Original Article
Prostate cancer

pISSN: 2287-4208 / eISSN: 2287-4690
World J Mens Health Published online Jan 15, 2026
https://doi.org/10.5534/wjmh.250298

The World Journal of MEN's HEALTH

Effects of Radiation Therapy on the Incidence of Bladder Cancer and Rectal Cancer in Patients with Prostate Cancer: A Nationwide Nested Case-Control Study in Korean Population

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Purpose: This study aimed to assess the risk of secondary bladder and colorectal cancers following radiotherapy for prostate cancer using a nationwide nested case-control design based on Korea's Health Insurance Review and Assessment database.

Materials and Methods: We conducted a nationwide nested case-control study using database, including men newly diagnosed with prostate cancer between 2011 and 2020. Patients were classified into radiotherapy and non-radiotherapy groups and matched 1:1 based on age, comorbidity index, and follow-up duration. Conditional logistic regression was used to assess the association between radiotherapy and secondary bladder and colorectal cancer incidences.

Results: In the crude cohort, radiotherapy was not significantly associated with secondary bladder or colorectal cancer. Kaplan–Meier analysis showed no significant differences in the cumulative incidence between radiotherapy and non-radiotherapy groups. However, nested case-control analysis revealed a significantly increased risk of secondary bladder cancer in the radiotherapy group (adjusted hazard ratio, 1.38; 95% confidence interval, 1.02 to 1.86), while no association was found for colorectal cancer (adjusted hazard ratio, 0.96; 95% confidence interval, 0.72 to 1.27).

Conclusions: Radiotherapy was linked to an increased bladder cancer risk but not colorectal cancer risk, underscoring the need for targeted long-term surveillance.

Keywords: Big data; Case-control studies; Prostatic neoplasms; Radiotherapy; Secondary malignancies

INTRODUCTION

Prostate cancer (PCa) represents a significant global health burden with varying incidence and mortality rates across countries. In the United States, more than two million men are estimated to be diagnosed with PCa [1]. In developed countries, such as Canada, PCa is the most common cancer among men, followed by

Received: Sep 16, 2025 **Revised:** Nov 12, 2025 **Accepted:** Nov 17, 2025 **Published online** Jan 15, 2026
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colorectal cancer (CRC), lung cancer, and bladder cancer (BC). It is the third leading cause of cancer-related deaths, accounting for 9.6% of these fatalities [2]. In Korea, PCa was the fourth most common cancer among men in 2017, followed by lung, stomach, and CRC, accounting for approximately 8.2% of all new cancer diagnoses in men [3]. Radiotherapy (RT) is the primary treatment approach for patients diagnosed with localized or locally advanced PCa [4,5].

Advancements in RT techniques, such as intensity-modulated radiation therapy and volumetric modulated arc therapy, have significantly improved dose conformity to the prostate and minimized exposure to surrounding healthy tissues. However, despite these technological improvements, and while RT offers excellent tumor control, the inherent trade-off between curative intent and potential long-term side effects, including the induction of secondary malignancies, remains a critical consideration for both patients and clinicians [6-8]. The well-established principle of radiation-induced carcinogenesis suggests that direct irradiation of the prostate and regional lymph nodes may increase the risk of secondary malignancies in the adjacent organs, particularly the bladder and colon, owing to their close anatomical proximity [9]. However, the reported association between RT and the incidence of secondary BC and CRC remains inconsistent across studies. While previous meta-analyses have persistently raised concerns regarding the increased risk of secondary malignancies following RT [9-11], the supporting evidence warrants careful interpretation. These analyses are often limited by substantial heterogeneity, variations in lag time definitions, and inconsistent inclusion criteria across studies, which may compromise the reliability of pooled estimates, particularly for secondary BC and CRC [12-20].

Although a few recent studies have begun to explore this association in Korean populations, comprehensive population-based analyses remain scarce [14,17]. Given the increasing use of RT and increasing survival of patients with PCa in Korea, there is a pressing need for robust epidemiologic evidence to clarify the magnitude and pattern of secondary cancer risks following RT. We aimed to evaluate the association between exposure to RT for PCa and the subsequent development of secondary BC and CRC through a nested case-control (NCC) study using the Health Insurance Review and Assessment (HIRA) database, with the ultimate goal of informing national public health policies, long-term cancer surveillance strategies, and individualized patient counseling.

MATERIALS AND METHODS

1. HIRA database

South Korea's National Health Insurance Service (NHIS) provides mandatory universal coverage to >50 million individuals (>98% of the population). The HIRA database comprises all nationwide reimbursement claims submitted to the NHIS, encompassing ICD-10-coded diagnoses, procedures, surgeries, treatments, and prescription medications. This study used fully anonymized HIRA claims data from 2009 through 2023. This study utilized the HIRA database, which, unlike overseas databases such as SEER, provides near-complete coverage of the entire 50 million Korean population, offering unique evidence on the risk of secondary cancers following PCa RT in an Asian population that has been underrepresented.

2. Study design, definitions, and clinical evaluation

This retrospective cohort study with an NCC design was conducted using claims data from the HIRA Service Database of South Korea. While existing SEER-based studies are largely limited to Western populations, this study targets all male patients newly diagnosed with 'prostate cancer' (ICD-10 code: C61.0) from January 1, 2011, to December 31, 2020, in Asia's largest single-insurer system, ensuring racial representativeness.

To ensure that our study cohort comprised genuine incident cases of PCa and to minimize prevalent user bias, we applied a two-year washout (look-back) period, which excluded all patients who were diagnosed with PCa in the two years prior to the cohort entry (2009 to 2010). This two-year period is a standard and empirically supported compromise in large claims data analysis, which balances the need to exclude prevalent cases with the need for sufficient statistical power for the subsequent analysis of rare events like secondary malignancy. The six-month exclusion period was implemented at the time of PCa diagnosis and initial treatment to rule out synchronous cancers or pre-existing but undiagnosed cancers (prevalent cases) explicitly. This pragmatic approach has been widely adopted in population-based cancer research to ensure that the

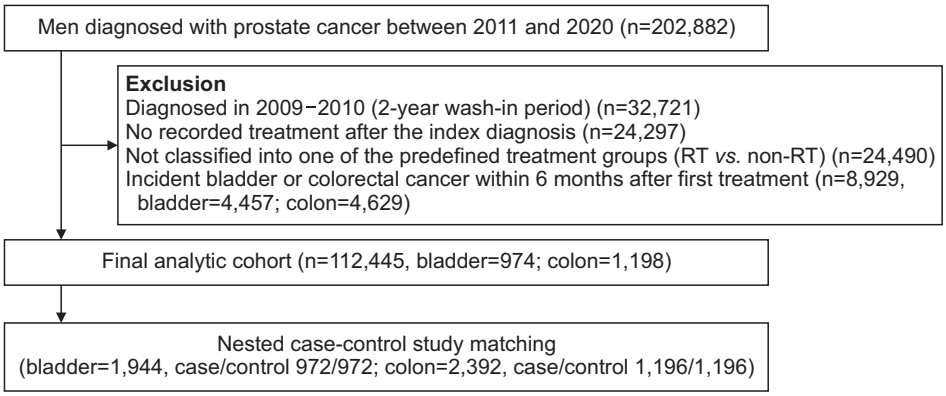

Fig. 1. Cohort selection and nested case–control matching flowchart for assessing secondary bladder and colorectal cancer risk in prostate cancer patients using national health insurance data (2011–2020). RT: radiotherapy.

secondary malignancies that are detected are new primary events occurring after the treatment exposure [8,21]. Additional exclusion criteria were as follows: (1) no record of treatment following the initial PCa diagnosis; (2) diagnosis of BC or CRC within six months after the first treatment; and (3) patients not classified into either the RT or non-RT treatment groups. Patients were categorized into RT and non-RT groups based on the presence of any RT claims, regardless of the modality. The follow-up period was defined as the interval from the date of initial treatment to the diagnosis of secondary cancer (for those with outcomes) or to December 31, 2023 (for those without outcomes). With the two-year washout applied, the actual follow-up duration is up to 10 years (based on the 2011 to 2020 diagnosis cohort), which is longer than many studies included in existing meta-analyses, allowing capture of late-onset secondary cancers.

Secondary malignancies were identified using ICD-10 codes: C67 for 'bladder cancer' and C18 and C20 for 'colorectal cancer.' To address the potential lag time bias and improve comparability between groups, we performed 1:1 NCC matching. Matching variables included age, Charlson Comorbidity Index (CCI) (incorporating 17 comorbidity variables), and follow-up duration (defined as the time from PCa diagnosis to the occurrence of secondary malignancy or censoring). Incorporating CCI into the matching variables is a sophisticated design unique to this study, considering that comorbidities can severely confound RT associations in elderly PCa patients, clearly distinguishing it from most existing studies that only match on age and follow-up period. The overall study design and cohort selection process are illustrated in the flowchart (Fig. 1).

3. Statistical analyses

Statistical analyses were performed on both the unmatched cohort and the matched case-control sets. Kaplan–Meier estimation was used to assess time-to-event outcomes in the full cohort. To evaluate the association between RT and the incidence of secondary BC and CRC, conditional logistic regression analysis was conducted using a NCC matched dataset. Matching variables included age, CCI and follow-up duration. The conditional logistic regression models were further adjusted for CCI to account for residual differences in comorbidity burden after matching, a step that strengthens causal inference compared to studies relying solely on age and follow-up matching. Descriptive statistics are presented as means±standard deviations for continuous variables and as numbers (percentages) for categorical variables. Baseline characteristics between the RT and non-RT groups were compared using Student's t-test for continuous variables and the chi-squared test for categorical variables. All statistical tests were two-sided, and a p-value<0.05 was considered statistically significant. Post-matching balance was rigorously assessed using standardized mean differences (SMDs); all SMDs for age, CCI, and follow-up duration were <0.05. Analyses were conducted using SAS Enterprise Guide version 7.13 (SAS Institute Inc.) and R version 4.0.2 (https://www.R-project.org).

4. Ethics statement

This study was approved by the Institutional Review Board of Gangnam Severance Hospital (approval number: 3-2024-0277) and was conducted in accordance with the principles of the Declaration of Helsinki. This study was conducted using a nationwide healthcare database and employed a retrospective observational

design. All data were anonymized prior to analysis, and no identifiable personal information was accessed. Given the minimal risk to participants and the impracticability of obtaining informed consent, the requirement for written informed consent was waived by the Institutional Review Board.

RESULTS

1. Baseline characteristics

Before matching, patients who developed secondary BC were significantly older than those who did not (mean age, 70.98 *vs.* 69.15 years; p<0.001), and had a higher prevalence of comorbidities such as chronic pulmonary disease (28.2% *vs.* 22.6%, p<0.001), vascular disease (11.8% *vs.* 8.9%, p=0.003), and diabetes mellitus without chronic complications (27.5% *vs.* 23.2%, p=0.002). The proportion of patients who received RT was slightly lower in the BC group than that in the non-BC group (12.3% *vs.* 14.7%, p=0.036). After 1:1 NCC matching, the two groups were well balanced in terms of age (mean, 70.98 years in both groups; p=0.956) and CCI (14.24 *vs.* 12.92, p=0.632). However, some differences in the comorbidities remained, including chronic pulmonary disease (28.2% *vs.* 22.3%, p=0.004) and vascular disease (11.8% *vs.* 8.8%, p=0.035; Table 1).

Similarly, in the CRC cohort, patients with secondary CRC were older than those without (mean age, 71.21

Table 1. Distribution of potential confounders by bladder cancer status before and after nested case–control matching in the entire cohort

Variable (1=yes, 0=no)	Entire cohort							
	Before nested case-control study				After nested case-control study			
	Total (N=112,445)	Bladder cancer		p-value	Total (N=1,948)	Bladder cancer		p-value
		0 (N=111,471)	1 (N=974)			0 (N=974)	1 (N=974)	
RTx				0.036				0.042
0	95,925 (85.3)	95,071 (85.3)	854 (87.7)		1,677 (86.1)	823 (84.5)	854 (87.7)	
1	16,520 (14.7)	16,400 (14.7)	120 (12.3)		271 (13.9)	151 (15.5)	120 (12.3)	
PAT_AGE	69.17±8.90	69.15±8.91	70.98±7.47	<0.001	70.98±7.44	70.97±7.41	70.98±7.47	0.956
CCI	12.02±40.97	12.00±40.65	14.24±68.12	0.305	13.58±60.96	12.92±52.86	14.24±68.12	0.632
MI				0.793				0.690
0	105,891 (97.6)	104,981 (97.6)	910 (97.4)		1,824 (97.3)	914 (97.1)	910 (97.4)	
1	2,646 (2.4)	2,622 (2.4)	24 (2.6)		51 (2.7)	27 (2.9)	24 (2.6)	
HF				0.262				0.902
0	100,949 (93.0)	100,089 (93.0)	860 (92.1)		1,725 (92.0)	865 (91.9)	860 (92.1)	
1	7,588 (7.0)	7,514 (7.0)	74 (7.9)		150 (8.0)	76 (8.1)	74 (7.9)	
Vascular				0.003				0.035
0	98,805 (91.0)	97,981 (91.1)	824 (88.2)		1,682 (89.7)	858 (91.2)	824 (88.2)	
1	9,732 (9.0)	9,622 (8.9)	110 (11.8)		193 (10.3)	83 (8.8)	110 (11.8)	
Cerebro				0.071				0.284
0	92,119 (84.9)	91,346 (84.9)	773 (82.8)		1,569 (83.7)	796 (84.6)	773 (82.8)	
1	16,418 (15.1)	16,257 (15.1)	161 (17.2)		306 (16.3)	145 (15.4)	161 (17.2)	
Dementia				0.181				0.017
0	107,393 (98.9)	106,473 (98.9)	920 (98.5)		1,857 (99.0)	937 (99.6)	920 (98.5)	
1	1,144 (1.1)	1,130 (1.1)	14 (1.5)		18 (1.0)	4 (0.4)	14 (1.5)	
CPD				<0.001				0.004
0	83,922 (77.3)	83,251 (77.4)	671 (71.8)		1,402 (74.8)	731 (77.7)	671 (71.8)	
1	24,615 (22.7)	24,352 (22.6)	263 (28.2)		473 (25.2)	210 (22.3)	263 (28.2)	
RD				0.265				0.490
0	105,472 (97.2)	104,570 (97.2)	902 (96.6)		1,816 (96.9)	914 (97.1)	902 (96.6)	
1	3,065 (2.8)	3,033 (2.8)	32 (3.4)		59 (3.1)	27 (2.9)	32 (3.4)	
PUD				0.068				0.179
0	84,382 (77.7)	83,679 (77.8)	703 (75.3)		1,436 (76.6)	733 (77.9)	703 (75.3)	
1	24,155 (22.3)	23,924 (22.2)	231 (24.7)		439 (23.4)	208 (22.1)	231 (24.7)	

Table 1. Continued

Variable (1=yes, 0=no)	Entire cohort							
	Before nested case-control study				After nested case-control study			
	Total (N=112,445)	Bladder cancer		p-value	Total (N=1,948)	Bladder cancer		p-value
		0 (N=111,471)	1 (N=974)			0 (N=974)	1 (N=974)	
Mild_liver				0.895				0.291
0	85,103 (78.4)	84,369 (78.4)	734 (78.6)		1,492 (79.6)	758 (80.6)	734 (78.6)	
1	23,434 (21.6)	23,234 (21.6)	200 (21.4)		383 (20.4)	183 (19.4)	200 (21.4)	
DB_without				0.002				0.030
0	83,344 (76.8)	82,667 (76.8)	677 (72.5)		1,400 (74.7)	723 (76.8)	677 (72.5)	
1	25,193 (23.2)	24,936 (23.2)	257 (27.5)		475 (25.3)	218 (23.2)	257 (27.5)	
DB_with				0.558				0.829
0	100,029 (92.2)	99,173 (92.2)	856 (91.6)		1,721 (91.8)	865 (91.9)	856 (91.6)	
1	8,508 (7.8)	8,430 (7.8)	78 (8.4)		154 (8.2)	76 (8.1)	78 (8.4)	
Hemi_para				0.899				0.574
0	107,192 (98.8)	106,270 (98.8)	922 (98.7)		1,848 (98.6)	926 (98.4)	922 (98.7)	
1	1,345 (1.2)	1,333 (1.2)	12 (1.3)		27 (1.4)	15 (1.6)	12 (1.3)	
Renal				0.192				0.559
0	104,104 (95.9)	103,216 (95.9)	888 (95.1)		1,777 (94.8)	889 (94.5)	888 (95.1)	
1	4,433 (4.1)	4,387 (4.1)	46 (4.9)		98 (5.2)	52 (5.5)	46 (4.9)	
Tumor				<0.001				<0.001
0	92,738 (85.4)	91,982 (85.5)	756 (80.9)		1,572 (83.8)	816 (86.7)	756 (80.9)	
1	15,799 (14.6)	15,621 (14.5)	178 (19.1)		303 (16.2)	125 (13.3)	178 (19.1)	
Sever_liver				0.273				0.124
0	108,153 (99.6)	107,220 (99.6)	933 (99.9)		1,868 (99.6)	935 (99.4)	933 (99.9)	
1	384 (0.4)	383 (0.4)	1 (0.1)		7 (0.4)	6 (0.6)	1 (0.1)	
Solid_tumor				0.087				0.073
0	106,861 (98.5)	105,935 (98.4)	926 (99.1)		1,850 (98.7)	924 (98.2)	926 (99.1)	
1	1,676 (1.5)	1,668 (1.6)	8 (0.9)		25 (1.3)	17 (1.8)	8 (0.9)	
ADIS_HIV				-				-
0	108,537 (100.0)	107,603 (100.0)	934 (100.0)		1,875 (100.0)	941 (100.0)	934 (100.0)	
1	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	
TF_CCI				0.002				0.005
0	37,310 (34.4)	37,034 (34.4)	276 (29.6)		611 (32.6)	335 (35.6)	276 (29.6)	
1	71,227 (65.6)	70,569 (65.6)	658 (70.4)		1,264 (67.4)	606 (64.4)	658 (70.4)	

Values are presented as number (%) or mean±standard deviation.
Percentages for comorbidities were calculated based on the number of patients with available data, excluding cases with missing values.
RTx: radiotherapy, PAT_AGE: patient age, CCI: Charlson Comorbidity Index, MI: myocardial infarction, HF: congestive heart failure, Vascular: peripheral vascular disease, Cerebro: cerebrovascular disease, Dementia: dementia, CPD: chronic pulmonary disease, RD: rheumatologic disease, PUD: peptic ulcer disease, Mild_liver: mild liver disease, DB_without: diabetes without chronic complication, DB_with: diabetes with chronic complication, Hemi_para: hemiplegia or paraplegia, Renal: renal disease, Tumor: any malignancy including leukemia and lymphoma, Sever_liver: moderate or severe liver disease, Solid_tumor: metastatic solid tumor, ADIS_HIV: AIDS/HIV, TF_CCI: presence of at least one of the above comorbidities.

vs. 69.15 years; p<0.001) and had a slightly lower rate of RT exposure (9.4% *vs.* 14.7%, p<0.001; Table 2). After matching, age and CCI were well balanced, and no significant differences were observed in most comorbidities, indicating successful matching.

2. Kaplan–Meier analysis of entire cohort

Kaplan–Meier curves were generated to assess the cumulative incidence of secondary BC and CRC among patients with PCa, stratified by RT status. Although the RT group showed a slightly higher cumulative incidence of both BC and CRC over time than the non-RT group, these differences were not statistically

Table 2. Distribution of potential confounders by colorectal cancer status before and after nested case–control matching in the entire cohort

Variable (1=yes, 0=no)	Entire cohort							
	Before nested case-control study				After nested case-control study			
	Total (N=112,445)	Colorectal cancer		p-value	Total (N=2,388)	Colorectal cancer		p-value
		0 (N=111,247)	1 (N=1,198)			0 (N=1,194)	1 (N=1,194)	
RTx				<0.001				0.026
0	95,925 (85.3)	94,840 (85.3)	1,085 (90.6)		2,128 (89.1)	1,047 (87.7)	1,081 (90.5)	
1	16,520 (14.7)	16,407 (14.7)	113 (9.4)		260 (10.9)	147 (12.3)	113 (9.5)	
PAT_AGE	69.17±8.90	69.15±8.91	71.21±7.36	<0.001	71.16±7.38	71.12±7.38	71.21±7.37	0.775
CCI	12.02±40.97	12.02±41.03	11.89±34.62	0.904	12.45±40.18	13.02±45.04	11.87±34.65	0.485
MI				0.724				0.197
0	105,891 (97.6)	104,766 (97.6)	1,125 (97.4)		2,256 (97.8)	1,135 (98.2)	1,121 (97.4)	
1	2,646 (2.4)	2,616 (2.4)	30 (2.6)		51 (2.2)	21 (1.8)	30 (2.6)	
HF				0.212				0.038
0	100,949 (93.0)	99,864 (93.0)	1,085 (93.9)		2,143 (92.9)	1,061 (91.8)	1,082 (94.0)	
1	7,588 (7.0)	7,518 (7.0)	70 (6.1)		164 (7.1)	95 (8.2)	69 (6.0)	
Vascular				0.322				0.730
0	98,805 (91.0)	97,744 (91.0)	1,061 (91.9)		2,114 (91.6)	1,057 (91.4)	1,057 (91.8)	
1	9,732 (9.0)	9,638 (9.0)	94 (8.1)		193 (8.4)	99 (8.6)	94 (8.2)	
Cerebro				0.604				0.563
0	92,119 (84.9)	91,145 (84.9)	974 (84.3)		1,936 (83.9)	965 (83.5)	971 (84.4)	
1	16,418 (15.1)	16,237 (15.1)	181 (15.7)		371 (16.1)	191 (16.5)	180 (15.6)	
Dementia				0.734				0.689
0	107,393 (98.9)	106,249 (98.9)	1,144 (99.0)		2,283 (99.0)	1,143 (98.9)	1,140 (99.0)	
1	1,144 (1.1)	1,133 (1.1)	11 (1.0)		24 (1.0)	13 (1.1)	11 (1.0)	
CPD				0.077				0.675
0	83,922 (77.3)	83,054 (77.3)	868 (75.2)		1,727 (74.9)	861 (74.5)	866 (75.2)	
1	24,615 (22.7)	24,328 (22.7)	287 (24.8)		580 (25.1)	295 (25.5)	285 (24.8)	
RD				0.670				0.919
0	105,472 (97.2)	104,352 (97.2)	1,120 (97.0)		2,236 (96.9)	1,120 (96.9)	1,116 (97.0)	
1	3,065 (2.8)	3,030 (2.8)	35 (3.0)		71 (3.1)	36 (3.1)	35 (3.0)	
PUD				0.672				0.527
0	84,382 (77.7)	83,490 (77.8)	892 (77.2)		1,769 (76.7)	880 (76.1)	889 (77.2)	
1	24,155 (22.3)	23,892 (22.2)	263 (22.8)		538 (23.3)	276 (23.9)	262 (22.8)	
Mild_liver				0.239				0.959
0	85,103 (78.4)	84,181 (78.4)	922 (79.8)		1,841 (79.8)	922 (79.8)	919 (79.8)	
1	23,434 (21.6)	23,201 (21.6)	233 (20.2)		466 (20.2)	234 (20.2)	232 (20.2)	
DB_without				0.081				0.656
0	83,344 (76.8)	82,482 (76.8)	862 (74.6)		1,731 (75.0)	872 (75.4)	859 (74.6)	
1	25,193 (23.2)	24,900 (23.2)	293 (25.4)		576 (25.0)	284 (24.6)	292 (25.4)	
DB_with				0.111				0.745
0	100,029 (92.2)	98,979 (92.2)	1,050 (90.9)		2,101 (91.1)	1,055 (91.3)	1,046 (90.9)	
1	8,508 (7.8)	8,403 (7.8)	105 (9.1)		206 (8.9)	101 (8.7)	105 (9.1)	
Hemi_para				0.652				0.847
0	107,192 (98.8)	106,053 (98.8)	1,139 (98.6)		2,276 (98.7)	1,141 (98.7)	1,135 (98.6)	
1	1,345 (1.2)	1,329 (1.2)	16 (1.4)		31 (1.3)	15 (1.3)	16 (1.4)	
Renal				0.356				0.599
0	104,104 (95.9)	102,990 (95.9)	1,114 (96.5)		2,220 (96.2)	1,110 (96.0)	1,110 (96.4)	
1	4,433 (4.1)	4,392 (4.1)	41 (3.5)		87 (3.8)	46 (4.0)	41 (3.6)	

Table 2. Continued

Variable (1=yes, 0=no)	Entire cohort							
	Before nested case-control study				After nested case-control study			
	Total (N=112,445)	Colorectal cancer		p-value	Total (N=2,388)	Colorectal cancer		p-value
		0 (N=111,247)	1 (N=1,198)			0 (N=1,194)	1 (N=1,194)	
Tumor				0.925				0.779
0	92,738 (85.4)	91,750 (85.4)	988 (85.5)		1,979 (85.8)	994 (86.0)	985 (85.6)	
1	15,799 (14.6)	15,632 (14.6)	167 (14.5)		328 (14.2)	162 (14.0)	166 (14.4)	
Sever_liver				0.612				0.753
0	108,153 (99.6)	107,003 (99.6)	1,150 (99.6)		2,298 (99.6)	1,152 (99.7)	1,146 (99.6)	
1	384 (0.4)	379 (0.4)	5 (0.4)		9 (0.4)	4 (0.3)	5 (0.4)	
Solid_tumor				0.660				0.871
0	106,861 (98.5)	105,722 (98.5)	1,139 (98.6)		2,274 (98.6)	1,139 (98.5)	1,135 (98.6)	
1	1,676 (1.5)	1,660 (1.5)	16 (1.4)		33 (1.4)	17 (1.5)	16 (1.4)	
ADIS_HIV				-				-
0	108,537 (100.0)	107,382 (100.0)	1,155 (100.0)		2,307 (100.0)	1,156 (100.0)	1,151 (100.0)	
1	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	
TF_CCI				0.757				0.702
0	37,310 (34.4)	36,908 (34.4)	402 (34.8)		793 (34.4)	393 (34.0)	400 (34.8)	
1	71,227 (65.6)	70,474 (65.6)	753 (65.2)		1,514 (65.6)	763 (66.0)	751 (65.2)	

Values are presented as number (%) or mean±standard deviation.
Percentages for comorbidities were calculated based on the number of patients with available data, excluding cases with missing values.
RTx: radiotherapy, PAT_AGE: patient age, CCI: Charlson Comorbidity Index, MI: myocardial infarction, HF: congestive heart failure, Vascular: peripheral vascular disease, Cerebro: cerebrovascular disease, Dementia: dementia, CPD: chronic pulmonary disease, RD: rheumatologic disease, PUD: peptic ulcer disease, Mild_liver: mild liver disease, DB_without: diabetes without chronic complication, DB_with: diabetes with chronic complication, Hemi_para: hemiplegia or paraplegia, Renal: renal disease, Tumor: any malignancy including leukemia and lymphoma, Sever_liver: moderate or severe liver disease, Solid_tumor: metastatic solid tumor, ADIS_HIV: AIDS/HIV, TF_CCI: presence of at least one of the above comorbidities.

significant (log-rank p>0.05 for both comparisons) (Fig. 2). These findings suggest that in the entire cohort, exposure to RT was not associated with a significantly increased risk of secondary BC or CRC during the follow-up period. All estimates were adjusted for age and CCI to account for baseline differences in comorbidity burden.

3. Association between RT and secondary malignancies

Table 3 summarizes the hazard ratios (HRs) for secondary BC and CRC associated with RT in patients with PCa, based on both the entire cohort and the NCC analyses.

In the entire cohort, RT was not significantly associated with the risk of secondary BC in either the unadjusted (HR, 1.12; 95% confidence interval [CI], 0.92 to 1.35; p=0.261) or adjusted model (HR, 1.11; 95% CI, 0.91 to 1.34; p=0.298). Similarly, no significant association was observed between RT and secondary CRC (adjusted HR, 0.83; 95% CI, 0.68 to 1.01; p=0.063), although a marginal trend toward reduced risk was noted. In contrast, the NCC analysis revealed a statistically significant association between RT and the risk of secondary BC. In the adjusted model, RT was associated with a 38% increased risk of developing BC (HR, 1.38; 95% CI, 1.02 to 1.86; p=0.037). This association remained consistent in the unadjusted model (HR, 1.36; 95% CI, 1.01 to 1.84; p=0.042). However, no significant association was found between RT and secondary CRC in the NCC analysis (adjusted HR, 0.96; 95% CI, 0.72 to 1.27; p=0.766).

DISCUSSION

In our large population-based cohort study, a significant increase in the incidence of secondary BC was observed in the RT group compared to the non-RT group following NCC analysis. However, no statistically significant difference was found in the incidence of CRC between the two groups.

Many studies have suggested a trend toward secondary cancer development due to ionizing radiation

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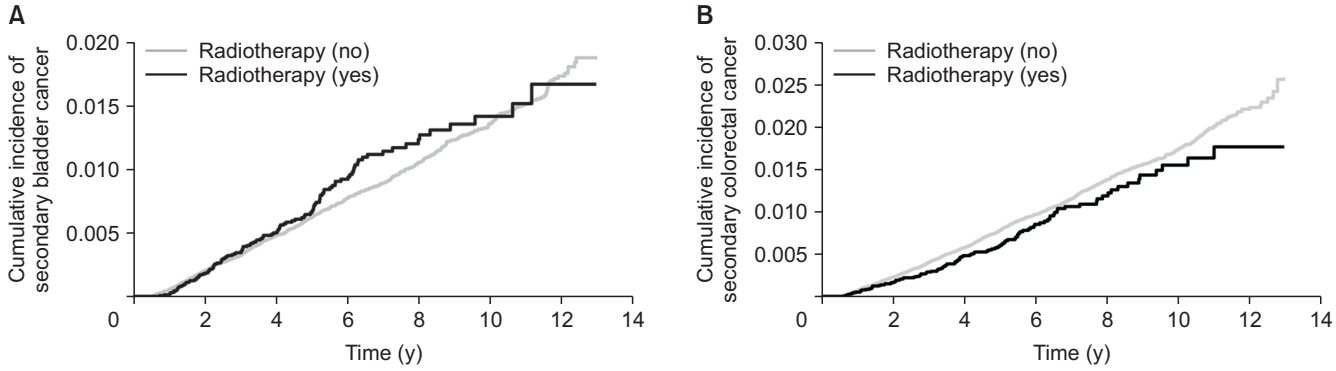

Fig. 2. Cumulative incidence of secondary bladder cancer (A) and secondary colorectal cancer (B) in prostate cancer patients after radiation therapy.

Table 3. HRs for secondary bladder and colorectal cancer associated with radiotherapy in prostate cancer patients: unadjusted and adjusted Cox regression in the entire cohort and conditional logistic regression in the nested case-control analysis

	Model	Variable	HR (95% CI)	p-value
Bladder cancer				
Entire cohort	Unadjusted	Radiotherapy (yes *vs.* ref)	1.12 (0.92–1.35)	0.261
	Adjusted[a]	Radiotherapy (yes *vs.* ref)	1.11 (0.91–1.34)	0.298
		Age (per year)	1.02 (1.02–1.03)	<0.001
		CCI (per point)	1.00 (1.00–1.00)	0.055
Nested case–control	Unadjusted	Radiotherapy (yes *vs.* ref)	1.36 (1.01–1.84)	0.042
	Adjusted[b]	Radiotherapy (yes *vs.* ref)	1.38 (1.02–1.86)	0.037
		CCI (per point)	1.00 (1.00–1.00)	0.282
Colorectal cancer				
Entire cohort	Unadjusted	Radiotherapy (yes *vs.* ref)	0.84 (0.69–1.02)	0.071
	Adjusted[a]	Radiotherapy (yes *vs.* ref)	0.83 (0.68–1.01)	0.063
		Age (per year)	1.03 (1.02–1.03)	<0.001
		CCI (per point)	1.00 (1.00–1.00)	0.998
Nested case–control	Unadjusted	Radiotherapy (yes *vs.* ref)	0.96 (0.72–1.27)	0.774
	Adjusted[b]	Radiotherapy (yes *vs.* ref)	0.96 (0.72–1.27)	0.766
		CCI (per point)	1.00 (1.00–1.00)	0.795

HR: hazard ratio, CI: confidence interval, CCI: Charlson Comorbidity Index.
[a]Adjusted for age and CCI.
[b]Conditioned on matching factors; additionally adjusted for CCI.

after RT for PCa [9,12-17,20]. However, the existing literature presents inconsistent findings regarding a clear increase in the development of secondary BC and CRC following RT for PCa. While some studies have demonstrated that RT elevates the risk of these secondary malignancies, others have reported either no discernible difference or only a modest, statistically insignificant increase in their incidence, suggesting that an elevated risk is not uniformly observed across all investigations [22,23].

Several large cohort studies have consistently demonstrated an elevated risk of secondary BC after RT for PCa. A Taiwanese nationwide study and SEER-based analyses both reported a higher incidence of BC in patients receiving RT compared with those undergoing surgery [12,15]. Similar findings have been observed in other population-based cohorts and competing-risk analyses, supporting the association between RT and secondary BC [1,24]. In our study, we also observed a modest but consistent increase in BC risk after RT, which is consistent with previous reports and suggests a reproducible, albeit variable, carcinogenic effect of RT on the bladder.

In contrast to the BC risk, studies on secondary CRC have yielded variable results. In one of the earliest studies, Baxter et al [13] investigated anatomical differ-

ences in radiation exposure and found a 1.70-fold higher adjusted hazard of CRC in RT recipients, suggesting that direct exposure plays a central role. Researchers have hypothesized that the anterior rectal wall, which lies directly posterior to the prostate, is subjected to a higher overall radiation dose than the bladder because radiation exposure to the bladder is generally limited to its base and neck [9]. Nevertheless, dose distribution alone cannot fully explain the observed differences in cancer risk, especially given the inconsistent definitions and overlap between rectal and colonic cancer classifications. Although some meta-analyses have shown higher relative risks for CRC than for BC, registry-based studies have consistently found a more pronounced increase in BC [1,12]. Building on these findings, more recent studies similarly reported that while both BC and CRC increased, the magnitude of the risk was greater for BC [15,24].

In studies on Korean populations, findings on secondary malignancies following RT have been inconsistent. One nationwide study reported an increased risk of both BC and CRC [17], whereas another registry-based study found no significant association [14], likely because of the limited statistical power of the smaller RT cohort. Notably, while the crude analyses in our study also showed no significant associations, the NCC analysis adjusted for age and CCI identified a statistically significant increase in BC risk following RT. Although our study included 112,445 patients, a sample size larger than that of previous domestic reports, the rarity of these events may limit statistical detection. Taken together, these mixed findings may reflect demographic or genetic differences and highlight the need for further large-scale, well-controlled studies in Korean populations.

A possible explanation for the inconsistent findings regarding secondary BC risk may be the very low absolute incidence of such events, despite the elevated relative risks reported in some studies [10,25]. Similarly, it has been noted that both BC and CRC occur at rates of only 1 to 4 cases per several hundred individuals over a lifetime, emphasizing that clinical decision-making should consider both relative and absolute risks [9]. Due to low event rates, study outcomes are highly sensitive to methodological differences, including cohort size, case definitions, and follow-up duration, making approaches that utilize very large administrative datasets valuable for enhancing statistical power. However, a major challenge remains in the limited availability of detailed smoking histories in many registries, despite smoking being a strong confounder of both BC and CRC. The absence of other key variables, including alcohol consumption and occupational exposure, further limits the accuracy of risk assessment [15,22]. In addition, studies differ widely in the lag times applied before counting second primary cancers, and variations in comorbidity adjustment methods can further distort risk estimates [9-11,26].

Our study makes several important contributions to the understanding of secondary BC and CRC risks after RT for PCa. By employing a robust NCC design and meticulously adjusting for confounding factors such as age and CCI, we were able to effectively isolate the specific impact of RT within Korea's extensive HIRA service database. Significantly, this research represents a crucial step forward in domestic studies utilizing nationwide claims data from the HIRA. While not the first to explore this area, it is the first to successfully detect a statistically significant increase in BC incidence, leveraging the strengths of the NCC analysis to address temporal considerations [14,17]. The consistent and significant findings derived from this comprehensive analysis underscore the importance of long-term surveillance for BC in patients with PCa treated with RT, providing valuable insights for clinical practice and patient counseling in Korea.

Our study has some limitations. First, our classification of treatment cohorts has a limitation regarding the active comparator. We acknowledge that comparing the RT group with patients undergoing radical prostatectomy is the most academically preferred method for isolating the pure effect of radiation. However, our NCC design inherently led to a lower final sample size. Furthermore, due to the extremely low incidence of secondary BC and CRC within this specific patient population, attempting to perform analyses using over two highly subdivided cohorts risked a loss of statistical power and undesirable results. This practical constraint led us to use the non-RT cohort, which groups patients receiving various other treatments, as the most feasible alternative to maintain statistical validity. Moreover, this approach simplifies the comparison group to maintain power when analyzing rare outcomes and is consistent with other domestic big data studies [27]. However, we recognize that this grouping may obscure treatment-specific effects and that the

comparison may not fully represent a radiation-free control. Second, another major limitation of our study stems from the intrinsic structural nature of the HIRA database. Since this data is based on insurance claims and billing records, it is inherently distinct from the detailed health screening data available on the NHIS. Therefore, we could not adjust for critical personal lifestyle variables such as smoking status, alcohol consumption, physical activity, and obesity. The absence of these data poses a significant limitation as smoking is a well-established risk factor for both BC and CRC. Although we adjusted for comorbidity burden using the CCI, the lack of these key lifestyle variables may limit the accuracy of our risk assessment. Future domestic studies can overcome this limitation by integrating NHIS health screening data to adjust for these variables and, thereby, strengthen the internal validity and causality assessment of the association between RT and secondary cancer incidence. Finally, our findings highlight the need for more granular comparisons among different RT modalities, including brachytherapy, and analyses that capture evolving treatment techniques and dose distributions over time [28-30]. However, recent studies have reported outcomes that diverge from common expectations, suggesting that further research is needed in this area [31].

CONCLUSIONS

Our HIRA database analysis, which employed an NCC design, revealed a statistically significant increase in the incidence of secondary BC after RT for PCa. Conversely, we observed no significant increase in the number of secondary CRC cases. These findings suggest the need for systematic long-term surveillance of secondary cancers, particularly BC, in patients with PCa who undergo RT. More comprehensive research is essential to elucidate the risks and mechanisms of secondary cancers, including BC, in this patient population.

Conflict of Interest

The authors have nothing to disclose.

Funding

This study was supported by the Korean Urological Association in 2024 (2024-KUA-003), and by a new faculty research seed money grant of Yonsei University College of Medicine for 2025 (2025-32-0036).

Acknowledgements

The authors would like to thank the Health Insurance Review and Assessment Service (HIRA) of Korea for providing access to the claims data used in this study.

Author Contribution

Conceptualization: JK, KSC, DKK. Data curation: JK, DKK. Formal analysis: JK, DKK. Funding acquisition: JK, DKK. Investigation: JK, JJ, HSL, SJ, DKK. Methodology: JK, JJ, HSL, SJ, SB, KSL, KCK, KSC, DKK. Project administration: JK, DKK. Resources: JK, DKK. Software: JK, KSC, DKK. Supervision: JK, KSC. Validation: JK, JJ, HSL, SJ, SB, KSL, KCK, DKK. Visualization: JK, HSL, SJ, DKK. Writing – original draft: JK, DKK. Writing – review & editing: JK, DKK.

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