British Journal of Cancer www.nature.com/bjc

ARTICLE

Clinical Study

Adjuvant radiotherapy and skin cancer risk in breast cancer survivors: a nationwide cohort study in Korea

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BACKGROUND: Adjuvant radiotherapy (RT) is standard for breast cancer, but its impact on skin cancer risk, especially in Asian populations, remains unclear despite advanced techniques. This study aimed to assess skin cancer incidence following RT in a large South Korean cohort.

METHODS: This retrospective cohort study, using South Korean Health Insurance Review and Assessment Service data (2009–2012), included 37,957 patients aged ≥20 with invasive breast cancer or ductal carcinoma in situ who underwent curative surgery. Prior malignancies or oncological treatment were excluded. Incidence of malignant melanoma and non-melanoma skin cancers were assessed. 1:1 propensity score matching was performed to balance confounders, resulting in 19,856 matched patients (9928 per group). Multivariable Cox proportional hazards models identified risk factors.

RESULTS: Post-matching, skin cancer incidence was comparable between RT and non-RT (NRT) groups (0.97% vs. 1.02%; $p = 0.720$). RT showed no significant association with overall skin cancer ($p = 0.604$), malignant melanoma ($p = 0.094$) or non-melanoma skin cancer ($p = 0.196$). Increased risk was associated with older age, mole presence (HR 5.254), pre-malignant skin lesions (HR 12.905), and lymphedema (HR 1.978).

CONCLUSION: Adjuvant RT did not increase skin cancer risk after breast cancer surgery. Dermatologic factors and lymphedema were principal predictors, emphasising vigilant follow-up in at-risk patients.

British Journal of Cancer; https://doi.org/10.1038/s41416-026-03485-z

INTRODUCTION

Since the publication of the National Surgical Adjuvant Breast and Bowel Project B-06 trial in 1985, adjuvant radiotherapy (RT) has been established as the standard treatment modality for breast cancer in combination with breast-conserving surgery [1–4]. However, subsequent studies have reported various radiation-induced toxicities, including a low but quantifiable risk of radiation-associated secondary malignancies [5–7]. A case-control study conducted in New Hampshire [8] demonstrated an increased risk of both basal cell carcinoma (odds ratio [OR] 3.30, 95% confidence intervals [CIs] 1.60–6.81) and squamous cell carcinoma (OR 2.94, 95% CIs 1.30–6.67) following therapeutic exposure to ionising radiation.

The widespread adoption of RT in breast cancer management has raised concerns regarding its potential contribution to the development of cutaneous malignancies. Reportedly, 13.0% of patients with breast cancer develop secondary malignancies, of which 3.4% are attributable to prior RT [9]. More recent population-based analyses using data from the Surveillance, Epidemiology, and End Results (SEER) database have documented a 12–57% increased risk of specific skin cancers in RT-treated patients with breast cancer compared with the general population [10, 11]. However, Asian populations remain markedly under-represented in these studies. Recent data from South Korea indicates a significant upward trend in the incidence of skin cancer. For instance, the prevalence of non-melanoma skin cancer rose from 6.32 per 100,000 in 2008 to 10.11 per 100,000 in 2016 [12], while that of melanoma also escalated from 4.4 per 100,000 to 5.9 per 100,000 over the same period [13]. This rapid increase underscores the importance of evaluating the long-term dermatological safety of radiotherapy in the growing population of breast cancer survivors.

Recent advancements in RT techniques, such as (ultra-) hypofractionation, reduced-dose irradiation, and intensity-modulated RT (IMRT), appear to have reduced post-RT toxicity compared with conventional RT [14–18]. Nevertheless, evidence regarding the impact of these techniques on the incidence of secondary malignancies is lacking. Moreover, there is a paucity of recent large-scale, long-term follow-up cohort studies evaluating the association between adjuvant RT and the risk of

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Received: 12 October 2025 Revised: 17 April 2026 Accepted: 20 May 2026
Published online: 12 June 2026

skin cancer in patients with breast cancer during the modern RT era.

In this study, we aimed to evaluate the risk of RT-associated skin cancers, including malignant melanoma and non-melanoma skin cancer, among patients with breast cancer in Korea.

METHODS

Study design

This retrospective observational study used data extracted from the Health Insurance Review and Assessment Service database of South Korea, which oversees reimbursement for the National Health Insurance (NHI) system. The NHI database contains comprehensive demographic and clinical information, including patients' medical histories, dates of diagnosis, diagnostic codes, treatment modalities, and prescription records. Diagnostic information was coded using the International Classification of Diseases, 10th revision (ICD-10) [19]. Given that the NHI monitors ICD-10 codes for treatments and prescriptions, the diagnostic coding in this database is considered reliable.

Regarding ethnicity, while the HIRA database does not explicitly record individual race, the South Korean population is characterised by high ethnic homogeneity. According to the 2015 Population and Housing Census by Statistics Korea, 98.1% and 97.3% of the population in 2010 and 2015, respectively, were Korean nationals [20]. Given that the majority of foreign residents were also of Asian descent, this cohort is effectively representative of an Asian population [21].

All data were anonymized in accordance with the privacy guidelines of the Health Insurance Portability and Accountability Act of Korea. The study protocol was approved by the Institutional Review Board (IRB of Seoul St. Mary's Hospital (local IRB number: KC22ZISI0340). Given that this was a retrospective study using de-identified data, the requirement for informed consent was waived.

Inclusion and exclusion criteria

Patients aged 20 years or older with medical records from January 1, 2007, to December 31, 2021, were initially screened. Individuals diagnosed with invasive breast cancer (ICD-10 code C50) or ductal carcinoma in situ (DCIS; ICD-10 code D05) between 2009 and 2012 were identified. Eligible patients were those who underwent curative surgery within one year of diagnosis, confirmed using the surgical procedure codes N7135-7139, P2124, and P2122 (Supplementary Table 1).

Patients were excluded if they had any other malignancy (including skin cancer or any ICD-10 C code) diagnosed within 2 years prior to or 6 months after breast cancer surgery. Patients who received chemotherapy, targeted therapy, or RT within 1 year prior to surgery were also excluded to reduce confounding bias.

Regarding RT techniques, national data indicate that the use of IMRT for breast cancer was negligible during the study period (2009–2012) due to restrictions in insurance coverage. Only 45 and 87 cases were reported nationwide in 2011 and 2012, respectively [22]. Therefore, vast majority of patients in this cohort received 3D-conformal radiotherapy (3D-CRT).

Enrolled patients were followed up until December 31, 2021, to assess the development of skin cancer according to the receipt of adjuvant RT. Patients without events during the follow-up period were censored on December 31, 2021. Neither human immunodeficiency infection (ICD-10 code B24) nor xeroderma pigmentosum (ICD-10 code Q821) was identified in this cohort.

Study endpoints and variable definition

The primary endpoint was the diagnosis of skin cancer following adjuvant RT, including melanoma (C43 for malignant melanoma) and non-melanoma skin cancer (C44 for non-melanoma skin cancer), as shown in Supplementary Table 2. Notably, ICD-10 codes C43 and C44 cover all types of skin cancers except for sarcomas.

Potential confounding variables included age, breast malignancy type (DCIS or invasive carcinoma), history of benign or pre-malignant skin conditions, specifically molar (ICD-10 code, D229), actinic keratosis or Bowen's disease (ICD-10 code, L570 or D049, respectively), receipt of chemotherapy, target therapy, hormonal therapy, and the presence of lymphedema. The relevant drug prescription codes are listed in Supplementary Table 3.

The Charlson Comorbidity Index (CCI), a well-known tool for estimating the 10-year survival rate of patients with multiple comorbidities, was analysed and used as a weighted index [23]. Patients diagnosed with xeroderma pigmentosum (ICD-10 code, Q821), a known predisposing condition for skin malignancies, were not presented in this study population.

To reduce confounding bias, patients who received RT were matched 1:1 with those who did not undergo RT, using propensity score matching based on age, sex, adjuvant treatment modality (hormonal therapy, chemotherapy, and targeted therapy), CCI score, presence of moles, and pre-malignant skin lesions [23]. Matching was performed using the nearest-neighbour greedy matching algorithm with a caliper of 0.001 to ensure close matches and avoid poor quality pairs. All matching procedures were conducted using the 'Matchit' package in R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). Logistic regression analysis was conducted using the previously mentioned confounding variables.

Statistical analysis

Continuous variables were compared between the two groups using an independent two-sample *t*-test, whereas categorical variables were compared using either the chi-square test or Fisher's exact test. Age was categorised into decade-based groups for categorical analysis.

The incidence of skin cancer was illustrated using Kaplan–Meier curves and compared between the two groups using the log-rank test. Cox proportional hazard analysis models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs), adjusting for potential confounders. Statistical significance was determined at a two-sided $p < 0.05$. Data analyses were conducted using the SAS software (version 9.4; SAS Institute, Cary, NC, USA).

Patient selection and enrollment

A total of 83,437 patients diagnosed with DCIS or invasive breast cancer between January 1, 2009, and December 31, 2012, were initially identified. Of these, 52,510 patients underwent breast cancer surgery within 1 year of diagnosis. In total, 14,553 patients were excluded based on the following criteria: diagnosis of another malignancy within 2 years prior to or 6 months following breast cancer surgery ($n = 3527$); receipt of any chemotherapy, targeted therapy, endocrine therapy, or radiation for cancer within 1-year prior to surgery ($n = 11,023$); or diagnosis of skin cancer within 2-years prior to surgery ($n = 88$). After applying the exclusion criteria, 37,957 patients were included in this study. Prior to propensity score matching, the RT group comprised 11,434 patients, and the non-RT (NRT) group comprised 26,523 patients (Fig. 1).

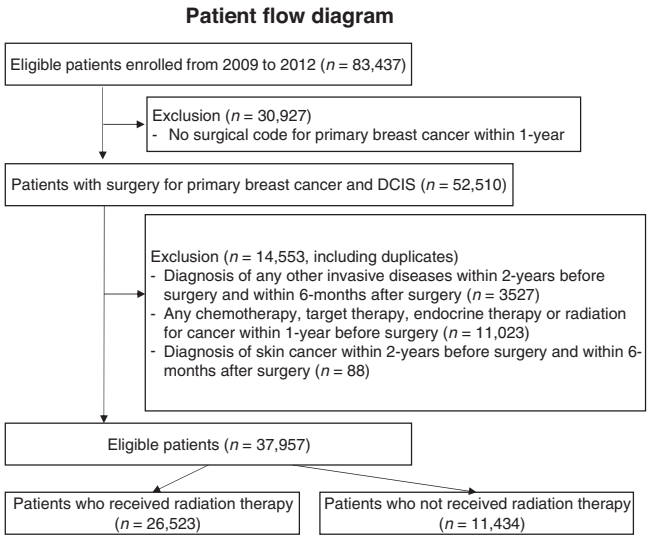

Fig. 1 Patient selection and enrollment flowchart. Flow diagram illustrating the step-by-step selection criteria and enrollment process of breast cancer patients from the Health Insurance Review and Assessment Service (HIRA) database of South Korea. Exclusions are explicitly detailed chronologically along with their corresponding sample sizes.

RESULTS

Baseline demographics and incidence of skin cancer

Table 1 compares the demographics and incidence of skin cancer between the two groups, including age, sex, CCI, treatment modalities, presence of molar or pre-malignant skin lesions (actinic keratosis or Bowen's disease), and lymphedema. A total of 37,796 (99.6%) patients were female. Among them, 32,372 (85.3%) patients were diagnosed with invasive breast cancer, and 5585 (14.7%) were diagnosed with DCIS. The most prevalent age group was the 40 s, comprising 13,986 patients (36.85%). Only 264 (0.7%) patients had one or more moles (ICD-10 code D229), and 285 (0.8%) had actinic keratosis or Bowen's disease (ICD-10 codes L570 and D049, respectively). Notably, 2487 (6.6%) patients developed lymphedema during the observational period. Overall, 402 patients (1.06%) developed a type of skin cancer (ICD-10 code C43 or C44), including 69 (0.18%) with malignant melanoma (ICD-10 code C43) and 338 (0.89%) with non-melanoma skin cancer (ICD-10 code C44).

Before matching, 11,434 (30.1%) and 26,523 (69.9%) patients were included in the RT and NRT groups, respectively. Both groups had the highest proportion of patients in their 40 s, with 3630 (31.8%) in the RT group and 10,356 (39.1%) in the NRT group ($p < 0.001$). Compared with the NRT group, the RT group had a lower rate of chemotherapy, endocrine therapy, HER2-targeted therapy, and lymphedema (all $p < 0.001$). Additionally, the presence of moles was lower in the RT group than in the NRT group (58 [0.51%] vs. 206 [0.78%] patients; $p = 0.004$).

After matching, 19,856 patients were included in the study, with 9928 patients in each group. The matched groups were well balanced in terms of age, sex, and other characteristics, including CCI, adjuvant treatment, diagnosis, and the presence of moles or lymphedema.

Before matching, the incidence of skin cancer was similar between the RT and NRT groups (121 [1.06%] vs. 281 [1.06%]; $p = 0.992$). Notably, 26 (0.23%) patients in the RT group and 43 (0.16%) in the NRT group developed malignant melanoma, whereas 97 (0.85%) patients in the RT group and 241 (0.91%) in the NRT group developed non-melanoma skin cancer ($p = 0.171$ and 0.566, respectively). After matching, 96 (0.97%) patients in the RT group and 101 (1.02%) patients in the NRT group developed skin cancer ($p = 0.720$); 18 (0.18%) patients with RT group and 9 (0.09%) in the NRT group developed malignant melanoma of the skin ($p = 0.083$); and 78 (0.79%) in the RT group and 93 (0.94%) in the NRT group developed non-melanoma skin malignancy ($p = 0.249$).

Risk factors associated with skin cancer

Table 2 presents the Cox proportional hazard models used to evaluate the risk factors for skin cancer (ICD-10 codes C43 and C44). RT was not a significant risk factor compared with NRT, both before and after matching (before matching, multivariable analysis, HR 1.057, 95% CIs 0.847–1.321, $p = 0.622$; after matching, multivariable analysis, HR 1.077, 95% CI 0.814–1.425, $p = 0.604$). Likewise, neither sex nor the type of systemic treatment was significantly associated with the development of skin cancer.

In the univariable analysis before matching, patients with DCIS had a 30% lower probability of developing skin cancer than those with invasive breast cancer (HR 0.70, 95% CI 0.511–0.961; $p = 0.027$). Each 10-year increase in age was associated with a higher risk of skin cancer, both before and after matching (before matching, multivariable analysis, HR 1.232, 95% CI 1.127–1.347, $p < 0.001$; after matching, multivariable analysis, HR 1.294, 95% CI 1.139–1.470, $p < 0.001$).

The presence of moles was associated with a 4- to 5-fold increased risk of skin cancer (before matching, multivariable analysis, HR 4.400, 95% CI 2.496–7.754, $p < 0.001$; after matching, multivariable analysis, HR 5.254, 95% CI 2.215–12.466, $p < 0.001$). Pre-malignant skin lesions, including actinic keratosis or Bowen's disease, were associated with a more than 10-fold increase in the risk of developing skin cancer (before matching, multivariable analysis, HR 10.327, 95% CIs 7.210–14.792, $p < 0.001$; after matching, multivariable analysis, HR 12.905, 95% CI 7.304–22.799, $p < 0.001$).

Lymphedema was also a significant risk factor for skin cancer both before and after matching (before matching, multivariable analysis, HR 1.599, 95% CI 1.155–2.216, $p = 0.005$; after matching, multivariable analysis, HR 1.978, 95% CI 1.144–3.419, $p = 0.015$).

Incidence and temporal risk of skin malignancies associated with RT

The median follow-up duration for patients who developed skin cancer (ICD-10 code, C43 or C44) was 138.0 months before matching (range, 105.4–164.6 months) and 138.1 months after matching (range, 106.1–164.6 months). Figure 2 demonstrates that the cumulative incidence of skin cancer did not differ significantly between the RT and NRT groups before and after matching (log-rank test, $p = 0.912$ and 0.651, respectively).

Figure 3 illustrates that RT was not a significant risk factor for developing malignant melanoma (Fig. 3a, before matching, $p = 0.178$; Fig. 3b, after matching, $p = 0.085$) or non-melanoma skin cancer (Fig. 3c, before matching, $p = 0.501$; Fig. 3d, after matching, $p = 0.211$). The annual hazard rate for skin cancer did not differ significantly according to the use of RT (Supplementary Fig. 1).

Subgroup analysis of risk factors for skin cancer: melanoma and non-melanoma

Subgroup analysis using Cox proportional hazards models (Supplementary Table 5) revealed that the presence of moles was associated with a significantly increased risk of developing malignant melanoma (HR 25.692, 95% CI 8.023–82.270; $p < 0.001$). Variables such as age, pre-malignant skin lesions, and lymphedema, which were significant for all skin cancers, were not significantly associated with the risk of melanoma. Although not significant, patients who received RT had a 50% lower risk of developing malignant melanoma than those who did not undergo RT (multivariable analysis after matching, HR 0.505, 95% CI 0.227–1.124; $p = 0.094$).

In the subgroup analysis of non-melanoma skin cancers (Supplementary Table 6), the significant risk factors included increasing age (HR 1.385, 95% CI 1.207–1.588, $p < 0.001$), actinic keratosis, Bowen's disease risk (HR 14.941, 95% CI 4.829–46.483, $p < 0.001$), and lymphedema (HR 1.991, 95% CI 1.104–3.591, $p = 0.022$). Receipt of RT was not significantly associated with non-melanoma skin cancers (HR 1.220, 95% CI 0.903–1.649; $p = 0.196$). Other treatments, including chemotherapy, endocrine therapy, and HER2-targeted therapy, demonstrated no significant association.

Consistent with the overall skin cancer findings, the annual hazard rate for each type of skin cancer (melanoma or non-melanoma skin cancer) showed no statistically significant differences between the RT and NRT groups before and after matching (Supplementary Fig. 2).

DISCUSSION

Although RT has demonstrated substantial benefits in breast cancer treatment, concerns regarding its potential adverse effects, particularly the risk of secondary skin cancer, persist [1, 5, 6, 8–11]. Given that patients with breast cancer receive radiation to the chest wall and axilla, we initially analysed the incidence of skin cancer occurring on the trunk (affected remaining ipsilateral breast, chest wall, and axilla) by evaluating specific ICD-10 codes (C435 for malignant melanoma and C445 for non-melanoma skin cancer). Among patients diagnosed with malignant melanoma and non-melanoma skin cancer, 31 of 69 (44.9%) and 173 of 338

Table 1. Comparison of clinical characteristics of patients with breast cancer according to receiving radiation therapy

	Total Cohort $n = 37,957$ (%)	Before matching			After matching		
		Patients with RT, $n = 11,434$ (%)	Patients without RT, $n = 26,523$ (%)	*P* value	Patients with RT, $n = 9928$ (%)	Patients without RT, $n = 9928$ (%)	*P* value
All skin cancer				0.992			0.720
No	37,555 (98.94)	11,313 (98.94)	26,242 (98.94)		9832 (99.03)	9827 (98.98)	
Yes	402 (1.06)	121 (1.06)	281 (1.06)		96 (0.97)	101 (1.02)	
Malignant melanoma				0.171			0.083
No	37,888 (99.82)	11,408 (99.77)	26,480 (99.84)		9910 (99.82)	9919 (99.91)	
Yes	69 (0.18)	26 (0.23)	43 (0.16)		18 (0.18)	9 (0.09)	
Non-melanoma skin cancer				0.566			0.249
No	37,619 (99.11)	11,337 (99.15)	26,282 (99.09)		9850 (99.21)	9835 (99.06)	
Yes	338 (0.89)	97 (0.85)	241 (0.91)		78 (0.79)	93 (0.94)	
Age (year)				<0.001			0.999
20–29	424 (1.12)	88 (0.77)	336 (1.27)		70 (0.71)	66 (0.66)	
30–39	4476 (11.79)	1065 (9.31)	3411 (12.86)		984 (9.91)	977 (9.84)	
40–49	13,986 (36.85)	3630 (31.75)	10,356 (39.05)		3416 (34.41)	3405 (34.30)	
50–59	10,969 (28.90)	2981 (26.07)	7988 (30.12)		2832 (28.53)	2845 (28.66)	
60–69	5306 (13.98)	1927 (16.85)	3379 (12.74)		1734 (17.47)	1741 (17.54)	
70–79	2479 (6.53)	1475 (12.90)	1004 (3.79)		846 (8.52)	852 (8.58)	
80–	317 (0.84)	268 (2.34)	49 (0.18)		46 (0.46)	42 (0.42)	
Gender				<0.001			>0.999
Male	161 (0.42)	116 (1.01)	45(0.17)		19(0.19)	19(0.19)	
Female	37,796 (99.58)	11,318 (98.99)	26,478 (99.83)		9909 (99.81)	9909 (99.81)	
CCI(weight number, mean ± SD)	4.006 ± 2.468	4.125 ± 2.498	3.954 ± 2.453	<0.001	3.997 ± 2.426	3.98 ± 2.4	0.617
Chemotherapy Not done				<0.001			0.955
	14,708 (38.75)	5852 (51.18)	8856 (33.39)		4529 (45.62)	4525 (45.58)	
Done	23,249 (61.25)	5582 (48.82)	17,667 (66.61)		5399 (54.38)	5403 (54.42)	
Endocrine treatment				<0.001			0.538
Not done	9900 (26.08)	3626 (31.71)	6274 (23.65)		2763 (27.83)	2802 (28.22)	
Done	28,057 (73.92)	7808 (68.29)	20,249 (76.35)		7165 (72.17)	7126 (71.78)	
HER2-target therapy				<0.001			0.911
Not done	33,250 (87.60)	10,239 (89.55)	23,011 (86.76)		8811 (88.75)	8806 (88.70)	
Done	4707 (12.40)	1195 (10.45)	3512 (13.24)		1117 (11.25)	1122 (11.30)	
Mole				0.004			0.618
No	37,693 (99.30)	11,376 (99.49)	26,317 (99.22)		9880 (99.52)	9875 (99.47)	
Yes	264 (0.70)	58 (0.51)	206 (0.78)		48 (0.48)	53 (0.53)	
Actinic keratosis or Bowen's disease				0.067			0.685
No	37,672 (99.25)	11,334 (99.13)	26,338 (99.30)		9877 (99.49)	9881 (99.53)	
Yes	285 (0.75)	100 (0.87)	185 (0.70)		51 (0.51)	47 (0.47)	
Diagnosis				<0.001			0.858
DCIS (D05)	5585 (14.71)	2434 (21.29)	3151 (11.88)		1937 (19.51)	1927 (19.41)	
Breast cancer (C50)	32,372 (85.29)	9000 (78.71)	23,372 (88.12)		7991 (80.49)	8001 (80.59)	
Lymphedema				<0.001			0.241
No	35,470 (93.45)	11,042 (96.57)	24,428 (92.10)		9556 (96.25)	9524 (95.93)	
Yes	2487 (6.55)	392 (3.43)	2,095 (7.90)		372 (3.75)	404 (4.07)	

RT Radiotherapy, *CCI* Charlson Comorbidity index, *SD* standard deviation, *HER2* human epidermal growth factor receptor 2, *DCIS* ductal carcinoma in situ

Table 2. Risk of developing all skin cancer from analyses using Cox proportional hazard models

	Before matching				After matching			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CIs)	*P* value	HR (95% CIs)	*P* value	HR (95% CIs)	*P* value	HR (95% CIs)	*P* value
Radiation therapy		0.912		0.622		0.651		0.604
No	Reference		Reference		Reference		Reference	
Yes	1.012 (0.818–1.252)		1.057 (0.847–1.321)		1.067(0.807–1.410)		1.077(0.814–1.425)	
Age (per 10-year)	1.255(1.157–1.361)	<0.001	1.232(1.127–1.347)	<0.001	1.340(1.191–1.508)	<0.001	1.294(1.139–1.470)	<0.001
Gender		0.381		0.335		0.859		0.793
Male	Reference		Reference		Reference		Reference	
Female	3.446(0.216–54.907)		3.939(0.243–63.824)		0.778(0.048–12.556)		0.686(0.042–11.338)	
CCI (weight number)	1.060(1.023–1.098)	0.001	1.034(0.997–1.073)	0.075	1.077(1.023–1.133)	0.005	1.046(0.992–1.104)	0.097
Mole		<0.001		<0.001		<0.001		<0.001
No	Reference		Reference		Reference		Reference	
Yes	4.408(2.482–7.829)		4.400(2.496–7.754)		5.071(2.087–12.324)		5.254(2.215–12.466)	
Actinic keratosis or Bowen's disease		<0.001		<0.001		<0.001		<0.001
No	Reference		Reference		Reference		Reference	
Yes	12.099(8.474–17.275)		10.327(7.210–14.792)		14.776(8.418–25.934)		12.905(7.304–22.799)	
Diagnosis		0.027		0.314		0.072		0.714
Breast cancer	Reference		Reference		Reference		Reference	
DCIS	0.701(0.511–0.961)		0.841(0.600–1.178)		0.693(0.464–1.033)		0.921(0.594–1.428)	
Lymphedema		0.002		0.005		0.021		0.015
No	Reference		Reference		Reference		Reference	
Yes	1.673(1.216–2.303)		1.599(1.155–2.216)		1.897(1.102–3.266)		1.978(1.144–3.419)	
Chemotherapy		0.278		0.391		0.500		0.716
Not done	Reference		Reference		Reference		Reference	
Done	1.119(0.913–1.372)		1.108(0.876–1.402)		1.102(0.831–1.461)		1.063(0.766–1.474)	
Endocrine therapy		0.863		0.760		0.476		0.610
Not done	Reference		Reference		Reference		Reference	
Done	0.981(0.786–1.224)		1.036(0.826–1.299)		0.896(0.661–1.213)		0.922(0.676–1.258)	
HER2-target therapy		0.129		0.382		0.162		0.353
Not done	Reference		Reference		Reference		Reference	
Done	1.239(0.940–1.633)		1.139(0.851–1.525)		1.331(0.892–1.985)		1.227(0.797–1.890)	

HR, hazard ratio; CCI, Charlson Comorbidity index; DCIS, ductal carcinoma in situ; HER2, human epidermal growth factor receptor 2

(51.2%) patients, respectively, had trunk involvement. However, because a definitive correlation between ipsilateral skin cancer and the radiation field could not be established, this analysis was ultimately excluded.

Owing to limitations in the claims data, the procedure codes for axillary surgery could not differentiate between sentinel lymph node biopsy and axillary lymph node dissection; therefore, the axillary surgical approach was excluded from this analysis. In addition, the use of claims data, rather than hospital-based electronical medical records, lack detailed clinical information, such as mortality data, TNM stage, histopathological subtype, and tumour biology, as well as specifics on target field, dose, or fractionation in radiotherapy records. Nevertheless, the inclusion of radiotherapy procedures coded under a breast cancer diagnosis validates their relevance to breast cancer treatment, a crucial point despite this intrinsic limitation of utilising the HIRA claims data.

Recent studies using the SEER database have revealed that RT in breast cancer treatment may increase the risk of skin cancer [10, 11]. For example, Luo et al. [11] analysed 520,977 patients with breast cancer from 1973 to 2018 and found that the HR for developing secondary cutaneous melanoma was 1.40 ($p < 0.001$) in the RT group compared with that in the NRT group. Similarly, Rezaei et al. [10] analysed 875,880 patients from the SEER database and reported a standardised incidence ratio (SIR) of 1.95 (95% CIs 1.37–2.68; $p < 0.05$) for patients who underwent total mastectomy followed by RT, whereas patients who did not receive RT group after total mastectomy group had an SIR of 1.12 (95% CI 0.92–1.34; $p < 0.05$).

This discrepancy between our findings and those of the SEER-based studies may be attributed to the limitations of our study, owing to its relatively small sample size. However, given that our study enrolled patients more recently (2009 to 2012) compared with preceding studies, it is more likely that recent advancements in RT techniques were incorporated into this cohort of patients, which may have resulted in the discrepancies regarding the impact on secondary skin malignancies after RT among patients with breast cancer. While specific codes for RT techniques were not identified for individual patients, national reimbursement for breast IMRT in South Korea was highly restricted until July 2015. National data indicate that only 45 and 87 breast cancer cases were treated with IMRT nationwide in 2011 and 2012, respectively, suggesting that our cohort primarily reflects the safety profile of

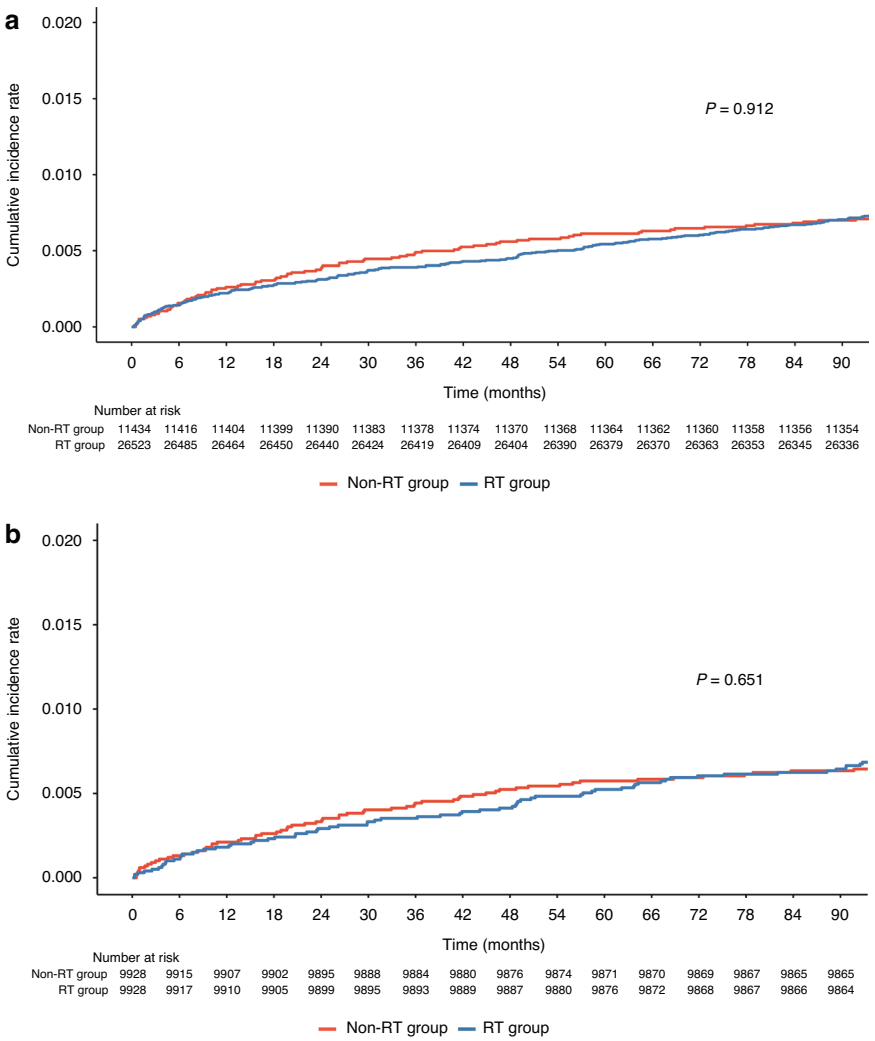

Fig. 2 Kaplan–Meier analysis of the incidence of skin cancer in breast cancer patients according to receiving radiation therapy. Before matching (median follow up 137.74 ± 16.55 months), there was no significant difference in the incidence of all skin cancer according to receiving radiation therapy (a, patients who did not receive radiation therapy, $n = 11{,}434$, patients who received radiation therapy $n = 26{,}523$, $p = 0.912$, log-rank test). After matching (median follow up 137.97 ± 16.45 months), there was no significant difference in the incidence of all skin cancer according to receiving radiation therapy as well (b, patients who did not receive radiation therapy, $n = 9928$, patients who received radiation therapy $n = 9928$, $p = 0.651$, log-rank test).

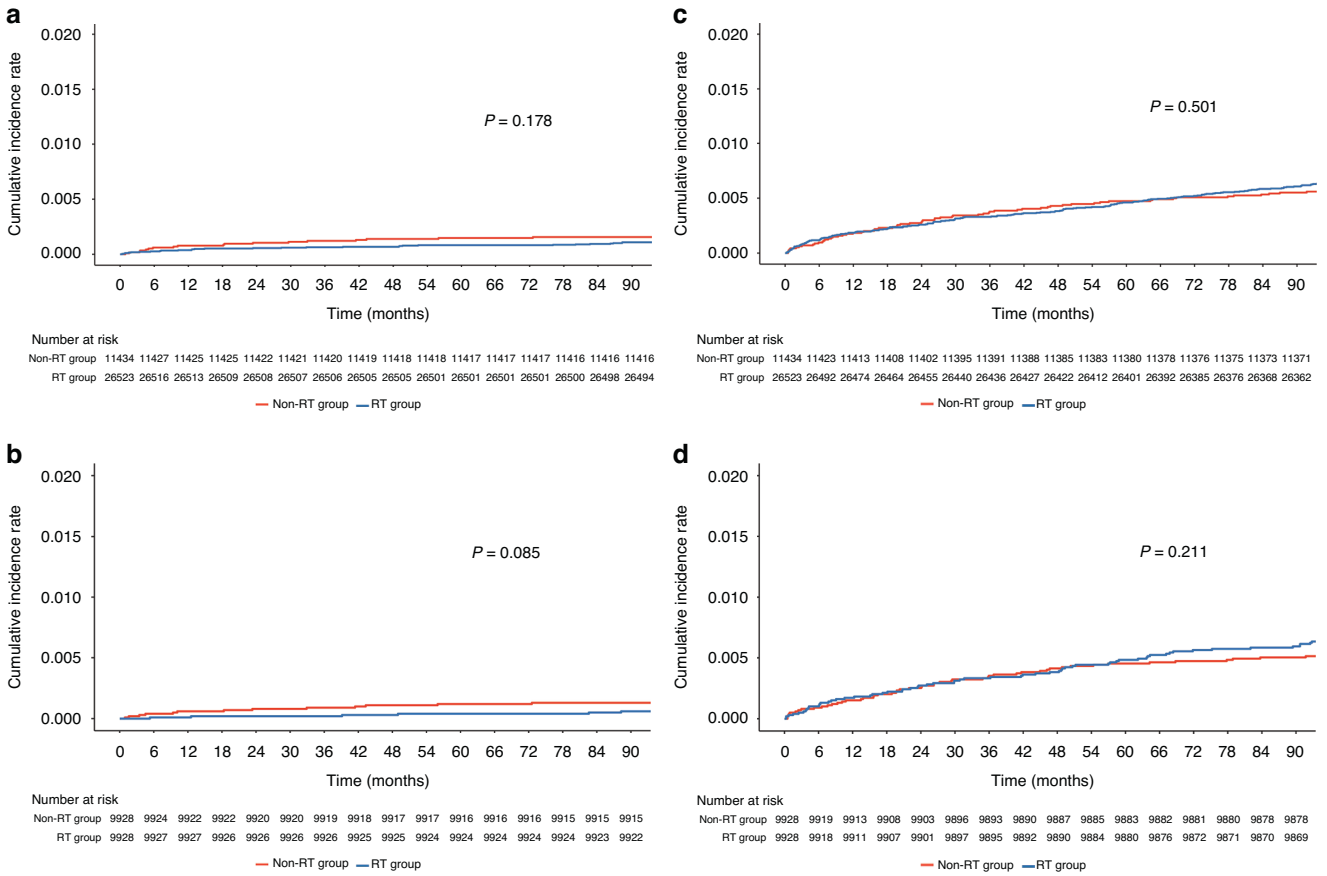

Fig. 3 Kaplan–Meier analysis of the incidence of types of skin cancer in breast cancer patients according to receiving radiation therapy. **a** Before matching (median follow up 137.87 ± 14.33 months), there was no significant difference in the incidence of malignant melanoma according to receiving radiation therapy (patients who did not receive radiation therapy, $n = 11,434$, patients who received radiation therapy $n = 26,523$, $p = 0.178$, log-rank test). **b** Before matching (median follow up 137.80 ± 16.08 months), there was no significant difference in the incidence of other skin cancers except malignant melanoma according to receiving radiation therapy (patients who did not receive radiation therapy, $n = 11,434$, patients who received radiation therapy $n = 26,523$, $p = 0.501$, log-rank test). **c** After matching (median follow up 138.10 ± 14.25 months), there was no significant difference in the incidence of malignant melanoma according to receiving radiation therapy (patients who did not receive radiation therapy, $n = 9,928$, patients who received radiation therapy $n = 9928$, $p = 0.085$, log-rank test). **d** After matching (median follow up 138.00 ± 16.09 months), there was no significant difference in the incidence of other skin cancers except malignant melanoma according to receiving radiation therapy (patients who did not receive radiation therapy, $n = 9928$, patients who received radiation therapy $n = 9928$, $p = 0.211$, log-rank test).

3D-CRT. Nevertheless, compared to older SEER-based studies that included patients from the 1970s and 80 s, an era characterised by 2D planning, our cohort represents the 3D-CRT era. Advancements such as de-escalation of RT, hypofractionation, and reduced-dose irradiation have been widely employed during this period owing to their non-inferior efficacy with fewer normal tissue effects compared with conventional RT [14–17]. While robust evidence is currently lacking, these advancements, including the shift toward 3D-CRT, may be a contributing factor to the non-increased incidence of secondary skin malignancies observed after breast cancer radiotherapy in our contemporary cohort. Therefore, this potential influence should be interpreted with caution, and further dedicated investigations are clearly warranted.

Another potential explanation for the discrepancy with previous studies may be the lack of data on other known risk factors for skin cancer, such as exposure to ultraviolet light. Importantly, racial composition may also account for this difference. While the SEER data consisted predominantly of 70–85% Caucasians and less than 10% Asians, our study primarily consisted of Asian patients [10, 11]. Numerous studies have shown that non-Hispanic white individuals are more vulnerable to skin cancer than Asians due to differences in melanin density and sensitivity to ultraviolet damage [24, 25]. The results of this study suggest that RT may pose a lower risk of skin cancer in Asian populations than in Western populations. Additionally, given that the latency period for radiation-induced non-melanoma skin cancer is presumed to be at least 20 years, and our study had a median follow-up time of 137 months, long-term follow-up is warranted to confirm these findings [8].

In the current study, we found that lymphedema, rather than RT, was associated with a 2-fold increased risk of developing any type of skin cancer. Consistently, a retrospective study by Anand et al. [26] at the Mayo Clinic revealed that lymphedema in the lower extremity was associated with a higher risk of non-melanoma skin cancers, with an HR of 2.65 (95% CI 1.17–5.99; $p = 0.02$). Although Stewart-Treves syndrome, a rare lymphangiosarcoma occurring after chronic lymphedema in post-mastectomy patients, was not evaluated in this study, the mechanism of lymphatic stasis may influence the development of soft tissue malignancy [27]. Lymphatic stasis may lead to localised immunosuppression and a growth factor-rich environment with vascular and lymphatic collaterals, which could contribute to the development of localised malignancy [27–29]. Although further research is needed to investigate the causal relationship with lymphedema and pre-malignant lesions, our findings underscore that early detection and management of lymphedema may be clinically

beneficial in reducing the risk of skin malignancies in this patient population.

Our study was based on a novel concept that sought to determine the incidence of skin cancer post-RT in patients with breast cancer in Korea, in which the data were based on a large cohort with a sufficient median follow-up time of more than 10 years. Another strength of our study is the inclusion of patients who underwent novel RT techniques, which appears to have made a difference compared with previous studies. However, its retrospective and observational nature, with a short 4-year enrollment period, may have introduced bias in the selection of cohort groups.

As racial and ethnicity significantly affects skin cancer risk, the specific demographic profile of our predominantly Korean study population imposes inherent limitations. We recognise that factors such as the Korean breast cancer cohort's relatively younger median age at diagnosis and low smoking prevalence compared to that of other ethnicities, combined with a follow-up period of 138 months, may be insufficient to capture outcomes with a known latency of over 20 years for radiation-induced skin cancers. Based on these limitations, caution is warranted against over-interpretation asserting long-term dermatological safety for the general population beyond this specific cohort.

Because the study was mainly conducted using ICD-10 codes, identifying whether skin malignancy developed in the irradiated field was nearly impossible. Specific codes denoting the affected site (e.g., ICD-10 code, C435 for malignant melanoma of the trunk) lack information on the lesion site and laterality, thereby obscuring the association between secondary skin cancer and irradiation. Nonetheless, since both the radiotherapy and non-radiotherapy groups were subject to the same background risk, and no differences were observed across anatomical sites, we consider the effect of uncaptured non-irradiated cancers to be minimised.

Although angiosarcoma is known to be associated with irradiation in patients with breast cancer, our study focused only on skin malignancies [30, 31]. Due to its low incidence rate, radiation-associated angiosarcoma (RAAS) was not included in the scope of the present analysis. Future large-scale studies with longer follow-up are warranted to specifically address the risk of RAAS following breast cancer treatment.

CONCLUSIONS

In this nationwide cohort study, radiotherapy was not associated with an increased risk of skin cancer in patients with breast cancer. Even after long-term follow-up and propensity score matching, no significant difference in the incidence of skin cancer was observed between the RT and NRT groups. Over the observed follow-up period, our findings show no detectable association between radiotherapy and an increased risk of skin cancer in this cohort, highlighting the need for continued surveillance and further investigation of non-radiotherapy related risk factors.

DATA AVAILABILITY

All data generated or analysed during this study are included in this research article and supplementary information files. However, the original data are prohibited from being exported outside due to NHI policy.

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AUTHOR CONTRIBUTIONS

CIY had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Conceptualisation: JHC, DK, and CIY; Data curation, HSL, SJ; Funding acquisition, CIY; Investigation, JHC, DK, HSL, SJ, and CIY; Methodology, JHC, DK, HSL, SJ, and CIY; Resources, HSL, SJ; Formal analysis, JHC, DK, and CIY; Supervision, WCP, JHS; Writing-original draft, JHC, DK, and CIY; Writing-review & editing, JAL, YJL, SYB and CIY.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study protocol was approved by the Institutional Review Board (Local IRB number: KC22ZISI0340) of Seoul St. Mary's Hospital. The need for informed consent was waived by the IRB due to the retrospective study design.

CONSENT FOR PUBLICATION

All authors have given consent for publication.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41416-026-03485-z.

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