

Haloperidol and Other Antipsychotics Exposure before Endometrial Cancer Diagnosis: A Population-based Case-control Study

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Objective: Endometrial cancer is the most common malignancy of the female genital tract worldwide, and the associated relationship between endometrial cancer formation and various antipsychotics need to be confirmed.

Methods: We conducted a case-control study by using data from Taiwan National Health Insurance Research Database to compare individual antipsychotic exposure between females with and without endometrial cancer. Among 14,079,089 females in the 12-year population-based national dataset, 9,502 females with endometrial cancer were identified. Their medical records of exposure to antipsychotics, including quetiapine, haloperidol, risperidone, olanzapine, amisulpride, clozapine, and aripiprazole, for up to 3 years before endometrial cancer diagnosis were reviewed. Daily dosage and cumulative exposure days were analyzed in the risky antipsychotic users. Additionally, the subsequent 5-year mortality rate of endometrial cancer among users of the risky antipsychotic were also analyzed.

Results: Among endometrial cancer patients, the proportion of those who have used haloperidol before being diagnosed with endometrial cancer is significantly higher than other antipsychotic users. The significant odds ratio (OR) and a 95% confidence interval of 1.75 (1.31–2.34) were noted. Furthermore, haloperidol users were associated with a significantly higher 5-year mortality rate after getting endometrial cancer than non-users.

Conclusion: There is a high correlation between the use of haloperidol and endometrial cancer formation. However, the underlying pathological biomechanisms require additional investigations.

KEY WORDS: Antipsychotic agents; Endometrial neoplasms; Haloperidol.

INTRODUCTION

Endometrial cancer is the most common gynecological malignancy in the world [1]. The use of psychotropic drugs had been reported as a risk factor for endometrial cancer in previous studies. In a case-control study with 41 endometrial cancer patients, 12% of cases had a history of

antipsychotic use, which was significantly higher compared to 3% of users in the control group [2]. In schizophrenic patients, a group of female most commonly used antipsychotics had a higher chance of endometrial cancer [3,4]. Generally, these studies speculated that antipsychotic-induced hyperprolactinemia, a common side effect of antipsychotics, is the main reason to cause endometrial cancer formation. Hyperprolactinemia caused by antipsychotics is associated with dopamine activity blockage of the hypothalamic-pituitary-gonadal axis [5]. This might result in menstrual cycle irregularity, galactorrhea, and reduced bone density because of an un-

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balanced endocrine state [6]. In fact, different antipsychotic agent affects prolactin level differently. Atypical antipsychotic agents, risperidone, paliperidone and amisulpride are often mentioned to cause high prolactin levels [5,7,8], but some atypical antipsychotics such as aripiprazole, the drug with dopamine partial agonistic function greatly reduce the probability of elevated prolactin [9]. Based on this hypothesis that the endometrial cancer development is associated with antipsychotic-induced hyperprolactinemia, the risk of endometrial cancer occurrence rate among the antipsychotic users should be positively related to their various effect on prolactin from each antipsychotic. Therefore, in this study, we wanted to know which antipsychotic drugs are highly related to the occurrence of endometrial cancer and whether the antipsychotics that are prone to cause hyperprolactinemia will have a high correlation with endometrial cancer. In addition, this study also investigates the subsequent mortality rates of the risky antipsychotic users after their endometrial cancer diagnosis. On the other way, because we believe that the safety of antipsychotics deserves cautious scrutiny in all-female antipsychotic users, not only female mental illness patients, and actually the studies have indicated that the number of off-label antipsychotics usage was actually large and increasing [10,11]. Therefore, this population-based case-control study focuses on the relationship in all-female antipsychotic users between various antipsychotic drugs and endometrial cancer development.

METHODS

We conducted a nationwide population-based case-control study by using data regarding patients with endometrial cancer obtained from the National Health Insurance Research Database (NHIRD).

Data Sources

The NHIRD was a nationwide electronic database in Taiwan that contains longitudinal medical records of beneficiaries enrolled in Taiwan's National Health Insurance System (NHIS). This health care system was established in 1995, and it covers 99% of the population in Taiwan or approximately 23.75 million people. The Registry of Catastrophic Illness Patient Database was a part of the NHIRD. The system recognizes 30 categories of catastrophic illnesses that require long-term care, including

cancers, chronic mental diseases, end-stage renal disease, and several autoimmune diseases. According to the privacy and strict confidentiality guidelines of personal electronic data protection regulations, the patients personal information was provided to researchers with anonymous identification numbers associated with relevant claims information, including sex, age, medical services received, drug prescriptions (specified according to the Anatomic Therapeutic Chemical classification of drugs [ATC]), and diagnoses (specified according to the International Classification of Diseases, Ninth Revision, Clinical Modification [ICD 9]). Therefore, patient consent was not required for NHIRD access. The ethical committee approved the present study based on the fulfillment of the conditions for exemption established by the Institutional Review Board of China Medical University (CMUH106-REC3-131). The Institutional Review Board also waived the consent requirement.

Identification of Study Sample

We included female patients who had received new diagnoses of a malignant neoplasm in their uterus (ICD 9 code 182) between January 2000 and December 2011. Cancer events were identified using the Registry of Catastrophic Illness Patient Database of the NHIRD. The time of participating in the NHIS was used as the entry date and year, and the time of the first diagnosis of endometrial cancer was used as the index date and year. The participants in the database who had received diagnoses of other cancers (ICD 9 codes 140–239) or those who had a medical record of < 3 years from their entry date to the index date were excluded. The control group was selected by frequency matching based on the same age, entry and index year of the case group from the NHIRD. However, the controls should not have a history of cancer or of receiving a hysterectomy following their entry date. The number of controls and patients with endometrial cancer were matched at a ratio of approximately 4:1. The ratios used in the analysis exhibited sufficient statistical power (Fig. 1).

Comorbidities

We had systemically identified the following potential confounding risk factors for endometrial cancer recorded between the entry date and index dates of the participants: hypertension (HTN; ICD 9 codes 401–405), diabetes

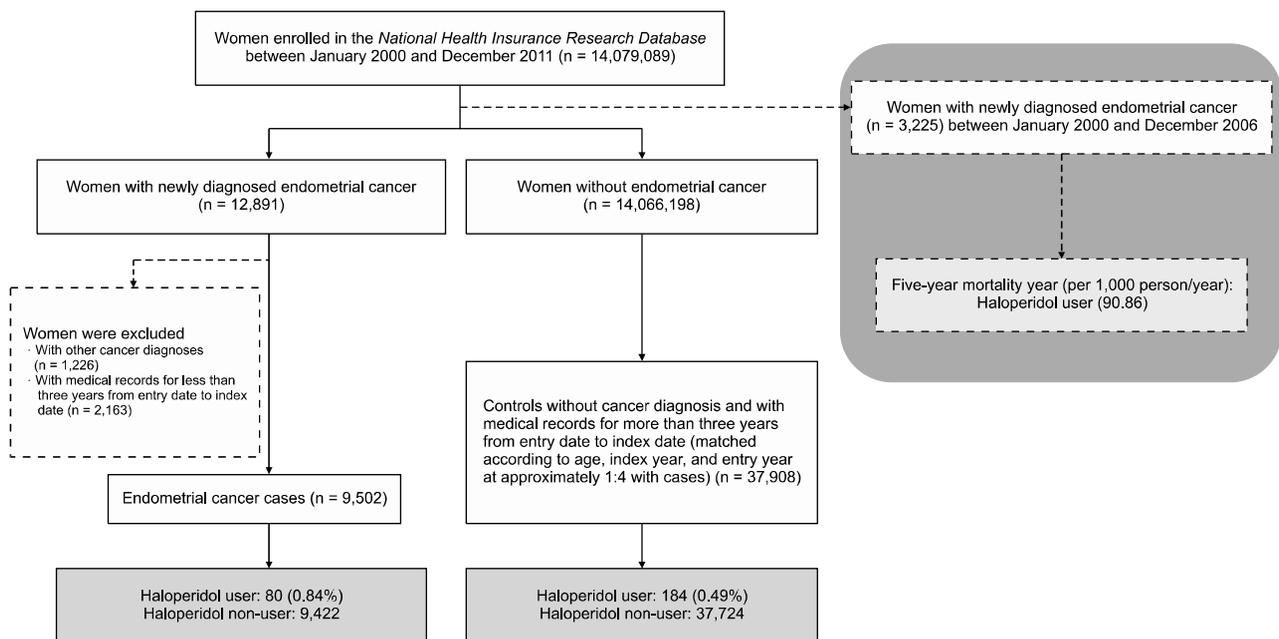


Fig. 1. Case of individuals with endometrial cancer selection, control selection and five-year mortality analysis.

mellitus (DM; ICD 9 code 250), hyperlipidemia (HL; ICD 9 code 272), and polycystic ovary syndrome (PCOS; ICD 9 code 256.4). These comorbidities were considered as a risk factors for endometrial cancer [12]. To ensure the validity of diagnoses, we had confirmed the diagnosis records in outpatient visit files at least 3 times or at least once for files regarding inpatient admission before defining the diagnoses.

Exposure to Female Hormones

The data of all participants inpatient and outpatient care orders with prescriptions of female hormones, such as estrogen and progesterone, were examined from their entry dates. The use of estrogen (ATC code L02AA) and progesterone (ATC code L02AB) were defined as potential confounding factors for endometrial cancer with any period or dosage of use indicated according to the medical records in this study.

Exposure to Antipsychotics

The data of inpatient and outpatient care orders of all participants with 3-year prescription records of antipsychotic drugs before their index date were collected from the NHIRD between January 1, 2000 and December 31, 2011. The data includes prescription dates, the daily dose prescribed, number of days of drug supply, and

number of pills per prescription. Considering the independent effects of each antipsychotic drug, several major antipsychotics drugs were analyzed separately in this study. Quetiapine (ATC code N05AH04), haloperidol (ATC code N05AD01), risperidone (ATC code N05AX08), olanzapine (ATC code N05AH03), amisulpride (ATC code N05AL05), clozapine (ATC code N05AH02), and aripiprazole (ATC code N05AX12) were selected as the major antipsychotics of interest. Because of genetic heterogeneity among patients and the lack of solid evidence of the biochemical effects of each type of antipsychotic drug on human cell mutations, this study selected to use the cumulative exposure days of more than 14 days as a wide range for the inclusion criteria. We defined antipsychotic “users” as patients who had cumulative exposure to an antipsychotic agent for more than 14 days within the 3-year medical record time frame before endometrial cancer diagnosis. “Nonusers” were defined as patients who had received fewer than 14 days of treatment with an antipsychotic drug. Moreover, after the comparison of various antipsychotics, we had separately compared the difference between different daily dosages and the different lengths of cumulative exposure days among the risky antipsychotics to explore the accumulative effect of their exposure on endometrial cancer development.

Five-year Mortality in Patients with Endometrial Cancer

We had identified females who received their first endometrial cancer diagnosis between January 1, 2000, and December 31, 2006, and calculated their 5-year mortality rate according to their medical records after endometrial cancer diagnosis. Furthermore, we had compared the mortality between haloperidol users and nonusers among the patients with endometrial cancer.

Statistical Analysis

In our analysis, age was considered as variable and participants were categorized into the following groups: 15–34, 35–49, 50–64, and ≥ 65 years. The continuous variable of age was presented as the mean and standard deviation. We had used the chi-square test for categorical variables and the student t-test for continuous variables to test the differences between patients with endometrial cancer and their corresponding control groups. We had used logistical regression to analyze the odds ratios (ORs) representing the risk of endometrial cancer among users of various antipsychotics and nonusers. The accompanying 95% confidence intervals (CIs) were calculated after adjusting for age, comorbidities, and female hormones exposure. The results were compiled in Model 1 and were with additional adjustments made for the effects of other

antipsychotics in Model 2. Logistic regression was also used to analyze ORs that represented the effects of various daily dosages and cumulative exposure days on endometrial cancer formation in haloperidol users. Finally, Cox proportional hazards models were used to compute the hazard ratios (HRs) and accompanying 95% CIs after adjusting for the aforementioned variables. All analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA). The level of significance was set at $p < 0.05$ for 2-tailed tests.

RESULTS

Participants' Characteristics

The medical records of 14,079,089 females from the NHIRD were analyzed in this study. In total, 9,502 females with endometrial cancer were included after some patients with other cancer diagnoses or incomplete medical records were excluded. Moreover, 37,908 cancer-free females were identified as controls for the patients with endometrial cancer. Table 1 lists the age distribution, comorbidities, female hormone exposure, and mental disorder condition of the patients with endometrial cancer and the cancer-free matched controls.

Table 1. Demographic and clinical characteristics of participants with endometrial cancer and their corresponding control groups

Variable	Endometrial cancer (n = 9,502)	Cancer-free matched control (n = 37,908)	<i>p</i> value
Age (yr)			0.99
15–34	435 (4.58)	1,740 (4.59)	
35–49	2,934 (30.9)	11,734 (31.0)	
50–64	4,712 (49.6)	18,789 (49.6)	
≥ 65	1,421 (15.0)	5,645 (14.9)	
Mean \pm SD	53.9 \pm 11.1	53.7 \pm 11.2	0.34
Comorbidity			
HTN	3,703 (39.0)	11,750 (31.0)	< 0.0001
HL	2,601 (27.4)	9,340 (24.6)	< 0.0001
DM	2,035 (21.4)	5,542 (14.6)	< 0.0001
PCOS	183 (1.93)	116 (0.31)	< 0.0001
Female hormone exposure before cancer diagnosis			
Progesterone	280 (2.95)	543 (1.43)	< 0.0001
Estrogen	263 (2.77)	6 (0.02)	< 0.0001
Mental disorder			0.12
No	8,469 (89.1)	33,570 (88.6)	
Yes	1,033 (10.9)	4,338 (11.4)	

Values are presented as number (%).

SD, standard deviation; HTN, hypertension; HL, hyperlipidemia; DM, diabetes mellitus; PCOS, polycystic ovary syndrome.

Antipsychotic Users between Endometrial Cancer

Patients and Controls

As presented in Table 2 the haloperidol users exhibited a significantly higher proportion in the endometrial cancer patients compared to the cancer-free participants among various antipsychotic drugs. The proportion of haloperidol users is 0.84%, and those accompanied with a significantly OR (95% CI) as 1.75 (1.31–2.34). Thus, a history of haloperidol exposure before endometrial cancer diagnosis was identified a stronger association to the patients with endometrial cancer.

Daily Dosage and Cumulative Exposure Days of Haloperidol

To understand the effects of haloperidol in endometrial cancer patients, we had analyzed the prescriptions of all haloperidol users according to different daily dosages and cumulative exposure days. The median daily dosage (1.5 mg/day) and median cumulative days of exposure (60 days) were used as cutoff values to establish 2 patient

groups. As presented in Supplementary Table 1 (available online) with the groups of both low and high daily dosage, haloperidol users exhibited a significantly higher endometrial cancer risk. The ORs (95% CIs) were 1.82 (1.25–2.66) for the low-dosage group and 1.67 (1.11–2.52) for the high-dosage group. Moreover, the groups of both short and long cumulative exposure days in haloperidol users were associated with significantly higher endometrial cancer risk, with ORs of (95% CIs) of 1.86 (1.28–2.71) and 1.63 (1.08–2.46), respectively.

Five-year Mortality Rate

Finally, as indicated in Table 3, we had observed a significant difference in the 5-year mortality rate between haloperidol users and nonusers among endometrial cancer patients. The HR (95% CI) of 1.89 (1.01–3.54) was noted after adjusting for age, comorbidities, and exposure to female hormones. Therefore, a history of haloperidol exposure among the females with endometrial cancer was correlated with significantly increased 5-year mortality.

Table 2. Odds ratios for endometrial cancer according to use of various antipsychotics patients with endometrial cancer vs. cancer-free matched controls

Antipsychotics user	Endometrial cancer (n = 9,502)	Cancer-free matched controls (n = 37,908)	Odds ratio (95% confidence interval)					
			Crude	p value	Model 1 ^a	p value	Model 2 ^b	p value
Quetiapine	58 (0.61)	224 (0.59)	1.03 (0.77–1.38)	0.82	0.89 (0.66–1.20)	0.43	0.81 (0.59–1.12)	0.19
Haloperidol	80 (0.84)	184 (0.49)	1.74 (1.34–2.27)	< 0.0001	1.63 (1.25–2.13)	0.0003	1.75 (1.31–2.34)	0.0001
Risperidone	58 (0.61)	193 (0.51)	1.20 (0.89–1.61)	0.22	1.09 (0.81–1.48)	0.58	1.02 (0.73–1.42)	0.92
Olanzapine	13 (0.14)	63 (0.17)	0.82 (0.45–1.50)	0.52	0.80 (0.44–1.46)	0.47	0.72 (0.38–1.36)	0.31
Amisulpride	9 (0.09)	44 (0.12)	0.82 (0.40–1.67)	0.58	0.77 (0.38–1.60)	0.49	0.69 (0.32–1.47)	0.34
Clozapine	11 (0.12)	35 (0.09)	1.25 (0.64–2.47)	0.51	1.23 (0.62–2.44)	0.55	1.14 (0.56–2.30)	0.72
Aripiprazole	9 (0.09)	34 (0.09)	1.06 (0.51–2.20)	0.88	1.07 (0.51–2.24)	0.86	1.13 (0.52–2.44)	0.76

Values are presented as number (%).

HTN, hypertension; HL, hyperlipidemia; DM, diabetes mellitus; PCOS, polycystic ovary syndrome.

^aAdjusted of age, HTN, HL, DM, PCOS, progesterone use and estrogen use. ^bAdditional adjustment of other antipsychotics use in Model 1.

Table 3. The five-year mortality rate of endometrial cancer patients between haloperidol users and non-users

Haloperidol	No.	Death No.	Person-years	Mortality rate	Hazard ratio (95% confidence interval)	
					Crude	Model ^a
User	29	10	110	90.86	2.09 (1.12–3.91)**	1.89 (1.01–3.54)*
Non-user	3,196	601	14,031	42.83	1.00	1.00

Mortality rate: per 1,000 person-years.

HTN, hypertension; HL, hyperlipidemia; DM, diabetes mellitus; PCOS, polycystic ovary syndrome.

^aAdjusted for age, HTN, DM, HL, PCOS, progesterone use and estrogen use, other antipsychotics use.

* $p < 0.05$, ** $p < 0.01$.

DISCUSSION

Understanding the relationship between various antipsychotics usage and endometrial cancer was the main goal of this study. We observed women with haloperidol exposure had a significantly higher proportion of diagnosis with endometrial cancer than various other antipsychotics exposure. Moreover, a significantly higher 5-year mortality rate was observed among endometrial cancer patients with haloperidol use history compared with those without haloperidol use after adjustment for confounding factors. The aforementioned results are the two major findings of this case-control study.

Previous studies found hyperprolactinemia had been viewed as an important factor for endometrial cancer development because it involves an imbalance of hormones [13] and causes neoplastic changes in the endometrial morphology [14,15]. Hyperprolactinemia was likely to cause amenorrhea, which leads to prolonged estrogen exposure and increases the risk of malignancies in the endometrium. Some studies had reported that amenorrhea was a risk factor for endometrial cancer [16,17]; although still some studies had reported contrary results [18,19]. Moreover, hyperprolactinemia may be viewed as an inflammatory state because it is a common symptom in many autoimmune diseases, such as systemic lupus erythematosus, multiple sclerosis and rheumatic arthritis; even though there exists no consistent relationship between the prolactin level and disease activity [20,21]. Additionally, women with hyperprolactinemia had abnormal autoantibody expression [22], a lower natural killer (NK) cell number [23], and dysregulated T cell function [24] compared with women with normal prolactin levels. In short, hyperprolactinemia-related changes affect the endocrine system, endometrium morphology and immunity. Hence, hyperprolactinemia was likely to be considered a critical factor for endometrial cancer formation. As for haloperidol, a typical antipsychotic agent with a relatively higher dopamine receptor blockage ability compared with atypical antipsychotics. According to a meta-analysis, haloperidol had a relatively higher possibility of causing hyperprolactinemia compared with the other 14 antipsychotics [25]; however, haloperidol was not the first or the only antipsychotic agent to cause hyperprolactinemia. Many other antipsychotic drugs that are prone to cause hyperprolactinemia had not been associated with endo-

metrial cancer formation according to our results of this present study. Therefore, the impact of haloperidol-induced hyperprolactinemia alone was not sufficient to explain the correlation with endometrial cancer formation.

From the biopathological views of the cancer formation, in addition to hyperprolactinemia, pro-tumorigenic inflammation and antitumor immunity changes are related to endometrial cancer development and progression [26-28]. For example, obese people, diabetic patients and older postmenopausal women are high-risk groups with endometrial cancer. Obese people and diabetic patients represent as in a chronic inflammatory states [29,30], and aging postmenopausal women represent immune senescence [31]. All these groups are related to impaired immunity. Hence, the possible role of haloperidol in endometrial cancer development through inflammation-like reactions and immunity changes warrants discussion. The inflammation affects every step of carcinogenesis, including tumor initiation, promotion, and progression. Firstly, an inflammatory microenvironment increases the mutation rate of normal cells. With genomic instability caused by inflammation, the cells serve as sources of reactive oxygen species (ROS) and reactive nitrogen intermediates in the tumor initiation phase, which can induce DNA damage. In fact, haloperidol can induce oxidative stress in inflammatory cells in a multimodal manner, such as by increasing the dopamine metabolism [32] and decreasing the intracellular glutathione level [33]. Earlier findings reported that the haloperidol exhibits an increased expression level of p53 in rat hippocampus and caudate putamen after 7 days of treatment [34], which indicates that exposure to haloperidol presents as a chemical stress for inducing ROS formation [35] and inflammation. Secondly, inflammation plays a crucial role as a tumor promotor in carcinogenesis. Several inflammation pathways are initiated by the signal transducer and activator of transcription 3 (STAT3) or nuclear factor- κ B (NF- κ B), with the possibility of carcinogenesis due to genetically altered cell proliferation [36]. In haloperidol, it not only increases the DNA binding activity of NF- κ B due to the inhibition of κ B (I κ B α) phosphorylation [34] but also increases the levels of the tumor necrosis factor- α (TNF- α) and NF- κ B p65 subunits [37,38] in a dose-dependent manner [39] in rat brains. If NF- κ B signaling of endometrium was activated by haloperidol, proinflammatory, proliferative, and prosurvival gene ex-

pression could be activated by haloperidol to promote tumor cell growth. In addition, the excess activity of the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway, which was associated with cellular growth and survival, was viewed as a possible therapeutic target in endometrial cancer [40]. Perifosine, a type of AKT inhibitor, was reported to treat endometrial cancer cells by inducing apoptosis [41]. By contrast, haloperidol works on increasing total AKT phosphorylation in mice brains [42]. Hence, elevated AKT phosphorylation levels suggest endometrial tumor proliferation and progression, which are likely to be induced by haloperidol exposure. This biological mechanism may lead to a poor prognosis of endometrial cancer, which was consistent with the results of this study, that is, users of haloperidol had a higher five-year mortality rate than non-users. Finally, uterine epithelial cells secrete unidentified and soluble mediators to regulate the dendritic cells (DCs) as the innate immunity of the uterus

[43], but haloperidol suppresses DC maturation and DC-mediated immunity had been reported in mice model [44]. NK cells, a type of innate immunity cells, play a critical role in host immunity against cancer. Previously, progesterin was used to treat endometrial atypical hyperplasia and well-differentiated adenocarcinoma by increasing the number of NK cells [45]; however, the suppression of splenic NK cell activity in mice after 5 days of treatment with haloperidol has been reported [46]. It represents haloperidol possible suppress the immunity in uterus.

In summary, in addition to hyperprolactinemia, inflammation-like effects and weakened immunity may be the possible causes why haloperidol becomes more likely to cause endometrial cancer development than other antipsychotics because of the unhealthy microenvironment. In brief, haloperidol plays a role in endometrial cell carcinogenesis, from cancer initiation to cancer progression, which was compatible with our major findings in this study (Fig. 2). However, further investigation was required

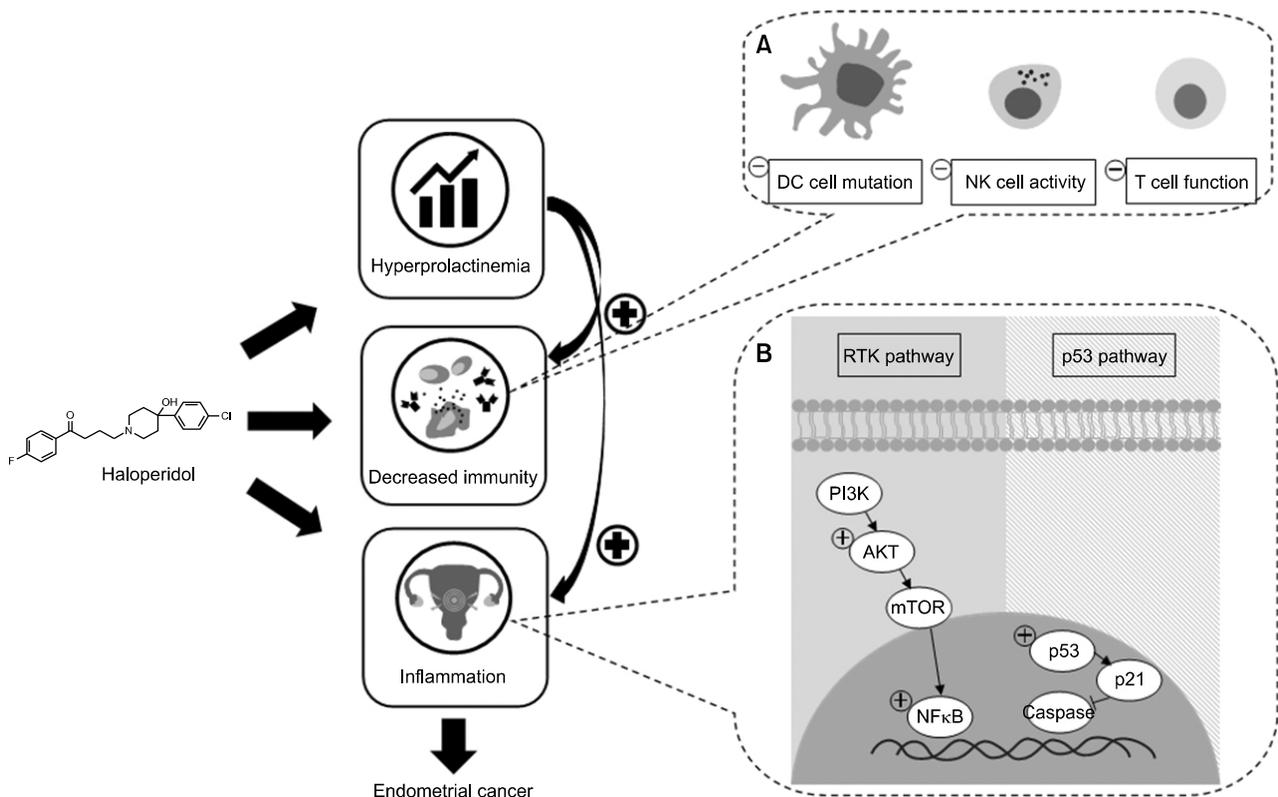


Fig. 2. The relationship between haloperidol and the formation of endometrial cancer. (A) Haloperidol may decrease immunity by suppressing DC cells mutation, reducing NK cells activity and affecting T cell function. (B) Haloperidol may cause inflammation by increasing the DNA binding activity of NF- κ B and p53 expression level.

DC cell, dendritic cell; NK cell, natural killer cell; RTK, receptor tyrosine kinase; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin; NF- κ B, nuclear factor κ B.

to elucidate biological mechanisms to define the effects of haloperidol on the human endometrial epithelium cell at each stage of endometrial cancer development.

Strengths and Limitations

To the best of our knowledge, this work was the first epidemiological study based on a nationwide population-based database to reveal that individual antipsychotic exposure precedes the diagnosis of endometrial cancer. Other studies had used various methods to examine the effects of antipsychotic agents on cancer development, such as converting antipsychotics into dosages equivalent to 10 mg of olanzapine [47], categorizing antipsychotics as atypical or typical [48], or grouping major cancers together in related analyses [49]. In this study, we inferred that each antipsychotic agent exhibits its unique features and different biomechanisms. Therefore, we chose to analyze individual exposures of selected antipsychotic agents. In addition, we had focused on all-female antipsychotic users, instead of just patients with mental illness, to understand the general effect of antipsychotics in the female. However, our study had some limitations because of its observational design. It lacks the data on cancer pathology and stages, and other endometrial-cancer-risk-related information, such as body mass index, prolactin level, lifestyle, supplements (including natural hormone replacements), family history, production times, and smoking habit.

The issue that antipsychotics may increase the opportunity of endometrial cancer should be focused. According to this study, female haloperidol users had a higher chance of getting endometrial cancer after a period of use. Moreover, the mortality rate of the haloperidol users with endometrial cancer was significantly higher than that of the non-users. Taken together, in clinical practice, we had recommended the selection of an antipsychotic apart from haloperidol as the first-line neuroleptic among studied 7 antipsychotics in treating female patients to reduce the possibility of endometrial cancer development after haloperidol exposure. In addition, the current haloperidol users of women should receive a regular clinical evaluation for endometrial cancer prevention.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization and study design: Wei-Ling Chen and Kuan-Pin Su. Data curation: Yan-Chiao Mao. Formal Analysis: Chih-Hsin Muo and Shih-Ping Liu. Interpretation of results: Wei-Ling Chen and Srinivasan Nithiyantham. Writing-original draft: Wei-Ling Chen. Writing-review and editing: Wei-Ling Chen, Srinivasan Nithiyantham, Chih-Pin Chuu, Min-Wei Huang, and Kuan-Pin Su. Visualization: Chih-Pin Chuu and Min-Wei Huang. All authors read and approved the final manuscript.

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