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Estrogen decrease coronary artery disease risk in patients with cervical cancer after treatment

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ABSTRACT

Background. The purpose of this study was to explore the possible association between coronary artery disease (CAD) risk and cervical cancer.

Methods. We used data from the National Health Insurance system of Taiwan to address the research topic. The exposure cohort contained 728 patients with cervical cancer. Each cancer patient was randomly frequency-matched with 4 participants by age, index-month, and index-year from the general population who did not have a cancer history before the index date (control group). Cox's proportion hazard regression analyses were conducted to estimate the relationship between cervical cancer and CAD risk.

Results. Among patients with cervical cancer, the overall risk for developing CADs was significantly lower than that of the control group [adjusted hazard ratio (aHR): 0.57, 95% confidence interval (95% CI): 0.41–0.79]. Further analyses revealed that the lower risk was observed only in patients with older age (aHR: 0.57, 95% CI: 0.40–0.82), a shorter follow-up duration (aHR: 0.47, 95% CI: 0.31–0.72), or with estrogen supplements (aHR: 0.39, 95% CI: 0.22–0.68).

Conclusions. The findings from this population-based study suggest that estrogen supplements are associated with a decreased CAD risk in patients with cervical cancer.

Introduction

Cancer has been the leading cause of death in Taiwan since 1982, and the age-adjusted incidence rate has increased steadily since then [1]. Because of earlier detection, improved diagnostic methods, more effective treatment, improved clinical follow-up after treatment, and an aging population, the proportion of long-term survivors is rising [2]. Consequently, surveillance and monitoring of cancer survivors has become a critical issue, not only for disease control, but also for cancer treatment and treatment-related health problems [3].

Cardiovascular disease is the second leading cause of death in Taiwan [4]. Cancer and cardiovascular disease will be a continuously major healthcare burden to Taiwanese society, and the related issues have aroused concern in the public health. Previous research has revealed higher risks for cardiovascular disease in survivors of some types of cancer; and treatment-related complications, as well as shared daily life risk factors, may contribute to cardiovascular disease [5–9]. We are interested in exploring whether any possible link exists between these 2 major public health threats. Cervical cancer, which is more commonly seen in developing rather than developed countries, is the fifth most common malignancy among Taiwanese women, with an age-adjusted incidence rate of 11.8 per 100,000 women in 2008 [1]. Little information is available regarding cardiovascular disease risk among cervical cancer patients. Maduro et al. discovered that an increased risk of developing a myocardial infarction was observed in a cohort of cervical cancer patients [10]. We are interested in knowing if the coronary artery disease (CAD) risk is also higher

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among Taiwanese women with cervical cancer, and designed a population-based retrospective cohort study to explore this possibility using the database from the National Health Insurance (NHI) system of Taiwan.

Methods

Data resources

This nationwide cohort study was based on the claims data of the universal health insurance program of Taiwan. This insurance program was implemented in 1995, covering more than 96% of the country's population and had contracted with 97% of the hospitals and clinics in Taiwan by the end of 1996. We used claims data from the National Health Insurance Research Database (NHIRD), consisting of registries and claims reported by contracted health care facilities. The NHIRD is managed by the National Health Research Institute (NHRI) in Taiwan, an autonomous organization established by the government and under the supervision of the Department of Health.

We used data subsets composed of one million insurants selected by NHRI using a systematically random sampling method in 2000, from the entire population (approximately 23 million) of enrollees in the insurance program between March 1995 and December 2000. This one million database contained inpatient and outpatient records, medication treatments and beneficiaries information included gender, birthday, living area etc. After creating the data subsets in 2000, it was updated approximately every other year for additional medical records in the subsequent years until December 31, 2009. A more detailed description of the NHIRD was previously described [11].

Study sample

This study design featured a study cohort and comparison cohort. We used the code of International Classification of Disease Diagnoses, Ninth revision (ICD-9-CM) to identify 869 patients with newly diagnosed cervical cancer (ICD-9-CM 180) from January 2000 to December 2008. We excluded patients who had other malignant cancer history (ICD-9-CM 140–208, n = 28) or had a history of CADs (ICD-9-CM 410–414, n = 113) before index date. The index date for the patients with cervical cancer was the date of diagnosed cervical cancer. After the inclusion and exclusion criteria were satisfied, our study cohort included 728 participants with cervical cancer. For the comparison group, we randomly selected 4 enrollees without a history of cervical cancer, with frequency matching of the case group by age, index-month, and index-year of diagnosis, using the same exclusion criteria in the same period.

Study end point

Using the unique patient identification number, we linked study participants to the registry for inpatient and outpatient claims data to identify new diagnoses of CADs as the outcome of this study. To ensure the validity of the diagnosis, only new patients with at least 3 CAD diagnoses to make sure a correct diagnosis during the follow-up period after the index date were eligible end points in the study cohort. We calculated person-years for each study participant until the CAD was diagnosed, or until December 31, 2009, for those censored for loss to follow-up, death, termination of insurance, or other causes.

In addition, we also searched for hypertension (ICD-9-CM: 401–405), diabetes mellitus (ICD-9-CM: 250), and hyperlipidemia (ICD-9-CM: 272) as co-morbidities at the baseline.

Statistical analysis

We compared the distributions of demographics and co-morbidities between cancer patients and non-cancer patients, and statistical significance was tested using the chi-square test. We also calculated the incidence density with person-years using these variables in the study cohort and comparison cohort. The univariate and multivariate Cox's proportion hazard regression analyses were used to estimate the effects of cervical cancer on the risk of CADs, adjusting for variables that were significantly related to cervical cancer from the prior chi-square analyses. The effects of estrogen supplements were then assessed using Cox's proportion hazard regression model. The hazard ratio (HR) and 95% confidence interval (CI) were calculated in the model.

All analyses were performed using SAS statistical software (Version 9.1 for Windows; SAS Institute, Inc., Cary, NC, USA). Results were considered to be statistically significant when two-tailed *P*-values were less than .05.

Results

Table 1 compares distributions of demographics and co-morbidities between the cervical cancer cohort and the comparison cohort. Compared to non-cancer group, cancer patients were more living in rural areas (38.9% vs. 33.4%, $P = .005$), more prevalent to have hyperlipidemia (16.4% vs. 12.9%, $P = .02$), and estrogen supplement (45.9% vs. 15.1%, $P < .0001$).

Table 2 presents the incidence densities and HR of CADs according to age and follow-up duration. Overall, the incidence rate of CADs in the study cohort was lower than in the comparison cohort (11.6 vs. 21.5 per 1000 person-years). The comparison cohort of 50 years of age or older had the highest incidence (33.5 per 1000 person-years).

The multivariate analysis for Cox's proportional regression model revealed that the risk of CADs was significantly lower in the cancer cohort than in the non-cancer cohort (HR = 0.57, 95% CI = 0.41–0.79) (Table 2). Compared with the non-cancer cohort of patients ≥ 50 years of age, the HR of CADs significantly decreased in patients with cervical cancer (HR = 0.57, 95% CI = 0.40–0.82) (Table 2). For the stratified analyses by follow-up duration, the HR of developing CADs was significantly lower in the cancer cohort within 3 years after the index date (HR = 0.47, 95% CI = 0.31–0.72).

Furthermore, the stratification analysis of estrogen supplements regarding the risk of CADs in association with cervical cancer is presented in Table 3. Compared to people without cancer and were not treated with estrogen supplement, patients with cervical cancer had lower risks but only for cervical cancer patients treated with estrogen supplement had a significantly lower risk for CADs (HR = 0.39, 95% CI = 0.22–0.68) (Table 3).

Table 1
Demographics and comorbidity of cervical cancer.

Variable	Comparison group N = 2912		Patients with cancer N = 728		*P*-value
	n	%	n	%	
Age, year					1.00
20–49	1204	41.4	301	41.4	
≥50	1708	58.7	427	58.7	
Mean (SD)†	54.8	(13.5)	55.0	(13.4)	
Urbanization					0.005
Rural	972	33.4	283	38.9	
Urban	1940	66.6	445	61.1	
Comorbidity					
Hypertension	806	27.7	211	29.0	0.48
Hyperlipidemia	478	16.4	94	12.9	0.02
Diabetes mellitus	287	9.9	67	9.2	0.60
Charlson score					0.53
0	2662	91.4	656	90.1	
1–2	195	6.7	57	7.8	
≥3	55	1.9	15	2.1	
Estrogen supplement	441	15.1	334	45.9	<0.0001

Chi-square test. †: SD, standard deviation.

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Table 2
Incidence and hazard ratio for CADs among age group and follow-up year.

	Comparison group N = 2912			Patients with cancer N = 728			Crude HR	(95% CI)	Adjusted HR	(95% CI)
	Person-years	CADs case	Incidence	Person-years	CADs case	Incidence				
Overall	14,564	313	21.5	3357	39	11.6	0.53	(0.38–0.74)***	0.57	(0.41–0.79)***
Age, year										
20–49	6589	46	7.0	1516	5	3.3	0.46	(0.18–1.16)	0.45	(0.18–1.14)
≥50	7975	267	33.5	1841	34	18.5	0.55	(0.38–0.78)***	0.57	(0.40–0.82)***
Follow-up duration (year)										
≤3	7507	227	30.2	1773	24	13.5	0.44	(0.29–0.67)***	0.47	(0.31–0.72)***
>3	7057	86	12.2	1584	15	9.5	0.78	(0.45–1.35)	0.82	(0.47–1.42)

Incidence, per 1000 person-years.
HR, hazard ratio.
Adjusted HR model: adjusted for age and hyperlipidemia.
*$P<0.05$, **$P<0.01$, ***$P<0.0001$.

The effect of different types of estrogen supplement was presented in Table 4. The incidences of CADs in cancer group were lower than controls in each medication group. Compared to control group, the risk of CADs was significantly lower only in "only estrogen" group (HR = 0.36, 95% CI = 0.18–0.72). Compared to none treatment group, people only treated with estrogen had a marginally lower risk, but the difference is not significant.

Discussion

We would like to know if patients with cervical cancer have a higher risk of developing CADs when compared to the general population without cancer. However, the results from this population-based cohort study indicated a reverse trend and showed that the overall CAD risk was significantly lower in the cervical cancer cohort. Sub-analyses revealed that the significantly lower risks were only seen in the patient group with older age, shorter follow-up duration, or estrogen supplement.

The age-adjusted cancer incidence rate in Taiwan has increased steadily, and in 2008, 297 new cases per 100,000 individuals resulted in the general population [1]. This trend is different from that of the U.S., where data from Surveillance Epidemiology and End Results showed that the overall cancer incidence rate decreased by 0.7% per year between 1999 and 2006 [12]. Because cancer continues to be a public health challenge in Taiwan, it has come to the attention of the government, resulting in population-based investigations regarding cancer-preventive epidemiology, as well as quality of life issues for cancer survivors. The NHI program provides comprehensive healthcare coverage, and the NHIRD contains data on ambulatory service records, hospital service records, and prescription claims. This database enabled us to select and examine patients who represented the underlying population. Previously, we used the data to evaluate the risk of malignancy for patients with various possible risk factors (e.g., diseases or medications), and discovered some compelling findings, which have been published or accepted for publication [13–15]. Because of the advance in cancer diagnosis and treatment, increasingly more cancer victims can now survive longer. We also aim to explore the risk of developing particular types of disease among the increasing number of cancer survivors. The current study used a similar design with a reverse direction (cancer is a risk factor instead of an end point) in attempting to determine whether survivors of cervical cancer are at a higher risk of developing CADs.

Table 1 revealed a significantly higher incidence of cervical cancer in the rural area. People living in the areas of higher urbanization levels may have been more frequently screened for cancer and more carcinoma in situ (CIS) diseases are supposed to be detected. CIS is not counted as a cervical cancer in the cancer registry, and then lower incidence rate of cervical cancer can be expected; however, due to the limitation of the database, it is difficult to verify from this study. We also found a significantly higher prevalence of estrogen supplement for cervical cancer patients, and it is not difficult to understand because surgical menopause in some young patients may make them start estrogen immediately to prevent the early menopause-related symptoms.

Previous studies have endeavored to discover a higher risk of cardiovascular diseases in some types of cancer. Cancer treatment with radiotherapy (RT) and/or chemotherapy (CT) may be associated with this excess risk [6,16–19]. Data regarding cardiovascular disease risk and cervical cancer are sparse [10,20]. Maduro et al. evaluated the risk of cardiovascular events in 277 patients with cervical cancer treated with RT or chemoradiation and found an increased risk for myocardial infarction. Whether this increased standardized incidence ratio is treatment-related or indicates a shared risk factor cannot be concluded [10]. Our results unexpectedly revealed a significantly lower risk of CADs among Taiwanese women with cervical cancer. Comparing the presence of CAD risk factors between the 2 groups in Table 1, patients with cervical cancer had a significantly lower hyperlipidemia than did the general population without cancer, which may have partially contributed to this result. Explaining why the significant difference is only seen in women ≥ 50 years or with a follow-up duration ≤ 3 years is difficult (Table 2). Only 5 CADs are in cervical cancer patients < 50 years, and the statistical significance is difficult to determine from a relatively small case number. One possible explanation for the lower risk of CADs in patients with follow-up duration ≤ 3 years is that cancer patients are usually eager to change their unhealthy behaviors (e.g., cigarette smoking, unhealthy diet, less regular exercise) immediately when

Table 3
Incidence and hazard ratio for CADs by estrogen supplement.

Cervical cancer	Estrogen supplement	N	Person-years	CADs case	Incidence	HR	(95% CI)	HR	(95% CI)
No	No	2471	11,869	264	22.2	1.00	(Reference)		
No	Yes	441	2696	49	18.2	1.05	(0.76–1.43)		
Yes	No	394	1432	26	18.2	0.74	(0.49–1.10)	1.00	(Reference)
Yes	Yes	334	1926	13	6.75	0.39	(0.22–0.68)**	0.51	(0.25–1.01)

Incidence, per 1000 person-years.
Adjusted model: adjusted for age and hyperlipidemia.
** $P<0.01$.

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Table 4
Incidence and hazard ratio for CADs by medication type.

	Comparison group N = 2912				Patients with cancer N = 728				Adjusted HR (95% CI)			
	N	Person-years	CADs case	Incidence	N	Person-years	CADs case	Incidence	Compared to comparison group		Compared to none	
None	2471	11,869	264	22.2	394	1432	26	18.2	0.73	(0.49–1.09)	1.00	(Reference)
Only estrogen	332	1935	34	17.6	294	1702	12	7.05	0.36	(0.18–0.72)**	0.74	(0.54–1.02)
Estrogen and progesterone	109	761	15	19.7	40	223	1	4.48	0.21	(0.03–1.61)	0.97	(0.58–1.61)

Incidence, per 1000 person-years.
HR, hazard ratio.
Adjusted HR model: adjusted for age and hyperlipidemia.
*$P<0.05$, **$P<0.01$, ***$P<0.0001$.

they are diagnosed with cancer, and the change may decrease the risk of subsequent CADs. When cancer is controlled temporarily, patients are less likely to strictly follow the "more healthy" behaviors.

The estrogen supplement, by contrast, has a more plausible interpretation for the results shown in Tables 3 and 4. Two observational studies have indicated that postmenopausal patients who receive hormone therapy (HT) have a lower rate of cardiovascular disease and cardiac death than those who do not receive it, thus suggesting the cardiovascular benefits of estrogen [21,22]. Our result is compatible with this finding. Despite being randomized prospective primary and secondary prevention trials, the Heart and Estrogen/Progestin Replacement Study (HERS II) and the Women's Health Initiative (WHI) have suggested that, contrary to expectations, HT may increase the risk of cardiovascular disease [23,24]. The reasons for this paradoxical characterization of HT as both beneficial and detrimental remain undetermined, but a new look at prospective data may indicate that HT has beneficial cardiovascular effects [25].

As the population from the current study is likely to have had surgical menopause and therefore start estrogen alone immediately at the onset of menopause, the newer information from the WHI indicated among postmenopausal women with prior hysterectomy followed up for 10.7 years, estrogen use for a median of 5.9 years was not associated with an increased or decreased risk of CADs [26]. Monkey studies have shown that estrogen deficiency during the premenopausal stage is extremely relevant regarding the progression of atherosclerosis. After several postmenopausal years, however, studies have shown that estrogen has no beneficial effects on atherosclerosis progression and may, in fact, be deleterious [27]. This observation may support our finding of shorter follow-up duration having a lower risk for CADs. However, there was no complete information for duration of medication exposure in the NHIRD database; therefore we cannot get the exact duration of estrogen exposure.

The current study still has limitations that must be addressed. First, the comparative analyses were not adjusted for potential confounders including smoking, drinking behavior, and some types of unhealthy choices because of the inherent shortcomings of the NHIRD database. Smoking is a well-known risk factor for CADs [28], and a higher proportion of smokers among cervical cancer patients has been observed [29]. Other types of unhealthy choices could be risk factors for cervical cancer as well, and could plausibly be associated with CADs. Second, radical surgery for younger women with cervical cancer does not require oophorectomy, and those patients do not need to have estrogen supplement. However, our database cannot clearly determine the surgical types by age group. An earlier study found aggressive characteristics of cervical cancer in young women in Taiwan [30], and oophorectomy may be needed for some young patients with advanced disease. Third, someone concerning the relatively lower CAD rate in the cervical cancer cases is related to patients' cancer death before they could get CADs. In fact, we used the person-years to measure the IR and it can eliminate the factor related to the different survival rates between two groups. The average follow-up durations were 4.61 and 5.00 years in cancer group and control group, respectively. The 5-year survival for patients with invasive cervical cancer (all stages) in Taiwan was 74.8% [31], and we still had enough patients to follow after 5 years. Fourth, the evidence derived from a cohort study is generally of lower methodological quality than that from randomized trials, because a cohort study design is subject to many biases related to adjustment for confounders. Despite our meticulous study design involving adequate control of confounding factors, a key limitation was that bias could still remain because of possible unmeasured or unknown confounders. Nevertheless, apart from these potential problems, the data on cervical cancer and CAD diagnosis were highly reliable.

In conclusion, this population-based retrospective cohort study unexpectedly discovered that patients with cervical cancer have a lower risk of developing subsequent CADs. The underlying mechanism remains unclear, and may be related to estrogen supplements. Additional large-scale studies are required to confirm our findings.

Conflicts of interest

The authors declare that they have no conflict of interest or financial interest invested in this work, either collectively or individually.

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