The Risk of Peripheral Arterial Disease in Long-Term Uterine Cancer Survivors: A Population-Based Study

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Abstract

Background: The risk of peripheral arterial disease (PAD) in long-term uterine cancer (UC) survivors remains unclear, especially in Asian patients, who are younger at the diagnosis of UC than their Western counterparts.

Methods: UC survivors, defined as those who survived for longer than 5 years after the diagnosis, were identified and matched at a 1:4 ratio with normal controls. Stratified Cox models were used to assess the risk of PAD.

Results: From 2000 to 2005, 1,889 UC survivors who received surgery alone or surgery combined with radiotherapy (RT) were classified into young (onset age <50 years, *n*=894) and older (onset age ≥50 years, *n*=995) groups. While compared with normal controls, the young patients with diabetes, hypertension, and receiving hormone replacement therapy (HRT) were more likely to develop PAD. In contrast, the risk of PAD was associated with adjuvant RT, obesity, hypertension, and HRT in the older group. Among the UC survivors, those who were diagnosed at an advanced age (>65 years, aHR³2.48, *P*£0.011), had hypertension (aHR=2.18, *P*=0.008) or received HRT (aHR=3.52, *P*=0.020) were at higher risk of PAD.

Conclusion: In this nationwide study, we found that the risk factors associated with PAD were similar in both cohorts except for adjuvant RT that was negligible in the young age group, but positive in the older group. Among the survivors, hypertension, advanced age, and HRT were more hazardous than RT. Secondary prevention should include PAD as a late complication in UC survivorship programs.

Background

Uterine cancer (UC) is the most common gynecologic malignancy in developed areas (1). The incidence of UC is increasing at a rate of 1-2% per year in Western and Asian countries (2, 3). In Western populations, 15% of UC patients are under the age of 50 years (4, 5), however, around 40% of UC patients in Taiwan are younger than 50 years of age (3). The patients with loco-regional disease in the United States, which comprises 89% of all cases of UC, have a great prognosis since the 5-year survival rates for local disease and regional disease are 95.3% and 67.5%, respectively (4, 5). Due to the high survival rate, UC survivorship care should include the management of many health issues, such as late side effects in post-treatment cancer survivors. The long-term survivors are commonly defined as patients who are alive more than 5 years after diagnosis (6). The well-being of long-term cancer survivors may do as well as persons with similar age and demographic characters (7). However, even 5 years or more after diagnosis, patients can continue to face the physical effect related to treatment. Thus, concerns have been raised about the detrimental impact of late complications owing to treatment in their survivorship (7, 8).

Surgery is the principal treatment for local-regional UC, and radiotherapy (RT) has become the standard adjuvant treatment of choice for patients with high-risk factors (9). Major pelvic surgery may result in lympho-vascular complications such as deep vein thrombosis or lymph edema (10, 11). In addition, RT

can cause local inflammation, oxidative stress, fibrosis and in-field cardiovascular disease (12). Several studies have reported that RT increased the risk of ischemic stroke in patients with head and neck cancers (13, 14).

Peripheral arterial disease (PAD) is a cardiovascular disease that encompasses all chronic arterial occlusive diseases of the arteries other than coronary arteries and the aorta caused by atherosclerosis. The most prevalent sites of PAD are the lower extremities, which may cause leg or pelvic pain, intermittent claudication, and limited mobilization. Women with PAD have been reported to have an increased prevalence of coexisting coronary artery disease and ischemic stroke, and higher all-cause mortality (15). The risk of PAD has been reported in cervical cancer patients (16, 17), however few studies have investigated the risk of PAD in UC survivors. A study from the US using the SEER Utah Cancer Registry revealed that among UC patients treated with surgery alone or surgery with adjuvant RT, the risk of PAD was 24% higher in the patients with RT than in those who received surgery alone during the first 5 years of follow-up. However, no long-term effect of adjuvant RT was observed 5 years after the diagnosis (2).

Since Asian patients with UC are younger on average, the risk of PAD in young survivors may be different from that in Western patients. To address this issue, we conducted a nationwide population-based study to assess the risk of PAD in UC long-term survivors, defined as patients who survived for more than 5 years after diagnosis. We also assessed whether age, treatment modality, income level, comorbidities, and hormone replacement therapy (HRT) are associated with the risk of PAD.

Methods

Data Sources

The data used in this study were sourced from the Registry of Catastrophic Illness (RCI) and Longitudinal Health Insurance Database 2005 (LHID2005), which are two subsets of records from the Taiwan National Health Insurance Research Database (NHIRD). The NHIRD is a nationwide database containing longitudinal medical records of beneficiaries enrolled in the National Health Insurance (NHI) program, which provides comprehensive health care coverage for over 98% of the Taiwanese population. The evaluation process for patients in the RCI database is conducted by a panel of specialists who follow a strict process of reviewing medical records, imaging, and pathology reports, therefore, it was used to identify patients with UC or other cancers. The LHID2005 contains original claims data for 1,000,000 beneficiaries randomly sampled from the entire population in 2005. All information on comorbidities and treatment modalities (for UC cases) from 1995–2012 was available for analysis from inpatient and outpatient records. This retrospective study was approved by the Institutional Review Board (IRB) of Chang Gung Medical Foundation (201600205B0). This study is based in part on data from the NHIRD provided by the NHI Administration, Ministry of Health and Welfare and managed by National Health Research Institutes. This is a secondary use of individuals' healthcare data and all personal information has been removed by de-identification, so that specific persons and their identities cannot be re-identified

or be linked to other database. In accordance with the Declaration of Helsinki, this study did not increase the risk of participants, and the IRB approves the waiver of the informed consent form.

Study Design

The primary endpoint of this study was the development of moderately severe PAD during the follow-up period (2005–2012). PAD was identified if the patients were hospitalized with a major or minor diagnosis of the following International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes: 440.0x, (atherosclerosis of the aorta), 440.2x (atherosclerosis of native arteries of the extremities), 440.8x (atherosclerosis of other specified arteries), 440.9x (generalized and unspecified atherosclerosis), 443.9x (peripheral vascular disease, unspecified), 444.0x (arterial embolism and thrombosis of the abdominal aorta), 444.2x (arterial embolism and thrombosis of other specified arteries), 447.8x (other specified disorders of arteries and arterioles), 447.9x (unspecified disorders of arteries and arterioles)

To evaluate the risk of PAD in UC survivors (ICD-9-CM code: 179 or 182), subgroup analysis was performed according to the age at the diagnosis of UC: < 50 years (young group) and ≥ 50 years (older group). For each group, two study cohorts were compared: a UC survivor group and a matched control group. The survivors were defined as those who survived for longer than 5 years after the diagnosis of UC, and the first day after 5 years of survivorship was defined as the index date. Originally, the UC group comprised 4,022 patients who were diagnosed between 2000 and 2005. However, 2,133 patients were excluded due to any one of the following criteria: aged < 20 or > 80 years at diagnosis of UC, survived for less than 5 years, developed second cancers during follow-up or PAD before the index date, incomplete individual information, and received treatment modalities other than surgery alone and surgery with adjuvant RT. Finally, 894 young and 995 older survivors were eligible for this study. Normal controls were matched using propensity score, calculated as the probability of being a case (UC) according to baseline variables, including age at the index date, sex, urbanization level, and income-related insurance payment. At a ratio of 1:4, four corresponding controls were selected for each UC case based on the closest propensity score. Thus, a total of 7,556 controls aged 25–85 years without any history of cancers or PAD before the index date were selected from the LHID2005. The index date of each control was assigned to be the same as that of the corresponding UC survivor. The survival time for all groups was defined as the number of years from the index date to a new diagnosis of PAD, withdrawal from the NHI program (mostly due to death, and a few cases owing to immigration, imprisonment, and others), or December 31, 2012, whichever occurred first. Comorbidities related to PAD including hypertension, diabetes, atrial fibrillation, hyperlipidemia, chronic kidney disease, morbid obesity and smoking-related diseases, and diagnoses of these comorbidities were confirmed by at least three clinical visits or at least one hospitalization during the 12 months prior to the index date. We identified HRT (G03C, G03F) according to the Anatomical Therapeutic Chemical Classification system, and retrieved prescription data from NHI files. The dosage of HRT was defined as the average number of days of taking HRT per year from the diagnosis of UC to the date of last follow-up.

Statistical Analysis

Baseline characteristics are presented as means with standard deviations or frequencies with percentages. Comparisons between UC survivors and controls were performed using generalized estimating equations (GEE) (18) which takes into account correlations within each cluster (1 UC case and 4 matched controls). Similarly, stratified Cox proportional hazards models were used to assess the risk of PAD between two groups, and the results are presented as crude hazard ratios (HRs) and adjusted HRs (aHRs) with *P* values. In addition, the cumulative incidence rates of PAD were calculated and compared between groups by applying a competing risk model proposed by Kalbfleisch and Prentice (19) and Gray (20). Among the UC survivors, risk factors related to PAD were assessed using a Cox proportional hazards models. Data were managed and analyzed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA). All statistical tests were two-sided at 0.05 level of significance.

Results

Characteristics of the Study Participants

From 2000 to 2005, a total of 1,889 eligible UC 5-year survivors were identified from the RCI, and 7,556 controls were selected from the LHID2005. The baseline characteristics are listed and two cohorts were comparable with respect to sex, age, and income-related insurance payment (all $P \geq 0.600$) for both age groups (Table 1). In the young group, the UC survivors had higher rates of comorbidities including hypertension (27.39% vs. 14.15%, $P < 0.001$), diabetes (18.34% vs. 5.54%, $P < 0.001$), hyperlipidemia (10.63% vs. 5.87%, $P < 0.001$), obesity (4.92% vs. 3.19%, $P = 0.010$) and duration of HRT (percentage of > 1 month: 15.44% vs. 6.10%, $P = 0.033$) than the matched controls. However, the controls had a higher rate of smoking-related diseases than the survivors (9.82% vs. 4.36%, $P < 0.001$). In contrast, compared with the older controls, the UC survivors had similar prevalence rates of all comorbidities, except for lower rates of morbid obesity (1.81% vs. 3.09%, $P = 0.031$) and smoking-related diseases (7.33% vs. 18.52%, $P < 0.001$), and a higher rate of diabetes (23.72% vs. 20.50%, $P = 0.026$).

Table 1
Characteristics of uterine cancer survivors and matched normal controls

Characteristic	UC survivors onset age <50 years (*n*=894)	Normal controls (*n*=3576)	*P* value	UC survivor onset age ≥50 years (*n*=995)	Normal controls (*n*=3980)	*P* value
Age at index date (years)	48.00 ± 5.63	47.82 ± 5.74		63.09 ± 6.83	63.23 ± 7.25	
25-40	88 (9.84)	352 (9.84)	1.00			1.00
40-45	121 (13.53)	484 (13.53)				
45-50	251 (28.08)	1004 (28.08)				
50-55	434 (48.55)	1736 (48.55)				
55-60				391 (39.30)	1564 (39.30)	
60-65				267 (26.83)	1068 (26.83)	
65-70				155 (15.58)	620 (15.58)	
>70				182 (18.29)	728 (18.29)	
Urbanization						
1 (least urbanized)	174 (19.46)	696 (19.46)	0.768	229 (23.01)	996 (23.01)	1.00
2	216 (24.16)	867 (24.24)		223 (22.41)	1184 (22.41)	
3	300 (33.56)	1197 (33.47)		296 (29.75)	892 (29.75)	
4	204 (22.82)	816 (22.82)		247 (24.82)	908 (24.82)	
Income-related insurance payment						
1 (lowest)	449 (50.22)	1793 (50.14)	0.600	665 (66.83)	2660 (66.83)	1.00
2	214 (23.94)	856 (23.94)		153 (15.38)	612 (15.38)	

Characteristic	UC survivors onset age <50 years (*n*=894)	Normal controls (*n*=3576)	*P* value	UC survivor onset age ≥50 years (*n*=995)	Normal controls (*n*=3980)	*P* value
3	146 (16.33)	587 (16.41)		132 (13.27)	528 (13.27)	
4 (highest)	85 (9.51)	340 (9.51)		45 (4.52)	180 (4.52)	
Morbid obesity[a]	44 (4.92)	111 (3.10)	0.010	18 (1.81)	123 (3.09)	0.031
Smoking-related diseases[b]	39 (4.36)	351 (9.82)	<0.001	73 (7.33)	737 (18.52)	<0.001
HRT[c]			0.033			0.108
0	548 (61.30)	2200 (61.52)		663 (66.63)	2781 (69.87)	
1-30 days	208 (23.27)	1158 (32.38)		229 (23.02)	774 (19.45)	
31-180 days	113 (12.64)	192 (5.37)		90 (9.05)	350 (8.79)	
>180 days	25 (2.80)	26 (0.73)		13 (1.31)	75 (1.88)	
Comorbidity						
Hypertension	244 (27.39)	506 (14.15)	<0.001	473 (47.54)	1779 (44.70)	0.094
Diabetes	164 (18.34)	198 (5.54)	<0.001	236 (23.72)	816 (20.50)	0.026
Atrial fibrillation	5 (0.56)	11 (0.31)	0.268	12 (1.21)	65 (1.63)	0.312
Hyperlipidemia	95 (10.63)	210 (5.87)	<0.001	179 (17.99)	750 (18.84)	0.532
Chronic kidney disease	7 (0.78)	15 (0.42)	0.173	11 (1.11)	35 (0.88)	0.511
PAD	8 (0.89)	19 (0.53)		19 (1.91)	66 (1.66)	
Mean follow-up after index date (years)	4.515	4.535		4.377	4.358	
Incidence per 100,000 person-years[d]	198.21	117.17	0.212	436.25	380.54	0.599

Characteristic	UC survivors onset age <50 years (*n*=894)	Normal controls (*n*=3576)	*P* value	UC survivor onset age ≥50 years (*n*=995)	Normal controls (*n*=3980)	*P* value
Treatment modality						
Surgery alone	727 (81.32)			694 (69.75)		
Surgery+RT	167 (18.68)			301 (30.25)		
Data are presented as n (%) or mean ± SD.						
UC survivors and the comparison group were matched by 5-year age group, sex, urbanization level, and income-related insurance payment.						
All *P* values were obtained from GEE models.						
UC, uterine cancer; RT, radiotherapy; HRT, hormone replacement therapy;						
PAD: peripheral arterial disease						
[a]morbid obesity (ICD-9 code: 278, 278.00, 278.01, and V778)						
[b]smoking related diagnoses (ICD-9 code: 305.1, 491.2, 492.8, 496, 523.6, 959.84, 649.0, and V15.82)						
[c]number of days of taking hormone replacement therapy (HRT) per year during the follow-up period. HRT was identified according to the Anatomical Therapeutic Chemical classification system and included estrogen only (G03C) and an estrogen-progesterone combination (G03F).						
[d]incidence per 100,000 person-years						

Risk Factors for a PAD Event in the Young Survivors

The crude incidence rates of PAD were higher in the young survivors than in the matched controls, but the difference was not significant (198.21 vs. 117.17 per 100,000 person-years, $P = 0.212$, Table 1). In univariate analysis, those who received HRT for longer than 1 month (HR ≥ 3.67, $P \leq 0.027$) or had any one of the following comorbidities were at a higher risk of developing PAD: diabetes (HR = 4.49, $P = 0.002$), hypertension (HR = 2.89, $P = 0.007$), hyperlipidemia (HR = 3.12, $P = 0.010$) (left panel, Table 2). The adjusted HRs also revealed that the young patients with diabetes (aHR = 2.93, $P = 0.033$), hypertension (aHR = 2.93, $P = 0.033$), and receiving HRT (aHR ≥ 2.89, $P \leq 0.038$) were more likely to develop PAD (right panel, Table 2). In contrast, both the surgery alone and surgery + RT subgroups had a similar risk to the normal controls (aHR = 0.75 and 0.34, respectively, both $P \leq 0.083$).

Table 2
Crude and adjusted hazard ratios for the occurrence of PAD in the young group using a stratified Cox model with withdrawal as a competing risk

	Crude HR (95% CI)		*P* value	Adjusted HR[a] (95% CI)		*P* value
Group (controls)	1		0.150	1		0.395
UC survivors[b]	1.68	(0.83–3.43)		0.66	(0.25-1.72)	
surgery alone[c]				0.75	(0.25-2.22)	0.601
surgery + RT[d]				0.34	(0.10-1.15)	0.083
Morbid obesity	1.36	(0.35-5.37)	0.659			
Smoking	1.83	(0.62-5.35)	0.271			
Diabetes	**4.49**	(1.76–11.44)	0.002	**2.93**	(1.09–7.92)	0.033
Hypertension	**2.89**	(1.33–6.27)	0.007	**3.61**	(1.43–9.08)	0.006
Hyperlipidemia	**3.12**	(1.31–7.46)	0.010			
Chronic kidney disease	4.00	(0.40–39.83)	0.237			
HRT						
0 days	1			1		
1-30 days	1.98	(0.82-4.75)	0.127	**2.89**	(1.06-7.91)	0.038
30-180 days	**3.67**	(1.16-11.58)	0.027	**5.65**	(1.62-19.65)	0.006
>180 days	**22.36**	(3.43-145.80)	0.001	**25.75**	(4.72-155.24)	<0.001

[a]adjusted HRs and *P* values were obtained from a multiple stratified Cox model, which included treatment modality and significant explanatory variables only.

[b]all UC survivors, regardless of treatment modality.

[c, d]treatment modalities (surgery alone and surgery with RT) were examined in the Cox model.

UC, uterine cancer; RT, radiotherapy; HRT, hormone replacement therapy; HR, hazard ratio; CI, confidence interval; PAD: peripheral arterial disease

Risk Factors for a PAD Event in the Older Survivors

In the older group, the crude incidence rates of PAD were not different between two groups (436.25 vs. 380.54 per 100,000 person-years, *P* = 0.599, Table 1). Consistently, univariate analysis also showed that the survivors were at a higher but not significant risk of PAD compared with the controls (HR = 1.17, *P* = 0.503). However, obesity, diabetes, hypertension and receiving HRT for longer than 6 months increased

the risk of PAD (HR = 6.00, *P* = 0.001; HR = 1.67, *P* = 0.021; HR = 2.24, *P* = 0.002; HR = 5.24, *P* = 0.002, respectively) (left panel, Table 3). Furthermore, the aHRs revealed that the older UC survivors who received RT after surgery had at least a 2-fold higher risk of PAD compared to the matched controls after adjusting for confounders (aHR = 2.12, *P* = 0.019) (right panel, Table 3). In addition, obesity (aHR = 5.55, *P* = 0.003), hypertension (aHR = 2.06, *P* = 0.005) and HRT for ≥ 180 days (aHR = 4.54, *P* = 0.013) were still positively associated with the risk of developing PAD.

Table 3
Crude and adjusted hazard ratios for the occurrence of PAD in the older group using a stratified Cox model with withdrawal as a competing risk

	Crude HR (95% CI)		*P* value	Adjusted HR[a] (95% CI)		*P* value
Group (controls)	1		0.503	1		
UC survivors[b]	1.17	(0.74–1.85)		1.29	(0.80-2.07)	0.299
surgery alone[c]				0.93	(0.47-1.84)	0.832
surgery + RT[d]				**2.12**	(1.13-3.95)	0.019
Morbid obesity	**6.00**	(2.08-17.29)	0.001	**5.55**	(1.82-16.94)	0.003
Smoking	0.92	(0.52-1.62)	0.769			
Comorbidity						
Diabetes	**1.67**	(1.08–2.59)	0.021			
Hypertension	**2.24**	(1.36–3.68)	0.002	**2.06**	(1.24–3.43)	0.005
Hyperlipidemia	1.59	(0.98–2.57)	0.062			
Chronic kidney disease	0.800	(0.11–5.63)	0.823			
HRT						
0 days	1			1		
1-30 days	0.68	(0.38-1.24)	0.208	0.60	(1.06-7.91)	0.100
30-180 days	1.01	(0.47-2.15)	0.979	0.82	(1.62-19.65)	0.615
>180 days	**5.24**	(1.81-15.23)	0.002	**4.54**	(1.38-14.91)	0.013

[a]adjusted HRs and *P* values were obtained from a multiple stratified Cox model, which included treatment modality and significant explanatory variables only.

[b]all UC survivors, regardless of treatment modality.

[c, d]treatment modalities (surgery alone and surgery with RT) were examined in the Cox model.

UC, uterine cancer; RT, radiotherapy; HRT, hormone replacement therapy; HR, hazard ratio; CI, confidence interval; PAD: peripheral arterial disease

The Risk of PAD in the UC Survivors

Among the 1,889 UC survivors, a comparison between treatment modalities revealed that RT increased the risk of PAD by 39%, but this was not significant after adjusting for other confounders (aHR = 1.39, *P* =

0.247). However, the risk of PAD was significantly increased among the survivors who were older (age at the index year > 65 years; aHR ≥ 2.48, $P < 0.011$), had hypertension (aHR = 2.18, $P = 0.008$), and received HRT for longer than 6 months per year from the diagnosis of UC (aHR = 3.52, $P = 0.020$) (Table 4).

Table 4
Adjusted hazard ratios for the occurrence of PAD in the UC survivors using a Cox proportional hazards model (*n*=1889)

	Adjusted HR	**95% CI**	**P value**
Treatment modality			
Surgery alone	1		0.247
Surgery with RT	1.39	(0.80-2.42)	
Age at index year (years)			
<55	1		
55-65	0.72	(0.35-1.48)	0.372
65-75	**2.48**	(1.23-4.99)	0.011
>75	**3.63**	(1.55-8.47)	0.003
Hypertension	**2.18**	(1.23-3.88)	0.008
HRT			
0 days	1		
1-30 days	0.53	(0.25-1.15)	0.108
30-180 days	1.08	(0.45-2.58)	0.864
>180 days	**3.52**	(1.22-10.13)	0.020
Adjusted HRs and *P* values were obtained from a multiple Cox model, which included treatment modality and significant explanatory variables only.			
UC, uterine cancer; RT, radiotherapy; HRT, hormone replacement therapy; HR, hazard ratio; CI, confidence interval; PAD: peripheral arterial disease			

Discussion

In this nationwide study, we found that the risk factors associated with PAD were similar in both cohorts except for adjuvant RT that was negligible in the young age group, but positive in the older group. In our study population, the young patients accounted for 47% of the total (894/1,889), which is much higher than that reported in Western populations (2, 5). Among the survivors, hypertension, advanced age, and HRT for longer than 180 days per year were more hazardous than RT.

PAD in the general population usually appears after the age of 50 years, and the prevalence then increases with age (21). This trend was also observed in the UC survivors in the present study. RT is a known cause of cardiovascular morbidity and mortality. The long-term effects on vascular endothelial damage and the possible mechanism of ionizing radiation on the progression of atherosclerotic plaque have been reported (22, 23). Although studies on the late vascular effects induced by RT have been performed in preclinical models, no clear correlations between individual changes and their time course after conventional fractionated RT have been identified. Accordingly, further studies are needed to investigate whether RT for UC increases the risk of PAD. In our analysis, RT did not cause PAD to occur earlier, but it increased the incidence of PAD in the older patients. People over 65 years of age often have multiple cardiovascular risk factors, and atherosclerosis can be accelerated by radiation (24).

In this study, we found that HRT was more associated with an increased risk of PAD than RT. A previous study reported that estrogen can regulate injury-induced chemokines and oxidative stress and that it has a vascular protective effect, but that it has no vascular protective effects on aging blood vessels (25). The “timing hypothesis” suggests that because the estrogen signaling pathway in older women has changed, estrogen has no vascular protective effect in patients with subclinical vascular diseases (25). Compared with the slow decline of estrogen levels in natural menopause over time, bilateral oophorectomy for UC treatment can lead to a sudden decrease in estrogen and menopause. This dramatic decline in estrogen has been associated with a higher cardiometabolic risk (26, 27). This may explain why HRT does not have a protective effect in UC patients, and even showed toxic effects on blood vessels in this study.

In this study, the UC survivors all had common risk factors for lower limb PAD, such as smoking, obesity, hypertension, and diabetes. Previous studies have reported that hypertension is a major risk factor for PAD regardless of age (2). In addition, the prevalence of PAD has been shown to increase with age and to be higher in people with metabolic syndrome and diabetes (15). We also found that the influence of diabetes and hyperlipidemia was more prominent in the young group. This may be because young UC patients usually have type I endometrial cancer, which is associated with obesity and metabolic syndrome. These are common risk factors for symptomatic PAD and can lead to chronic atherosclerosis (4, 15)

There are several strengths to this study. The first study examining RT effect on long-term UC survivors, and the use of a nationwide database allowed for a large sample size, homogeneous population, and long follow-up period. In addition, we could evaluate the temporal relationship regarding the use of HRT. Nevertheless, the major limitation is that data on other covariates including body mass index, use of contraceptives, self-pay medications, reproductive history, smoking status, details of treatment such as volume of radiation are not provided in NHIRD. We also lacked information of histology and staging at the initial diagnosis, which are major factors for survival. However, endometrial adenocarcinoma comprises approximately 90% of all UC (4) and we only included patients who had surgery alone or surgery combined with adjuvant RT, which are the main treatments for loco-regional disease.

Conclusions

We used a nationwide population-based database to explore the risk of PAD among long-term UC survivors. Among them, the correlation between adjuvant RT and PAD was far weaker than the correlations of hypertension, diabetes, and long duration of HRT. Therefore, young patients should pay special attention to monitoring PAD when using HRT. The development of PAD is an important risk factor for severe vascular diseases, such as ischemic stroke and coronary artery disease. Consequently, future survivorship care should include PAD as a late complication to ensure proper prevention and management.

Abbreviations

UC, uterine cancer; RT, radiotherapy; PAD, peripheral arterial disease; SEER, Surveillance, Epidemiology, and End Results; US, United States; HRT, hormone replacement therapy; RCI, Registry of Catastrophic Illness; LHID, Longitudinal Health Insurance Database; NHIRD, National Health Insurance Research Database; NHI, National Health Insurance; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; GEE, generalized estimating equations; HR, hazard ratios; aHR, adjusted HR; Institutional Review Board (IRB)

Declarations

Ethics approval and consent to participate: This study was approved by the Institutional Review Board of Chang Gung Medical Foundation (201600205B0). The IRB approves the waiver of the informed consent form.

Consent for publication: Not applicable.

Availability of data and material: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest/Competing interests: The authors have no relevant financial or non-financial interests to disclose.

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