Original Contribution

Use of Selective Serotonin Reuptake Inhibitors and the Risk of Breast Cancer

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Selective serotonin reuptake inhibitors (SSRIs) were introduced in 1987 and, by 1997, were prescribed to 58% of Americans receiving outpatient treatment for depression. In 1992, a study reported that one of the SSRIs, fluoxetine, accelerated the growth of mammary tumors in rodents. By use of data from 1988 to 2002 from their hospital-based, case-control surveillance study, the authors examined the relation between use of SSRIs and risk of breast cancer. Nurse interviewers administered standard questionnaires to patients admitted to hospitals in three US centers to obtain information on demographic, medical, and lifestyle factors and to elicit a history of drug use, including antidepressants. Cases comprised 2,138 women with primary invasive breast cancer, and controls comprised 2,858 women admitted with nonmalignant diagnoses unrelated to SSRI use. The authors used multivariate conditional logistic regression models to estimate odds ratios for breast cancer among regular users of SSRIs compared with nonusers. The odds ratio was 1.1 (95% confidence interval: 0.8, 1.7) for regular use of SSRIs and 0.7 (95% confidence interval: 0.4, 1.5) for use of 4 or more years. Odds ratios were not elevated for any specific SSRI. These data provide some assurance that the use of SSRIs does not increase the risk of breast cancer.

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

Abbreviations: CI, confidence interval; OR, odds ratio; SSRI, selective serotonin reuptake inhibitor.

Fluoxetine (Prozac; Eli Lilly and Company, Indianapolis, Indiana), the first selective serotonin reuptake inhibitor (SSRI), was approved on December 29, 1987, for the treatment of depression. It was followed by sertraline (Zoloft; Pfizer, Inc., New York, New York) in 1991, paroxetine (Paxil; GlaxoSmithKline, London, United Kingdom) in 1992, citalopram (Celexa; Forest Pharmaceuticals, Inc., St. Louis, Missouri) in 2000, and escitalopram (Lexapro; Forest Pharmaceuticals) in 2002. According to the 1997 Medical Expenditure Panel Survey, SSRIs were prescribed to 58 percent of Americans who received outpatient treatment for depression (1). Fluoxetine and paroxetine have been found to reduce the number and intensity of hot flashes in women who have had breast cancer or are at high risk, and the drugs are prescribed for hot flashes to an unknown extent (2). In 2003, Zoloft ranked 12th in the United States in terms of number of prescriptions dispensed (3).

Concern was raised about the tumor-promoting potential of fluoxetine in 1992 when it was reported that clinically relevant doses of the drug accelerated the growth of mammary tumors in rodents (4). It was suggested that fluoxetine acted as a tumor promoter in the presence of a carcinogen by binding to antiestrogen-binding site/intracellular histamine receptors (H₁c) (5, 6). The drug is structurally similar to the prototype compound N,N-diethyl-2-[4-(phenylmethyl) phenoxy]ethanamine hydrochloride, which binds to the same receptors and plays a role in growth regulation. However, a later study conducted by the Food and Drug Administration...
reported that fluoxetine did not significantly stimulate tumor cell proliferation, DNA synthesis, or colony formation in several human and murine cell lines, including the human breast cancer cell line MCF-7 (7).

Five epidemiologic studies have assessed SSRI use and breast cancer risk (8–11). One study reported a nonsignificant twofold increase in risk among women who had used SSRIs for 36 or more months (8), and another reported a nonsignificant sevenfold increase in risk among paroxetine users (9), but both results were based on small numbers. A study using Medicare and Medicaid databases reported a hazard ratio of 1.04 for women who filled a prescription for fluoxetine compared with women who had filled a prescription for any other medication (10). In an analysis of the General Research Practice Database, the odds ratio for breast cancer among users of SSRIs was 0.98 (95 percent confidence interval: 0.81, 1.19) (11). In an assessment of SSRI use and breast cancer risk in our hospital-based, case-control surveillance study using data reported through 1996, the odds ratio was 1.8 (95 percent CI: 1.0, 3.3) for recent users of SSRIs based on 22 case users (12). Here, we present an update using data from patients admitted through 2002. We also have accrued enough subjects to evaluate more informatively duration of use and specific SSRIs.

**MATERIALS AND METHODS**

Data were collected from patients admitted to hospitals in New York, New York, Philadelphia, Pennsylvania, and Baltimore, Maryland, from 1988 through 2002. The population base for the study comprised people living in ZIP codes within 50 miles of a participating hospital. Nurse interviewers visited the hospitals from one to three times per week, depending on the size of the institution. On visit days, all patients meeting study criteria were identified through examination of admission lists and ward logs. Eligible patients were aged 18–79 years, were under the care of a physician participating in the study, did not have certain excluded diagnoses (e.g., psychiatric diagnoses), were able to complete the interview (e.g., not deaf), and lived in an eligible ZIP code.

Nurse interviewers administered standard questionnaires to obtain information on demographic factors, medical and reproductive history, and habits such as smoking and alcohol consumption. Histories of drug use were elicited by asking about 43 indications for use that included those for which SSRIs are used (i.e., nerves, depression, mood elevators, emotional disorders, psychiatric problems). For each episode of use, the drug name and the duration, timing, and frequency of use were recorded. Details of the diagnosis were abstracted from discharge summaries and pathology reports. From 1988 through 1997, 95 percent of patients approached for an interview participated. Since 1998, 88 percent of patients have participated. The study was approved by the institutional review boards of all participating institutions.

**Cases and controls**

The breast cancer cases comprised 2,138 women aged 24 through 73 years with a first occurrence of primary invasive breast cancer diagnosed within the previous year and no concurrent or previous cancer other than nonmelanoma cancer of the skin.

The control group comprised 2,858 patients admitted with nonmalignant diagnoses that we judged to be unrelated to the use of SSRIs, who were frequency matched to the cases in up to a 4:1 ratio based on 5-year age group, study center, and year of interview (four categories). Controls had no history of cancer other than nonmelanoma cancer of the skin. Controls included subjects admitted to the hospital for trauma (25.1 percent); acute infection (10.9 percent); hernias, disorders of the bowel, and gallbladder (39.6 percent); and other conditions (e.g., pelvic inflammatory disease, herniated or ruptured disc) (24.5 percent).

**Statistical analysis**

We defined regular use of SSRIs as use on at least 4 days per week for at least 3 continuous months. Any other use was considered sporadic. Individuals whose use occurred exclusively within the year before admission were excluded from the analysis (12 cases and 21 controls). Duration of regular use was summed over all lifetime episodes.

Odds ratios for breast cancer among regular users of SSRIs compared with never use of an SSRI were calculated by use of conditional logistic regression models that accounted for the matching variables. Among controls, the prevalence of regular use of SSRIs increased with age and year of interview. We estimated the association of SSRI use with breast cancer risk using three models: model 1 accounted for the matching variables only; model 2 added breast cancer risk factors that were associated with SSRI use in our data (alcohol consumption, cigarette use, parity, and age at first birth).


<table>
<thead>
<tr>
<th>Year of interview</th>
<th>Cases (%)</th>
<th>Controls (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 2,138)</td>
<td>(n = 2,858)</td>
</tr>
<tr>
<td>1988–1990</td>
<td>32.0</td>
<td>26.8</td>
</tr>
<tr>
<td>1991–1992</td>
<td>27.5</td>
<td>20.4</td>
</tr>
<tr>
<td>1993–1996</td>
<td>25.5</td>
<td>34.5</td>
</tr>
<tr>
<td>1997–2002</td>
<td>15.0</td>
<td>18.3</td>
</tr>
<tr>
<td>Area</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baltimore</td>
<td>7.7</td>
<td>11.0</td>
</tr>
<tr>
<td>New York</td>
<td>34.5</td>
<td>16.3</td>
</tr>
<tr>
<td>Philadelphia</td>
<td>57.8</td>
<td>72.7</td>
</tr>
</tbody>
</table>
religion, family history of breast cancer, and race); and model 3 added other breast cancer risk factors: presence of benign breast disease, parity, menopausal status, age at menopause, age at first birth, body mass index, and age at menarche. Results from model 2 differed from results from model 1, but addition of the variables in model 3 did not alter the odds ratios. Thus, the odds ratios from models 1 and 2 are presented.

### RESULTS

The prevalence of regular SSRI use among subgroups of controls, adjusted for age, year of interview, and study center, was as follows: infection, 2.9 percent; hernias and bowel and gallbladder disorders, 2.2 percent; trauma, 2.3 percent; and other conditions, 2.0 percent. The prevalence of SSRI

### TABLE 2. SSRI* use among cases and controls, New York, New York, Philadelphia, Pennsylvania, and Baltimore, Maryland, 1988–2002†

<table>
<thead>
<tr>
<th>SSRI use</th>
<th>Cases (no.)</th>
<th>Controls (no.)</th>
<th>ORᵢ, 95% CI</th>
<th>ORᵢ, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No use</td>
<td>2,047</td>
<td>2,743</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Regular use</td>
<td>59</td>
<td>65</td>
<td>1.5</td>
<td>1.0, 2.1</td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>6</td>
<td>5</td>
<td>2.1</td>
<td>0.6, 7.2</td>
</tr>
<tr>
<td>1–&lt;2 years</td>
<td>21</td>
<td>18</td>
<td>1.9</td>
<td>1.0, 3.6</td>
</tr>
<tr>
<td>2–&lt;4 years</td>
<td>18</td>
<td>20</td>
<td>1.6</td>
<td>0.8, 3.1</td>
</tr>
<tr>
<td>≥4 years</td>
<td>14</td>
<td>22</td>
<td>0.9</td>
<td>0.5, 1.9</td>
</tr>
<tr>
<td>Continuing use</td>
<td>48</td>
<td>50</td>
<td>1.5</td>
<td>1.0, 2.3</td>
</tr>
<tr>
<td>Discontinued use</td>
<td>11</td>
<td>15</td>
<td>1.3</td>
<td>0.6, 3.0</td>
</tr>
<tr>
<td>Sporadic use</td>
<td>19</td>
<td>26</td>
<td>1.1</td>
<td>0.6, 2.1</td>
</tr>
<tr>
<td>Unknown use</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* SSRI, selective serotonin reuptake inhibitor; OR, odds ratio; CI, confidence interval.
§ In addition to the matching variables, adjusted for alcohol consumption (former, current, never), religion (Catholic, Jewish, Protestant, other), family history of breast cancer (yes, no), and race (White, other).
use among controls has increased from less than 1 percent prior to 1993, to 1.8 percent from 1993 to 1996, to 8.0 percent from 1997 to 2002. The majority of use was of fluoxetine (60 percent), followed by sertraline (24 percent) and paroxetine (12 percent). All use was daily use.

Cases were older than controls (table 1). Most cases and controls were from Philadelphia, and the distribution of year of interview was similar for cases and controls.

Regular use of SSRIs was not associated with breast cancer risk after adjustment for other risk factors (odds ratio (OR) = 1.1, 95 percent CI: 0.8, 1.7) (table 2). The odds ratio was 0.7 (95 percent CI: 0.4, 1.5) for use of 4 or more years. The confidence intervals for all duration categories included 1.0. The odds ratios were similar whether use was recent (continued into the year of interview) (OR = 1.2, 95 percent CI: 0.8, 1.8) or had stopped at least a year prior to interview (OR = 1.1, 95 percent CI: 0.5, 2.6). The odds ratio for sporadic use did not differ from 1.0 (table 2). Overall and duration-specific odds ratios were similar for pre- and post-menopausal women (data not shown).

The odds ratios for regular use of fluoxetine, sertraline, and paroxetine did not differ significantly from 1.0 (table 3). There was no indication that odds ratios increased as duration of use increased, although numbers were small. There were not enough users of escitalopram or citalopram for separate analysis.

**DISCUSSION**

Use of SSRIs overall was not associated with breast cancer risk in these data, nor was there an association with long-term use or with specific drugs. No increase was seen for recent use, in contrast to our earlier report where the odds ratio for recent SSRI use was 1.8. The present report is based on more than twice as many SSRI users, and the previously observed increase in risk was probably due to chance.

A limitation of the study is that drug use was self-reported. However, since SSRIs were introduced relatively recently and are taken daily, use was likely to be well remembered. A validation study of antidepressant use that compared self-report with physician report found a kappa of 0.60 and percent agreement of 80 percent for ever use, and accuracy of reporting was the same for cases and controls (13). We do not believe recall bias played a role because neither interviewers nor study subjects were aware of the hypothesis, and antidepressant use was ascertained along with all other drugs used for a long list of indications. With regard to selection bias, we chose controls with diagnoses that are not known to be related to the use of SSRIs, and the similarity of the age-standardized prevalences of SSRI use among subgroups of controls supports this assumption. Adjustment was made for breast cancer risk factors that were associated with SSRI use.

Our results did not confirm the finding of an increased risk for paroxetine reported in one study (8). In that Canadian, population-based, case-control study, the odds ratio for ever use of an SSRI or for ever use of fluoxetine was slightly less than 1.0, but the odds ratio for ever use of paroxetine was 7.2 (95 percent CI: 0.9, 58.3), based on only nine cases and one control (9). We also did not confirm an increased risk for long-term users reported in a population-based, case-control study in North Carolina (8). In that study, the odds ratio for invasive breast cancer was 1.0 (95 percent CI: 0.7, 1.5) for any use (70 cases and 55 controls), but it was 2.2 (95 percent CI: 0.8, 6.3) for use of 36 or more months (13 cases and five controls) (8).

In conclusion, our data provide some assurance that the use of SSRIs, even for 4 or more years, does not increase the risk of breast cancer. Monitoring of longer term use will be worthwhile if it becomes apparent that an appreciable number of women remain on these commonly used medications for decades.

**ACKNOWLEDGMENTS**

Conflict of interest: none declared.

**REFERENCES**