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Antipsychotic Drug Use and Postmenopausal Breast Cancer Risk in the Women's Health Initiative (WHI): A Prospective Cohort Study

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Antipsychotic Drug Use and Postmenopausal Breast Cancer Risk in the Women's Health Initiative (WHI): A Prospective Cohort Study

A Thesis Presented

By

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ABSTRACT

ANTIPSYCHOTIC DRUG USE AND POSTMENOPAUSAL BREAST CANCER RISK IN THE WOMEN'S HEALTH INITIATIVE (WHI): A PROSPECTIVE COHORT STUDY

MAY 2019

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Breast cancer is the most prevalent form of cancer and the second leading cause of mortality, affecting 1 in 9 women in the United States. Recent studies have shown that antipsychotic drug use is associated with increased prolactin levels, which, in turn, is associated with increased risk of breast cancer. However, studies of the association between antipsychotic drug use and the risk of breast cancer are sparse and have largely been conducted in homogenous populations. Therefore, we evaluated this relationship in postmenopausal women (N = 119 524) in a diverse population of the Women's Health Initiative (WHI) cohort. Antipsychotic drug use was self-reported and in situ and invasive breast cancer cases were confirmed by medical records for the WHI clinical trial (CT) and the WHI observational study (OS), from 1993 through 2018. We used Cox proportional hazards regression to model breast cancer risk against antipsychotic drug use while adjusting for dietary and lifestyle factors. Overall, antipsychotic users made up 0.41% of this population. There was no overall association between antipsychotic drug use and postmenopausal breast cancer risk (HR = 1.01, 95% CI = 0.73 – 1.40). Among typical antipsychotic drug users, there was a suggested two-fold increased risk in

developing in situ breast cancer (HR = 2.02, 95% CI = 0.84, 4.86). Thus, antipsychotic drug use does not appear to increase breast cancer risk overall, but the potential association between antipsychotics and in situ breast cancer merits further study.

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CHAPTER I

BACKGROUND AND SIGNIFICANCE

A. Introduction

In recent years, both cancer incidence and mortality are increasing rapidly on a global scale.[1] Among women in the United States, breast cancer is the most prevalent form of cancer and the second leading cause of cancer mortality, affecting 1 in 9 women.[2,3] According to the American Cancer Society, approximately 266, 120 new cases of invasive breast cancer will be diagnosed and 40, 920 deaths will occur in women in 2018.[4] According to the 2018 statistics from the World Health Organization, the age adjusted incidence rates for breast cancer among females in North America is 84.8 per 100, 000 women.[5]

There are both modifiable and non-modifiable risk factors associated with breast cancer. Women who have inherited mutations to certain genes, such as BRCA1 and BRCA2, are at higher risk of developing postmenopausal breast cancer.[6] In addition, women with early onset of menses or menopause after the age of 55 are at an increased risk of postmenopausal breast cancer. Late age at menopause significantly increases postmenopausal breast cancer risk due to longer estrogen exposure among those entering menopause at older ages.[7] Having a family history of breast cancer also increases the risk of breast cancer, especially when it involves a first-degree relative.[6] Some modifiable factors include obesity, being physically active as well as moderately consuming alcohol.[6] Certain forms of hormone replacement therapy (HRT) as well as current use of oral contraceptives have been found to increase breast cancer risk.[6]

Another potential modifiable factor is medication use, particularly antipsychotic drug use. In the United States, psychiatric medication sales are among the five top drug sales in the

country.[8] Based on data extracted from the IQVia Total Patient Tracker Database, approximately 6, 430, 052 adults aged 45 and above use antipsychotics.[9] While these statistics do not differentiate between men and women, data has shown that nearly twice as many women compared to men reported taking psychiatric drugs.[10]

B. Physiology of Exposure-Outcome Relationship

There is one potential mechanism that describes the physiological relationship between antipsychotic drug use and risk of breast cancer. Antipsychotics, also known as neuroleptics, serve as dopamine antagonizers that block post-synaptic D2 receptors located in the pituitary gland.[8] This blockade occurs in the mesolimbic and mesocortical areas of the brain, and is integral to antipsychotic efficacy.[11] Prolactin (PRL) is a 199-amino acid polypeptide hormone secreted in the lactotroph cells within the anterior pituitary.[11] PRL secretion is controlled by both peptide and steroid hormones as well as neurotransmitters, which act as inhibitory and stimulatory factors. With regards to humans and animals, dopamine is the main prolactin-inhibiting factor. Once dopamine binds to dopamine D_2 receptors on the membrane of the lactotroph cells, this stimulation causes effects on PRL gene transcription. Elevated PRL levels are a common adverse effect of antipsychotic drug use, especially with typical antipsychotics (first-generation drugs).[12,13] In contrast, atypical antipsychotics (second-generation drugs) cause smaller PRL elevations, with risperidone being an exception, as it has been shown to cause a significant increase in PRL levels compared to the other atypical antipsychotics.[12,14]

PRL physiologically causes breast enlargement in pregnancy and is responsible for milk production during lactation.[11] High levels of PRL, otherwise known as hyperprolectinemia, can increase the risk of breast cancer.[15] For example, in the 1990s, there was evidence that related

PRL and breast cancer through a study that showed how activation of the prolactin receptor (PRLR) induced mammary carcinomas in transgenic mice.[16] In addition, another study showed that human breast cancer cells had a higher expression of PRLR levels as compared to normal breast tissue.[17] Cells in breast carcinomas are highly sensitive to PRL stimulation through these receptors.[18] Apart from having a paracrine effect, it was also suggested that PRL has an autocrine effect on breast cancers and stimulates the growth of malignant neighboring cells in the breast in the presence of a carcinoma.[19] To further support those claims, a study conducted by Tworoger et al. involving the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII) cohort showed an increased risk for higher proximate prolactin levels (RR, >15.7 vs. 8.1 ng/mL [i.e. top vs. bottom quartiles] =1.20, 95% CI = 1.03 – 1.40, p-trend = 0.005). More interestingly, the positive association was stronger for ER+ disease (RR = 1.28, p-trend = 0.003) and postmenopausal women (RR = 1.37, p-trend = 0.0002)..[20] Therefore, we propose to investigate the relationship between antipsychotic drug use and breast cancer risk among postmenopausal women using data from all eligible participants enrolled in the Women's Health Initiative.

CHAPTER II

STUDY DESIGN AND METHODS

A. Study Population

The study population was drawn from the WHI cohort. Our analyses included all postmenopausal women from both the clinical trial (CT) and observational study (OS) aged 50-79 years old enrolled in 1997 and followed-up through March 21, 2018 (N = 161 808). Participants had to be able as well as willing to provide written informed consent and planned to reside within the same area for at least 3 years after enrollment.

Participants were excluded from both the CT and OS if they had medical conditions predictive of a survival time of less than 3 years as well as having conditions or characteristics inconsistent with study participation and adherence.[21] These conditions included alcoholism, drug dependency, mental illness and dementia. Participants were also excluded if they were active in another randomized controlled clinical trial. In addition, any competing risks were a cause for exclusion, which included invasive cancer in the past 10 years, breast cancer at any time or suspected breast cancer at baseline screening, acute myocardial infarction, stroke, transient ischemic attack in the past six months, chronic active hepatitis and cirrhosis.[21] Each CT component had its own specific exclusionary criteria, which is described in further detailed elsewhere.[21] For the purposes of our study, we excluded women with a personal history of breast cancer (N = 10 421).

B. Outcome Assessment

Postmenopausal breast cancer was assessed through annual self-report in which participants were required to report physician diagnosis of new cancer, a malignant tumor or growth of any type. From this self-reported information, medical records were retrieved and all cases were adjudicated, whereby cases were confirmed by a team of internal physicians within the WHI. Additionally, information on disease stage, subtype and tumor characteristics were collected. Incident cases of breast cancer was measured by assessing the questionnaires filled out in the WHI. We then categorized participants into "Yes" for those diagnosed with breast cancer and "No" for participants free of the disease.

C. Exposure Assessment

An inventory of current medications was collected at Screening Visit 1 (SV1) to ensure participants were not taking any protocol-excluded medications or supplements as well as to collect baseline information. Each participant was required to bring all their medications during the clinical visit, which was to be placed in a WHI bag. This includes all prescription medications, over-the-counter (OTC) medications, vitamins, minerals and bulk fiber supplements. If the participant forgot to bring any of her medications, this information was then collected during SV2. Each medication was then entered into a database after information on name as well as dosage of these medications were obtained by a research nurse.

For our study, we examined risk according to typical and atypical antipsychotic use based on medical data within the WHI with a TCCODE subcode of 590000, which was then further categorized based on similarities in molecular structure and chemical composition. Typical antipsychotics included phenothiazines (Fluphenazine, Chlorpromazine; TCCODE 592000),

butyrophenones (Haloperidol; TCCODE 591000), thioxanthenes (Thiothixene, Flupenthixol; TCCODE 593000) and indole derivatives (Molindone; TCCODE 591600). On the other hand, atypical antipsychotics comprised benzisoxales (Risperidone; TCCODE 590700), dibenzapines (Clozapine, Olanzipine,; TCCODE 591500) quinolinone derivatives (Aripiprazole; TCCODE 592500) and others. We then categorized participants into “Non-Users and “Users”, who were then categorized further into “Atypical antipsychotic” and “Typical antipsychotic”.

CHAPTER III

DATA ANALYSIS

Baseline descriptive statistics were calculated for all initial covariates based on antipsychotic drug use and postmenopausal breast cancer diagnosis (Table 1 and Table 2). Potential covariates were identified based on *a priori* knowledge of potential confounders of this relationship. T-tests and chi-square tests were performed for all continuous and categorical variables, respectively.

Cox proportional hazards models were used to estimate the hazard ratio (HR) and confidence intervals (CI) for the association between antipsychotic drug use and risk of postmenopausal breast cancer. As this was a survival analysis, censoring events were taken into consideration to define when follow-up ended for each participant. For participants diagnosed with breast cancer, follow-up ended when first diagnosed with breast cancer. Censoring for invasive breast cancer occurred at the first diagnosis of invasive breast cancer and censoring for in situ breast cancer occurred at the first diagnosis of in situ breast cancer. There was a small number of participants who were first diagnosed with in situ breast cancer and then proceeded to develop invasive breast cancer. Under that circumstance, the latter diagnosis was used as the time to event for the total breast cancer analysis. On the other hand, censoring for non-cases occurred at the end of follow-up or in the event of death. An unadjusted HR was calculated as well as age- and multivariable adjusted HR, controlling for potential confounders. Univariable Cox models were used to determine which covariates were to be included in the initial multivariable model, whereby covariates with $p < 0.25$ were included. Backward elimination and weighted likelihood-ratio tests were used to assess statistical significance of each covariate to

ensure a parsimonious yet reasonable model. This process was repeated until all covariates had a >10% change in the beta values obtained. Covariates included in the final multivariable model were alcohol intake, age, BMI, first-degree family history of breast cancer, education, ethnic group, HRT use, HT arm enrollment,

parity, smoking status, Healthy Eating Index (HEI) score,[22] total energy expended from recreational physical activity and age at menopause. All analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, North Carolina) and all tests of statistical significance were based on two-sided p-values set at 0.05.

CHAPTER IV

RESULTS

Within the WHI cohort, there were 161 808 eligible participants who were enrolled. Our study had a total of 119 524 participants after applying an exclusion criterion of having ever been diagnosed with breast cancer. Among those eligible in this analysis, 119 166 (99.6%) were not antipsychotic drug users whereas 478 (0.40%) reported being users (Table 1). The mean age (SD) at enrollment was 63.1 (7.2) for non-users and 62.2 (7.2) for users. Compared to non-users, users were more likely to be overweight, had less than $35 000 in family income and were current drinkers *(P<0.05).* Overall, participants who were non-users and users of antipsychotic drugs had a statistically significant difference across all levels of each covariate *(P < 0.05),* except for ethnic group, education, HRT use and female relative having had breast cancer.

In regards to postmenopausal breast cancer diagnosis, 9559 (8.0%) participants were diagnosed with the disease (Table 2). The majority of cases were aged 60 to 69, overweight, white, never smokers, current drinkers and current HRT users. Breast cancer cases were slightly younger at enrollment (mean, 62.6; SD, 6.9), on average, compared to non-cases (mean, 63.1; SD, 7.2).

Table 3 describes the distribution of cancer subtypes by antipsychotic drug use in this particular cohort. Among antipsychotic users, there was no variation in disease subtype (ER/PR positive or ER/PR negative) compared to non-users as this was not statistically significant *(P = 0.73).*

Table 4 describes the association between antipsychotic drug use and postmenopausal breast cancer diagnosis, stratified by both types of breast cancer as well as types of

antipsychotics. This table provides the multivariable adjusted HRs with respective confidence intervals at 95% as well as their p-values. Overall, there was no association between antipsychotic drug use and breast cancer *risk (multivariable-adjusted HR = 1.01, 95% CI = 0.73 – 1.40).* Among participants who used atypical antipsychotics, there was not an increased risk in developing invasive breast cancer *(multivariable-adjusted HR = 1.15, 95% CI = 0.37 - 3.56).* Similarly, typical antipsychotic users were not at an increased risk for in situ breast cancer *(multivariable-adjusted HR = 2.02, 95% CI = 0.84 - 4.86).*

CHAPTER V

DISCUSSION

In this prospective cohort study of postmenopausal women, we observed no association between antipsychotic drug use at baseline and breast cancer risk. Null findings were observed between atypical antipsychotic drug use and invasive breast cancer as well as between typical antipsychotic drug use and in situ breast cancer.

Several prior epidemiologic studies support a potential relationship between antipsychotic drug use and breast cancer risk, but the data are inconsistent. From the six prior epidemiologic studies, results varied between null findings and an increased association. Study populations within those studies also included both pre- and post-menopausal women. As ours is the first study to look solely at postmenopausal women, these results may be able to provide an association of the underlying mechanism between antipsychotic drug use and postmenopausal breast cancer.

Our finding of no association between antipsychotic drugs and breast cancer risk is in agreement with two prospective cohort studies[23,24] and one retrospective cohort study.[25] One study conducted by Chou et al. found an almost two-fold increase in breast cancer risk with antipsychotic drug use *(HR = 1.94, 95% CI = 1.43 – 2.63).* However, this study utilized a highly selective population of schizophrenic patients, who may not be representative of the general population. Two separate studies conducted by Pottegard et al. and Wang et al. also reported a statistically significant 18% and 16% increase, respectively, in breast cancer risk among antipsychotic users. However, these studies included all women over the age of 18. Our results

may differ from those studies due to our study population being of older, postmenopausal women compared to that of populations inclusive of younger women.

Our study found a two-fold increased risk of in situ breast cancer among typical antipsychotic drug users, although this result was not significant, It is possible that women with current antipsychotic prescriptions visit their health care providers more often to get both treatment and continuous prescriptions and as such, they may receive referrals for regular screening mammography during these clinic visits. Compared to unscreened populations, screening mammography is known to lead to an increased diagnosis of in situ breast cancer. Therefore, the potential association observed among in situ breast cancer cases may be due to screening artifacts rather than an association of true etiology.

One limitation of our study is the potential non-differential misclassification of exposure assessment. As antipsychotic drug use was measured by having each participant fill a WHI bag with current medication, it is possible that participants incorrectly or incompletely filled these bags due to stigma surrounding antipsychotics. Also, while the advantage of this is the ability to determine actual medication usage of these women. this only accounts for current medications. Thus, prior antipsychotic use or recent discontinuation of antipsychotics would have been missed, identifying these women as non-users. This is a major limitation as there is potential for some women to be past antipsychotic users who will not be represented in this cohort due to the nature of the exposure assessment. This will then cause an underestimation of the true risk, which would potentially explain our null findings.

While our study adjusted for potential confounders such as alcohol consumption, obesity, physical activity and diet, these covariates were only collected at baseline. As all these covariates are not fixed and can change over time due to varying behaviors and environmental factors, there

is potential for residual confounding. This is a major limitation of our study as we were unable to incorporate changes to these factors over time due to the nature of its assessment.

While the study started off with significant power due to its large sample size, this was significantly reduced when we stratified by type of antipsychotic as well as type of breast cancer. Due to the major reduction in numbers, power was then compromised and not adequate enough to capture significant results, causing an increase in type II error.

Strengths of our study included its prospective study design as well as extensive data on potential confounders. To the best of our knowledge, this is the first study to look at the association between typical vs. atypical antipsychotic drug use and risk of developing either in situ or invasive breast cancer among postmenopausal women. This study also utilized a relatively diverse cohort within the American population, allowing for a large sample size. While the majority of our study population was white, there were also women of other races who participated, making it less homogenous than prior studies. The WHI study also has over 25 years of follow-up, providing strong epidemiologic data as well as breast cancer information. We expect the biologic and physiologic mechanism to remain the same among all postmenopausal women regardless of geographic location or race, making these results potentially generalizable to different populations of postmenopausal women. Additionally, many studies had short follow-up times, which makes it difficult to fully understand the impact of antipsychotics drug on breast cancer, as risk for this disease is likely to occur over a period of many years.

In summary, our study does not show an overall association between antipsychotic drug use and breast cancer risk, though there appears to be suggestive evidence that antipsychotic drugs may increase the risk of in situ breast cancer. While this finding was only borderline significant, it is important to note how our power was compromised due to small numbers after

stratification. To support these findings, additional research should include looking at not just breast cancer, but also stratifying it by invasive and in situ breast cancer along with the different classes of antipsychotics. This additional data will not only increase the abundance in the literature but improve our understanding on whether antipsychotics increase breast cancer risk among postmenopausal women. This can then be used for meta-analyses to increase statistical power.

Table 1: Distribution of baseline characteristics by antipsychotic drug use in the Women's Health Initiative (WHI) Study

	Antipsychotic Drug Use		P-value[a]
	No	Yes	
Number of participants	119 166 (99.6)	478 (0.4)	
Mean age at enrollment (years, SD)	63.1 (7.2)	62.2 (7.2)	<0.0001
Mean age at menopause (years, SD)	48.1 (6.4)	47.6 (6.8)	<0.0001
Age group at screening			0.11
<50 - 59	42 349 (35.5)	182 (38.1)	
60 - 69	53 720 (45.1)	208 (43.5)	
70 - 79+	25 119 (21.1)	88 (18.4)	
BMI			0.007
Underweight/Normal	42 349 (35.5)	138 (28.9)	
Overweight	41 377 (34.7)	176 (36.8)	
Obese/Extremely obese	35 440 (29.7)	164 (34.4)	
Ethnic group			0.56
White	99 764 (83.7)	408 (85.4)	
Black/African-American	9944 (8.3)	38 (8.0)	
Other	9458 (7.9)	32 (6.7)	
Education			0.3
Didn't go to school/Some high school/Vocational or training school	37 619 (31.6)	139 (29.1)	
Some college degree	46 447 (39.0)	184 (38.5)	
Some higher/professional degree	35 100 (29.5)	155 (32.4)	
Family income			<0.0001
Less than $35 000	47 350 (39.7)	270 (56.5)	
$35 000 to less than $100 000	59 964 (50.3)	180 (37.7)	
$100 000 and more	11 852 (10.0)	28 (5.9)	
Parity			<0.0001
Nulliparous	13 950 (11.7)	86 (18.0)	
3 or less	69 444 (58.3)	274 (57.3)	
4 and more	35 772 (30.0)	118 (24.7)	
Smoking status			<0.0001
Never smoker	60 391 (50.7)	211 (44.1)	
Past smoker	50 515 (42.4)	193 (40.4)	
Current smoker	8260 (6.9)	74 (15.5)	

Table 1 (Continued): Distribution of baseline characteristics by antipsychotic drug use in the Women's Health Initiative (WHI) Study

	Antipsychotic Drug Use		P-value[a]
	No	Yes	
Alcohol intake			<0.0001
Never drinker	12 498 (10.5)	49 (10.3)	
Past drinker	21 651 (18.2)	173 (36.2)	
Current drinker	85 017 (71.3)	256 (53.6)	
HRT use			0.85
Never user	36 460 (30.6)	143 (29.9)	
Past user	26 659 (22.4)	112 (23.4)	
Current user	56 047 (47.0)	223 (46.7)	
HT arm			0.1
Not randomized	99 332 (83.4)	417 (87.2)	
E-alone intervention	3530 (3.0)	6 (1.3)	
E-alone control	3602 (3.0)	10 (2.1)	
E + P intervention	6420 (5.4)	21 (4.4)	
E + P control	6282 (5.3)	24 (5.0)	
Female relative had breast cancer			0.48
No	97 334 (81.7)	397 (83.1)	
Yes	21 832 (18.3)	81 (17.0)	

Abbreviations: SD, standard deviation; BMI, body mass index; HRT, hormone replacement therapy; CaD, calcium and vitamin D; DM, dietary modification; HT, hormone therapy

[a] P values were calculated using a two-sample t-test for continuous variables and chi-square test for categorical variables

Table 2: Distribution of baseline characteristics by postmenopausal breast cancer diagnosis in the Women's Health Initiative (WHI) Study

	Postmenopausal Breast Cancer		P-value[a]
	No	Yes	
Number of participants	110 085 (92.0)	9559 (8.0)	
Mean age at enrollment (years, SD)	63.1 (7.2)	62.6 (6.9)	<0.0001
Mean age at menopause (years, SD)	48.0 (6.4)	48.6 (6.1)	<0.0001
Age group at screening			<0.0001
<50 - 59	37 135 (33.7)	3374 (35.3)	
60 - 69	49 478 (45.0)	4450 (46.6)	
70 - 79+	23 472 (21.3)	1735 (18.2)	
BMI			0.0008
Underweight/Normal	39 256 (35.7)	3231 (33.8)	
Overweight	38 181 (34.7)	3372 (35.3)	
Obese/Extremely obese	32 648 (29.7)	2956 (30.9)	
Ethnic group			<0.0001
White	91 780 (83.4)	8392 (87.8)	
Black/African-American	9363 (8.5)	619 (6.5)	
Other	8942 (8.1)	548 (5.7)	
Education			<0.0001
Didn't go to school/Some high school/Vocational or training school	35 194 (32.0)	2564 (26.8)	
Some college degree	42 842 (39.0)	3789 (39.6)	
Some higher/professional degree	32 049 (29.1)	3206 (33.5)	
Family income			<0.0001
Less than $35 000	44 384 (40.3)	3236 (33.9)	
$35 000 to less than $100 000	54 947 (50.0)	5197 (54.4)	
$100 000 and more	10 754 (9.8)	1126 (11.8)	
Parity			<0.0001
Nulliparous	12 766 (11.6)	1270 (13.3)	
3 or less	63 975 (58.1)	5743 (60.1)	
4 and more	33 344 (30.3)	2546 (26.6)	
Smoking status			<0.0001
Never smoker	55 196 (50.8)	4686 (49.0)	
Past smoker	46 418 (42.2)	4290 (44.9)	
Current smoker	7751 (7.0)	583 (6.1)	

Table 2 (Continued): Distribution of baseline characteristics by postmenopausal breast cancer diagnosis in the Women's Health Initiative (WHI) Study

	Postmenopausal Breast Cancer		P-value[a]
	No	Yes	
Alcohol intake			<0.0001
Never drinker	11 693 (10.6)	854 (8.9)	
Past drinker	20 298 (18.4)	1526 (16.0)	
Current drinker	78 094 (70.9)	7179 (75.1)	
HRT use			<0.0001
Never user	34 022 (30.9)	2581 (27.0)	
Past user	24 938 (22.7)	1833 (19.2)	
Current user	51 125 (46.4)	5145 (53.8)	
HT arm			<0.0001
Not randomized	91 588 (83.2)	8161 (85.4)	
E-alone intervention	3339 (3.03)	197 (2.1)	
E-alone control	3360 (3.05)	252 (2.6)	
E + P intervention	5921 (5.4)	520 (5.4)	
E + P control	5877 (5.3)	429 (4.5)	
Female relative had breast cancer			<0.0001
No	90 464 (82.2)	7267 (76.0)	
Yes	19 621 (17.8)	2292 (24.0)	

Abbreviations: SD, standard deviation; BMI, body mass index; HRT, hormone replacement therapy; CaD, calcium and vitamin D; DM, dietary modification; HT, hormone therapy

[a] P values were calculated using a two-sample t-test for continuous variables and a chi-square test for categorical variables

Table 3: Distribution of cancer subtypes by antipsychotic drug use in the Women's Health Initiative (WHI) Study

	Antipsychotic Drug Use		P-value[a]
	No	Yes	
Breast cancer insitu			0.29
No	117 373 (98.5)	468 (97.9)	
Yes	1793 (1.5)	10 (2.1)	
Breast cancer invasive			0.07
No	111 293 (93.4)	30 (94.9)	
Yes	7873 (6.6)	24 (5.0)	
Subtype			0.71
ER/PR positive	5777 (84.1)	20 (87.0)	
ER/PR negative	1093 (15.9)	3 (13.0)	

Abbreviations: ER, estrogen receptor; PR, progesterone receptor

[a]P values were calculated using a two-sample t-test for continuous variables and a chi-square test for categorical variables

Table 4: Estimated hazards ratios for the effects of antipsychotic drug use on breast cancer diagnosis (N = 119 524)

	All breast cancer						
	N[a]	Age-Adjusted	95% CI	p-value[b]	Hazards Ratio	95% CI	p-value[b]
Any antipsychotic	9563						
No	9530	1			1		
Yes	33	0.99	0.73, 1.33	0.94	1.01	0.73, 1.40	0.95
Atypical antipsychotic	9563						
No	9561	1			1		
Yes	2	1.2	0.45, 3.19	0.72	0.95	0.31, 2.94	0.93
Typical antipsychotic	9563						
No	9551	1			1		
Yes	12	0.92	0.56, 1.5	0.74	0.89	0.50, 1.57	0.68

Multivariable Cox model adjusted for age, alcohol intake, BMI, female relative having had breast cancer, education, ethnic group, HRT use, HT arm enrollment, parity, smoking status, dietary measures, total energy expended from recreational physical activity and age at menopause

[a]N refers to cases only

[b]P values were calculated using a two-sample t-test for continuous variables and a chi-square test for categorical variables

Table 5: Estimated hazards ratios for the effects of antipsychotic drug use on invasive breast cancer diagnosis (N = 119 524)

	Invasive breast cancer						
	N[a]	Age-Adjusted	95% CI	p-value[b]	Hazards Ratio	95 % CI	p-value[b]
Any antipsychotic	7899						
No	7875	1			1		
Yes	24	0.84	0.59, 1.20	0.33	0.88	0.60, 1.29	0.5
Atypical antipsychotic	7899						
No	7897	1			1		
Yes	2	1.47	0.55, 3.40	0.44	1.15	0.37, 3.56	0.82
Typical antipsychotic	7899						
No	7891	1			1		
Yes	8	0.69	0.37, 1.29	0.25	0.71	0.35, 1.41	0.33

Multivariable Cox model adjusted for age, alcohol intake, BMI, female relative having had breast cancer, education, ethnic group, HRT use, HT arm enrollment, parity, smoking status, dietary measures, total energy expended from recreational physical activity and age at menopause

[a]N refers to cases only

[b]P values were calculated using a two-sample t-test for continuous variables and a chi-square test for categorical variables

Table 6: Estimated hazards ratios for the effects of antipsychotic drug use on in situ breast cancer diagnosis (N = 119 524)

	In situ breast cancer						
	N[a]	Age-Adjusted	95% CI	p-value[b]	Hazards Ratio	95% CI	p-value[b]
Any antipsychotic	1805						
No	1795	1			1		
Yes	10	1.68	0.99, 2.85	0.05	1.68	0.93, 3.04	0.09
Atypical antipsychotic	1805						
No	1805	1			1		
Yes	0	--[c]	--[c]	0.91	--[c]	--[c]	0.91
Typical antipsychotic	1805						
No	1800	1			1		
Yes	5	2.11	1.00, 4.42	0.05	2.02	0.84, 4.86	0.12

Multivariable Cox model adjusted for age, alcohol intake, BMI, female relative having had breast cancer, education, ethnic group, HRT use, HT arm enrollment, parity, smoking status, dietary measures, total energy expended from recreational physical activity and age at menopause

[a]N refers to cases only

[b]P values were calculated using a two-sample t-test for continuous variables and a chi-square test for categorical variables

[c]Not available due to very small numbers

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