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Original Article

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Increased cardiovascular disease risk among adolescent and young adult survivors of cervical cancer

Hea Lim Choi [1,2,*] **Danbee Kang** [2,3,*] **Hyunsoo Kim** [3] **Juhee Cho** [2,3,4] **Keun Hye Jeon** [5] **Wonyoung Jung** [6] **Yoo-Young Lee** [7] **Su-Min Jeong** [8,9] **Dong Wook Shin** [2,10,11]

[1]Department of Family Medicine/Executive Healthcare Clinic, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
[2]Department of Clinical Research Design and Evaluation, Samsung Advanced Institute for Health Sciences & Technology (SAIHST), Sungkyunkwan University, Seoul, Korea
[3]Center for Clinical Epidemiology, Samsung Medical Center, Sungkyunkwan University, Seoul, Korea
[4]Department of Epidemiology and Medicine, and Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins Medical Institutions, Baltimore, MD, USA
[5]Department of Family Medicine, CHA Gumi Medical Center, CHA University, Gumi, Korea
[6]Division of Cardiology, Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA
[7]Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[8]Department of Medicine, Seoul National University College of Medicine, Seoul, Korea
[9]Department of Family Medicine, Seoul National University Hospital, Seoul, Korea
[10]Department of Digital Health, Samsung Advanced Institute for Health Sciences & Technology (SAIHST), Sungkyunkwan University, Seoul, Korea
[11]Department of Family Medicine/Supportive Care Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

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Correspondence to
Dong Wook Shin
Department of Family Medicine/Supportive Care Center, Samsung Medical Center, Sungkyunkwan University School of Medicine; Department of Clinical Research Design and Evaluation, Samsung Advanced Institute for Health Science & Technology (SAIHST), Sungkyunkwan University, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea.
Email: dwshin.md@gmail.com

Su-Min Jeong
Department of Medicine, Seoul National University College of Medicine, 1 Gwanak-ro, Gwanak-gu, Seoul 08826, Korea.
Email: smjeong.fm@snu.ac.kr

*Hea Lim Choi and Danbee Kang contributed equally to the article.

ABSTRACT

Objective: To investigate the incidence and risk factors of cardiovascular disease (CVD) in adolescent and young adult survivors of cervical cancer.
Methods: This retrospective cohort study used data from the Korean National Health Insurance Service. Adolescent and young adult (AYA) cervical cancer survivors (n=7,803) were matched with non-cancer controls (n=23,327) using 1:3 propensity score matching, and hazard ratios (HRs) for CVD were determined using Cox regression models. Multivariable Cox regressions were used to assess CVD incidence according to cancer treatment and identify risk factors.
Results: A total of 7,803 AYA survivors with cervical cancer were analyzed in this study during a median 8.9 years of follow-up. They developed any CVD with an adjusted HR of 1.47 (95% confidence interval [CI]=1.33–1.62) compared with the non-cancer controls. Those who underwent concurrent chemoradiotherapy had markedly elevated risks of heart failure (subHR=2.66; 95% CI=1.24–5.72), ischemic heart disease (subHR=1.78, 95% CI=1.11–2.86), deep vein thrombosis (subHR=15.32; 95% CI=9.16–25.63), and pulmonary embolism (subHR=14.99; 95% CI=6.31–35.62). Diabetes, hypertension and chemoradiation therapy were identified as potential risk factors that increase the risk of CVD by 1.55-fold, 1.62-fold and 2.64-fold, respectively.
Conclusion: These findings indicate a need to pay increased attention to cardiovascular health management in adolescent and young adult cervical cancer survivors, particularly those treated with chemoradiotherapy.

Keywords: Adolescent Health; Cervical Cancer; Cardiovascular Disease; Young Adult

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ORCID iDs
Hea Lim Choi
https://orcid.org/0000-0001-9021-5870
Danbee Kang
https://orcid.org/0000-0003-0244-7714
Hyunsoo Kim
https://orcid.org/0000-0001-5241-289X
Juhee Cho
https://orcid.org/0000-0001-9081-0266
Keun Hye Jeon
https://orcid.org/0000-0003-2294-0637
Wonyoung Jung
https://orcid.org/0000-0003-4749-4637
Yoo-Young Lee
https://orcid.org/0000-0001-5902-9877
Su-Min Jeong
https://orcid.org/0000-0001-9588-1928
Dong Wook Shin
https://orcid.org/0000-0001-8128-8920

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

Data Availability
The data that support the findings of this study are available from the National Health Insurance Service (NHIS), but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. However, the data are available from the authors upon reasonable request and with permission from the NHIS.

Author Contributions
Conceptualization: C.H.L., K.D., C.J., J.K.H., J.S.M., S.D.W.; Data curation: C.H.L., K.D., K.H., C.J., J.S.M.; Formal analysis: C.H.L., K.D., K.H., C.J.; Funding acquisition: J.S.M.; Investigation: C.H.L., K.D., C.J., J.K.H., J.S.M., S.D.W.; Methodology: K.D., K.H., C.J.; Project administration: S.D.W.; Resources: K.D.,

Synopsis
This study reports a 47% increase in cardiovascular disease risk among adolescent and young adult cervical cancer survivors compared to non-cancer controls. Those who received chemoradiotherapy had an increased risk of heart failure, ischemic heart disease, and venous thromboembolism, emphasizing the need for targeted cardiovascular care.

INTRODUCTION

Cervical cancer is one of the most common cancers among females globally. Although the overall incidence of cervical cancer has declined in many countries, it remains a serious health problem, particularly in low- and middle-income countries. In 2022, approximately 660,000 new cases of cervical cancer were reported worldwide, with about 88% occurring in low- and middle-income countries [1,2]. The increasing incidence of cervical cancer among adolescents and young adults (AYAs) is also noticeable [3,4].

The age range of 15–39 years was selected based on the definition of AYA cancer patients outlined by organizations like the National Cancer Institute and the World Health Organization. This population represents a unique demographic within oncology due to the biological, psychosocial, and survivorship challenges they face, which differ from other age groups [5-7]. According to Surveillance, Epidemiology, and End Results Program report from 2017–2021 [8], 13.8% of new cervical cancer cases globally were among young patients, and in South Korea, the incidence rate of cervical cancer patients in their 20s and 30s rose to 20%–50% between 2013 and 2016 [9]. This trend is attributed to societal changes and earlier sexual experiences among young Korean females. In response, South Korea adjusted the age of eligibility for free cervical cancer screenings from 30 to 20 starting in 2016, aligning with the age recommended by the Centers for Disease Control and Prevention in the United States [10].

While advancements in chemotherapy (CTx), radiation therapy (RT), and surgical techniques have reduced cancer-related mortality, many cervical cancer survivors still experience early mortality due to comorbidities or other health complications, which may be indirectly related to cancer or its treatment [11]. In South Korea, young cervical cancer patients generally show a better 5-year relative survival rate than their older counterparts, highlighting the importance of addressing non-cancer comorbidities [12]. Cardiovascular disease (CVD)-related mortality and morbidity among AYA patients with cervical cancer are critical factors in determining their long-term prognosis [13], especially when they survive the cancer. CVD encompasses a range of conditions, including ischemic heart disease, heart failure (HF), stroke, and other vascular disorders. The relationship between cancer treatments and cardiovascular toxicity is well-established, particularly with therapies such as CTx and radiotherapy, which have been shown to increase the risk of CVD through mechanisms such as direct myocardial damage, endothelial dysfunction, and accelerated atherosclerosis [14-16].

Despite the different treatment approaches for cervical cancer in young adults—such as efforts to preserve ovarian function—the effects of these treatment on CVD risk among AYA cervical cancer survivors still require further investigation. Prior studies have generally lacked adequate follow-up periods [17] or sufficient sample sizes [18] and have primarily focused on Caucasian patients [17,18]. A recent cohort study in Korea [19] found no higher CVD risk in

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gynecological cancer survivors than in the general population but did not specifically analyze cervical cancer among AYA patients. Therefore, this study investigates the risk of CVD in AYA cervical cancer survivors and further evaluate the risk according to treatment modality.

MATERIALS AND METHODS

1. Data sources

We performed a retrospective, population-based cohort study using data from the Korean National Health Insurance Service (K-NHIS) from 2005 to 2020. Korea has a mandatory social insurance system with insurance premiums determined by income level and not by health status. The K-NHIS is the single insurer in Korea and covers approximately 97% of the population, with the remaining 3% being beneficiaries of the Medical Aid Program. Data on the use of medical facilities and records of prescriptions with International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) diagnosis codes are gathered by the NHIS. The K-NHIS claims database also includes information on demographics, medical treatments, procedures, prescription drugs, diagnostic codes, and hospital use. Vital status and causes of death were obtained from death certificates collected by Statistics Korea at the Ministry of Strategy and Finance of South Korea [20]. Use of the K-NHIS database was approved by the NHIS review committee. The Institutional Review Board of Samsung Medical Center (SMC) approved this study and waived the requirement for informed consent because the K-NHIS data were de-identified (SMC 2022-03-028).

2. Study population

We included Korean adults aged 15–39 years between 2006 and 2019. Data access is restricted by the NHIS's data share policy; we selected all patients with cancer, defined as the presence of an ICD-10 code C or the special copayment reduction code for cancer (V193), between 2006 and 2019 and a 4 times larger sample of age- matched adults who did not develop cancer during the study period (n=3,352,310). To select newly diagnosed cancer as the exposure and incident cases of CVD as the outcome, we excluded 109,269 participants who had any cancer (n=45,732) or any CVD (n=66,317) before January 1, 2006.

Among the AYA cancer survivors, we selected cervical cancer (ICD-10: C53) survivors, defined as those who underwent cervical cancer surgery alone, surgery combined with radiotherapy or concurrent chemoradiotherapy (CCRT), or CCRT alone. Those who underwent CTx for exclusively palliative purposes were excluded.

In this study, we chose to emulate a target trial sequentially, as a series of nested cohorts [21,22]. We began with the initially eligible participants (n=3,243,041), and every 6 months, if a patient was eligible for our target cohort (still without cancer or CVD and alive in the previous 6 months), we created a copy of that patient. Thus, the number of cloned patients aged 15–39 years between 2006 and 2019 was 62,985,785. We checked every 6 months to see if the participants were eligible until June 1, 2019. Then we excluded participants who had any cancer (n=1,570,072) or a history of CVD (n=1,859,670) at each baseline (n=59,561,447). As all participants were females with cervical cancer, we only included women in the data set (n=35,746,969) and then generated propensity score (PS) and selected the control group at a 1:3 ratio using PS matching (control: 23,327; cancer: 7,803) (**Fig. 1**). The detailed methods for the sequential cohort design process are presented in **Fig. S1**.

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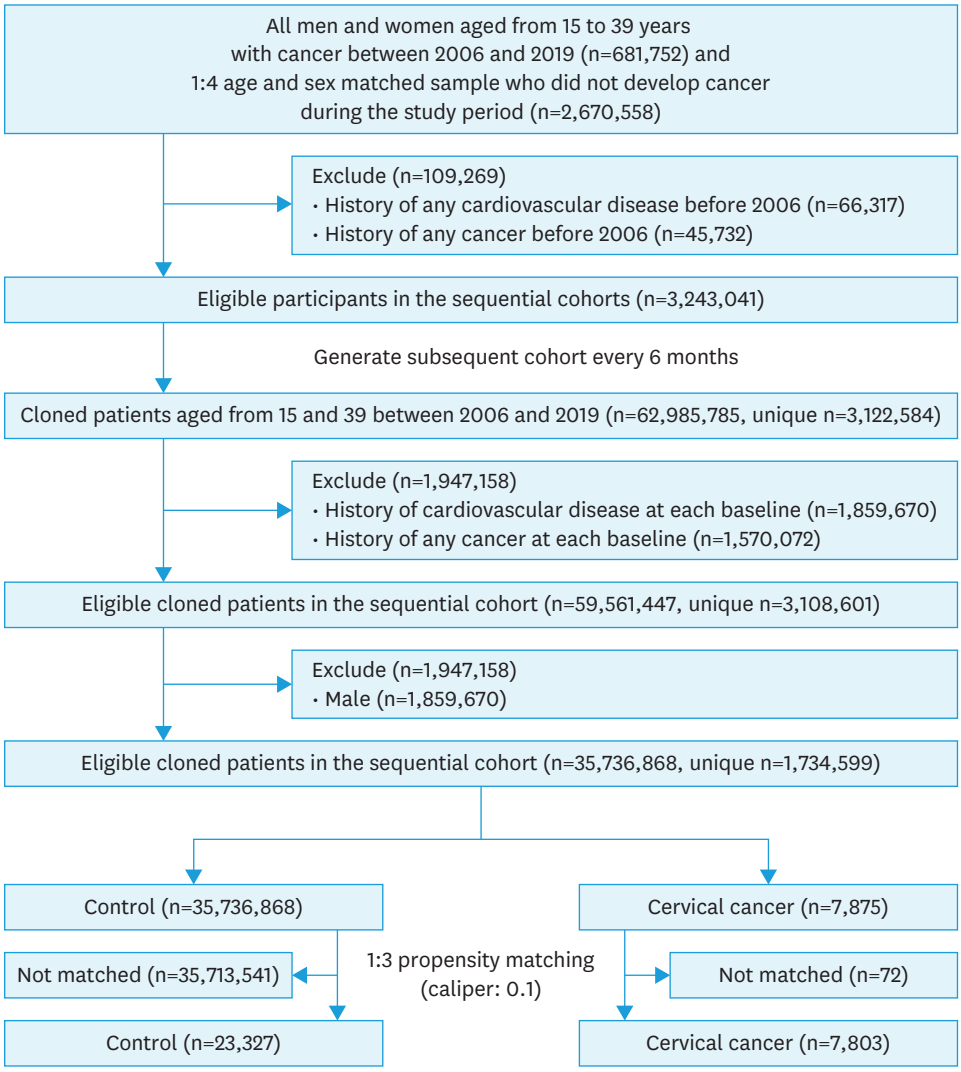

Fig. 1. Flow chart of study population selection.

3. Definition of AYA cervical cancer survivors

The main exposure was an incidence of cancer between 15 and 39 years old. To define incident cancer, we used a special registration code V193 in addition to the ICD-10 diagnosis code. The NHIS has established a special co-payment reduction program to enhance health coverage and relieve the financial burden of patients with cancer. Once cancer patients are registered in the system, they pay only 5% of the total medical bill incurred for cancer-related medical care. Because enrollment in this co-payment reduction program is indicated by a special co-payment reduction code for cancer (V193) and requires a medical certificate from a physician, the cancer diagnoses included in this study are considered to be sufficiently reliable. This method has been used in previous studies [23].

4. Study outcomes

The primary endpoint was a composite of any cardiac outcome (myocardial infarction [MI], stroke, HF, ischemic heart disease, cerebrovascular disease, atrial fibrillation, arrhythmia, cardiomyopathy, valvular heart disease, venous thromboembolism [VTE]). The cardiovascular

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outcomes were identified by diagnostic records (ICD-10 codes) from both outpatient visits and hospitalizations (**Table S1**).

5. Covariates

For the covariates, we included age, sex, comorbidities, income, and residential area at baseline. Co-morbidities during the year prior to baseline were obtained from claims data and defined using ICD-10 codes. Data on income at the time of the first screening exam was obtained from the insurance eligibility database. Income level was categorized by percentile groups (≤30th, >30th–≤70th, and >70th percentile). Residential area at the time of the first screening exam was classified as metropolitan or rural. Metropolitan areas were defined as Seoul, 6 metropolitan cities, and 15 cities with a population >500,000 that have been officially designated as municipal cities.

6. Statistical analysis

The participants were classified into 2 groups based on whether they developed cervical cancer or not. In this process, we performed logistic regression to generate PS scores, and the covariate of PS included age, sex, income, residential area, and the presence of comorbidities (diabetes mellitus, hypertension, and hyperlipidemia) at cohort entry. We then performed PS matching at a 1:3 ratio using greedy matching methods with a caliper <0.1 and no replacement. The standardized mean difference (SMD) between the cervical cancer and control groups was estimated to compare the distribution of variables used for matching. The variables used for matching were updated based on the first date of each subsequent cohort.

The primary endpoint was the development of CVD. Each endpoint was analyzed separately, and for each endpoint analysis we included only participants who had not experienced that endpoint prior to that cohort. We followed the participants from the baseline of each subsequent cohort until the development of CVD, death, or December 2020, whichever occurred first. After completing all the processes, we pooled the data from all trials into a single model and included the baseline day of each cohort.

The cumulative incidence of each outcome was estimated using the Kaplan-Meier method, and log rank tests were applied to evaluate differences between groups. We calculated hazard ratios (HRs) with 95% confidence intervals (CIs) for the incidence of clinical outcomes using a Cox regression model with robust variance estimators to adjust for within-pair dependence. Covariates with SMD >0.1, which can provide evidence of an imbalance between matched groups, were adjusted for the survival analysis. We examined the proportional hazards assumption using plots of the log(-log) survival function and Schoenfeld residuals.

In the sensitivity analysis to account for competing risks due to mortality, we fitted a proportional sub-distribution hazards regression model [24] with death as the competing event. In the subgroup analysis, we analyzed the incidence of CVD by types of cancer treatment. For this analysis, the control group consisted of all participants without cancer at baseline. We also performed a multivariable Cox regression to find risk factors for incident CVD among cervical cancer survivors.

All p-values were 2-sided, and a p-value of less than 0.05 was considered to be significant. Analyses were performed using SAS® Visual Analytics (SAS Institute Inc., Cary, NC, USA) and R 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

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RESULTS

The mean age of the study participants was 34 years (**Table 1**). All SMDs for differences between the control and cervical cancer groups were less than 0.1. Among AYA cervical cancer survivors, 30.8% received CTx, and 34.9% and 30.7% of patients received surgery only or conization only, respectively.

During the follow-up (median 8.0 years), 1,853 participants developed any CVD (**Table 2**). The cumulative incidence of any CVD was consistently higher in AYAs with cervical cancer than in those without cervical cancer during the entire follow-up period (**Fig. 2A**). The HR for any CVD in participants with cervical cancer compared with those without it was 1.47 (95% CI=1.33–1.62). The association remained significant in the competing risk analysis (subHR=1.35; 95% CI=1.23–1.49) (**Table 2**).

When we compared the development of each type of CVD, the cumulative incidence of CVD was consistently higher in participants with cervical cancer than in controls throughout the entire follow-up period. The differences were particularly high for deep vein thrombosis (DVT; **Fig. 2B**) and pulmonary embolism (PE; **Fig. 2C**). Compared with the participants without cervical cancer, the subHRs for DVT and PE for participants with cervical cancer were 6.19 (95% CI=4.43–8.65) and 3.99 (95% CI=2.17–7.35), respectively (**Table 2**).

In the subgroup analysis, AYA cervical cancer survivors who had received both CTx and RT had a higher risk of CVD whether or not they received surgery (Surgery + CTx + RT subHR=1.82, 95% CI=1.51–2.18; CCRT subHR=2.14, 95% CI=1.67–2.75), compared with those who received other treatments. Although the risks of HF, ischemic heart disease, and atrial fibrillation (AF) were higher in cancer survivors than in those without cancer, the risks of DVT

Table 1. Baseline characteristics of study participants before and after 1:3 propensity score matching

Variables	Unmatched			Matched		
	Control (n=35,736,868)	Cancer (n=7,875)	SMD	Control (n=23,327)	Cancer (n=7,803)	SMD
Age (yr)	30.0±6.2	34.3±3.7	0.842	34.3±4.0	34.3±3.7	0.01
Income						
Medical Aid	571,417 (1.6)	117 (1.5)	0.069	335 (1.4)	110 (1.4)	−0.002
≤30th	8,642,677 (24.2)	2,308 (29.3)	0.116	6,744 (28.9)	2,276 (29.2)	0.006
31th–70th	14,856,833 (41.6)	3,475 (44.1)	0.051	10,390 (44.5)	3,447 (44.2)	−0.007
>70th	10,606,922 (29.7)	1,856 (23.6)	−0.139	5,511 (23.6)	1,851 (23.7)	0.002
Residential area, metropolitan	1,035,692 (2.9)	119 (1.5)	−0.095	15,884 (68.1)	5,269 (67.5)	
Comorbidities	24,749,484 (69.3)	5,309 (67.4)	−0.041			
Diabetes, yes				902 (3.9)	281 (3.6)	−0.014
Hypertension, yes	892,838 (2.5)	284 (3.6)	0.064	1,410 (6.0)	473 (6.1)	0.001
Hyperlipidemia, yes	1,607,109 (4.5)	477 (6.1)	0.07	1,716 (7.4)	570 (7.3)	−0.002
Type of treatment						
Conization only				-	2,395 (30.7)	-
Radiotherapy only				-	30 (0.4)	-
Surgery				-	2,726 (34.9)	-
Surgery + RT				-	243 (3.1)	-
Surgery + CTx				-	432 (5.5)	-
Surgery + CTx + RT				-	1,334 (17.1)	-
CCRT (CTx + RT)				-	643 (8.2)	
Conization to surgery (n=4,735)*				-	2,103 (44.4)	-
Cisplatin (n=2,409)†				-	2,397 (99.5)	

Values are presented as number (%) or mean ± standard deviation.
CTx, chemotherapy; RT, radiation therapy; SMD, standardized mean difference.
*Patient who received surgery; †Patient who received chemotherapy.

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Table 2. HRs (95% CIs) for incident cardiovascular disease associated with adolescent and young adult cervical cancer

Variables	No. of cases(1,000 person-years)		Adjusted HR*(95% CI)	SubHR†(95% CI)
	Control	Cancer		
Any cardiovascular disease	1,281 (7.21)	572 (10.54)	**1.47 (1.33–1.62)**	**1.35 (1.23–1.49)**
Ischemic heart disease (I20–I25)	393 (2.16)	146 (2.61)	1.22 (1.01–1.47)	1.11 (0.92–1.34)
Myocardial infarction (I21–I22)	19 (0.10)	7 (0.12)	1.23 (0.519–2.94)	1.10 (0.46–2.62)
Cerebrovascular disease (I63–I69)	345 (1.88)	143 (2.55)	**1.37 (1.13–1.66)**	**1.24 (1.02–1.51)**
Stroke (I60–I64)	139 (0.76)	53 (0.94)	1.25 (0.91–1.71)	1.14 (0.83–1.56)
Ischemic stroke (I63–I64)	99 (0.54)	38 (0.67)	1.26 (0.86–1.83)	1.15 (0.79–1.67)
Hemorrhagic stroke (I60–I62)	45 (0.25)	15 (0.27)	1.09 (0.61–1.95)	1.00 (0.55–1.78)
Heart failure (I50)	103 (0.56)	48 (0.85)	**1.52 (1.08–2.14)**	1.39 (0.99–1.96)
Cardiomyopathy (I42–I43, I23.5)	23 (0.13)	8 (0.14)	1.15 (0.51–2.56)	1.04 (0.46–2.32)
Valvular heart disease (I01–I08, I34–I37)	19 (0.10)	5 (0.09)	0.867 (0.32–2.32)	0.78 (0.29–2.10)
Arrhythmia (I47–I49)	507 (2.80)	190 (3.41)	**1.21 (1.03–1.43)**	1.12 (0.95–1.32)
Arterial fibrillation (I48)	60 (0.33)	23 (0.41)	1.24 (0.77–2.01)	1.14 (0.71–1.85)
Venous thromboembolism				
Deep vein thrombosis (I80.1–I80.3)	51 (0.28)	105 (1.87)	**6.62 (4.74–9.25)**	**6.19 (4.43–8.65)**
Pulmonary embolism (I26)	18 (0.10)	24 (0.42)	**4.21 (2.29–7.76)**	**3.99 (2.17–7.35)**

Values are presented as number (%). Bolded figures indicate a p-value of less than 0.05.
CI, confidence interval; HR, hazard ratio.
*All the covariates including age, sex, income, residential area, and the presence of comorbidities (diabetes mellitus, hypertension, and hyperlipidemia) were well matched.
†SubHRs for events were modeled with mortality as a competing risk.

(Surgery + CTx + RT subHR=12.52, 95% CI=8.17–19.18; CCRT subHR=15.32, 95% CI=9.16–25.63) and PE (Surgery + CTx + RT subHR=10.74, 95% CI=5.08–22.72; CCRT subHR=14.99, 95% CI=6.31–35.62) were particularly increased in survivors who had received both CTx and RT, compared with other treatments (**Table 3**).

Among the cervical cancer survivors, those who underwent surgery and CCRT (HR=1.95; 95% CI=1.53–2.48) or CCRT without surgery (HR=2.64; 95% CI=1.96–3.55) had a higher risk of CVD than others, after adjusting for traditional confounders (**Table 4**).

Table 3. HRs (95% CIs) for incident cardiovascular disease associated with adolescent and young adult cervical cancer by treatment type

Variables	SubHR (95% CI)				
	Conization only	Surgery only	Surgery + CTx + RT	CCRT (CTx + RT)	Cisplatin use
Any cardiovascular disease	1.13 (0.95–1.35)	**1.20 (1.02–1.40)**	**1.82 (1.51–2.18)**	**2.14 (1.67–2.75)**	**1.77 (1.53–2.04)**
Ischemic heart disease (I20–I25)	1.03 (0.74–1.43)	0.88 (0.64–1.20)	1.52 (1.07–2.15)	**1.78 (1.11–2.86)**	**1.43 (1.08–1.88)**
Myocardial infarction (I21–22)	0.55 (0.07–4.11)	0.86 (0.20–3.70)	2.76 (0.82–9.33)	2.06 (0.28–15.34)	2.04 (0.69–6.00)
Cerebrovascular disease (I63–I69)	0.90 (0.62–1.31)	**1.50 (1.14–1.96)**	1.21 (0.80–1.83)	1.59 (0.93–2.71)	1.26 (0.92–1.72)
Stroke (I60–I64)	0.60 (0.29–1.22)	1.29 (0.82–2.02)	1.00 (0.49–2.04)	1.96 (0.92–4.19)	1.39 (0.87–2.22)
Ischemic stroke (I60–I62)	0.21 (0.05–0.85)	1.56 (0.96–2.55)	1.05 (0.46–2.41)	1.97 (0.80–4.82)	1.36 (0.78–2.39)
Hemorrhagic stroke (I63–I64)	1.38 (0.59–3.24)	0.54 (0.17–1.75)	0.77 (0.19–3.18)	1.72 (0.42–7.09)	1.29 (0.55–3.01)
Heart failure (I50)	0.61 (0.27–1.39)	1.34 (0.80–2.25)	**2.04 (1.12–3.71)**	**2.66 (1.24–5.72)**	**2.16 (1.37–3.40)**
Cardiomyopathy (I42–I43, I23.5)	-	1.07 (0.32–3.52)	1.51 (0.36–6.40)	**4.98 (1.50–16.53)**	2.09 (0.76–5.51)
Valvular heart disease (I01–I08, I34–I37)	0.54 (0.07–4.09)	1.72 (0.59–5.02)	-	-	-
Arrhythmia (I47–I49)	1.27 (0.98–1.66)	0.88 (0.67–1.17)	**1.38 (1.00–1.90)**	1.28 (0.79–2.08)	1.28 (0.99–1.65)
Atrial fibrillation (I48)	0.68 (0.25–1.87)	1.38 (0.71–2.71)	2.02 (0.93–4.43)	-	1.45 (0.72–2.91)
Venous thromboembolism					
Deep vein thrombosis (I80.1–I80.3)	1.82 (0.90–3.69)	**4.70 (2.98–7.43)**	**12.52 (8.17–19.18)**	**15.32 (9.16–25.63)**	**12.34 (8.54–17.84)**
Pulmonary embolism (I26)	0.58 (0.08–4.30)	**2.28 (0.84–6.19)**	**10.74 (5.08–22.72)**	**14.99 (6.31–35.62)**	**9.74 (5.07–18.74)**

The non-cancer control group was the reference in all analyses. SubHRs for events were modeled with mortality as a competing risk. Bolded figures indicate a p-value of less than 0.05.
CI, confidence interval; CTx, chemotherapy; HR, hazard ratio; RT, radiation therapy.

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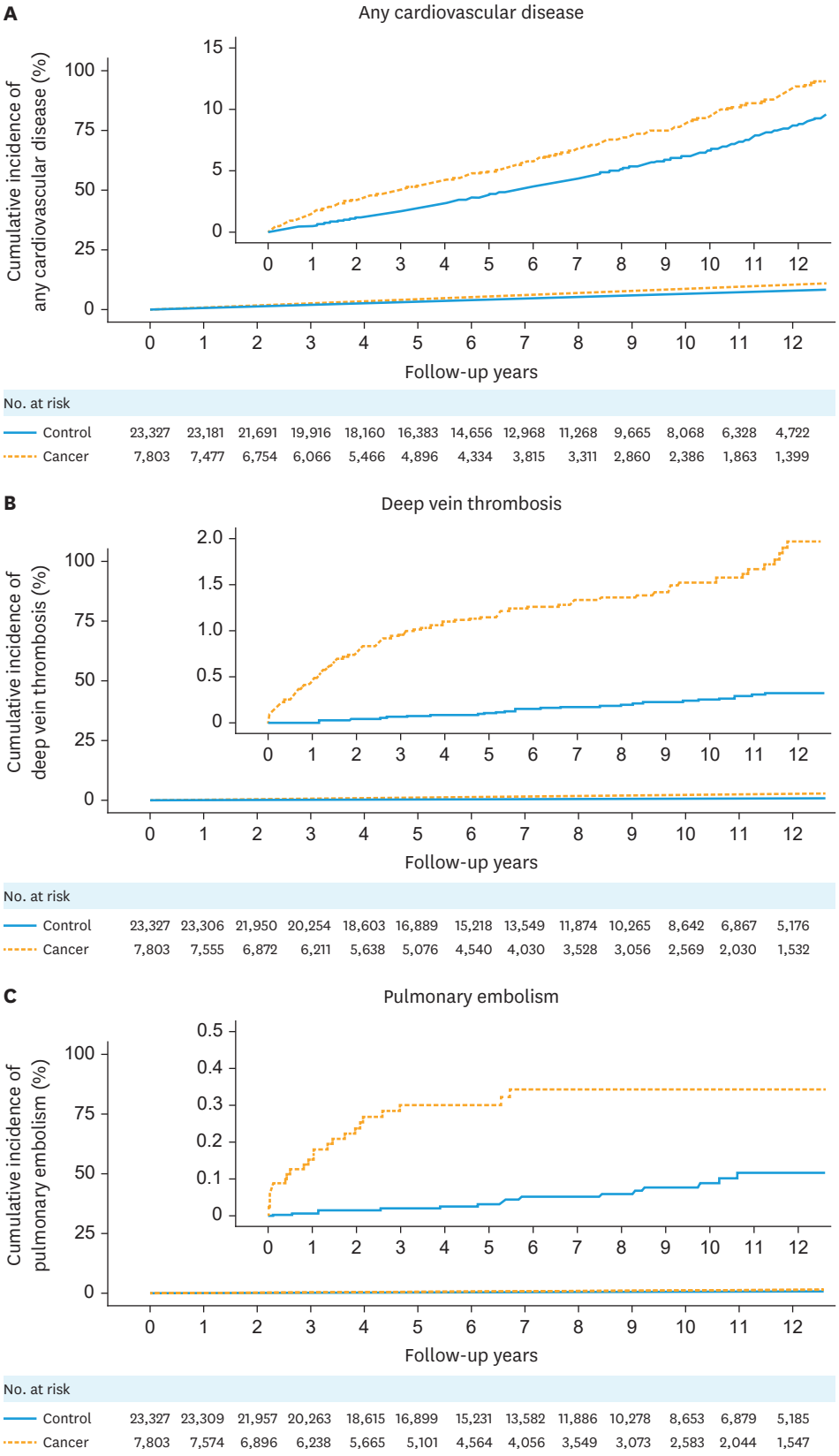

Fig. 2. Kaplan-Meier curves for the incidence of (A) any cardiovascular disease, (B) deep vein thrombosis, and (C) pulmonary embolism.

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Table 4. Risk factors for cardiovascular disease in the adolescent and young adult cervical cancer group

Variables	Crude HR (95% CI)	Adjusted HR* (95% CI)
Treatment		
Conization only	Reference	Reference
Surgery only	1.09 (0.87–1.35)	1.03 (0.82–1.29)
Radiotherapy only	1.43 (0.35–5.79)	1.25 (0.31–5.05)
Surgery + Radiotherapy	1.24 (0.76–2.02)	1.18 (0.72–1.93)
Surgery + Chemotherapy	1.13 (0.76–1.68)	1.12 (0.75–1.66)
Surgery + RT + CTx	2.03 (1.60–2.59)	1.95 (1.53–2.48)
CCRT (CTx + RT)	2.79 (2.09–3.74)	2.64 (1.96–3.55)
Cisplatin (n=2,409)		
No	Reference	Reference
Yes	1.89 (1.60–2.23)	1.87 (1.58–2.21)

CI, confidence interval; CTx, chemotherapy; HR, hazard ratio; RT, radiation therapy.
*Adjusted for age at diagnosis, income, residential area, comorbidities, and the treatments listed in the table.

DISCUSSION

This study revealed that AYA survivors with cervical cancer had a 47% increased risk of CVD, consistently higher than non-cancer controls throughout the entire follow-up period. AYA cervical cancer survivors who underwent conization alone exhibited a 1.21-fold elevated risk of CVD, particularly arrhythmia and DVT. The risk of CVD intensified with more complex treatments, such as exposure to cisplatin CTx, which increased the risk of HF, AF, DVT, and PE.

In contrast to prior studies that reported an increased risk of MI in cervical cancer patients [25,26], we did not find a statistically significant increase in MI risk, likely due to the low number of cases. Previous research suggested that cervical cancer patients undergoing chemoradiation therapy tend to be healthier overall compared to those with other treatments, potentially lowering their risk of MI [27]. We speculate that the lower number of MI cases in our study is due to this better general health among AYA patients undergoing chemoradiation therapy.

Our data show that the risk of cerebrovascular disease, including both ischemic stroke (ICD I63–I64) and cerebrovascular diseases without obstructions (ICD I65–I69), increased by 1.24-fold in AYA cervical cancer survivors. Unlike breast or head and neck cancer which is often associated with a higher stroke risk after radiotherapy [28], reports on stroke risk in cervical cancer patients are scarce, except for a Taiwanese population-based study that showed increased risk after radiotherapy [29]. Therefore, further investigation is needed to elucidate the association between cervical cancer and cerebrovascular disease to fill the gap in knowledge.

In this study, AYA cervical cancer survivors who underwent surgery and CCRT had a 2.04-fold increased risk of HF compared with the control group, and those treated with chemoradiotherapy alone had a 2.66-fold increased risk. Furthermore, those treated with platinum-based CTx exhibited an HR of 2.16, suggesting that the use of cisplatin has a substantial effect. This finding is significant since platinum-based CTx has not been widely reported to be highly associated with heart failure, other than MI or thromboembolic events [30]. The mechanism by which platinum-based CTx induces heart failure is speculated to involve direct damage to myocardial cells and harm to the vascular endothelium, potentially leading to systolic dysfunction [31,32]. Notably, the toxic effects of CTx accumulate over time and are influenced by the timing of treatment. In other words, young patients undergoing

CTx are at a higher risk of developing cardiac dysfunction than older patients due to their continued cancer therapy which results in exceeded capacity for reserve compensatory activity with diminished myocardial contractility [32].

In this study, we report a significant increase in the risk of DVT and PE among AYA cervical cancer survivors, with HRs of 6.19 and 3.99, respectively. Our findings align with previous studies that reported the incidence of VTE among cervical cancer patients [27,33-35]. However, unlike previous studies that observed a plateau in the risk of VTE after about 5 years [27], identified increased age as a risk factor [34], and reported a lower incidence of VTE in Asian patients [36], our data indicate a sustained increase in the risk of DVT and PE among Korean AYAs with cervical cancer. Our findings show that not only surgery, a well known risk factor for VTE, but also surgery plus CCRT and CCRT alone increase the risk of VTE. Given the limited incidence of chemoradiation-induced VTE and the need to further elucidate the mechanism underlying VTE induced by chemoradiotherapy, future investigations are warranted.

Our data also show a 21% increased risk for arrhythmia among AYA cervical cancer survivors, and that risk increased to 38% among those who underwent surgical treatment with CCRT. Platinum-based CTx is reported to cause arrythmia such as atrial fibrillation [30,37,38], and atrial fibrillation is reported to be one of the common early complications following surgery [39]. However, our study did not show an increased risk of either atrial fibrillation or valvular disease due to the small number of cases. Nonetheless, the risk of cardiomyopathy was increased by 4.98-fold in those who underwent CCRT. As previously mentioned, CTx can directly harm myocardial cells and lead to cardiac dysfunction. Consistent with the elevated risk of HF, the increased risk of cardiomyopathy among AYA cervical cancer survivors could have resulted from CCRT.

Our study showed heightened risk of CVD in AYA cervical cancer survivors, particularly those undergoing chemoradiotherapy. Previous studies suggest that even subtle myocardial cell injury in young adolescents could produce marked sequelae compared with those seen in adults, given the longer survival period and the need for subsequent cardiac growth [40]. Therefore, it is crucial to provide tailored cardiovascular health management for AYA cervical cancer survivors.

Furthermore, given that platinum-based CTx-induced cardiotoxicity is quite uncommon, our findings highlight the need for future research to investigate whether cardiotoxicity is more prevalent among younger cancer patients or if there are ethnic differences.

To the best of our knowledge, this is the first large population-based study to investigate the CVD risk of AYA cervical cancer survivors according to their treatment modalities. Nevertheless, our study has several limitations to be considered. First, our reliance on administrative data meant that we lacked detailed clinicopathological information, including cancer stage and histology, and other prognosis-related measures, which may have influenced both treatment options and CVD outcomes. This confounding issue could not be fully addressed, which might have impacted the association between treatment and CVD risk. However, it was possible to make inferences about such details from the information we had about the treatments administered to each patient. Second, the use of claims data introduces the possibility of inaccurate outcome definitions, potentially leading to either an underestimation or an overestimation of the actual incidence. In addition, surveillance bias cannot be ruled out because cancer survivors are more likely than the control group to visit the hospital. Third, this

study focused on Korean individuals, whose AYA cancer incidence patterns might differ from those of Western populations, so it might be difficult to generalize the results.

In conclusion, we investigated the risk of CVD among AYA cervical cancer survivors while emphasizing the effects of treatment modalities on that risk. This study highlights the need for preventive measures and careful monitoring of CVD incidence among AYA cervical cancer survivors.

SUPPLEMENTARY MATERIALS

Table S1

Definition of outcomes

Fig. S1

Study scheme. The sequential cohort design was emulated several times in a sequence of nested cohort, to coincide group assignment and start of follow-up, thus avoiding immortal-time bias. This figure illustrates the construction of the observations in each nested cohort, including their respective group assignment (cancer or not), measurement of confounders, and follow-up. A hypothetical cohort is presented for simplicity. (A) The figure demonstrates the construction of the first emulated cohort. At the initial baseline (cohort 0, C0), no patient had cervical cancer. Therefore, the target cohort was not emulated, as a comparison between patients with and without cancer was not feasible. At cohort 1 (C1), 5 patients (P5 to P9) developed cervical cancer and were compared to the 4 patients (P1 to P4) who did not develop cervical cancer. Group assignment in this cohort was determined based on the patients' cervical cancer status at the start of cohort 1. Baseline confounders for the first nested trial were measured at the beginning of cohort 1 (indicated by the red rectangle). Follow-up for the first emulated trial was restarted at cohort 1 to align with eligibility criteria, group assignment, and time-zero. (B) The figure illustrates the construction of the second cohort. At cohort 2 (C2), 3 patients (P1, P2, and P4) did not develop cancer and 1 patient (P3) developed cervical cancer. Patients who had already developed cervical cancer in the previous nested trial (cohort 1) are no longer eligible for this cohort. In this second nested trial, the treatment assignment for cloned copies of eligible patients was determined based on their cervical cancer status at the beginning of cohort 2 (indicated by the blue rectangle). Baseline confounders for the second nested cohort were measured at this same timepoint. Follow-up was then restarted at cohort 2 for this nested trial. Each of these nested cohort datasets was then combined into a unique dataset comprising cloned copies of participants, assigned group status, reset follow-up, and baseline confounders for each nested cohort. Propensity score matching was applied to the stacked cohort of observations, adjusting for confounders measured at the baseline of each nested cohort. Follow-up continued until the incidence of cardiovascular disease, death or the last available date.

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