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Psychotropic medication use and postmenopausal breast cancer risk

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Abstract

Background—Prior studies evaluating psychotropic medications in relation to breast cancer risk are inconsistent and have not separately evaluated invasive and *in situ* disease.

Methods—We estimated hazard ratios (HR) and 95% confidence intervals (CI) for the association of psychotropic medication use (any, typical antipsychotics, atypical antipsychotics, lithium) with invasive and *in situ* breast cancer risk among Women's Health Initiative participants (N=155,737).

Results—Prevalence of psychotropic medication use was low (n=642; 0.4%). During an average 14.8 (SD 6.5) years of follow-up, 10,067 invasive and 2,285 *in situ* breast were diagnosed. Any psychotropic medication use was not associated with invasive breast cancer risk compared to non-users (HR 0.82, 95% CI 0.57–1.18). *In situ* breast cancer risk was higher among "typical" antipsychotic medication users compared with non-users (HR 2.05, 95% CI 0.97–4.30).

Conclusions—Findings do not support an association of psychotropic medication use with invasive breast cancer risk. The possible elevation in *in situ* breast cancer risk associated with "typical" antipsychotics could not be explained by differences in screening mammography utilization and merits further study.

Impact—Our findings contribute to knowledge of the safety profile of psychotropic medications and may be useful to clinicians and patients considering use of these medications.

Introduction

An estimated 268,600 new female breast cancer (BC) cases are expected in 2019 (1). Psychotropic medications have been associated with modest increases in BC risk in some (2–4), but not other (5–7), epidemiologic investigations. Elevated prolactin levels are a

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common adverse effect of psychotropic drugs, especially with typical antipsychotics (first-generation drugs). In contrast, atypical antipsychotics (second-generation drugs), except for risperidone, cause smaller prolactin elevations. Higher circulating prolactin levels are associated with higher BC risk, especially for hormone-receptor positive and postmenopausal disease (8). Given prior inconsistent results, we prospectively evaluated associations between psychotropic medication use and postmenopausal BC risk within the Women's Health Initiative (WHI) cohort, a large prospective population-based cohort with high quality data on medication use and adjudicated BC outcomes.

Methods

WHI enrolled postmenopausal women ages 50–79 years into observational study (OS) or clinical trial (CT) components from 1993–1997 at 40 clinical centers nationwide (N=161,808). Participants provided written informed consent at enrollment, and IRB approval was obtained at each clinical center. For this analysis we excluded participants with a personal BC history (N=5,397) or <1 day follow-up time (N=674), giving a final analytic cohort of 155,737 postmenopausal women.

Participants brought all current prescription and non-prescription medications and supplements to their baseline visit. A research nurse recorded each medication name and dosage. We classified reported antipsychotic medications as "typical" (fluphenazine, chlorpromazine, haloperidol, thiothixene, flupenthixol, and molindone) or "atypical" (risperidone, clozapine, olanzapine, and aripiprazole) based on their structures and mechanisms of action using UpToDate® (Waltham, MA). Participants were categorized as using any psychotropic medications (no, yes) and separately by use of typical (no, yes) or atypical (no, yes) antipsychotics or lithium (no, yes); users of typical antipsychotics who did not also use atypical antipsychotics were classified as "no" for atypical use, and vice versa. BC cases were centrally adjudicated using medical records.

We compared baseline descriptive statistics between users and non-users of psychotropic medications. Hazard ratios (HR) and 95% confidence intervals (CI) examining associations of psychotropic medications with BC were estimated using Cox proportional hazards regression models. Follow-up time began at enrollment; participants were censored at either BC diagnosis, death, loss to follow-up, or March 31, 2018, whichever came first. We decided *a priori* to adjust for age and WHI study arm (OS vs CT) and arm of hormone therapy clinical trial given known differences in BC risk across these groups; these adjusted HRs changed <2% when additional variables were included (i.e. characteristics summarized in Table 1). Thus, our final model adjusted for age and the WHI study participation variables.

We performed sensitivity analyses among the subgroup of women with regular mammograms during the first 10 years of follow-up, as determined by study protocol for CT participants or self-report of ≥6 mammograms during the 10 year period for OS participants (N=133,754). We repeated analyses restricting to estrogen-receptor positive (ER+) BCs. We also incorporated medication use at the year 3 follow-up visit, and repeated analyses as described above, starting follow-up time at year 3, and also estimating HRs for the

consistency of psychotropic medication use between baseline and year 3 (never used, initiated use, stopped use, consistent use).

Results

Prevalence of psychotropic medication use was low (n=642; 0.4%), with most users taking either a typical antipsychotic (n=272; 42.4%) or lithium (n=326; 50.8%) (Table 1). During an average 14.8 (SD 6.5) years of follow-up, 10,097 invasive and 2,285 *in situ* BCs were diagnosed (Table 2). The average age at BC diagnosis was 72.0 years (range 50–99). No association between any psychotropic medication use and invasive BC was observed (HR 0.82, 95% CI 0.57–1.18); likewise, there was no association of typical or atypical antipsychotics or lithium with invasive BC risk. Psychotropic medication use was positively associated with increased *in situ* BC risk (HR 1.66, 95% CI 0.98–2.81), which likely was driven by typical antipsychotic use (HR 2.05, 95% CI 0.97–4.30); results were similar when restricted to participants with regular mammograms (HR 1.87, 95% CI 0.84–4.16). Results were similar when restricting to ER+ cancers and when modeling psychotropic medication use at year 3. No associations were observed between consistency of psychotropic medication use at baseline and year 3 and invasive or *in situ* BC risk (data not shown).

Discussion

Our results do not support an association between psychotropic medication use and subsequent invasive BC risk. We did observe a suggestive two-fold increase in *in situ* BC risk associated with typical antipsychotic use, which persisted among the subgroup of women with regular mammograms. The consistency of these results suggests that screening differences between users and non-users may not fully account for the elevated risk. However, our findings were limited by a small number of psychotropic medication users, including only 7 typical antipsychotic users later diagnosed with *in situ* BC, and thus should be interpreted cautiously. We are unaware of a potential biologic mechanism that would result in psychotropic medications increasing only *in situ* BC risk. Additional limitations include the potential for underreporting of psychotropic medications if women selectively chose not to bring such medications to their clinical visit, as well as the inability to distinguish between diagnostic and screening mammograms for OS participants. Prior studies have either included only invasive cases (2) or have not stratified analyses by invasiveness (3–7), thus additional evaluations, perhaps with pooled data across multiple studies, are needed. Overall, our findings contribute to knowledge of the safety profile of psychotropic medications and may be useful to clinicians and patients considering use of these medications.

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Abbreviations:

BC	breast cancer
CI	confidence interval
CT	clinical trial
ER	estrogen receptor
HR	hazard ratio
OS	observational study
WHI	Women's Health Initiative

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Table 1.

Descriptive characteristics of participants at baseline, N=155,737

	Psychotropic Drug Use		
Characteristic	**Users (N=642)**	**Non-Users (N=155,095)**	**P value**
Age, years; Mean (SD)	62.14 (7.20)	63.19 (7.22)	0.0003
White; N (%)	526 (82.2)	128,048 (82.8)	0.45
Married; N (%)	292 (45.7)	96,463 (62.5)	<0.0001
College degree; N (%)	286 (45.0)	60,614 (39.4)	0.01
Body mass index, kg/m^2; Mean (SD)	29.02 (6.19)	27.98 (5.94)	<0.0001
Obese; N (%)	228 (36.1)	46,417 (30.2)	0.0003
Current Smoker; N (%)	105 (16.6)	10,679 (7.0)	<0.0001
≥1 Alcoholic drink/week; N (%)	158 (24.8)	57,509 (37.4)	<0.0001
Healthy Eating Index score; Mean (SD)[1]	63.66 (10.13)	65.05 (10.43)	0.0007
First degree relative with breast cancer; N (%)	103 (16.0)	26,753 (17.2)	0.42
Ever had a mammogram; N (%)	622 (97.2)	148,694 (96.4)	0.27
History of benign breast disease; N (%)	141 (23.1)	31,370 (21.4)	0.30
Nulliparous; N (%)	116 (18.3)	18,104 (11.7)	<0.0001
Age at menopause; Mean (SD)	47.26 (6.98)	48.09 (6.45)	0.002
Current postmenopausal hormone therapy use; N (%)	263 (41.0)	63,934 (41.3)	0.76
Observational study participant; N (%)	416 (64.8)	87,508 (56.4)	<0.0001
Typical antipsychotic use; N (%)[2]	272 (42.4)	n/a	--
Atypical antipsychotic use; N (%)[2]	59 (9.2)	n/a	--
Lithium use; N (%)[2]	326 (50.8)	n/a	--

n/a: not applicable

[1]Healthy Eating Index score calculated based on U.S. Department of Agriculture guidelines, where a higher score indicates a diet that more closely adheres to the guidelines

[2]Some participants used more than one type of psychotropic medication, therefore the sum of typical, atypical, and lithium users is greater than the total number of users of any medication

Table 2.

Multivariable adjusted associations between psychotropic medication use at baseline and incident breast cancer, N=155,737[1]

	Full Study Population N=155,737				Regular Mammogram Users N=133,754			
	Cases	**Person-Years**	**Adjusted HR (95% CI)**	**P value**	**Cases**	**Person-Years**	**Adjusted HR (95% CI)**	**P value**
Invasive breast cancer								
Any psychotropic drug use								
No	10,067	2,292,928	1 (ref)	--	9,274	2,022,856	1 (ref)	--
Yes	30	8,358	0.82 (0.57–1.18)	0.29	29	7,116	0.89 (0.62–1.28)	0.53
Typical antipsychotic use								
No	10,087	2,297,891	1 (ref)	--	9,294	2,027,051	1 (ref)	--
Yes	10	3,395	0.67 (0.36–1.25)	0.21	9	2,922	0.66 (0.35–1.28)	0.22
Atypical antipsychotic use								
No	10,093	2,300,660	1 (ref)	--	9,299	2,029,485	1 (ref)	--
Yes	4	626	1.45 (0.54–3.87)	0.46	4	487	1.78 (0.67–4.75)	0.25
Lithium use								
No	10,079	2,296,770	1 (ref)	--	9,285	2,026,046	1 (ref)	--
Yes	18	4,516	0.92 (0.58–1.46)	0.72	18	3,926	1.01 (0.64–1.61)	0.96
In situ breast cancer[2]								
Any psychotropic drug use								
No	2,271	2,291,956	1 (ref)	--	2,153	2,021,940	1 (ref)	--
Yes	14	8,340	1.66 (0.98–2.81)	0.06	13	7,098	1.67 (0.97–2.88)	0.07
Typical antipsychotic use								
No	2,278	2,296,919	1 (ref)	--	2160	2,026,135	1 (ref)	--
Yes	7	3,376	2.05 (0.97–4.30)	0.06	6	2,903	1.87 (0.84–4.16)	0.13
Lithium use								
No	2,278	2,295,780	1 (ref)	--	2159	2,025,112	1 (ref)	--
Yes	7	4516	1.53 (0.73–3.22)	0.26	7	3926	1.64 (0.78–3.44)	0.19

[1] All models adjusted for age, OS vs CT participation, HT trial arm

[2] Estimates for atypical antipsychotic medication use are not estimable because no users were diagnosed with in situ breast cancer

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