ORIGINAL ARTICLE

Dopamine Antagonists and the Development of Breast Cancer

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Background: Although animal studies have raised the possibility that prolactin-elevating dopamine antagonists used to treat psychotic disorders may initiate and promote breast cancers, epidemiologic studies in humans have been limited and inconsistent.

Methods: A retrospective cohort study was conducted of 52 819 women exposed and 55 289 not exposed to dopamine antagonists between January 1, 1989, and June 30, 1995. All participants were 20 years or older, initially free of breast cancer, and enrolled in the Medicaid or the Pharmaceutical Assistance to the Aged and Disabled programs of New Jersey. Incident breast cancer cases were identified through the New Jersey Cancer Registry and definitive breast cancer surgeries. Adjusted hazard ratios of breast cancer were calculated from multivariable proportional hazards models.

Results: Use of antipsychotic dopamine antagonists was associated with a 16% increase in the risk of breast cancer (adjusted hazard ratio, 1.16; 95% confidence interval, 1.07-1.26), with a dose-response relationship between larger cumulative dosages and greater risk. The increased risk was also seen in women who used prolactin-elevating antiemetic dopamine antagonists despite having different breast cancer risk profiles than antipsychotic dopamine antagonist users. Dopamine antagonist use was not associated with risk of colon cancer, a control condition not related to elevated prolactin levels. The increased risk of breast cancer among dopamine antagonist users was not explained by increased surveillance or protopathic bias.

Conclusions: Antipsychotic dopamine antagonist use may confer a small but significant risk of breast cancer. In light of the small hazards and the possibility of residual confounding, these findings should lead to follow-up investigations but not to changes in treatment strategies.

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EACH YEAR, more than 180 000 cases of breast cancer are diagnosed and 44 000 breast cancer deaths occur in the United States alone.[1] Such burdens confer high priority on the identification of modifiable risk factors, including the use of medications that may initiate or promote breast malignancies. Laboratory studies[2] have raised the possibility that some centrally acting dopamine antagonists used to treat psychotic disorders may increase the risk of breast malignancies. It is well established that at therapeutic dosages, some of these drugs cause dose-dependent increases in serum prolactin levels, with significantly greater increases in women than in men given comparable doses.[3] In animals, increased prolactin levels can cause malignant transformation of breast tissue.[4] Elevated prolactin levels also promote tumor growth in rodents with induced mammary malignancies.[5-7] The Food and Drug Administration has required product label warnings for conventional neuroleptics since the 1970s based on a possible association with breast cancer.

Previous epidemiologic studies of this issue have been limited and have produced inconsistent findings. Early studies[8-10] comparing cancer mortality rates between psychiatric inpatients and other populations produced variable results, in part because of inappropriate statistical analyses.[11,12] Of studies that compared breast cancer incidence rates between dopamine antagonist users and other populations, one attributed significantly increased risk to use of these drugs,[13] but its methods have been questioned.[14-16] Another study[17] reported significantly increased breast cancer risks among dopamine antagonist users at 2 of 3 study sites. Other studies[18-22] found no significant associations, but their statistical power was limited.[23] One investigation[24] reported a significant reduction in breast cancer risk among haloperidol users; however, in a subsequent reanalysis,[25] this finding was not replicated.

Important methodologic issues in these previous studies include small sample sizes, imprecise means of ascertaining drug exposures, and unadjusted confounding by important risk factors. Surveillance bias is another important concern because psychiatric patients, especially those with psychotic disorders, have been shown to be less likely to receive screening, diagnostic, and therapeutic interventions for comorbid medical conditions such as cancer.[26-28]

Because of the common use of dopamine antagonists in the general population and the even more intensive exposure in oncology populations,[29] the effect of these drugs on the occurrence and course of breast cancer is a persistent and important question that has drawn new impetus from the current availability of atypical agents (eg, clozapine, olanzapine, and quetiapine) that do not elevate prolactin levels.[2]

The public health importance of the underlying question and the difficulty of conducting appropriate randomized trials makes it imperative to address the methodologic shortcomings of earlier epidemiologic studies. For these reasons, we used objective assessments of medication use based on actual drug dispensing rather than patient reports of use to minimize information biases. We separately identified the risks associated with cumulative dosages, pharmacologic classes, and specific agents. We used a rigorous means to identify incident breast cancer cases, including a population-based cancer registry. We looked for unadjusted confounding by examining the breast cancer risk among users of antiemetic dopamine antagonists because these agents elevate prolactin levels, but patients taking antiemetics presumably have a different breast cancer risk profile than patients with psychotic disorders. We assessed the impact of differential surveillance by comparing the rates of mammography and visits to general medical providers by antipsychotic dopamine antagonist users vs nonusers. We also examined whether dopamine antagonist use was associated with colon cancer, a control condition not related to elevated prolactin levels that would be affected by biased surveillance in a manner similar to breast cancer. Finally, we investigated whether patients with occult tumors were given dopamine antagonists for symptoms caused by undiagnosed breast cancer (protopathic bias[30]) by removing cases diagnosed within 3 months of initiating use and within 12 months of initiating use.

METHODS

STUDY POPULATION

All women 20 years or older who used at least 1 medical service or prescription in each of 2 consecutive 6-month periods were eligible for study participation. These requirements helped ensure that all participants were enrolled in their benefits programs (described herein) and capable of using services in a uniform 1-year period, during which exposure variables and other covariates could be assessed. The index date for each woman was considered to be the earliest date after completion of this yearlong eligibility period.

We then identified an exposed cohort of all eligible women who filled any prescriptions for the following dopamine antagonists in the year before their index date: acetophenazine maleate, chlorpromazine, chlorprothixene, clozapine, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, perphenazine, pimozide, promazine hydrochloride, risperidone, thioridazine, thiothixene, and trifluoperazine hydrochloride. We also identified women who filled prescriptions for 2 other dopamine antagonists not used for psychiatric indications: prochlorperazine, used as an antiemetic agent, and metoclopramide hydrochloride, used as an antiemetic and prokinetic agent. These women served in subanalyses as positive controls (ie, they were exposed to dopamine antagonists that elevate prolactin levels but were likely to have a different profile of breast cancer risk factors than women taking antipsychotic drugs).

We also identified an unexposed cohort of eligible women who filled a prescription for a random medication other than a dopamine antagonist during the year before their index date. Dopamine antagonist users and nonusers were frequency matched by calendar year of birth and by year and month of their first qualifying prescription. Any woman selected as a nonuser who previously or subsequently filled a prescription for a dopamine antagonist was excluded.

We removed all prevalent cases of breast cancer by excluding any woman with any of the following before, on, or 3 months after the index date: a diagnosis of breast cancer in the New Jersey (NJ) Cancer Registry, an *International Classification of Diseases, Ninth Revision, Clinical Modification,* diagnosis code for breast cancer,[31] a breast cancer surgical procedure,[31,32] a diagnosis-related group code for a breast cancer hospitalization,[33] or a prescription for tamoxifen citrate.

DATA SOURCES

NJ Medicaid Program

New Jersey Medicaid provides coverage for medication prescriptions and health care services. For this study, information was available from January 1, 1989, to June 30, 1995, and included demographic characteristics and dates of enrollment; hospitalization, outpatient, and nursing home use data (including admission and discharge dates, physician encounters, diagnoses, and procedures); and data for all filled prescriptions (including medication, quantity dispensed, number of days supply, and prescription date). The NJ Medicaid program has no deductibles, no maximum benefit, and no copayment for prescription drugs. Because it covers elderly patients receiving long-term care and younger patients with chronic mental illness, Medicaid includes many individuals receiving antipsychotic medications. The indigent status of Medicaid enrollees results in essentially no out-of-pocket health care use, ensuring comprehensive ascertainment of all filled prescriptions and use of services in Medicaid reimbursement files.

NJ Pharmaceutical Assistance to the Aged and Disabled Program

The NJ Pharmaceutical Assistance to the Aged and Disabled (PAAD) program provided additional information on nonindigent patients for the same period. The PAAD program is a state-specific program of reimbursement for the drug expenses of nonindigent elderly (aged ≥65 years) and disabled citizens. During the study, the NJ PAAD program had the highest income ceiling of any such program nationally (recipients could have an annual income of up to $15 700 if single and $19 250 if married), producing a recipient population that was both large and less poor than the Medicaid population.

NJ Medicare

Medicare data used in the present study included both Part A data on hospitalizations and nursing home stays and Part B data

on outpatient professional services and procedures, covering essentially all NJ residents older than 65 years.

NJ Cancer Registry

Since 1978, state law has mandated that hospitals, physicians, dentists, and clinical laboratories report all new cancer cases within 6 months to the NJ Cancer Registry.[34] A standardized reporting system (*ICD-Oncology Version 2*) is used to classify pathologic, histologic, and staging information. Neighboring states provide information to the NJ Cancer Registry on NJ residents diagnosed as having cancer outside of NJ. The NJ Cancer Registry data are periodically matched to information from reporting hospitals and physicians; state death, motor vehicle, and income tax records; and federal databases such as the National Death Index. Information on approximately 90 000 breast cancer cases was available and last updated for this study in July 1996. Data included information on demographic variables, diagnosis, tumor characteristics, treatments received, and survival.

We identified Medicaid beneficiaries younger than 65 years and then all Medicare beneficiaries 65 years and older who were also enrolled in either Medicaid or the PAAD program (because the latter 2 programs provide comprehensive data on all prescription drug use). Information on all filled prescriptions, procedures, physician encounters, hospitalizations, long-term care, and any breast cancer information on individuals available in the NJ Cancer Registry was assembled into a relational database. Personal identifiers were transformed into anonymous, coded study numbers to protect the privacy of all patients. The study protocol was approved by the institutional review boards of the Harvard School of Public Health and the NJ Cancer Registry.

DOPAMINE ANTAGONIST EXPOSURE DEFINITIONS

Use of Dopamine Antagonists

We identified all prescriptions for a dopamine antagonist filled by patients during an exposure assessment period consisting of the year before the index date. We recorded whether patients were exposed to any dopamine antagonists, individual agents, and pharmacologic classes, including phenothiazines (acetophenazine, chlorpromazine, fluphenazine, mesoridazine, perphenazine, promazine, thioridazine, and trifluoperazine), thioxanthenes (chlorprothixene and thiothixene), and butyrophenones (haloperidol). We also identified exposure to the antiemetic agents prochlorperazine and metoclopramide.

Cumulative Dopamine Antagonist Dosage

Using the quantity dispensed and number of days supply data recorded on prescriptions, we calculated the total dosage of all prescriptions during the exposure assessment period. To standardize comparisons between agents, dosages were converted to chlorpromazine-equivalent milligrams (cpz-eq.mg) using established equivalencies.[35] We used the distribution of cumulative dosages to divide exposed individuals into 4 equal-sized groups (quartiles).

CANCER CASE DEFINITIONS

A woman was considered to be an incident breast cancer case if she received a first diagnosis of breast cancer in the NJ Cancer Registry at least 3 months after her index date. Data from the NJ Cancer Registry used in this study had been last updated in July 1996. Therefore, all living patients who had not received a diagnosis of breast cancer by June 30, 1996, were considered censored on that day. In addition, we considered as cases women who had a first claim for 1 of the following breast cancer surgeries indicative of incident breast cancer: a mastectomy,[31,32] a lumpectomy plus an axillary node biopsy,[31,32] or a hospitalization for breast cancer surgery.[33] Of the 2467 incident breast cancer cases in the present study, 98 (4%) were identified through breast cancer surgeries alone. The date of breast cancer onset was taken as the earliest date a woman was identified through the NJ Cancer Registry or breast cancer surgery claims. This case definition, based on new NJ Cancer Registry diagnoses and breast cancer surgeries, correctly identifies more than 90% of the incident breast cancer cases estimated to occur in the population.[36]

We also identified cases of the control outcome, incident colon cancer, as women who had both of the following at least 3 months after the index date: a new diagnosis of colon cancer[31] plus a first colectomy or colon excision procedure.[31,32] The date of onset of colon cancer was considered the date of diagnosis or the date of colon cancer surgery, whichever was earlier.

OTHER COVARIATES

We defined the following potential confounders and covariates during the year before the index date.

Sociodemographic Characteristics

Program enrollment information was used to determine age, race, and socioeconomic status (lower socioeconomic status was defined as being enrolled in Medicaid, and relatively higher socioeconomic status was defined as being enrolled in the PAAD program).

Factors Potentially Related to Breast Cancer Diagnosis

Using all filled prescriptions in the year before the index date, we recorded whether patients had filled any prescriptions for estrogens. We used the presence of specific *International Classification of Diseases, Ninth Revision, Clinical Modification,* diagnostic codes[31] to define subjects who had several clinical conditions related to breast cancer development, including benign mammary dysplasia, obesity, and malignancies other than breast cancer. We also scanned diagnostic information from all inpatient and outpatient encounters to calculate a modified Charlson score, a commonly used measure of the extent of comorbid illness that was originally developed using a population of patients with breast cancer.[37,38]

Health Care Use

Health care use was assessed in the year before the index date by calculating the number of days medically hospitalized, the number of days psychiatrically hospitalized, the number of outpatient medical visits, the number of outpatient psychiatric visits, and the number of days spent in a nursing home. To assess whether dopamine antagonist users were more or less likely to be screened for breast cancer, we also measured rates of mammography in all study groups.

STATISTICAL ANALYSES

Initially, we calculated the crude incidence rates of developing breast cancer for women with any dopamine antagonist use and for women in levels of all other covariates. To examine the independent effect of the use of antipsychotic dopamine antagonists on developing breast cancer while controlling for potential confounders, we constructed a multivariable proportional hazards model.[39] Variables representing age, race, and antipsychotic dopamine antagonist use were introduced into the model first. All remaining covariates were then subjected

Table 1. Characteristics of Users and Nonusers of Dopamine Antagonists*

Characteristic	Users (n = 52 819)	Nonusers (n = 55 289)	*P* Value†
Age, %			.64
<40 y	23.6	23.5	
40-49 y	10.9	10.7	
50-59 y	9.3	9.2	
60-69 y	14.0	14.2	
70-79 y	19.2	19.5	
≥80 y	23.0	23.0	
Race, %			.001
White	76.8	70.5	
Nonwhite	23.2	29.5	
Socioeconomic status, %			.001
Medicaid	70.5	60.9	
PAAD	29.5	39.1	
Clinical characteristics, %‡			
Benign breast disorders	2.4	3.0	.001
Obesity	2.3	2.1	.02
Nonbreast malignancy	9.2	7.3	.001
Charlson comorbidity score, mean	1.0	0.8	.001
Any estrogen use, %	7.2	10.5	.001
Medical hospital days in previous year, mean No.	9.1	4.1	.001
Medical outpatient visits in previous year, mean No.	3.7	4.8	.001
Psychiatric hospital days in previous year, mean No.	2.0	0.1	.001
Psychiatric outpatient visits in previous year, mean No.	1.6	0.4	.001
Nursing home use in previous year, %	23.3	11.0	.001

*PAAD indicates Pharmaceutical Assistance to the Aged and Disabled program eligibility.

†All *P* values are 2-sided and were obtained from *t* tests (for continuous variables) and χ^2 tests (for categorical variables).

‡Based on the presence of *International Classification of Diseases, Ninth Edition, Clinical Modification*, diagnostic codes corresponding to these conditions.

to a forward stepwise selection procedure with a selection criterion of $P<.20$. Next, each covariate not included by the stepwise selection procedure was individually added back; any variable whose inclusion changed the parameter estimate for dopamine antagonist use by 10% or more was included in the final model. We derived asymptotic 95% confidence intervals (CIs) from the Fisher information matrix.

In subset analyses, we estimated the independent risks associated with use of different cumulative doses, pharmacologic classes, and specific agents by substituting variables representing these exposures into the final multivariable proportional hazards model. We also examined the hazard associated with the antiemetic agents prochlorperazine and metoclopramide. We evaluated whether our results could have been affected by patients with occult breast tumors who were prescribed dopamine antagonists for symptoms related to an as-yet undiagnosed breast malignancy (protopathic bias[30]) by restricting the analyses to breast cancer cases diagnosed at least 1 year after the index date. To investigate the time course over which the effects of dopamine antagonist use might emerge, we reran the final model among strata of women defined by their number of years of follow-up. In subanalyses, we controlled for the effects of schizophrenia or other psychotic disorders by inserting variables representing these diagnoses into the final model. We also assessed whether there were significant interactions between dopamine antagonist use and either age or psychotic disorder diagnoses.

To investigate whether the degree of medical surveillance received by antipsychotic dopamine antagonist users vs nonusers could have affected the results, we constructed 2 multivariable logistic regression models. The dependent variable in the first model was mammography in the year before the index date. The dependent variable in the second model was having greater than the median number of outpatient medical visits in the year before the index date. Into each model, we added variables representing dopamine antagonist use, age, and nursing home use. Last, we constructed a multivariable proportional hazards model of developing the control outcome of colon cancer, into which we added variables representing age, race, and dopamine antagonist use; the remaining covariates were then selected as described earlier.

RESULTS

Characteristics of dopamine antagonist users and nonusers are given in **Table 1**. One quarter of all participants were younger than 40 years, and one quarter were 80 years and older. Most women were white and were enrolled in Medicaid, more so among dopamine antagonist users than nonusers. Users of these agents were less likely to be exposed to estrogens. Compared with nonusers, users were more likely to have some conditions potentially related to developing breast cancer (ie, obesity and nonbreast malignancies) but less likely to have others (ie, benign breast disorders); they also had higher comorbid illness severity scores. Users had fewer outpatient medical visits but used more medical and psychiatric inpatient, psychiatric outpatient, and nursing home services.

Table 2 provides case counts, person-years of follow-up, crude incidence rates, and adjusted hazard ratios (HRs) of breast cancer for variables included in the final multivariable proportional hazards models. Dopamine antagonist users had a slightly higher crude incidence rate of breast cancer (5.72×10^{-3} person-years) than nonusers (5.18×10^{-3} person-years). After adjustment for potential confounders, antipsychotic dopamine antagonist use was associated with a modest but significantly increased risk of developing breast cancer (adjusted HR, 1.16; 95% CI, 1.07-1.26).

We also observed significant relationships between some established risk factors and the development of breast cancer.[40-45] Breast cancer risks increased with age to a maximum for women aged 60 to 69 years; risks began to decline thereafter for women aged 70 to 79 years and 80 years and older. Women with the lowest socioeconomic status (eligible for Medicaid) had a significantly lower risk of breast cancer relative to the less poor (eligible for the PAAD program). There was also a tendency for nonwhites to have lower risks than whites. Significantly elevated risks were observed among women with benign breast conditions and nonbreast malignancies. We also observed a tendency for women with obesity to be at greater risk of breast cancer. Women with more severe comorbid illness and greater numbers of outpatient medical visits were significantly more likely to be diagnosed as having breast cancer.

The median cumulative dosage of dopamine antagonist was 11 700 cpz-eq.mg (25%-75% interquartile

Table 2. Case Counts, Person-years of Follow-up, Crude Incidence Rates, and Adjusted Hazard Ratios of Incident Breast Cancer for Variables in the Final Proportional Hazards Model*

Variable	Breast Cancer Cases, No. (N = 2467)	Follow-up, Person-years	Crude Incidence Rate, $\times 10^{-3}$ Person-years	Adjusted Hazard Ratio (95% CI)†
Dopamine antagonist use				
Yes	1239	216 517	5.72	1.16 (1.07-1.26)
No	1228	237 242	5.18	1.00
Age, y				
<40	250	116 301	2.15	1.00
40-49	297	53 671	5.53	1.79 (1.53-2.08)
50-59	342	45 069	7.59	2.50 (2.15-2.90)
60-69	571	67 017	8.52	2.72 (2.37-3.11)
70-79	569	89 973	6.32	2.06 (1.79-2.38)
≥80	438	81 729	5.36	1.78 (1.53-2.08)
Race				
Nonwhite	590	126 878	4.65	0.94 (0.85-1.05)
White	1877	326 881	5.74	1.00
Socioeconomic status				
Medicaid	1446	298 893	4.84	0.86 (0.78-0.95)
PAAD	1021	154 867	6.59	1.00
Benign breast disorders				
Yes	152	12 716	11.95	1.85 (1.57-2.19)
No	2315	441 043	5.25	1.00
Obesity				
Yes	68	10 227	6.65	1.23 (0.96-1.57)
No	2399	443 532	5.41	1.00
Nonbreast malignancies				
Yes	316	32 753	9.65	1.51 (1.32-1.72)
No	2151	421 007	5.11	1.00
Charlson comorbidity score				
0	1229	261 904	4.69	1.00
1	721	124 077	5.81	1.06 (0.96-1.17)
≥2	517	67 777	7.63	1.15 (1.02-1.30)
Medical outpatient visits, No.				
0	804	176 783	4.55	1.00
1-4	529	103 056	5.13	1.20 (1.07-1.35)
5-9	512	84 199	6.08	1.33 (1.18-1.50)
≥10	622	89 721	6.93	1.44 (1.28-1.63)
Nursing home use				
Yes	275	57 352	4.79	0.95 (0.82-1.11)
No	2192	396 408	5.53	1.00

*CI indicates confidence interval; PAAD, Pharmaceutical Assistance to the Aged and Disabled program eligibility.
†From the final multivariable proportional hazards model that included all of the variables listed.

range, 2800-43 599 cpz-eq.mg). The **Figure** shows the adjusted HRs associated with quartiles of cumulative dosages of dopamine antagonists. The 2 lowest quartiles were not associated with elevated breast cancer risks, whereas the 2 highest quartiles were significantly associated with elevated risks. There was a generally monotonic dose-response relationship between higher cumulative dosages and greater breast cancer risks.

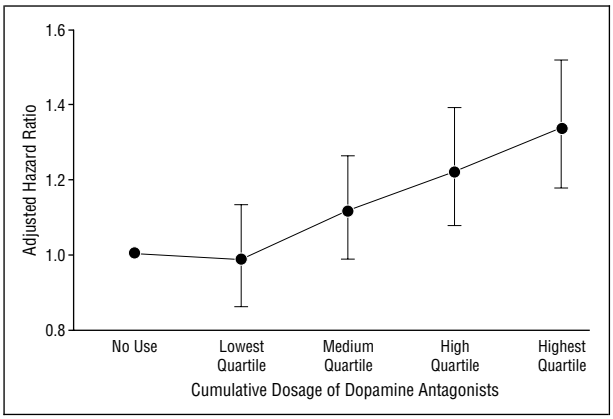
Case counts, person-years of follow-up, crude incidence rates, and adjusted HRs associated with pharmacologic classes of antipsychotic dopamine antagonists are given in **Table 3**. Phenothiazines were associated with significantly elevated hazards of developing breast cancer, and there was a nonsignificant trend toward increased risk for thioxanthene use. Butyrophenone use was not associated with a statistically significant elevated risk. Among individual agents, there were significantly elevated risks only for use of trifluoperazine (adjusted HR, 1.30; 95% CI, 1.06-1.60) and thioridazine (adjusted HR, 1.15; 95% CI, 1.00-1.31); however, many of these drug-specific estimates had limited power owing to the infrequent use of most individual agents. Use of prolactin-elevating antiemetic medications was also associated with a significantly increased breast cancer risk (adjusted HR, 1.11; 95% CI, 1.00-1.22). Although there was a suggestion of a dose-response relationship between higher cumulative dosages of antiemetic agents and greater breast cancer risks, study power to examine this issue was limited.

In a separate multivariable model of colon cancer, dopamine antagonist users were not at increased risk of being diagnosed as having this control condition (adjusted HR of colon cancer, 1.00; 95% CI, 0.86-1.17), despite the fact that colon cancer would likely have been affected by surveillance bias in a manner similar to breast cancer.

To further investigate whether surveillance bias might explain the associations observed between antipsychotic dopamine antagonist use and breast cancer risk, we constructed separate multivariable logistic regression models to measure the likelihood of being screened for breast cancer. Antipsychotic dopamine antagonist us-

ers were significantly less likely than nonusers to have mammography (adjusted OR of mammography, 0.88; 95% CI, 0.82-0.95) and frequent outpatient medical visits (adjusted OR of having greater than the median number of visits, 0.71; 95% CI, 0.69-0.73).

To examine whether the results were affected by a protopathic bias, we then restricted the final multivariable proportional hazards model of breast cancer to cases diagnosed at least 1 year after the index date; the adjusted HR in this restricted analysis was virtually unchanged from that given in Table 2 (adjusted HR for antipsychotic dopamine antagonist use, 1.17; 95% CI, 1.07-1.29). When we adjusted the final model of breast cancer for diagnoses of schizophrenia and other psychotic disorders, we likewise observed no change in the elevated risk of breast cancer (adjusted HR, 1.16; 95% CI, 1.07-1.26). When the final model was rerun among strata defined by the duration of follow-up, the greatest risks from dopamine antagonist use emerged among women followed for 6 years or longer (adjusted HRs [95% CIs] for dopamine antagonist use among women followed for <2, 2-3, 4-5, and ≥6 years were 1.09 [0.96-1.23], 1.08 [0.94-1.23], 1.17 [0.97-1.41], and 2.37 [1.25-4.47], respectively). There were no significant interactions between antipsychotic dopamine antagonist use and either age or diagnoses of psychotic disorders in relation to the risk of developing breast cancer.



Adjusted hazard ratios and 95% confidence intervals of developing breast cancer associated with quartiles of the cumulative dosage of dopamine antagonists obtained from a multivariable proportional hazards model. The dosage ranges for the lowest, medium, high, and highest quartiles correspond to <2800, 2800-11 699, 11 700-43 599, and ≥43 600 chlorpromazine-equivalent milligrams, respectively. The model was also adjusted for the covariates given in Table 2.

COMMENT

We found that women who use antipsychotic and antiemetic dopamine antagonists that elevate prolactin levels have a modest but significantly increased risk of developing breast cancer, which increases in a monotonic, dose-dependent fashion with exposure to larger cumulative dosages.

It is critically important to consider whether these findings are the result of methodologic limitations or a true biological relationship between these agents and breast cancer. Differential surveillance for breast cancer between antipsychotic dopamine antagonist users and nonusers is an important possibility, especially if women who used these drugs had greater opportunity to be diagnosed as having breast cancer than nonusers. However, a growing body of literature indicates that psychiatric patients, especially those with psychotic disorders, are less likely to be screened for, diagnosed as having, and treated for comorbid medical disorders.[26-28] Consistent with these studies, we found that antipsychotic dopamine antagonist users were significantly less likely to have mammograms and outpatient medical visits through which breast cancers would be diagnosed. We did not observe any relationship between use of these agents and colon cancer. If antipsychotic dopamine antagonist users were at increased risk of being diagnosed as having breast cancer simply because of more intensive surveillance, they would also be expected to show increased risks for all cancers detectable by screening.

We considered whether residual confounding by risk factors for which we lacked information (eg, reproductive history and family history) or had incomplete information (eg, body mass index and socioeconomic status) could explain our results. One concerning possibility is that antipsychotic dopamine antagonist users may have a greater risk of breast cancer because they forego having children or have them later in life. However, women who used antiemetic dopamine antagonists were also at increased risk of breast cancer. Antiemetic users are unlikely to share the same breast cancer risk profile as antipsychotic drug users, but they are exposed to agents that elevate prolactin levels. In addition, for confounding to

Table 3. Case Counts, Person-years of Follow-up, Crude Incidence Rates, and Adjusted Hazard Ratios of Breast Cancer Associated With Classes of Dopamine Antagonists*

Pharmacologic Class	Breast Cancer Cases, No.	Follow-up, Person-years	Crude Incidence Rate, $\times 10^{-3}$ Person-years	Adjusted Hazard Ratio (95% CI)†
Phenothiazines‡	508	89 916	5.65	1.19 (1.08-1.32)
Thioxanthenes§	100	18 071	5.53	1.14 (0.94-1.40)
Butyrophenones‖	240	46 269	5.19	1.05 (0.92-1.21)

*CI indicates confidence interval.
†Adjusted hazard ratios were obtained from a multivariable proportional hazards model of developing breast cancer. In addition to variables representing antipsychotic medication use, the model was adjusted for the covariates depicted in Table 2.
‡Includes acetophenazine maleate, chlorpromazine, fluphenazine, mesoridazine, perphenazine, promazine hydrochloride, thioridazine, and trifluoperazine hydrochloride.
§Includes chlorprothixene and thiothixene.
‖Includes haloperidol.

have caused a spurious association between dopamine antagonist use and increased breast cancer risk, these agents would have to have been preferentially prescribed to women with breast cancer risk factors. For many risk factors, this seems unlikely given the product label warnings about the potential for breast cancer required since the 1970s by the Food and Drug Administration on all conventional antipsychotic dopamine antagonists. It seems more likely that clinicians might have avoided prescribing them to women at increased risk of breast cancer because of such warnings, causing us to underestimate the true hazards of breast cancer with their use. Nevertheless, we cannot rule out the possibility of residual confounding by risk factors such as reproductive history at this time.

Might residual confounding by the indications for antipsychotic drug use explain these observations? Although schizophrenia and other psychotic disorders are no longer thought to be risk factors for developing cancer,[11] we investigated this possibility by adjusting our results for the presence of a diagnosis of schizophrenia or other psychotic disorders. There was little change in the observed risk function.

We considered the possibility that breast cancer outcomes were misclassified, such as would happen if incident breast cancer cases were underreported to the NJ Cancer Registry by health care facilities, laboratories, and providers. To guard against this possibility, we also identified cases through claims for definitive breast cancer surgeries (eg, mastectomies). Underascertainment may have been further mitigated by agreements that provide the NJ Cancer Registry with cancer information on residents diagnosed out of state, the fact that Medicare claims are recorded for NJ residents regardless of the state in which care was received, and substantial financial barriers faced by public entitlement recipients to going out of state to receive care.

We also considered the possibility that exposure status was misclassified. However, psychiatric conditions requiring these drugs are usually chronic; therefore, use of these agents during the exposure assessment period was likely to have been indicative of use before and after the study in most patients. It also seems likely that any misclassification of dopamine antagonist use would be unrelated to the outcomes of interest, thereby biasing away from finding an association between dopamine antagonist use and increased breast cancer risks.

Protopathic bias might have occurred if women experienced an emergence of psychopathologic symptoms requiring dopamine antagonist therapy because of a prevalent but not yet formally diagnosed breast tumor. If antipsychotic drugs were used to treat such exacerbations, they would spuriously seem to cause breast cancer. We reduced the chances of such a bias in our main analyses by excluding any cases diagnosed before or 3 months after the earliest onset of dopamine antagonist therapy. We also excluded cases diagnosed within 1 year after the index date in subanalyses and found that the significantly elevated risk of breast cancer among antipsychotic dopamine antagonist users persisted.

If these findings are validated in other studies, they raise the question of whether dopamine antagonists might act as modest initiators or promoters of breast malignancies. Results of earlier animal studies[3,4] suggest that elevated prolactin levels, through which these agents presumably act, can play both roles. However, long lag periods are generally thought to be required between tumor initiation and the diagnosis of breast malignancies.[46,47] For this reason, our findings that dopamine antagonists can affect the development of breast cancer within 6 to 7 years are most compatible with tumor-promoting effects rather than with direct tumor initiation. However, our findings could still be compatible with tumor-initiating effects if dopamine antagonist use during the study was a marker of women with chronic psychotic disorders who used prolactin-elevating agents in the remote past.

Other factors in this study associated with breast cancer are consistent with those identified in previous epidemiologic studies[40-45] and provide some reassurance concerning the validity of these analyses. Breast cancer risks increased with age to a maximum for women in their 60s; the rate of increase slowed for women in later decades of life, and it began to decline beyond the seventh decade; hormonal factors such as menopause and decreased surveillance and diagnosis among the elderly may underlie these findings.[40] Similarly, the lower risk we observed among poor women (eligible for Medicaid) may be explained by differences in reproductive patterns (eg, greater parity, lower age at first birth, and lower age at menarche) or surveillance and diagnosis.[42] We also confirmed increased hazards for women with other established risk factors, including benign breast disease,[43] obesity,[44] and nonbreast malignancies.[45] The increased risk in patients with more comorbid illness and more outpatient medical visits may be owing to higher levels of surveillance for breast cancer in these populations.

These findings must be confirmed in additional rigorous pharmacoepidemiologic studies. Such studies will need to be adequately powered and, ideally, be capable of differentiating between potential tumor-promoting and tumor-initiating effects. Greater quantification of the risks associated with individual agents, including newer atypical antipsychotic agents that do not cause an increase in prolactin concentration (eg, clozapine, olanzapine, and quetiapine) is also necessary and may shed light on biological mechanisms through which dopaminergic antagonists may affect breast cancer outcomes. Future studies should anticipate important methodologic pitfalls, such as the decreased surveillance for breast cancer experienced by antipsychotic medication users in routine care settings.

The clinical implications of these findings are limited at this time. First, these results should be viewed as preliminary. Until the relationships identified herein are confirmed, these findings do not warrant changes in patients' antipsychotic medication regimens. Even if replicated, clinicians should keep in mind and reassure their patients who have been exposed that the magnitude of the risk observed, although statistically significant, is small in absolute terms. To illustrate this point, the etiologic

fraction among the exposed based on the risk observed in this study is only 0.138; this means that even if our results are verified, there is less than a 14% chance that a dopamine antagonist user who develops breast cancer did so on the basis of her antipsychotic drug use. Finally, these results have important implications for the general medical care given to psychiatric patients. We found that women who use antipsychotic medications are less likely to receive breast cancer surveillance through mammography and outpatient medical visits. Rather than receiving such diminished levels of care, our results suggest that patients with psychotic disorders may require enhanced monitoring for cancer and care of their general medical disorders.

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