | 0.8, 1.7 | 0.8 | 0.5, 1.4 |
| Antidepressant subgroups | | | | | | | | |
| Tricyclic medication use | 48 | 6.9 | 42 | 6.0 | 1.2 | 0.8, 1.8 | 0.8 | 0.5, 1.5 |
| SSRI* medication use | 22 | 3.2 | 24 | 3.4 | 0.9 | 0.5, 1.7 | 0.7 | 0.3, 1.5 |
| MAOI* medication use | 2 | 0.3 | 1 | 0.1 | 2.0 | 0.2, 22.5 | | —† |
| Atypical medication use | 4 | 0.6 | 4 | 0.6 | 1.0 | 0.3, 4.1 | | — |

* AOR, age-adjusted odds ratio estimate; CI, confidence interval; MVOR, multivariate odds ratio estimate, adjusted for age, clinical depression, benign proliferative breast disease (and age at menopause for selective serotonin reuptake inhibitors (SSRIs)); MAOI, monoamine oxidase inhibitor.

† —, sample size too small.

**TABLE 2. Age-adjusted and multivariate-adjusted odds ratio estimates and 95% confidence interval associated with tertiles of duration of antidepressant medication use, tricyclic, and selective serotonin reuptake inhibitor medication use, Ontario, Canada, 1995–1996**

| Variable | AOR* | 95% CI* | MVOR* | 95% CI |
|---|---|---|---|---|
| Duration of antidepressant medication use | | | | |
| No antidepressant use | 1.0 | | 1.0† | |
| Tertile 1 (≤5 months) | 1.0 | 0.5, 2.0 | 0.6 | 0.2, 1.4 |
| Tertile 2 (6–24 months) | 0.9 | 0.5, 1.8 | 0.7 | 0.3, 1.6 |
| Tertile 3 (≥25 months) | 1.6 | 0.9, 2.8 | 1.1 | 0.5, 2.4 |
| Duration of tricyclic antidepressant medication use | | | | |
| No TCA* antidepressant use | 1.0 | | 1.0‡ | |
| Tertile 1 (≤6 months) | 0.8 | 0.4, 1.8 | 0.6 | 0.2, 1.5 |
| Tertile 2 (7–24 months) | 0.8 | 0.3, 2.0 | 1.0 | 0.4, 2.8 |
| Tertile 3 (≥25 months) | 2.5 | 1.2, 5.1 | 2.1 | 0.9, 5.0 |
| Duration of SSRI* antidepressant medication use | | | | |
| No SSRI antidepressant use | 1.0 | | 1.0§ | |
| Tertile 1 (≤6 months) | 1.2 | 0.4, 3.5 | 1.1 | 0.4, 3.5 |
| Tertile 2 (7–22 months) | 0.9 | 0.3, 2.4 | 0.6 | 0.2, 1.9 |
| Tertile 3 (≥23 months) | 0.9 | 0.3, 2.6 | 0.7 | 0.2, 2.2 |

* AOR, age-adjusted odds ratio estimate; CI, confidence interval; MVOR, multivariate odds ratio estimate; TCA, trichloroacetic acid; SSRI, selective serotonin reuptake inhibitor.
† Adjusted for age, clinical depression, and benign proliferative breast disease.
‡ Adjusted for age, clinical depression, benign proliferative breast disease, hysterectomy, and age at first pregnancy.
§ Adjusted for age, clinical depression, and hysterectomy.

imipramine was associated with a statistically nonsignificant elevated breast cancer risk. The use of doxepin or sertraline was associated with a statistically nonsignificant reduced risk of breast cancer, after controlling for confounders in the multivariate model.

To investigate the data further, associations between various aspects of antidepressant medication use (e.g., SSRI use, age at first use) and breast cancer risk were assessed stratified by menopausal status. The results in each stratum were similar to those found when the strata were combined (data not shown). In addition, household income, age group, history of clinical depression, body mass index, family history of breast cancer, and benign proliferative breast disease were not effect modifiers of the association between any antidepressant medication use, SSRI use, or tricyclic use and breast cancer risk (data not shown). Education level was not an effect modifier of the odds ratio associated with SSRI use or any antidepressant medication use. However, the interaction between education level and tricyclic antidepressant medication use was of borderline significance; there was an elevated breast cancer risk associated with tricyclic medication use *only* among women with less than a grade 12 education

**TABLE 3. Age-adjusted and multivariate-adjusted odds ratio estimates and 95% confidence interval for specific antidepressant medication use, Ontario, Canada, 1995–1996**

| Antidepressant*,† | Cases | | Controls | | AOR‡ | 95% CI‡ | MVOR‡ | 95% CI |
|---|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | | | | |
| Fluoxetine | 21 | 3.0 | 15 | 2.1 | 1.4 | 0.7, 2.8 | 0.9 | 0.4, 2.0 |
| Sertraline | 3 | 0.4 | 8 | 1.1 | 0.4 | 0.1, 1.4 | 0.3 | 0.1, 1.2 |
| Paroxetine | 9 | 1.3 | 1 | 0.1 | 9.1 | 1.2, 72.5 | 7.2 | 0.9, 58.3 |
| Amitriptyline | 28 | 4.0 | 29 | 4.1 | 1.0 | 0.6, 1.7 | 0.7 | 0.4, 1.4 |
| Imipramine | 12 | 1.7 | 7 | 1.0 | 1.7 | 0.7, 4.5 | 1.0 | 0.3, 3.0 |
| Doxepin | 5 | 0.7 | 8 | 1.1 | 0.6 | 0.2, 2.0 | 0.4 | 0.1, 1.4 |

* Used for >2 weeks and started at least 6 months prior to diagnosis date.
† Referent was no antidepressant medication use.
‡ AOR, age-adjusted odds ratio estimate; CI, confidence interval; MVOR, multivariate odds ratio estimate, adjusted for clinical depression and benign proliferative breast disease (with the exception of paroxetine, which was not adjusted for benign proliferative breast disease because of nonconvergence).

(MVOR = 3.4, 95 percent CI: 0.7, 16.1) (data not shown).

## DISCUSSION

Results from this study do not support the hypothesis of an increased breast cancer risk associated with "ever" use of antidepressant medications, although the use of tricyclic antidepressant medications for at least 2 years' duration was associated with a twofold elevation in breast cancer risk, and use of paroxetine, an SSRI, was associated with a sevenfold elevation in risk. We found no association between "ever" or duration of SSRI use and breast cancer risk.

Three other studies have evaluated the breast cancer risk associated with exposure to antidepressant medications (7, 8, 10). In contrast to our findings, Kelly et al. (8) found that "ever" use of SSRIs was associated with an elevated risk of breast cancer, and the magnitude of this risk increased with increasing duration of use. With findings similar to ours, they found that "ever" use of tricyclic medications was not associated with an elevated risk of breast cancer. It is possible that the association between SSRI use and breast cancer risk reported by Kelly et al. (8) was not seen in our study because of our limited power to detect this association. Alternatively, it is possible that their findings are spurious or are confounded by uncontrolled factors such as depression.

To date, no other study has evaluated both the association between tricyclic and SSRI antidepressant medications and breast cancer in women. Wallace et al. (7) found that "ever" use of antidepressant medications (tricyclics and monoamine oxidase inhibitors combined) was associated with a statistically significant elevated risk of breast cancer; further analysis, however, indicated that socioeconomic status was an effect modifier. Unfortunately the results were not stratified by socioeconomic status so the findings are difficult to interpret. In comparison, our study found an interaction between education level and tricyclic antidepressant medication use that was of borderline significance; there was an elevated breast cancer risk associated with tricyclic medication use *only* among women with less than a grade 12 education. This finding should be interpreted cautiously because multiple comparisons were made.

Our study does not support the hypothesis of Brandes et al. (5) that antidepressants are tumor promoters, as we found no statistically significant reduction in breast cancer risk associated with recent use of antidepressant medications. We also were unable to identify a specific latency period relevant to the antidepressant-breast cancer hypothesis.

Of the six most commonly reported antidepressant medications evaluated, only paroxetine was associated with an increase in breast cancer risk, and the odds ratio estimate was of substantial magnitude and of borderline statistical significance. Whether this is a chance finding can only be determined by further studies; however, this finding has two plausible biologic mechanisms. Paroxetine has been shown to stimulate prolactin secretion (18), which has been implicated in the etiology of breast cancer (19); and paroxetine is a potent inhibitor of the cytochrome P450 2D6 enzyme (20), which is thought to be associated with human cancer risk (21). Similar to our findings, a postmarketing surveillance study that evaluated the use of 215 various types of medications with 56 cancer outcomes found no excess risk of breast cancer associated with amitriptyline or imipramine, although more recent antidepressants, such as paroxetine, were not evaluated (22, 23).

Experimental evidence suggests that there are several plausible biologic mechanisms to support the hypothesis that antidepressant medication use may be associated with breast cancer risk. Antidepressants have been shown to interfere with the cytochrome P450 enzyme system (20, 24–27) that is involved with the metabolism of both carcinogens (28, 29) and estrogen (30–32), both of which are known to play a role in the development of breast cancer. In addition, antidepressants have been shown to increase prolactin secretion in humans, which is thought to be associated with the development of breast cancer (18, 33–47).

It is interesting to note that, among our control subjects, benign proliferative breast disease was strongly associated with antidepressant medication use and was also found to be a confounder of the antidepressant-breast cancer relation evaluated in our study. It is not clear whether the controls diagnosed with benign proliferative breast disease were more likely to use antidepressants, or whether antidepressant medication use contributed to the development of benign proliferative breast disease in the controls. With the exception of an anecdotal report (48), a relation between benign proliferative breast disease and antidepressant medication use has not been reported in the literature. Benign breast disease lesions may be cancer precursors with the *ability* to progress to breast cancer (49, 50). It is also possible that some risk factors may be related to the development of both benign proliferative breast disease and breast cancer.

It is unlikely that selection bias or uncontrolled confounding biased the results of our study. Both our cases and controls were selected from population-based sampling frames. It is unlikely that the opportunity for diagnosis of breast cancer would be differential according to antidepressant medication use. In addi-

tion, selection bias with respect to controls is very unlikely since it is not possible that the sampling of controls from the Ministry of Finance database was in any way related to antidepressant medication use. Furthermore, our data are consistent with those of previous studies in identifying known risk factors for breast cancer, and potential confounders were controlled for in our multivariate analysis.

Recall bias is of particular concern in case-control studies because cases may remember or report exposures differently than do controls. In an attempt to reduce the opportunity for recall bias in the reporting of antidepressant medication use, material sent to subjects did not state the specific research hypotheses. In addition, our questionnaire addressed a wealth of environmental factors, making it difficult for participants to determine the study hypothesis.

In an attempt to assess the misclassification of self-reported antidepressant medication use, we have previously compared antidepressant medication use reported by female cancer cases and controls participating in the Enhanced Cancer Surveillance study with physician-reported antidepressant medication use (51). We found substantial agreement between subject- and physician-reported antidepressant medication use for "ever" use and for use of specific antidepressant medications, while moderate agreement was observed for duration of use and date of first use. Although these findings suggest that nondifferential misclassification is minimal with respect to the self-reported dichotomous variables, some attenuation of our odds ratio estimates toward the null hypothesis would still be expected (52). The effect of nondifferential misclassification on the degree of attenuation toward the null is usually greatest when the prevalence of exposure differs substantially from 50 percent (53), as is the case for the antidepressant medication use. In addition, nondifferential misclassification of categorized variables or any differential misclassification could have biased odds ratio estimates either toward or away from the null hypothesis (52, 54).

Because of both the paucity of epidemiologic studies and their inconsistent findings, further studies are needed regarding the association between antidepressant medication use and breast cancer risk. Evidence to date does not support a change in the current use of antidepressant medications, although there may be an effect from long-term use.

Future studies should be able to adequately evaluate the breast cancer risk associated with various subgroups of antidepressant medication types and assess benign proliferative breast disease risk in relation to antidepressant use. Future studies should also evaluate other cancer sites that have been identified in the literature as potentially associated with antidepressant medication use (e.g., ovarian cancer and melanoma) (55, 56). Further experimental studies would be helpful to elucidate the underlying biologic mechanisms by which antidepressant medications could influence breast cancer risk.

## ACKNOWLEDGMENTS

This research was performed within the context of the Enhanced Cancer Surveillance project, sponsored by the Laboratory Centre for Disease Control, Health Canada (contract no. H4078-3-C119/01-SS). Michelle Cotterchio was a research student of the National Cancer Institute of Canada supported with funds provided by the Canadian Cancer Society.

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