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Risk of Pelvic Insufficiency Fractures in Cervical Cancer Survivors: Using the National Claim Database

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ABSTRACT

Background: Cervical cancer, one of the most prevalent cancers among women worldwidely, has seen improved survival rates due to advancements in pelvic radiation therapy (RT). Several risk factors for pelvic insufficiency fracture (PIF) have been reported in patients with cervical cancer. This study aimed to estimate the incidence of PIFs in patients with cervical cancer and assess the potential risk factors for PIF using a national claim database.
Methods: A total of 13,480 cervical cancer patients were identified during 2007 to 2016 from linkage between the Korea National Health Insurance Service and Korea Central Cancer Registry. Patients were identified and divided into PIF and non-PIF groups. The incidence of PIFs was estimated and risk factors for PIFs, including age, type of medical institution, residential area, insurance type, Surveillance, Epidemiology, and End Results summarized stage, RT and comorbidities, were assessed using multivariate Cox proportional hazards regression analysis.
Results: In a cohort of 13,480 patients diagnosed with cervical cancer, PIF occurred in 134 (1.0%). Among the variables, older age (adjusted hazard ratio [aHR], 1.063; 95% confidence interval [CI], 1.047–1.079; $P < 0.001$) and RT (aHR, 1.829; 95% CI, 1.235–2.710; $P = 0.003$) were significantly associated with occurrence of PIF.
Conclusion: The incidence of PIFs in cervical cancer survivors was 1.0% in this national claim database study and it demonstrated that RT and older age were significantly associated with an increased risk of PIF. Our findings suggest that clinicians should be aware of the risk of PIF, especially in older patients who underwent RT.

Keywords: Cervical Cancer; Radiation Therapy; Pelvic Insufficiency Fracture; National Claim Database; Korea

INTRODUCTION

Cervical cancer is one of the most prevalent cancers among women worldwidely.[1] Although screening and vaccination programs have advanced, cervical cancer remains a significant cause of morbidity and mortality in women.[2] In the United States, it is projected that

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Disclosure
The authors have no potential conflicts of interest to disclose.

Data Availability Statement
The data that support the findings of this study are available from Korean National Health Insurance Service (KNHIS). Restrictions apply to the availability of these data, which were used under license for this study from KNHIS. Data may be available from KNHIS with an additional permission for this study from them.

Author Contributions
Conceptualization: Lee YK, Yoon BH. Data curation: Lee YK, Bak JK. Formal analysis: Yoo BN. Funding acquisition: Lee YK, Bak JK. Investigation: Chung YK. Methodology: Jeon YJ. Software: Jeon YJ. Validation: Park JW. Visualization: Yoo BN. Writing - original draft: Park KT. Writing - review & editing: Park KT, Park JW.

2,001,140 new cancer cases and 611,720 cancer-related deaths will occur in 2024.[3] Radiation therapy (RT) is an important treatment for locally advanced cervical cancer, and it also decreases the risk of recurrence and improves overall survival rates.[4]

Despite its efficacy, however, it is also associated with various complications in the pelvic region, including gastrointestinal, genitourinary, hematologic, and skeletal complications.[5] Especially, radiation-induced pelvic insufficiency fracture (PIF) has a significant impact on the quality of life and morbidity in cervical cancer patients, because it is a type of stress fracture that is hard to be healed.[6,7] The incidence of these fractures in patients with pelvic malignancies has been widely reported to range from 1.7% to 45.2%.[8-13]

However, PIF in cervical cancer patients is often underestimated and little known, because it is difficult to diagnose and differentiate from bone metastasis.[14] This study aimed to estimate the incidence of PIFs in cervical cancer survivors and assess the potential risk factors for PIF using a national claims database.

METHODS

Data source and linking

Our analysis was based on data obtained from the Korean National Health Insurance Service (KNHIS) and the Korea Central Cancer Registry (KCCR). The majority of Koreans (97%), except for Medicaid beneficiaries, are covered by mandatory universal health insurance. The KNHIS database comprehensively documents all information related to reimbursements for outpatient visits and hospital admissions.[15] This includes medical diagnoses classified according to the International Classification of Diseases, 10th revision (ICD-10), as well as procedures, prescriptions, and associated costs. Furthermore, the database records beneficiary qualification details, such as age, monthly insurance premiums (used as an indicator for household income status), and disability status.[16]

The Korean Ministry of Health and Welfare established the KCCR to systematically collect data on cancer incidence and to facilitate the provision of insurance benefits to cancer patients. All cancer cases in Korea are registered in the KCCR, with diagnoses based on the ICD-10 classification. Since 1999, the KCCR has systematically produced population-based cancer incidence data, and "Cancer Incidence in Five Continents, Vol. 9" was published based on the KCCR database from 1999 to 2002, emphasizing the dataset's completeness and validity.[17] The cancers recorded in the KCCR were classified based on the International Classification of Diseases (ICD) for Oncology, 3rd edition. The KCCR dataset includes comprehensive patient information such as age at diagnosis, cancer-specific details including date of diagnosis, tumor site, histological type, Surveillance, Epidemiology, and End Results (SEER) summarized stage, as well as information for first-line treatment such as surgery, chemotherapy, and RT.[18] For determining multiple primary cancers, the definitions provided by the International Agency for Research on Cancer were adhered. These two databases were integrated by cross-referencing with patient personal information (name, date of birth).[19]

Study population: identification of eligible patient

We included 22,735 patients who were diagnosed with cervical cancer by ICD-10 code (C530, C539) between January 1, 2007, and December 31, 2016. We excluded patients with distant metastasis or unknown SEER summarized stage data (n = 3,763), patients with

previous osteoporosis medication history (n = 1,988), those who were diagnosed with other cancers during the study period (n = 1,112), and those who died within 6 months of cervical cancer diagnosis (n = 991). We also excluded patients with a previous medication history of glucocorticoid for more than 90 days (n = 964), patients with recurrence of cervical cancer within the study period (n = 147), and those with a previous history of PIF as main or sub-diagnosis (n = 131). Additionally, we excluded patients with registration without a diagnosis date (n = 48), duplicate registration of death in the same ID (n = 27), duplicate and incorrect registration of cancer registration data (n = 22), and those within the wash-out period of 1 year in 2007 (n = 2,475).[20,21] In total, 13,480 cervical cancer patients were included in the analysis (**Fig. 1**).

Outcome measures

The primary outcome of this study was the incidence of PIFs in cervical cancer survivors. PIFs were defined as patients having ICD-10 codes for pelvis fracture (S321, S323, S324, S325, S326, S328, S329, M484, M843, and M849) when they were hospitalized or visited the emergency room. RT was identified by using procedure codes (HD061, HD081, HZ271, HD022, HD052, HD053, HD054, HD055, HD056, HD057, HD058, and HD059) corresponding to RT.

To assess risk factors associated with fracture, we examined the following variables: age at diagnosis, type of medical institution (hospital, general hospital, or tertiary hospital), residential area (urban or rural), insurance type (self-employed/employee insured or Medical-aid beneficiary), income level (quintile distribution), SEER summarized stage (localized or regional), RT status, medical comorbidities, and Charlson Comorbidity Index (CCI).

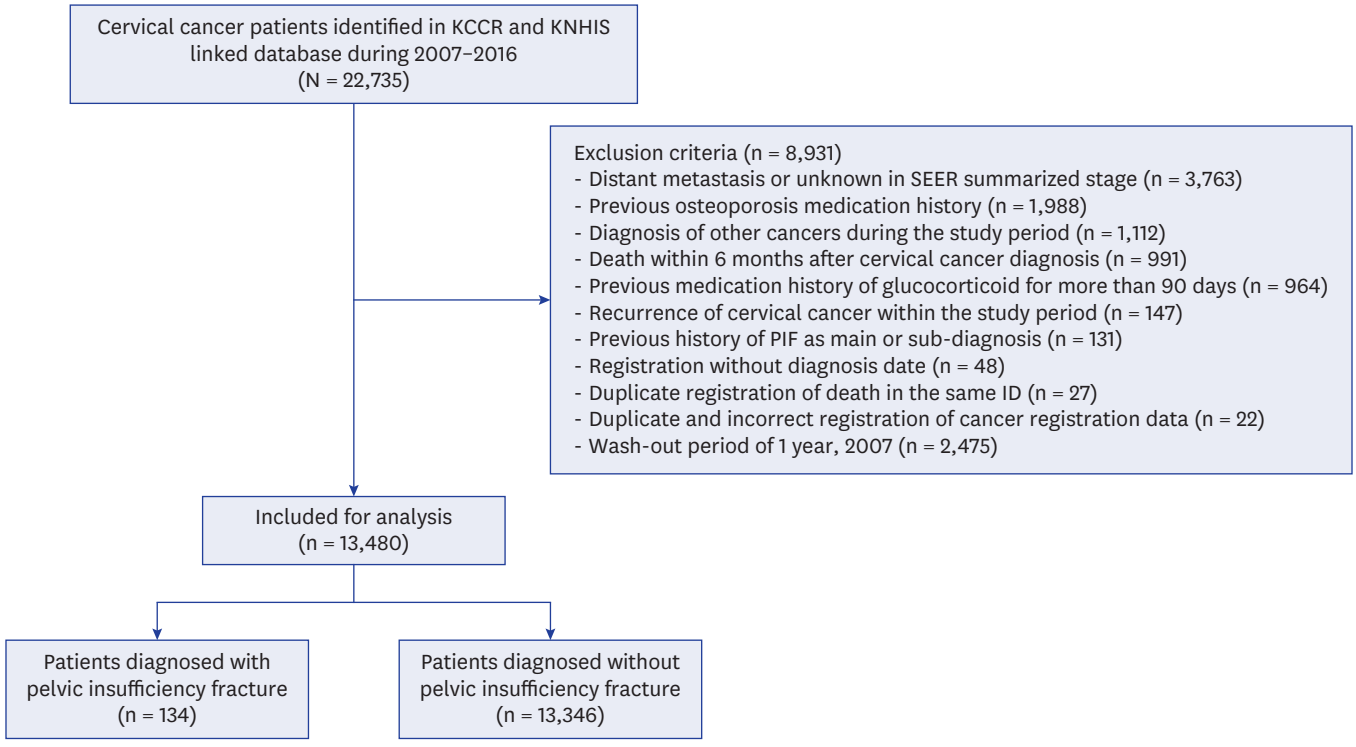

Fig. 1. Flow chart for the selection of the study population.
KCCR = Korea Central Cancer Registry, KNHIS = Korean National Health Insurance Service, SEER = Surveillance, Epidemiology, and End Results, PIF = pelvic insufficiency fracture.

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Patients were enrolled in this study cohort on the date of their cervical cancer diagnosis and were followed up until the first occurrence of a fracture, death, censoring, or the end of the study period on December 31, 2016.

Statistical analysis

Baseline characteristics of the study population were assessed using descriptive statistics. The χ^2 tests were used to analyze differences in categorical variables (e.g., age group, type of medical institution, urbanity, insurance type, income level, SEER summarized stage, RT status, and comorbidities) based on the occurrence of PIF. Independent *t*-tests were also employed to compare the means of continuous variables (e.g., age and CCI) between two groups. A Cox proportional hazards regression model was employed to analyze factors associated with PIF in cervical cancer survivors. The confounding factors were considered, including age at diagnosis, type of medical institution, residential area, insurance type, SEER summarized stage, RT status, and comorbidities. The assumption of proportional hazards was assessed before all analyses. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). The *P* values < 0.05 indicated statistical significance.

Ethics statement

As this was a retrospective study only utilizing the patient data that were already acquired from the routine treatment process, the consent to participate and study protocol was exempted by the Institutional Review Board (IRB)/Ethics Committee of Seoul National University Bundang Hospital of Korea (IRB No. X-1801-447-908) because it did not involve human subjects, and all data provided by the KCCR and KNHIS were anonymized. And this study was conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

Characteristics of the study population and incidence of PIFs

A total of 13,480 cervical cancer survivors were included in the final analysis. The average age at diagnosis of cervical cancer was 49.3 ± 12.4 years. In a cohort of 13,480 patients with cervical cancer, 134 patients of PIFs were identified, resulting in an incidence rate of 1.0%. Among the 3,020 patients who underwent RT, 39 patients (1.3%) had PIFs. There was no difference in the incidence of PIFs by medical institution ($P = 0.846$), residential area ($P = 0.607$), and income level ($P = 0.133$).

However, patients with medical-aid beneficiary showed a higher risk of PIFs than patients with self-employed or employee insured. Patients with regional stage had a higher risk of PIF than localized disease ($P = 0.005$). The RT showed a marginal level of significant tendency for the occurrence of PIF ($P = 0.061$). There was a significant difference in the occurrence of PIF among patients with ischemic heart disease ($P = 0.049$), peripheral vascular disease ($P < 0.001$), chronic lung disease ($P < 0.001$), connective tissue disease ($P = 0.032$), peptic ulcer disease ($P = 0.007$), mild liver disease ($P = 0.022$), and diabetes both with and without complications ($P = 0.001$ and $P = 0.005$, respectively). Additionally, patients diagnosed with PIF had a significantly higher CCI ($P < 0.001$) (**Table 1**).

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Table 1. Demographics of cervical cancer survivors

Variables	Total (N = 13,480)	Patients with		*P* value
		PIF (n = 134)	Non-PIF (n = 13,346)	
Age group, yr				< 0.001
≤ 39	2,922 (21.7)	8 (6.0)	2,914 (21.8)	
40–49	4,455 (33.0)	22 (16.4)	4,433 (33.2)	
50–59	3,485 (25.8)	21 (15.7)	3,464 (26.0)	
60–69	1,604 (11.9)	39 (29.1)	1,565 (11.7)	
≥ 70	1,014 (7.5)	44 (32.8)	970 (7.3)	
Age, yr	49.3 ± 12.4	61.6 ± 13.6	49.2 ± 12.3	< 0.001
Type of medical institution				0.846
Hospital	290 (2.1)	2 (1.5)	288 (2.2)	
General hospital	4,021 (29.8)	39 (29.1)	3,982 (29.8)	
Tertiary hospital	9,169 (68.0)	93 (69.4)	9,076 (68.0)	
Residential area				0.607
Urban	9,822 (72.9)	95 (70.9)	9,727 (72.9)	
Rural	3,658 (27.1)	39 (29.1)	3,619 (27.1)	
Insurance type				< 0.001
Self-employed or employee insured	12,868 (95.5)	120 (89.5)	12,748 (95.5)	
Medical-aid beneficiary	612 (4.5)	14 (10.4)	598 (4.5)	
Income level (quintile)				0.133
Q1	2,706 (21.4)	33 (27.7)	2,673 (21.4)	
Q2	2,488 (19.7)	23 (19.3)	2,465 (19.7)	
Q3	2,437 (19.3)	15 (12.6)	2,422 (19.4)	
Q4	2,482 (19.7)	19 (16.0)	2,463 (19.7)	
Q5	2,513 (19.9)	29 (24.4)	2,484 (19.9)	
SEER summarized stage				0.005
Localized	8,884 (65.9)	73 (54.5)	8,811 (66.0)	
Regional	4,596 (34.1)	61 (45.5)	4,535 (34.0)	
Radiation therapy				0.061
Yes	3,020 (22.4)	39 (29.1)	2,981 (22.3)	
No	10,460 (77.6)	95 (70.9)	10,365 (77.7)	
Comorbidities				
Myocardial infarction	12 (0.1)	1 (0.7)	11 (0.1)	0.113
Ischemic heart disease	139 (1.0)	4 (3.0)	135 (1.0)	0.049
Peripheral vascular disease	520 (3.9)	15 (11.2)	505 (3.8)	< 0.001
Cerebrovascular disease	300 (2.2)	6 (4.5)	294 (2.2)	0.127
Chronic lung disease	1,380 (10.2)	26 (19.4)	1,354 (10.1)	< 0.001
Connective tissue disease	121 (0.9)	4 (3.0)	117 (0.9)	0.032
Peptic ulcer disease	1,291 (9.6)	23 (17.2)	1,111 (82.8)	0.007
Mild liver disease	643 (4.8)	12 (9.0)	631 (4.7)	0.022
Diabetes without complications	818 (6.1)	17 (12.7)	801 (6.0)	0.001
Diabetes with complications	320 (2.4)	9 (6.7)	311 (2.3)	0.005
Hemiplegia	28 (0.2)	0 (0.0)	28 (0.2)	1.000
Renal disease	70 (0.5)	0 (0.0)	70 (0.5)	1.000
Moderate or severe liver disease	11 (0.1)	0 (0.0)	11 (0.1)	1.000
CCI	0.4 ± 0.9	0.9 ± 1.2	0.4 ± 0.9	< 0.001

Values are presented as number (%) or mean ± standard deviation.
PIF = pelvic insufficiency fracture, SEER = Surveillance, Epidemiology, and End Results, CCI = Charlson Comorbidity Index.

The risk for PIFs in post-RT cervical cancer survivors

In univariate analysis, older age (crude hazard ratio [cHR], 1.079; 95% confidence interval [CI], 1.065–1.093; $P < 0.001$), medical-aid beneficiary (cHR, 2.616; 95% CI, 1.504–4.550; $P < 0.001$), regional SEER stage (cHR, 1.904; 95% CI, 1.354–1.2677; $P < 0.001$), and RT (cHR, 2.223;, 95% CI, 1.514–3.265; $P < 0.001$) were associated with the occurrence of PIFs. It was revealed that older age (adjusted hazard ratio [aHR], 1.063; 95% CI, 1.047–1.079; $P < 0.001$) and RT (aHR, 1.829; 95% CI, 1.235–2.710; $P = 0.003$) were associated with the occurrence of PIF in multivariate analysis (**Table 2**).

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Table 2. Hazard risk of pelvis insufficiency fracture in cervical cancer survivors

Variables	Univariate model		Multivariate model	
	Crude HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Age group, yr				-
≤ 39	1 (ref)		-	
40–49	1.838 (0.818–4.129)	0.140	-	
50–59	2.309 (1.023–5.213)	0.044	-	
60–69	8.899 (4.159–19.042)	< 0.001	-	
≥ 70	19.943 (9.385–42.380)	< 0.001	-	
Age, yr	1.079 (1.065–1.093)	< 0.001	1.063 (1.047–1.079)	< 0.001
Type of medical institution				
Hospital	1 (ref)		1 (ref)	
General hospital	1.312 (0.317–5.434)	0.708	0.970 (0.232–4.049)	0.966
Tertiary hospital	1.327 (0.327–5.387)	0.692	1.166 (0.286–4.757)	0.830
Residential area		0.508		0.673
Urban	1 (ref)		1 (ref)	
Rural	1.134 (0.781–1.647)		1.084 (0.744–1,581)	
Insurance type		< 0.001		0.493
Self-employed or employee insured	1 (ref)		1 (ref)	
Medical-aid beneficiary	2.616 (1.504–4.550)		1.225 (0.686–2.189)	
Income level (quintile)				-
Q1	1 (ref)		-	
Q2	0.726 (0.426–1.236)	0.238	-	
Q3	0.496 (0.270–0.914)	0.024	-	
Q4	0.621 (0.353–1.091)	0.098	-	
Q5	0.951 (0.578–1.567)	0.845	-	
SEER summarized stage		< 0.001		0.120
Localized	1 (ref)		1 (ref)	
Regional	1.904 (1.354–2.677)		1.320 (0.929–1.875)	
Radiation therapy		< 0.001		0.003
No	1 (ref)		1 (ref)	
Yes	2.223 (1.514–3.265)		1.829 (1.235–2.710)	
Comorbidities				
Myocardial infarction	6.805 (0.951–48.680)	0.056	3.370 (0.457–24.870)	0.233
Ischemic heart disease	3.512 (1.298–9.501)	0.013	1.120 (0.405–3.098)	0.827
Peripheral vascular disease	3.242 (1.895–5.546)	< 0.001	1.318 (0.747–2.326)	0.341
Cerebrovascular disease	2.307 (1.017–5.231)	0.045	0.821 (0.353–1.910)	0.647
Chronic lung disease	2.163 (1.410–3.319)	< 0.001	1.273 (0.811–1.998)	0.294
Connective tissue disease	3.216 (1.188–8.701)	0.022	2.018 (0.728–5.593)	0.177
Peptic ulcer disease	1.957 (1.249–3.067)	0.003	1.225 (0.767–1.956)	0.395
Mild liver disease	2.139 (1.182–3.871)	0.012	1.586 (0.855–2.941)	0.143
Diabetes without complications	2.417 (1.453–4.020)	< 0.001	0.896 (0.506–1.586)	0.706
Diabetes with complications	2.952 (1.501–5.806)	0.002	1.258 (0.593–2.670)	0.550
Hemiplegia	0 (0, Inf)	0.992	0 (0, Inf)	0.995
Renal disease	0 (0, Inf)	0.993	0 (0, Inf)	0.995
Moderate or severe liver disease	0 (0, Inf)	0.994	0 (0, Inf)	0.998
CCI	1.463 (1.305–1.641)	< 0.001	-	-

HR = hazard ratio, CI = confidence interval, CCI = Charlson Comorbidity Index.

DISCUSSION

The incidence of PIFs in cervical cancer patients was 1.0%, with older age and RT identified as significant risk factors for PIFs in this national claim database study. To the best of our knowledge, this is the first study to investigate the incidence of PIFs in cervical cancer survivors using a national claim database.

Previous studies, using advanced imaging techniques such as magnetic resonance imaging (MRI) and bone scans, have reported that the incidence of PIFs after RT ranged from 1.7

to 45.2%.[9-13] In this study, we revealed an incidence of 1.0% (134 patients) among 13,480 cervical cancer survivors. The incidence of PIFs in this study was much lower than those after RT in previous studies that used X-ray, computed tomography (CT), or MRI to diagnose PIF. A possible explanation for the lower incidence of PIFs in our study, compared to previous reports, could be attributed to differences in the study design including diagnostic methods.[13,22] It is difficult to diagnose PIF with a plain radiograph.[14] And, previous studies using CT or MRI could easily demonstrated a higher incidence of PIFs, because of the superior sensitivity of the diagnosis technique.[7] However, our study using national registry data relies on diagnostic codes for pelvis fracture, potentially leading to under-coding of PIFs and under-estimation of the incidence of PIFs.

Because PIFs following RT can often be asymptomatic or the symptom often vague, these fractures may be overlooked or mistaken for post-RT discomfort.[14] A retrospective study analyzing pelvic MR images of 510 patients found PIFs in 100 patients, and among them, only 43 patients (43%) experienced pelvic pain.[9] Similarly, Oh et al.[23] reported that only 48 patients (57.3%) had pelvic pain, while 35 patients (42.6%) had asymptomatic PIFs. Differentiating between pathological fractures due to metastasis and insufficiency fractures also can be challenging.[24] Although bone scans have been known as the diagnostic tool of choice for PIF, MRI has proven to be most sensitive imaging tool in distinguishing between insufficiency fractures and bone metastasis recently.[25] A meta-analysis by Chung et al.[7] focusing on PIF following RT in cervical cancer patients demonstrated that studies using MRI reported significantly higher incidences of PIFs compared to those using other diagnostic tools, highlighting the superior sensitivity of MRI. Therefore, it is crucial to consider advanced imaging techniques such as MRI and bone scans for patients with suspected PIFs, regardless of the presence of symptoms like pain, to ensure accurate diagnosis and appropriate management.

RT was a significant risk factor for PIF in present results, supported by previous studies.[9,26] RT induces injury to the microvasculature of mature bone, resulting in occlusion of microcirculation and, consequently, injury to the periosteal vasculature.[27] Radiation exposure impacts the proliferation and function of osteoblasts, including collagen production, and can induce cell cycle arrest in osteoblasts.[28] Additionally, the increased number of osteoclasts after RT suggests that it contributes to radiation-induced bone loss.[29] Radiation also leads to adipocyte infiltration in bone marrow, altering the microenvironment and potentially affecting bone quality, ultimately resulting in an increased susceptibility to traumatic or stress fractures.[30] Though there are limited data clarifying the effect of RT on the bone turnover process, recent studies show high serum markers, bone-specific alkaline phosphatase, which indicates a high bone turnover process resulting in the overall reduction of bone mass.[31]

Several studies have reported that older women, particularly those over 50 and postmenopausal, are associated with an increased risk of PIF following RT.[10,11,13,22] According to a systematic review on radiation-induced PIF in patients with gynecologic malignancies, postmenopausal status was identified as the most common risk factor for PIF.[32] Oh et al.[23] compared the 5-year cumulative incidence of PIFs following RT in cervical cancer patients and reported a significant increase with patient age. Consistently, our study also found that older age is a significant risk factor for PIF.

This study has several limitations. First, we used ICD-10 codes to identify patients with PIF in the national claim database. Incidence based on insurance claim records might be

underestimated, because all patients with PIFs may not be coded in this nationwide database, as reported elsewhere.[33-36] Second, we could not include other confounders such as bone mineral density[12,22], body mass index,[22,23] smoking status,[13] or steroid use[10] due to database limitations. This might affect our results. Third, it was not easy to distinguish between high energy and low energy trauma patients, because the distinction between high and low-energy fractures could not be made by using the ICD-10 coding system. However, the high-energy trauma that led to the fracture is spontaneously excluded because traffic accidents and industrial accidents are covered by different insurance systems.[37] In addition, these diagnostic criteria using ICD code could be found in several studies on fractures among cancer survivors.[20,21] Therefore, our study without radiographic measurement could be justified.

In conclusion, the incidence of PIFs was 1.0% in cervical cancer survivors in this national claim database study in Korea. This study demonstrated that RT and older age are significantly associated with an increased risk of PIFs in cervical cancer survivors. Our findings suggest that clinicians should be aware of the risk of PIFs, especially in older patients who underwent RT.

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