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Aspirin associated with a decreased incidence of uterine cancer

A retrospective population-based cohort study

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Abstract

Aspirin (ASA) exerts an anti-tumor effect via the COX pathway. Clinical studies on the chemopreventive effects of ASA on uterine cancer (UC) remain inconsistent. We used population-based retrospective cohort study to evaluate the UC in ASA users in Taiwanese women. From insurance claims data, we identified 23,342 women received ASA treatment between 2000 and 2010 and a comparison group of same sample size randomly selected from the same database matched by the propensity score. The incidence of UC in the ASA cohort was 10% of that in the comparison group (0.28 vs 2.73 per 10,000 person-years). The Poisson regression analysis estimated adjusted incidence rate ratio (IRR) was 0.10 (95% confidence interval (CI) = 0.09–0.11) for ASA users relatives to comparisons after controlling for covariates. The UC incidence in ASA users decreased with age, from 0.61 per 10,000 person-years in the 20 to 39 years old (adjusted IRR = 0.21, 95% CI = 0.15–0.29) to 0.21 per 10,000 person-years in the 65 to 80 years old (adjusted IRR = 0.15, 95% CI = 0.12–0.16). The incidence was higher in longer term users. Hormone therapy of estradiol was associated with the increase of UC risk in both cohorts, but less in ASA users than comparisons (1.34 vs 4.75 per 10,000 person-years). This study suggests that ASA use was associated with a decreased risk of UC. Further prospective randomized clinical trials are warranted to confirm the association.

Abbreviations: ASA = aspirin, BMI = body mass index, CAD = coronary artery disease, CHF = congestive heart failure, CI = confidence interval, COPD = chronic obstructive pulmonary disease (COPD), COX = cyclooxygenase, COX-2 = cyclooxygenase-2, DM = diabetes mellitus, HR = hazard ratio, HT = hormone therapy, HTN = hypertension, IRR = incidence rate ratio, LHID2000 = Longitudinal Health Insurance Database 2000, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, NSAID = nonsteroidal anti-inflammation drug, OR = odds ratio, PCOS = polycystic ovary syndrome, PG = prostaglandin, PGE2 = prostaglandin E2, RCIPD = Registry of Catastrophic Illness Patient Database, RR = relative risk, UC = uterine cancer.

Keywords: aspirin, cohort, non-steroidal anti-inflammatory drugs, population, uterine cancer

1. Introduction

Uterine cancer is the most common gynecological malignancy in developed countries. Endometrial cancer was the sixth most common female malignancy worldwide in the Global Cancer Statistics 2018, with 382,069 new cases and 89,929 deaths from the disease.[1] The age-standardized incidence is 11.1 per 100,000 and the mortality rate is 2.0 per 100,000 in highly-developed

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The research ethics committee of China Medical University Hospital in Taichung, Taiwan was consulted and approved (IRB permit number: CMUH-104-REC2–115). No consents are needed from study population.

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The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

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regions.[1] In Taiwan, the age-specific incidence of uterine cancer (UC) was 12.5 per 100,000 in 2006 to 2010.[2] The incidence rate of UC has increased over the past 20 years, which has been attributed to obesity, diabetes, increasing age, reduced parity, physical inactivity, excess exogenous estrogen, and tamoxifen use after breast cancer.[3] Current evidence suggests that chronic inflammation related to obesity in conjunction with estrogen exposure can be a potential pathogenesis of UC.[4,5]

It is hypothesized that nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce inflammation and angiogenesis by inhibiting the cyclooxygenase (COX) and decreasing the production of prostaglandin (PG), which therefore may decrease tumor growth and cancer risk.[6] Additionally, prostaglandin E2 (PGE2) promotes cancer progression via the enhancement of cell proliferation, elevation of cytokines and tumor growth factors, upregulation of angiogenesis, inactivation of apoptosis, stimulation of invasion, induction of the transition from epithelial to mesenchymal phenotype, dysregulation of stem cell homeostasis, and suppression of immune response.[7] On the other hand, acquired evidence implies that NSAIDs have potential chemopreventive effects for endometrial cancers that overexpress cyclooxygenase-2 (COX-2). [8–10]

Aspirin, a widely used NSAID, has been used as an analgesic and for the primary prevention of cardiovascular diseases for decades.[8] Aspirin (ASA) also exerts an anti-tumor effect via the COX pathway to cause platelet-associated dysfunction.[9] Recent studies have elucidated that aspirin can reduce the risk of several types of cancer, including gastric, esophageal, colorectal, pancreatic, ovarian, breast, and prostate cancers, and small intestine neuroendocrine tumor.[10] The prevalence of ASA prescription in Taiwan was 12.4%.[11]

However, clinical studies on the chemopreventive effects of ASA in UC prevention remain inconsistent and uncertain.[12–15] Bodelon et al performed a population-based case-control study in western Washington State, and failed to find NSAIDs was associated with the decreasing incidence of endometrial cancer.[13] In a prospective study, Viswanathan et al followed up 82971 women for 24 years and found 747 women developed endometrial cancer, but not associated with ASA usage.[14] Prizment et al conducted a prospective study recruiting 20,000 women aged 58 to 76 years. During a 15-year period, they also found no association between ASA usage and endometrial cancer.[15] On the contrary, Zhang et al concluded in a systemic study, based on 7 cohort studies and 6 case-control studies, that ASA significantly reduced risk of endometrial cancer, especially in obese women (reduced 7% of the risk).[12] A recent pooled analysis showed that the weekly use of ASA was associated with a decreased endometrial cancer risk for 14% in overweight and obese women.[16] Taken together, studies on ASA in the prevention of UC remain inconclusive and study in an Asian population is limited.

Therefore, we hypothesized that the ASA usage might be associated with decreasing UC risk in Asian women. This study used claims data of National Health Insurance (NHI) of Taiwan to assess this relationship

2. Materials and methods

2.1. Data source

The NHI program was established in 1995 with more than 99% of Taiwan's population covered.[17] The present study used Longitudinal Health Insurance Database 2000 (LHID 2000), with claims data of 1 million patients randomly selected from 23 million insured population in National Health Insurance Research Database (NHIRD). The 1-million database was established by the Bioresource Center at Taiwan's National Health Research Institutes. The skill of linear congruential random number generation developed by Park and Miller (1998) was used to select the 1-million sample.[18] They randomly selected 20 groups of persons from all insured people, each group consisted of 50,000 persons. Distributions of sex, age and income of the first group of 50,000 persons, the 1-million sample and all insured people were similar (http://nhird.nhri.org.tw/date_01.html).

There were no significant Differences in age and gender distributions of insured people were similar in LHID2000 and NHIRD. In the database, information was available on patient demographic status, inpatient and outpatient medical records, including medications, treatments and costs. The NHIRD also includes a sub data set of the Registry of Catastrophic Illness Patient Database (RCIPD), for which patients who have been registered in are eligible for medical services. The patients with UC are eligible to be included in the RCPID. This study was approved by the International Review Board, China Medical University and Hospital Research Ethics Committee (IRB permit number: CMUH-104-REC2-115).

2.2. Sampled participant

From LHID2000, we screened for women aged 20 to 80 years who had been prescribed to receive ASA for at least 30 days life time in 2000 to 2010 as the ASA cohort (Fig. 1). The index date was the first date to receive aspirin by prescription (ATC code: B01AC06). We excluded the patients who had been diagnosed with cancer (ICD-9-CM code 140–208) or hysterectomy before index date or within 1 year after the index date or withdrew from the insurance program before the index date.

From the same database, we randomly selected a group of women without ASA usage and histories of hysterectomy and cancer as the comparison group with the sample size similar to ASA group, frequency matched by propensity scores. Propensity score matching was used to optimize comparability between cohorts with and without ASA usage. We estimated the propensity score for each person using multivariable logistic regression to estimate the probability of the disease, with receipt of ASA use as the dependent variable. Age, comorbidities, medications and index year were used as independent variables. Though some unmeasurable confounders could still exist disproportionally in the study groups, we expected the potential of propensity score matching could balance distributions of measured covariates optimally, as a randomized trial does.

2.3. Comorbidities and medications

In the propensity score estimation, we included comorbidities of hypertension (HTN) (ICD-9-CM code 401–405), diabetes mellitus (DM) (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), stroke (ICD-9-CM codes 430–438), coronary artery disease (CAD) (ICD-9-CM codes 410 to 413, 414.01 to 414.05, 414.8, 414.9), congestive heart failure (CHF) (ICD-9-CM codes 398.91, 402.01, 402.11, 402.91, 428), chronic obstructive pulmonary disease (COPD) (ICD-9-CM code 491, 492, 496) and polycystic ovary syndrome (PCOS) (ICD-9-CM code 256.4), because these disorders are prevalent in most populations.

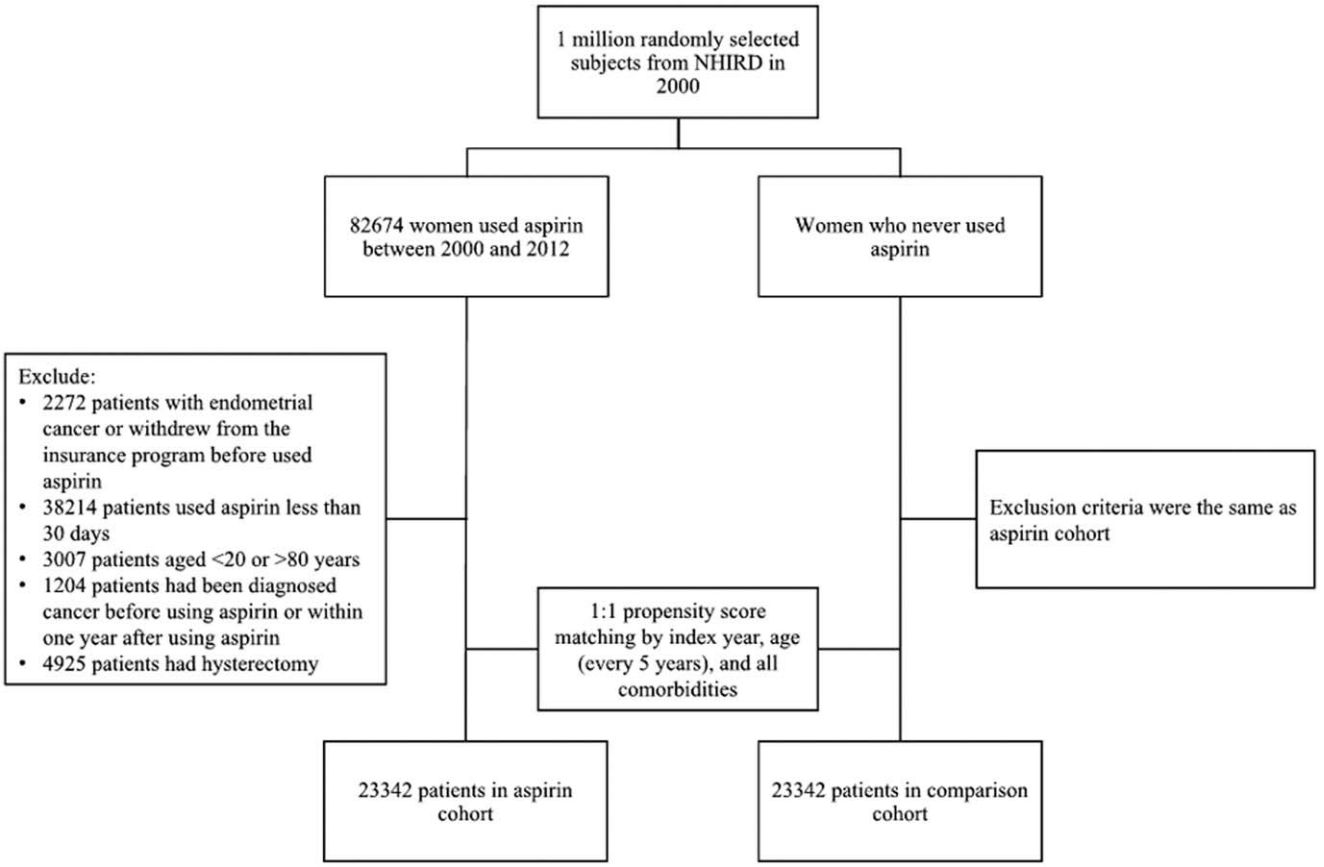

Figure 1. Flow chart for establishing aspirin usage cohort and controls using the National Health Insurance Research Database.

And the diagnosis of PCOS was based on blood tests for luteinizing hormone, follicle-stimulating hormone and testosterone (NHI codes: 09078B2, 09126B, 09126C, 09078B1, 09125B, 09125C, 09064B2, 09121B, and 09121C) and/or ultrasonography (NHI code: 19003C). We also assessed the relationships with prescriptions for Estradiol and Premarin in the database (ATC codes G03C) during the study period. Women were considered as hormone therapy users if they received hormone therapy for more than 30 days. Obesity (278), tamoxifen use (ATC code: L02BA01), menopause (627), history of benign endometrial pathology (621.0, 621.3, 621.31, 621.32, and 621.33) were also included as comorbidities.

2.4. Outcome

Women in both ASA and comparison groups were followed up until the date they were diagnosed with UC, they withdrew from the insurance or died, or the end of 2013. Follow-up person-years were calculated for each woman, and incidence of UC was estimated for each cohort.

2.5. Statistical analysis

Baseline characteristics of covariates were compared between the 2 study cohorts. Distributions of categorical variables were presented with number and percentage, compared using Chi-squared test. Mean ages were examined using t-test. We used Kaplan–Meier methods to estimate and plot the cumulative incident UC for the 2 cohorts, examined the Log-rank test. We compared the incidence of UC for the whole cohorts and by age groups (20–39, 40–64 and 65–80 years). The ASA group to the comparison group incidence rate ratio (IRR) and 95% confidence interval (CI) were calculated using Poisson regression analysis. Adjusted IRR was calculated after controlling for all covariates; no overdispersion was observed. In the distribution of days of ASA uses in all women, we further assessed the incidence of UC for shorter term users (quartile 1: 58–413 days, median 139 days) and longer users (quartile 3: 1127–2620 days, median 1823 days). We also assessed the risk associated with medications of of estradiol, Premarin and tamoxifen and with their interactions. SAS statistical software (Version 9.4 for Windows; SAS Institute, Inc., Cary, NC) was used for statistical analyses. The analysis with a p-value of less than 0.05 was considered to be statistically significant.

3. Results

3.1. Patients characteristics

Each study cohort consisted of 23,342 women, with the mean age slightly younger in the ASA group than comparisons, but significant (Table 1). The median follow-up time was similar in both groups. The baseline prevalence rates of COPD, PCOS, obesity, menopause, and history of benign endometrial pathology were similar in two groups. However, the ASA group was more prevalent than the comparison group in hypertension,

Table 1

Baseline characteristics compared between cohorts with and without aspirin usage.

	Aspirin		
	Yes (n = 23342)	No (n = 23342)	*P* value
Age, yr			<.0001
20–39	1988 (8.52)	1886 (8.08)	
40–64	13904 (59.6)	14603 (62.6)	
65–80	7450 (31.9)	6853 (29.3)	
Mean (SD)	57.0 (12.1)	57.3 (12.8)	.01
Follow-up duration, years			
Mean (SD)	7.54 (3.66)	7.69 (3.93)	<.0001
Comorbidity, n (%)			
Hypertension	4220 (18.1)	3560 (15.2)	<.0001
Diabetes	4072 (17.4)	3858 (16.5)	.01
Hyperlipidemia	4827 (20.7)	4466 (19.1)	<.0001
Stroke	2630 (11.2)	2794 (11.9)	.01
CAD	3689 (15.8)	4113 (17.6)	<.0001
CHF	1672 (7.16)	1877 (8.04)	.0003
COPD	1933 (8.28)	1883 (8.07)	.39
PCOS	116 (0.50)	99 (0.42)	.24
Obesity	324 (1.39)	307 (1.32)	.49
Menopause	1866 (7.99)	1870 (8.01)	.94
History of benign endometrial pathology	359 (1.54)	357 (1.53)	.94
Medication			
Estradiol	1441 (6.17)	1811 (7.76)	<.0001
Premarin	3211 (13.7)	3917 (16.8)	<.0001
Tamoxifen	256 (1.10)	162 (0.69)	<.0001

CAD = coronary artery disease, CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, PCOS = polycystic ovary syndrome.

hyperlipidemia, DM, stroke, CAD and CHF. The prevalence of hormone therapy (estradiol and Premarin) was higher in the comparison group than in the ASA group. Whereas there were more tamoxifen users in the ASA group.

3.2. Risk of uterine cancer

The cumulative incidence of UC was 0.2% greater in the comparison group than in the ASA group ($P < .001$) (Fig. 2). Table 2 shows the incident UC in the ASA cohort was near10% that in the comparison group (5 vs 49 cases, or 0.28 vs 2.73 per 10,000 person-years), with an adjusted IRR of 0.10 (95% CI = 0.09–0.11) for ASA users.

3.3. Uterine cancer risk by age

Table 2 also shows that the UC incidence in ASA users decreased with age, from 0.61 per 10,000 person-years in 20 to 39 years old to 0.27 in 40 to 64 years old and 0.21 in 64 to 80 years old. The corresponding adjusted IRRs were 0.24 (95% CI = 0.18–0.32), 0.08 (95% CI = 0.06–0.09) and 0.15 (95% CI = 0.12–0.18), relative to comparisons.

3.4. The length of ASA use and UC risk

Table 3 shows that most women in the ASA group (69.3%, n = 16171) were shorter term users. The UC incidence was lower in the shorter-term users than in the longer term users, with adjusted IRRs of 0.24 (95% CI = 0.19–0.30) and 0.05 (95% CI = 0.04–0.06), respectively.

3.5. The interaction between ASA and hormone therapy on uterine cancer incidence

Taking estradiol was associated with an increase of UC risk in both groups, but with the incidence lower in ASA users than in non-users (1.34 vs 4.75 per 10,000 person-years) (Table 4).

4. Discussion

After a median follow-up period of 7.5 years, our large population-based study revealed a strong inversed association between ASA use and UC risk. The ASA use is associated with reducing the risk for 90% (IRR 0.1, 95% CI: 0.09–0.11). Our data also show that the benefit it brings to users might be greater for older women. Our results confirm findings in previous studies indicating that ASA could be associated with a reduced UC risk.[12,19]

Observational studies have focused on examining the association between ASA use and endometrial cancer risk, but reported inconsistent results. A recent meta-analysis of 12 studies elucidated that ASA use was associated with a reduced risk of endometrial cancer for 7% (RR 0.93, 95% CI: 0.88–0.99) in the

Table 2

Incidence of uterine cancer by age in women with or without aspirin.

					IRR (95% CI)	
	N	UC, n	PY	IR	Crude	Adjusted*
Overall						
Comparisons	23,342	49	179,654	2.73	1 (reference)	1 (reference)
Aspirin group	23,342	5	176,171	0.28	0.10 (0.09–0.11)	0.10 (0.09–0.11)
20–39, years						
Comparisons	1988	5	17,881	2.80	1 (reference)	1 (reference)
Aspirin group	1886	1	16,379	0.61	0.21 (0.15–0.29)	0.24 (0.18–0.32)
40–64, years						
Comparisons	13,904	37	111,486	3.32	1 (reference)	1 (reference)
Aspirin group	4603	3	112,496	0.27	0.08 (0.06–0.09)	0.07 (0.06–0.09)
65–80, years						
Comparisons	7450	7	50,287	1.39	1 (reference)	1 (reference)
Aspirin group	6853	1	47,296	0.21	0.15 (0.12–0.18)	0.15 (0.12–0.18)

CI = confidence interval, IR = incidence rate per 10000 person-years, IRR = incidence rate ratio, PY = person-years, UC = uterine cancer.
* Measured after controlling for age, comorbidities, and medications listed in Table 1.

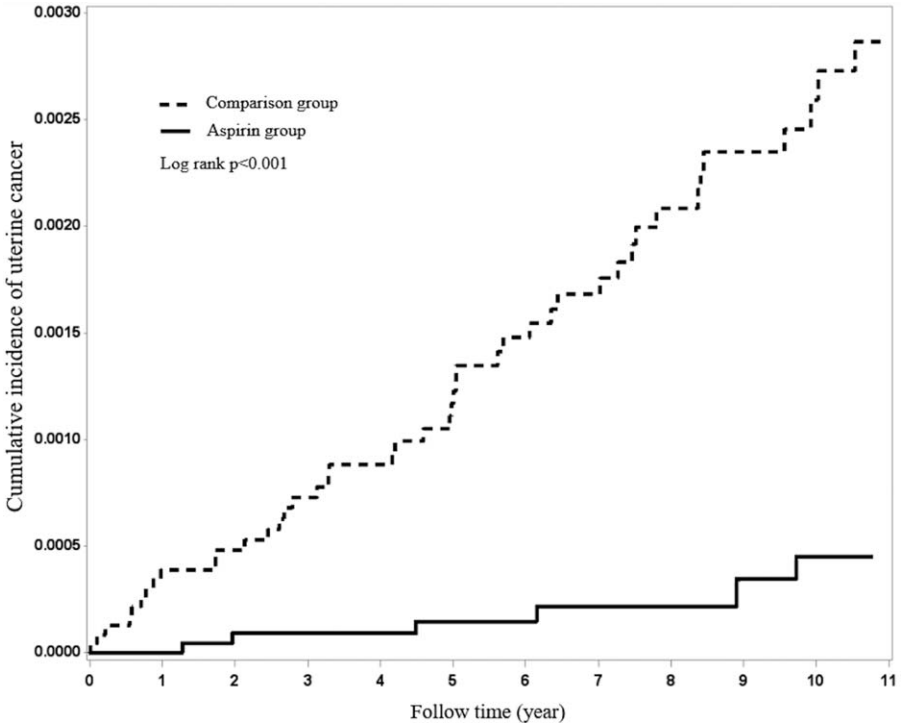

Figure 2. Kaplan-Meier curves revealed an accumulated incidence of uterine cancer for women with aspirin usage (solid line) and the comparison group (dashed line) by the end of follow-up.

pooled analysis.[12,19] The chemopreventive effect of aspirin is particularly significant among obese women.[12,19] Another recent pooled analysis showed weekly use of ASA was associated with a decreased incidence of endometrial cancer among both overweight and obese women with similar odds ratios of 0.86 (95% CI = 0.76–0.98) and 0.86 (95% CI: 0.76–0.97), respectively.[16] A recent case-control study using the insurance claims data of Taiwan also showed a decreased overall cancer risk with an adjusted OR of 0.95 (95% CI: 0.94–0.96).[20] All these beneficial associations between ASA use and reductions of endometrial cancer are not so strong as our findings between the ASA use and the UC risk.

The frequency, duration, and dosage of ASA uses have also been investigated. A follow-up study in the US found the high ASA use decreased risk of endometrial cancer was greater for high ASA uses (HR 0.64, 95% CI: 0.41–1.01; $P = .03$) than the low uses (HR 0.77, 95% CI: 0.54–1.09), but not significant.[21] Verdoodt et al found the high frequent ASA users could be benefited with reduced risks for 37% in case-control studies and for 20% in cohort studies, but no duration-response relationship was observed. With a 14-year follow-up period, our findings suggest that shorter-term ASA users (58–413 days) was associated with a 74% reduction in the risk (IRR 0.24, 95% CI: 0.19–0.30), and long-term users (1127–2620 days) might have further reduced risk (IRR 0.05, 95% CI: 0.04–0.06). The dramatic findings deserve additional assessment for confirmation.

Estrogen has been shown to up-regulate COX-2 expression for 2.8 fold and PGE2 synthesis for 1.5 folds in human uterine microvascular endothelial cells.[22] Nasir et al also reported that there is strong and frequent expression of COX-2 protein in human endometrial carcinoma based on in vivo studies.[23] Logically, we hypothesized to observe a chemopreventive effect of ASA for hormone therapy (HT) users. Our findings indicate that women taking ASA are at a reduced risk of endometrial cancer despite the use of estradiol, with an adjusted IRR of 0.46 (95 CI: 0.34–0.63) for UC. Among HT never users, ASA usage was associated with a prominently decreased incidence of UC (IRR 0.12; 95 CI: 0.11–0.14). Extensive studies have provided robust evidence that estrogen therapy is linked with higher risks

Table 3

Incidence of uterine cancer in shorter and longer terms of aspirin usage.

		Days	UC			IRR (95% CI)	
Aspirin usage	N	[Q1, Q3]	n	PY	Rate	Crude	Adjusted*
Comparisons	23,342		49	179,654	2.73	1 (reference)	1 (reference)
Shorter term	16,171	58–413	2	125,550	0.16	0.26 (0.21–0.33)	0.24 (0.19–0.30)
Long term	7171	1127–2620	3	50,621	0.59	0.05 (0.04–0.07)	0.05 (0.04–0.06)

CI = confidence interval, IRR = incidence rate ratio, PY = person-years, Rate = per 10,000 person-years, UC = uterine cancer.
* Measured after controlling for age, comorbidities, and medications listed in Table 1.

Table 4

Incidence of uterine cancer associated with estradiol, Premarin, and tamoxifen.

Group	Estr	Prem	Tamo	N	UC, n	PY	IR	IRR (95% CI)	
								Crude	Adjusted*
Comparison	N	N	N	19,134	34	139,447	2.44	1 (reference)	1 (reference)
	Y	N	N	780	3	6322	4.75	1.94 (1.60–2.35)	1.49 (1.23–1.81)
	N	Y	N	2523	9	25236	3.57	1.46 (1.29–1.65)	1.12 (0.99–1.27)
	N	N	Y	210	0	1624	0.00	–	–
	Y	Y	N	649	3	6565	4.57	1.87 (1.54–2.27)	1.28 (1.05–1.55)
	Y	N	Y	7	0	56	0.00	–	–
	N	Y	Y	34	0	357	0.00	–	–
	Y	Y	Y	5	0	47	0.00	–	–
Aspirin	N	N	N	18,348	4	130,203	0.31	0.12 (0.11–0.14)	0.12 (0.11–0.14)
	Y	N	N	952	1	7473	1.34	0.54 (0.40–0.75)	0.46 (0.34–0.63)
	N	Y	N	3041	0	28,834	0.00	–	–
	N	N	Y	116	0	1037	0.00	–	–
	Y	Y	N	839	0	8190	0.00	–	–
	Y	N	Y	9	0	89	0.00	–	–
	N	Y	Y	26	0	226	0.00	–	–
	Y	Y	Y	11	0	119	0.00	–	–

CI = confidence interval, Estr = estradiol, IR = incidence rate per 10,000 person-years, IRR = incidence rate ratio, Prem = premarin, PY = person-years, Tamo = tamoxifen, UC = uterine cancer.
* Measured after controlling for age, comorbidities, and medications listed in Table 1.

of endometrial cancer,[24] associated with a duration- and dose-dependent relationship.[25] The reduced UC risk for women taking HT might be due to ASA usage in our study.

In our study, potential bias might exist. Table 2 shows that the incidence rate of UC in the comparison group are higher in young women than in the elderly. This is somewhat different from reported statistics. Lai et al. reviewed the UC distribution among countries and found 8.4% of cancer cases in women below the age of 40, 65% in 40 to 64 years old and 26.6% in the elderly.[2] In the USA, the uterine cancer incidence rate is in the same trend.[26] Our study cohorts were generated from database of 1 million insured people, which was randomly selected from NHIRD. There was no significant difference in the distribution of age and gender between the two databases. In addition, we were unable to assess the UC incidence by body mass index (BMI). A recent meta-analysis showed that odds ratios of endometrial cancer were 1.43 (95% CI: 1.30–1.56) for overweight women and 3.33 (95% CI: 2.87–3.79) for obese women.[27] Information on BMI is unavailable in NHIRD. In Taiwan, 18.3% and 1.2% women aged between 20 and 64 overweight and obesity, respectively.[28] The proportion of overweight and obesity in women in Taiwan was similar to that in other Asian countries,[28] but lower than that in Western countries.[29] This may reflect on the incidence of UC. In the USA, the incidence is 26.2 per 100,000[30], while it is 12.4 per 100,000 in Taiwan.[2] After propensity score matching, we assumed proportions of obesity were the same in both groups.

This study represents the largest evidence-based study quantifying the decreased UC risk associated with using ASA. The population-based cohort design could minimize selection bias. We obtained reliable drug exposure from the administrative prescription database rather than self-reported data. The information on ASA use in previous cohort studies[6,15,21,31] was mainly based on interviews or questionnaires, which may be susceptible to misclassification error and recall bias. Our study has also adjusted for potential confounding factors. Moreover, the data from nationwide healthcare registers provides representative information of the general population and the comparison women are drawn from the same population.

We acknowledge several limitations of this study. First, we assessed the length of ASA uses instead of ASA dose. Generally, there is a consensus that low-dose aspirin can be used for cardiovascular disease prevention in Taiwan.[32,33] One retrospective study by Matsuo et al. suggested benefit of low-dose ASA in improving survival of endometrial cancer, with a hazard ratio of 0.23 (95% CI = 0.08–0.64) compared with non-users.[34] Second, the effort of propensity score matching failed to establish the two study cohorts with similar distributions for some baseline variables.[35] We therefore estimated the adjusted IRR after controlling these baseline variables. Third, we were unable to assess the cancer risk associated with the family history of gynecologic or colorectal cancer due to the lack of information on it. Lastly, the ASA exposure was based on prescription information only; we thus were unable to determine whether the patients had actually adhered to medication compliance. In addition, information on over-the-counter medications of ASA and other types of NSAID was also unavailable. The risk might be overestimated or underestimated due to the misclassification.

5. Conclusions

In conclusion, our findings suggest that the ASA use was associated with a decreased risk of UC. This association remains significant for the shorter-term users. Our findings add to the literature implicating that the anti-cancer effect of ASA is particularly notable for UC. Further prospective randomized clinical trials are warranted to confirm our findings.

Author contributions

Pei-Chen Li: manuscript preparation; Fung-Chang Sung, Yu-Cih Yang, WeiShan Chen: data analysis, manuscript preparation; Jen-Hung Wang: study design; Shinn-Zong Lin: study design; Dah-Ching Ding: study concepts, design and manuscript preparation. Dah-Ching Ding and Fung-Chang Sung manuscript revision.

Formal analysis: Fung-Chang Sung.

Writing – original draft: Pei-Chen Li.

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