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Increased second primary liver cancer risk in young breast cancer patients undergoing radiotherapy and chemotherapy: a nationwide population-based study

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► ***Original article***

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ABSTRACT

***Background*:** Although chemotherapy (CT) and radiotherapy (RT) are important breast cancer (BC) treatment modalities, they can cause other cancers. However, second cancers of liver and stomach tend to be ignored during BC treatment. In this study, the incidence patterns of second primary cancer of liver and stomach were analyzed. ***Materials and Methods*:** The insurance claim data of patients that underwent definitive surgery from 2009 to 2010 were analyzed. Standardized incidence ratios (SIRs) were used to estimate the relative risks of second primary liver cancer (SPLC) and second primary stomach cancer (SPSC). In addition, hazard ratios (HRs) of risk factors were analyzed. Data were obtained on 21,024 BC patients that underwent definitive mastectomy. ***Results*:** The median follow-up period was 105.5 months. Overall SIRs for SPLC and SPSC were 7.26 ($p<0.01$) and 2.92 ($p<0.01$). In the young age group (aged 20–39 years), the crude HR for CT was 2.27 ($p < 0.05$) and the age/RT adjusted HR was 2.37 ($p<0.05$). RT also showed a tendency to induce SPLC. The effect of CT peaked within 5 years after treatment, whereas the effect of RT gradually increased after 5 years. ***Conclusion*:** This study shows CT and RT both increase the risk of SPLC in BC patients and that these increases are greater in young BC patients. Times to SPLC occurrence after RT and CT were found to differ.

INTRODUCTION

Breast cancer (BC) is a highly prevalent solid cancer among Korean women but has a high cure rate due to recent treatment developments [1, 2]. However, some studies have reported that the rate of second primary cancer (SPC) in BC patients is higher than in the general population [3-7]. Genetic predisposition and lifestyle may cause other cancers in BC patients, but several studies have reported that radiation therapy (RT) and chemotherapy (CT) for BC are underlying causes of SPC [8-10]. In clinics, the risk of developing SPC is often not considered when deciding on a treatment modality. However, BC patients have much longer life expectancies than patients with other organ cancers. The 5- and 10-year overall survival rates for all stages BC are 91.2% and 84.8%, respectively [11]. Moreover, BC patients are relatively young at disease onset [12].

In BC, CT is an important treatment modality that improves survival and is administered to most patients, except those with early-stage disease [13, 14]. However, it has been established that CT may cause cancer [9]. RT is also an important treatment modality [8], and the majority of patients that undergo breast-conserving surgery receive RT [15]. Remaining breast tissues and regional lymph node chains are included in irradiation fields, as are liver and stomach. In fact, planned target volumes and penumbra areas include liver and stomach in both high and low radiation dose regions. Although some studies have already been undertaken on radiation-induced SPC, the majority have addressed thyroid and lung cancer [16-19], few studies have sought to determine patterns of second primary liver cancer (SPLC) or second primary stomach cancer (SPSC) after RT.

SPC for liver and stomach included in the RT field tend to be overlooked, but may be an important factor in treatment choices in young BC patients. First of all, we thought that the quantification of SPC risk is necessary. We analyzed the prevalence of SPLC and SPSC according to the treatment modalities, such as CT and RT, in BC patients underwent curative mastectomy, using the database accumulated in the Health Insurance Review & Assessment Service (HIRA) in the South Korea. The age pattern and onset time of SPC occurrence were also analyzed.

MATERIALS AND METHODS

The Korean National Health Insurance (NHI) System is a national system that covers almost all residents. Data such as sex, age, diagnosis,

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prescriptions, and procedures for nearly all medical claims in South Korea are stored in the HIRA database. The present study was conducted on a nationwide cohort using this database. The subjects were 21,024 patients diagnosed with BC from January 2009 to December 2010 that underwent definitive surgery. Patients with distant metastasis or a concurrent malignancy at time of BC diagnosis were excluded. The institutional review board (IRB) of Dongguk University Gyeongju Hospital approved the study (IRB no. 110757-201905-HR-07-02).

The study population consisted of patients diagnosed with BC (C50) according to the Korean Classification of Disease, sixth edition (KCD-6), a version of the International Classification of Disease 10 (ICD-10) modified for the Korean health care system. BC subgroups, that is, nipple and areola (C500), central portion (C501), upper inner quadrant (C502), lower inner quadrant (C503), upper outer quadrant (C504), lower outer quadrant (C505), axillary tail (C506), overlapping lesion (C508), and unspecified (C509), were included. Patients that underwent definitive surgery were identified using procedure codes corresponding to total mastectomy (N7131), partial mastectomy (N7133), or radical mastectomy (N7135). The occurrences of liver cancer (C22) and gastric cancer (C16) after curative BC treatment were monitored until December 2018. Risks associated with treatment modalities, age at BC diagnosis, the time of SPC occurrence, and comorbid diseases were analyzed. Metastatic liver and stomach cancer were excluded. The irradiation field is widened in patients with positive axillary nodes and this extension covers the breast lymphatic drainage system. Therefore, irradiation field sizes were classified according to axillary node involvement.

Standardized incidence ratios (SIRs) were used to estimate the relative risks (RRs) of SPLC and SPSC development. SIRs were calculated with respect to the South Korean female population. Reference incidences of liver and stomach cancer were obtained from the Korean Statistical Information Service. Expected numbers of liver or stomach cancer cases were calculated using reference incidence rates. SIRs were then calculated by dividing the numbers of observed liver or stomach cancer cases by expected numbers. The statistical significances of SIRs were analyzed using the exact test based on the assumption that the occurrences of liver or stomach cancer exhibit a Poisson distribution. The Cox proportional hazards regression model was used to estimate hazard ratios (HRs) of SPLC and SPSC after RT or CT. HRs and 95% confidence intervals (CIs) were estimated using univariate or multivariate Cox models. *P* values of <0.05 were considered statistically significant, and the analysis was performed using R 3.6.3.

RESULT

Details of 21,014 patients that underwent curative mastectomy between 2009 and 2010 were obtained from HIRA, but 235 cases with missing last follow-up data were excluded from the analysis. Median patient age was 48 years; the age distribution of patients is provided in figure 1. RT and CT were performed in 67.6% and 34.1% of the patients, respectively, and 21.6% received RT and CT. Axillary node metastasis was found at diagnosis in 14.8% of patients, and all received curative treatment (table 1). The median follow-up period was 105.5 months (1.1–121.7 months).

Overall SIRs for SPLC and SPSC in patients with BC underwent curative treatment were 7.26 (95% CI 6.37–8.24, $p < 0.001$) and 2.92 (95% CI 2.58–3.29, $p < 0.001$), respectively, and these represented significant increases. Notably, in the young age group (aged 20–39 years) the SIR of SPLC was 45.17 (95% CI 30.01–65.28, $p < 0.001$) and the SIR of SPSC was 3.56 (95% CI 1.99–5.88, $p < 0.001$). Details are presented in table 2.

In BC patients treated with curative aim, CT was found to be an important factor causative factor of SPLC (figure 2). In particular, the HR of SPLC was significantly higher in the young age group than in the older age group (>40 years old). The crude HR was 2.27 (95% CI 1.06–4.85, $p<0.05$) and the age/RT adjusted HR was 2.37 (95% CI 1.09–4.99, $p<0.05$) (table 3). Furthermore, in the young age group, RT showed a tendency to induce SPLC. The crude HR of SPLC in the young age group was 1.80 (95% CI 0.73–4.44) and the age/CT adjusted HR was 1.85 (95% CI 0.75–4.56), which was not a statistically meaningful difference. No difference was observed according to the irradiated field. Like SPLC, SPSC also showed had a higher HR in the young age group, but this was not statistically significant (table 3).

Analysis of times of SPC occurrence revealed the effect of CT on SPLC was remarkable within the 5 years following treatment (figure 3). In particular, the incidence of SPLC within 5 years of CT was high in the young age group ($p<0.017$). The incidence of SPSC was elevated in the young age group, but it was not statistically significant. On the other hand, there was no statistically significant difference in the incidence of SPLC and SPSC within 5 years after RT. The incidence of SPLC after CT increased non-significantly from 5 years post-treatment (figure 4). In the young age group, unlike that observed during the first 5 years after treatment, no further increase in SPLC was observed during further follow-up. RT increased the incidence of SPLC non-significantly in the young age group.

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Table 1. Demographic factors and comorbidities in the study population.

Parameter	No. of cases	%
Total	20779	100.00%
Age		
≤19	6	0.03%
20–39	3141	15.12%
40–59	14455	69.57%
≥60	3177	15.29%
Comorbidities		
Hypertension	3477	16.73%
Dyslipidemia	2158	10.39%
Diabetes mellitus	1643	7.91%
Axilla involve	3071	14.78%
Treatments		
Radiotherapy	14038	67.56%
Chemotherapy	7083	34.09%
Radiotherapy + chemotherapy	4494	21.63%

Table 2. Standardized incidence ratios of liver and stomach cancer development after mastectomy for BC in patients treated curatively in South Korea from 2009 to 2010.

Age group	Obs.	Exp.	SIR	95% CI	p-value
All age	20,779				
Liver	239	32.935	7.257	6.366–8.237	<0.001
Stomach	269	92.046	2.922	2.584–3.293	<0.001
20–39 yrs	3,141				
Liver	28	0.620	45.168	30.014–65.280	<0.001
Stomach	15	4.211	3.562	1.994–5.875	<0.001
≥40 yrs	17,632				
Liver	211	32.315	6.529	5.678–7.472	<0.001
Stomach	254	87.834	2.892	2.547–3.270	<0.001

Obs.: observed cases, Exp.: expected cases, SIR: standardized incidence ratio, CI: confidence interval

Table 3. Crude and adjusted hazard ratios for liver and stomach cancer after radiotherapy or chemotherapy.

Age group	Liver cancer		Stomach cancer	
	Radiotherapy	Chemotherapy	Radiotherapy	Chemotherapy
All age (n = 20,779)				
Crude HR	0.987 (0.750–1.298)	1.333 (1.029–1.726)*	0.841 (0.654–1.081)	0.983 (0.763–1.267)
Adjusted HR 1	0.969 (0.737–1.275)	1.396 (1.077–1.810)*	0.809 (0.629–1.041)	1.073 (0.831–1.385)
Adjusted HR 2	0.994 (0.755–1.308)		0.813 (0.631–1.046)	
Adjusted HR 2-1	0.856 (0.640–1.145)		0.802 (0.617–1.043)	
Adjusted HR 3		1.395 (1.075–1.811)*		1.055 (0.816–1.362)
Adjusted HR 4	0.883 (0.659–1.183)	1.342 (1.032–1.744)*	0.807 (0.620–1.051)	1.052 (0.813–1.361)
20–39 yrs (n = 3,141)				
Crude HR	1.799 (0.729–4.441)	2.271 (1.064–4.849)*	1.239 (0.390–3.939)	1.283 (0.465–3.539)
Adjusted HR 1	1.799 (0.728–4.443)	2.301 (1.078–4.912)*	1.200 (0.378–3.811)	1.346 (0.488–3.713)
Adjusted HR 2	1.846 (0.748–4.560)		1.215 (0.382–3.864)	
Adjusted HR 2-1	1.630 (0.633–4.196)		1.448 (0.449–4.668)	
Adjusted HR 3		2.336 (1.094–4.989)*		1.354 (0.491–3.739)
Adjusted HR 4	1.699 (0.659–4.380)	2.299 (1.075–4.920)*	1.472 (0.456–4.754)	1.380 (0.500–3.811)
≥40 yrs (n = 17,632)				
Crude HR	0.915 (0.686–1.221)	1.255 (0.949–1.658)	0.881 (0.688–1.128)	1.002 (0.771–1.304)
Adjusted HR 1	0.899 (0.674–1.200)	1.301 (0.983–1.721)	0.850 (0.664–1.089)	1.060 (0.814–1.380)
Adjusted HR 2	0.918 (0.687–1.226)		0.887 (0.692–1.137)	
Adjusted HR 2-1	0.793 (0.583–1.077)		0.775 (0.592–1.015)	
Adjusted HR 3		1.292 (0.976–1.711)		1.039 (0.797–1.355)
Adjusted HR 4	0.812 (0.596–1.105)	1.237 (0.596–1.105)	0.778 (0.593–1.020)	1.031 (0.790–1.346)

Adjusted HR 1: age, comorbidity; Adjusted HR 2: 1 + chemo; Adjusted HR 2-1= 1+axilla; Adjusted HR 3=1+rt; Adjusted HR 4 = 2 + axilla or 3 + axilla, * :p < 0.05

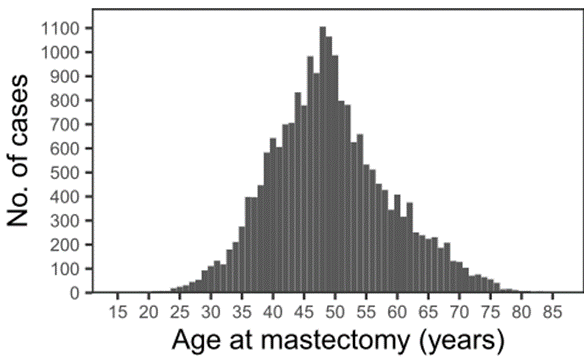
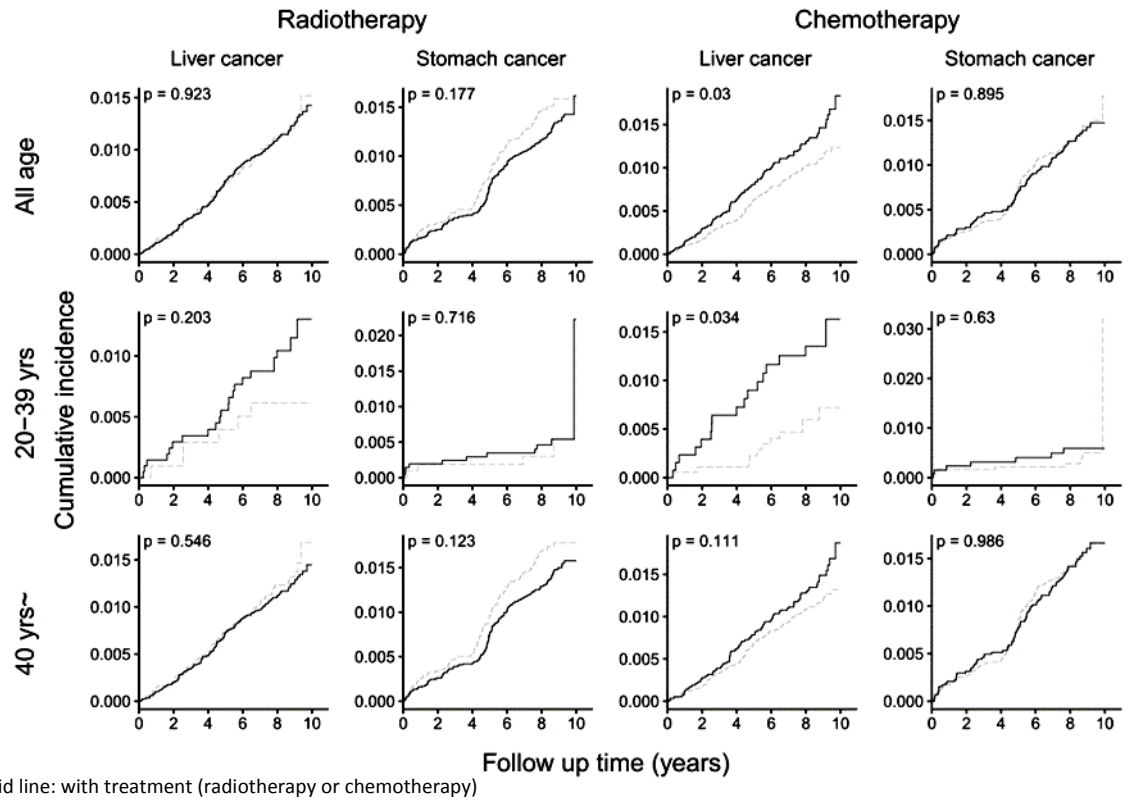


Figure 1. Age distribution of patients that underwent mastectomy from 2009 to 2010 in South Korea.

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Black solid line: with treatment (radiotherapy or chemotherapy)
Gray dashed line: without treatment (radiotherapy or chemotherapy)

Figure 2. Cumulative incidence curves for liver and stomach cancer after mastectomy with or without radiotherapy or chemotherapy.

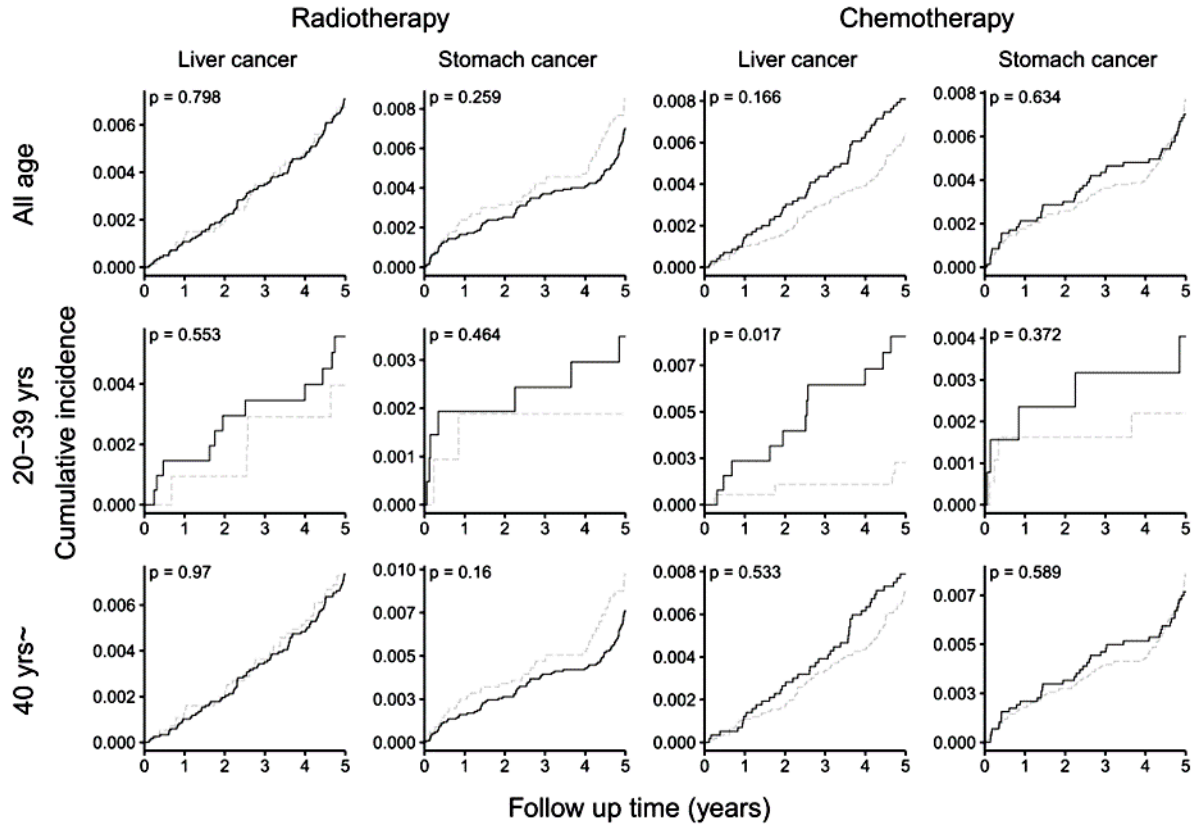


Figure 3. Cumulative incidence curve of liver and stomach cancer over the first 5 years after mastectomy with or without radiotherapy or chemotherapy.

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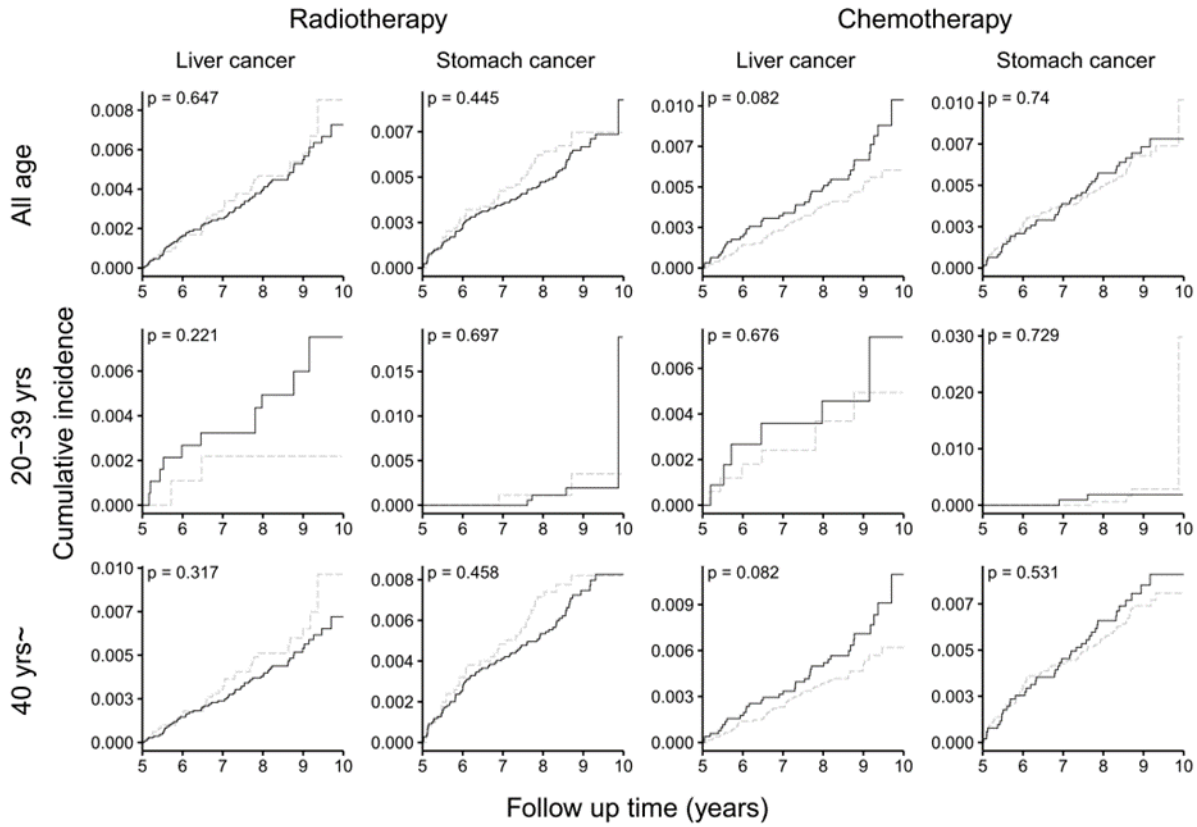


Figure 4. Cumulative incidence curves of liver and stomach cancer from 5 years after mastectomy with or without radiotherapy or chemotherapy.

DISCUSSION

RT and CT are known causes of SPC [8-10]. Japanese epidemiological studies on atomic bomb survivors, clearly demonstrated a correlation between radiation exposure and cancer [20, 21], and several studies have also indicated a link between RT for BC and second cancers [22, 23]. For example, in an Italian study of 5,248 BC patients, the RR of solid cancer after RT was found to be 1.84 [8]. Other studies have reported an association between CT and SPC in BC. Wei *et al.* reported that CT in BC increased the incidences of all cancers except lymphoma, myeloma, and chronic lymphocytic leukemia [9]. In an analysis of childhood cancer survivors, the incidence of a subsequent malignant neoplasm was observed to be 2.8-fold higher in patients that received CT [24]. The SIRs of SPLC and SPSC were also increased in our study, especially, the SIR of SPLC was increased highly in the young age group.

Some previous studies have addressed the incidence of SPC by BC patient age, but few have focused on its incidence among younger patients. According to Hung *et al.*, the SIR of SPC in BC patients was 2.17 for all ages, but 29.70 in 30 to 39-year-olds [25]. And, according to a study of 53,783 BC patients in Taiwan, the SIR of SPC was 0.96 for patients over 50 years and 1.43 for those under 50 [26]. Sun *et al.* conducted a cohort study on 55,318 BC patients and concluded age was the most important risk factor of second primary thyroid cancer; patients ≥ 55 and 20-54 years had adjusted HRs of 1.16 and 2.34, respectively ($p<0.001$) [18]. These findings demonstrate further analysis of SPC by organ type is required in younger BC patients.

Several macroscopic statistical studies have investigated the incidence of SPC after RT in BC patients [8, 22, 27]. In particular, a number of studies have examined SPCs of the thyroid and lung. Huang et al. reported the HR of primary lung cancer was 10 times higher in BC patients than received RT than in those that did not [28], and Grantzau *et al.* reported that primary lung cancer increased by 8.5% per Gy after RT for BC [29]. Thus, it seems likely that the risks of SPLC and SPSC are increased by RT, because liver and stomach are partially included in lower margins of irradiation fields. In the present study, we focused on the incidences of SPLC and SPSC in BC patients that had received different treatments. Based on consideration of the penumbra region and planned target volumes, substantial proportions of liver and stomach are exposed to high-dose radiation and almost all regions of liver and stomach are exposed to low-dose radiation [30]. In our study, the CT HRs of SPLC were significantly increased in the young group. These observations suggest CT is a major risk factor of SPLC.

In the present study, RT was not found to have a significant causative effect on SPC, which may have been due to the short follow-up period. However, it

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has been reported that SPC caused by radiation usually manifests at 5–20 years after treatment. Zhang et al. reported that the RR of SPC was 1.08 (95% CI 0.71–1.65) at 5–9 years after RT, 1.34 (95% CI 0.71–2.52) at 10-14 years, and 1.13 (95% CI 0.46–2.77) at 10–14 years [8]. However, our study had a median follow-up period of only 105.5 months, and thus, the impact of RT on SPC may have been muted. Nevertheless, we did observe that the incidence of SPLC after RT gradually increased every year from 5 years post-mastectomy in the young age group (figure 4), which suggests that the incidence of SPLC may increase after 10 years post-RT. Unfortunately, the HIRA system was commissioned in the late 2000s, and thus, most patients had a follow-up period of less than 10 years.

Since the present study was based on insurance claim codes, specific information about the RT regimens used, such as about planning techniques, radiation doses, and CT combinations and cycle numbers were not available. In addition, information was lacking on the laterality of BC, which may affect the occurrence of SPLC or SPSC after RT. However, the present study was performed on a large number of patients, and thus, we believe our findings are statistically meaningful. This study shows that CT and RT increase the incidence of SPLC in BC patients. CT was found to affect incidences during the first 5 years after treatment, whereas RT had a gradually increasing effect from 5 years after treatment. Notably, both CT and RT increased the incidence of SPLC in the young age group, and thus, we suggest further studies to determine the effect of RT and CT in young BC patients by organ type.

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***Conflict of Interest*:** The authors have no potential conflict of interest to declare.

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***Authors' contributions*:** IS and HJ contributed equally to conception, design, acquisition of data, and wrote the manuscript.

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