Second primary malignancies associated with radiation therapy in cervical cancer patients diagnosed between 1975 and 2011: a population-based competing-risk study

Yijun Wu[1,2#], Yuming Chong[2#], Chang Han[2#], Kai Kang[1,2], Zhikai Liu[1], Fuquan Zhang[1]

[1]Department of Radiation Oncology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; [2]Peking Union Medical College, Eight-year MD program, Chinese Academy of Medical Sciences, Beijing, China

Contributions: (I) Conception and design: Y Wu, C Han; (II) Administrative support: Z Liu, F Zhang; (III) Provision of study materials or patients: C Han, K Kang; (IV) Collection and assembly of data: C Han, Y Chong; (V) Data analysis and interpretation: Y Wu, Y Chong; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Zhikai Liu, MD; Fuquan Zhang, MD. Department of Radiation Oncology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China. Email: liuzk2009@126.com; zhangfq_pumc@163.com.

Background: Cervical cancer is a major health threat for women. Radiotherapy plays an important role in the treatment of cervical cancer. However, its overall benefit has been questioned due to the risk of second primary malignancies.

Methods: The Surveillance, Epidemiology, and End Results (SEER) database was used to search for cervical cancer patients diagnosed between January 1975 and November 2011. Factors that could possibly affect the occurrence of second primary malignancies included the year of diagnosis, gender, ethnicity, histologic type, SEER cancer stage, histology, grade, and whether surgery, chemotherapy, or radiotherapy were used. Age-adjusted and propensity scoring matching (PSM)—adjusted competing-risk analysis was applied for analysis.

Results: Of the 23,112 patients identified through SEER, 14,800 (64.0%) received radiotherapy. Second malignancies were diagnosed in 2,545 (11.0%) cases. PSM-adjusted competing analysis revealed that patients receiving radiotherapy had a significantly higher risk of developing a second cancer in the colon, rectum and anus [hazard ratio (HR): 1.43; 95% confidence interval (CI): 1.09–1.87; P=0.01], lung and bronchus (HR: 1.41; 95% CI: 1.13–1.76; P=0.002), corpus uteri (HR: 3.71; 95% CI: 1.71–8.06; P<0.001), ovary (HR: 2.79; 95% CI: 1.38–5.64; P=0.004), and urinary bladder (HR: 2.18; 95% CI: 1.35–3.54; P=0.002). However, radiotherapy significantly lowered the risk of second cancers in the female breast (HR: 0.67; 95% CI: 0.52–0.86; P=0.002). Age-adjusted competing-risk analysis showed generally consistent results.

Conclusions: Radiotherapy increased the risk of second cancers among cervical cancer patients. Those who underwent radiotherapy had a significantly higher risk of developing a second cancer in the colon, rectum and anus, lung and bronchus, corpus uteri, ovary, and urinary bladder.

Keywords: Cervical cancer; second malignancy; radiotherapy; competing-risk regression; propensity score matching analysis

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Introduction

Cervical cancer is estimated to be the fourth most common cancer in women, with 570,000 cases and 311,000 deaths in 2018 (1). Radiotherapy can be used for the treatment of cervical cancer as a single modality or in combination with surgery or chemotherapy. However, a consensus has not been reached on the overall benefit of radiotherapy. Although radiotherapy has equivalent efficacy with surgery in the control of first cancer sites (2,3), its side effects, especially the risk of second primary malignancy, have generated concerns about its use.

Cancer survivors are reported to be more predisposed to second primary malignancies (4). A study by Kleinerman *et al.* found that cervical cancer patients who underwent radiotherapy had a higher risk of developing second malignancies compared with the general population (5). Chaturvedi *et al.* confirmed in their study of 104,760 1-year survivors that the risk of second malignancies was significantly higher at sites close to the cervix as a result of heavy irradiation (6). A previous study based on Surveillance, Epidemiology, and End Results (SEER) cancer registries suggested only a small proportion of second cancers were likely related to radiotherapy and that other factors including lifestyle and genetics had a greater influence (7).

As radiotherapy is an effective treatment modality, it is important to explore whether or not it increases the risk of second malignancies. This study performed competing-risk analysis using data from SEER to evaluate the impact of radiotherapy on the long-term risk of second malignancies. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/atm-21-1393).

Methods

Data source and cohort

The National Cancer Institute's SEER program is an authoritative database for cancer statistics. This study performed statistical analysis on data from 9 registries including Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah. Cervical cancer patients aged minimum 20 years and diagnosed between January 1975 and November 2011 were selected for further screening. Those who met the following criteria were excluded: (I) patients whose cervical cancer was not considered the first primary cancer, (II) patients with incomplete survival and follow-up information, and (III) patients who died within 5 years after the diagnosis of primary cervical cancer. The SEER registries used for analyses were last updated November 2016, and thus all enrolled patients had survived at least 5 years since diagnosis of the initial cervical cancer, revealing the long-term effect of radiation exposure on the incidence of second malignancies (8). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Study parameters

Patient information was extracted from the database using SEER*Stat software 8.3.6. The following information was obtained from the database: year of diagnosis (1975–1984, 1985–1994, 1995–2004, or 2005–2011), age (20–39, 40–64, or ≥65), gender (male or female), ethnicity [White, Black, others (American Indian/Alaskan Native, Asian/Pacific Islander), or unknown], histologic type (squamous, adenocarcinoma, or others), SEER cancer stage (localized, regional, distant, or unknown), histology (squamous cell carcinoma: codes 8070–8076 and 8084; adenocarcinoma: codes 8140, 8144, 8210, 8255, 8260–8263, 8310, 8323, 8384; or others), grade (well differentiated, moderately differentiated, poorly differentiated, undifferentiated, or unknown), whether a surgery was given (yes or no), whether chemotherapy was used (yes or no), and whether radiotherapy was used (yes or no).

Statistical analysis

SPSS version 25.0 (IBM Corporation, Armonk, NY, USA) and R software 3.6.3 (http://www.r-project.org) were used to perform statistical analysis. Statistical significance was achieved at a P value <0.05 (2 sides). Patient clinical information was recorded in the form of count or percentage, and Pearson's chi-square test was used to make comparisons.

Age-adjusted competing-risk regression analysis using the R package "cmprsk" was performed to assess the association between radiotherapy and second malignancies in order to avoid risk estimation bias caused by conventional statistical methods which improperly process data of patients who die before the event of interest, who do not experience the event before the end of follow-up, or who are lost to follow-up (9,10). For the calculation of the whole risk of second malignancies, competing events were death and occurrence of second malignancies; for the calculation of the risk of single site second malignancies, competing

events were death and other malignancies. Further, to ensure there were consistent distributions of clinical information for patients receiving radiotherapy and those not receiving radiotherapy, the competing-risk regression model was adjusted by propensity score matching (PSM). In the process of patient matching, each patient in one group was matched to a possible patient in the other group, with all unmatched patients excluded from the PSM-adjusted competing-risk regression model.

Results

Patient information

A total of 23,112 cervical cancer patients were identified for this study and enrolled for further analysis. Among them, 14,800 (64.0%) patients received radiotherapy. Univariate analysis and multivariate logistic regression were applied to identify the difference between patients with radiotherapy and those without radiotherapy (*Table 1*). The proportion of cervical cancer patients receiving radiotherapy has increased since 1975. Radiotherapy was more likely to be used in young patients [40–64 *vs.* 20–39: odds ratio (OR) 0.205, 95% confidence interval (CI): 0.183–0.229, P<0.001; ≥65 *vs.* 20–39: OR: 0.526, 95% CI: 0.476–0.582, P<0.001]; black patients (OR: 5.828; 95% CI: 2.742–12.389; P<0.001); patients from other races (OR: 5.729; 95% CI: 2.682–12.236; P<0.001); patients of unknown race (OR: 7.600; 95% CI: 3.551–16.266; P<0.001); patients histologically diagnosed as adenocarcinoma (OR: 1.547; 95% CI: 1.383–1.729; P<0.001) or other types (OR: 1.306; 95% CI: 1.131–1.508; P<0.001); patients with regional invasion (OR: 1.025; 95% CI: 0.871–1.207; P=0.765), distant metastasis (OR: 7.397: 95% CI: 6.226–8.788; P<0.001), or unknown SEER stage (OR: 4.903; 95% CI: 3.616–6.649; P<0.001); patients with moderately differentiated cancer (OR: 1.637; 95% CI: 1.428–1.876; P<0.001), poorly differentiated cancer (OR: 2.156; 95% CI: 1.964–2.366; P<0.001), undifferentiated cancer (OR: 2.829; 95% CI: 2.57–3.113; P<0.001), or unknown grade (OR: 2.078; 95% CI: 1.589–2.716; P<0.001); patients without surgery (OR: 2.910; 95% CI: 2.497–3.392; P<0.001); and patients undergoing chemotherapy (yes *vs.* no/unknown: OR: 0.072; 95% CI: 0.062–0.084; P<0.001).

Relation between radiotherapy and occurrence of second malignancies

Out of a total of 23,112 cervical cancer patients, second malignancies were diagnosed in 2,545 (11.0%) cases (*Table 2*). The top 12 most common sites of second malignancies were the lung and bronchus (N=535, 21.0%); female breast (N=522, 20.5%); colon, rectum, and anus (N=347, 13.6%); urinary bladder (N=108, 4.2%); lymphoma (N=108, 4.2%); ovary (N=71, 2.8%); vagina (N=67, 2.6%); corpus uteri (N=58, 2.3%); pancreas (N=57, 2.2%); vulva (N=55, 2.2%); stomach (N=48, 1.9%); and kidney (N=46, 1.8%; *Figure 1*).

Competing-risk analysis revealed that radiotherapy significantly increased the risk of second malignancies [hazard ratio (HR): 1.62; 95% CI: 1.50–1.75; P<0.001] and that it was significantly associated with higher risk of death (HR: 2.62; 95% CI: 2.49–2.75; P<0.001; *Figure 2*). The cumulative incidence for the top 12 most common second malignancies is shown in *Figure 3*.

Additionally, we analyzed changes in trends of the occurrence of second primary malignancies following the diagnosis of primary cervical cancer (*Figure 4*). The results demonstrated that the incidence of second malignancies declined as survival time increased among both populations of patients: those receiving radiotherapy (RT group) and those not receiving radiotherapy (no-RT group). Interestingly, the RT group started to show more second malignancies 10–15 years after diagnosis of primary cervical cancer.

Age-adjusted competing-risk analysis

Generally, patients receiving radiotherapy had a higher risk of developing second malignancies (HR: 1.35; 95% CI: 1.24–1.47; P<0.001; *Table 2*). Compared with cervical cancer patients not receiving radiotherapy, those who received radiotherapy had a significantly higher risk of developing a second cancer in the small intestine (HR: 4.84; 95% CI: 1.31–17.8; P=0.018), lung and bronchus (HR: 1.35; 95% CI: 1.24–1.47; P<0.001), corpus uteri (HR: 6.09; 95% CI: 3.11–11.90; P<0.001), ovary (HR: 2.61; 95% CI: 1.52–4.49; P<0.001), and urinary bladder (HR: 2.25; 95% CI: 1.47–3.44; P<0.001). However, radiotherapy significantly reduced the occurrence of second malignancies in the female breast (HR: 0.74; 95% CI: 0.61–0.90; P=0.002).

PSM-adjusted competing-risk analysis

Clinical information was further analyzed by PSM-adjusted competing-risk model using the nearest neighbor matching algorithm with a caliper of 0.1. After matching with a ratio of 2 (patients receiving radiotherapy: patients not receiving

Table 1 Univariate and multivariate analysis of patient information for factors that affected the application of radiotherapy

Patient characteristics	Total (N=23,112)	No radiation (N=14,800)	Radiation (N=8,312)	P value	Logistic regression		
					OR	95% CI	P value
Year of diagnosis							
1975–1984	6,683 (28.9%)	4,075 (27.5%)	2,608 (31.4%)	<0.001	Reference		
1985–1994	6,597 (28.5%)	4,381 (29.6%)	2,216 (26.7%)		5.326	4.613–6.148	<0.001
1995–2004	6,237 (27%)	4,147 (28%)	2,090 (25.1%)		3.158	2.742–3.638	<0.001
2005–2011	3,595 (15.6%)	2,197 (14.8%)	1,398 (16.8%)		1.787	1.553–2.056	<0.001
Age, years							
20–39	9,144 (39.6%)	7,377 (49.8%)	1,767 (21.3%)	<0.001	Reference		
40–64	11,035 (47.7%)	6,234 (42.1%)	4,801 (57.8%)		.205	0.183–0.229	<0.001
≥65	2,933 (12.7%)	1,189 (8%)	1,744 (21%)		.526	0.476–0.582	<0.001
Race							
White	17,599 (76.1%)	11,478 (77.6%)	6,121 (73.6%)	<0.001	Reference		
Black	3,010 (13%)	1,826 (12.3%)	1,184 (14.2%)		5.828	2.742–12.389	<0.001
Others	2,290 (9.9%)	1,295 (8.8%)	995 (12%)		5.729	2.682–12.236	<0.001
Unknown	213 (0.9%)	201 (1.4%)	12 (0.1%)		7.600	3.551–16.266	<0.001
Histologic type							
Squamous	16,505 (71.4%)	10,052 (67.9%)	6,453 (77.6%)	<0.001	Reference		
Adenocarcinoma	3,392 (14.7%)	2,415 (16.3%)	977 (11.8%)		1.547	1.383–1.729	<0.001
Other	3,215 (13.9%)	2,333 (15.8%)	882 (10.6%)		1.306	1.131–1.508	<0.001
SEER stage							
Localized	15,856 (68.6%)	12,646 (85.4%)	3210 (38.6%)	<0.001	Reference		
Regional	5,602 (24.2%)	1,108 (7.5%)	4,494 (54.1%)		1.025	0.871–1.207	0.765
Distant	427 (1.8%)	93 (0.6%)	334 (4%)		7.397	6.226–8.788	<0.001
Unknown	1,227 (5.3%)	953 (6.4%)	274 (3.3%)		4.903	3.616–6.649	<0.001
Grade							
Well differentiated	2,121 (9.2%)	1,524 (10.3%)	597 (7.2%)	<0.001	Reference		
Moderately differentiated	5,211 (22.5%)	2,813 (19%)	2,398 (28.8%)		1.637	1.428–1.876	<0.001
Poorly differentiated	4,317 (18.7%)	1,911 (12.9%)	2,406 (28.9%)		2.156	1.964–2.366	<0.001
Undifferentiated	354 (1.5%)	170 (1.1%)	184 (2.2%)		2.829	2.57–3.113	<0.001
Unknown	11,109 (48.1%)	8,382 (56.6%)	2,727 (32.8%)		2.078	1.589–2.716	<0.001
Surgery							
Yes	20,872 (90.3%)	14,248 (96.3%)	6,624 (79.7%)	<0.001	Reference		
No	2,240 (9.7%)	552 (3.7%)	1,688 (20.3%)		2.910	2.497–3.392	<0.001
Chemotherapy							
Yes	2,901 (12.6%)	329 (2.2%)	2,572 (30.9%)	<0.001	Reference		
No/unknown	20,211 (87.4%)	14,471 (97.8%)	5,740 (69.1%)		0.072	0.062–0.084	<0.001

OR, odds ratio; CI, confidence interval; SEER, Surveillance, Epidemiology, and End Results.

Table 2 The risk of second malignancies among cervical cancer patients after radiotherapy

Second malignancy	Age-adjusted competing-risk regression				PSM-adjusted competing-risk regression			
	N	Events	HR (95% CI)	P value	N	Events	HR (95% CI)	P value
All sites	23,112	2,545	1.35 (1.24–1.47)	<0.001	10,270	1,465	1.28 (1.15–1.42)	<0.001
Oral cavity and pharynx		42	1.40 (0.72–2.73)	0.32		21	2.02 (0.85–4.80)	0.11
Digestive system								
Esophagus		15	1.22 (0.41–3.60)	0.72		5	1.00 (0.17–6.02)	1
Stomach		48	1.63 (0.91–2.92)	0.1		26	1.52 (0.70–3.27)	0.29
Small intestine		15	4.84 (1.31–17.8)	0.018		4	1.51 (0.21–10.7)	0.68
Colon, rectum, and anus		347	1.54 (1.22–1.94)	<0.001		211	1.43 (1.09–1.87)	0.01
Hepatobiliary system		37	0.98 (0.48–2.00)	0.960		28	0.99 (0.46–2.11)	0.97
Pancreas		57	1.30 (0.73–2.29)	0.37		33	1.12 (0.56–2.23)	0.75
Others		15	–	–		–	–	–
Respiratory system								
Lung and bronchus		535	1.35 (1.24–1.47)	<0.001		318	1.41 (1.13–1.76)	0.002
Others		23	–	–		–	–	–
Melanoma of the skin		43	0.54 (0.26–1.12)	0.096		25	0.72 (0.31–1.66)	0.43
Female breast		522	0.74 (0.61–0.90)	0.002		286	0.67 (0.52–0.86)	0.002
Female genital system								
Cervix uteri		38	0.88 (0.40–1.95)	0.75		18	0.76 (0.28–2.02)	0.58
Corpus uteri		58	6.09 (3.11–11.9)	<0.001		31	3.71 (1.71–8.06)	<0.001
Ovary		71	2.61 (1.52–4.49)	<0.001		34	2.79 (1.38–5.64)	0.004
Vagina		67	1.35 (0.75–2.43)	0.31		40	1.37 (0.74–2.55)	0.32
Vulva		55	1.79 (0.97–3.29)	0.061		35	1.80 (0.93–3.49)	0.083
Others		15	–	–		–	–	–
Urinary system								
Urinary bladder		108	2.25 (1.47–3.44)	<0.001		68	2.18 (1.35-3.54)	0.002
Kidney		46	0.97 (0.49–1.91)	0.93		26	0.80 (0.36–1.80)	0.6
Others		18	–	–		–	–	–
Nervous system		22	1.64 (0.62–4.33)	0.32		10	1.52 (0.44–5.21)	0.51
Endocrine system								
Thyroid		36	0.98 (0.44–2.21)	0.96		16	0.91 (0.33–2.50)	0.85
Others		2	–	–		–	–	–
Lymphatic/hematopoietic diseases								
Lymphoma		108	1.08 (0.73–1.61)	0.69		60	1.08 (0.65–1.81)	0.76
Myeloma		22	0.74 (0.30–1.82)	0.51		15	0.55 (0.18–1.72)	0.3
Leukemia		40	1.15 (0.57–2.36)	0.69		23	0.98 (0.42–2.25)	0.95
Other tumors		140	–	–		16	–	–

HR, hazard ratio; CI, confidence interval; PSM, propensity score matching.

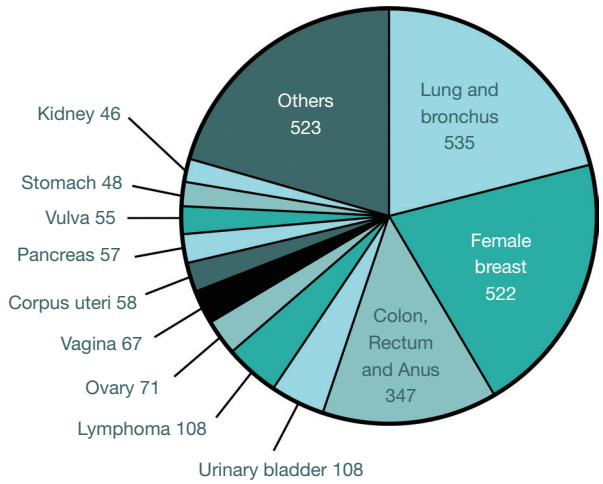

Figure 1 Sites of second malignancies after radiotherapy among cervical cancer patients.

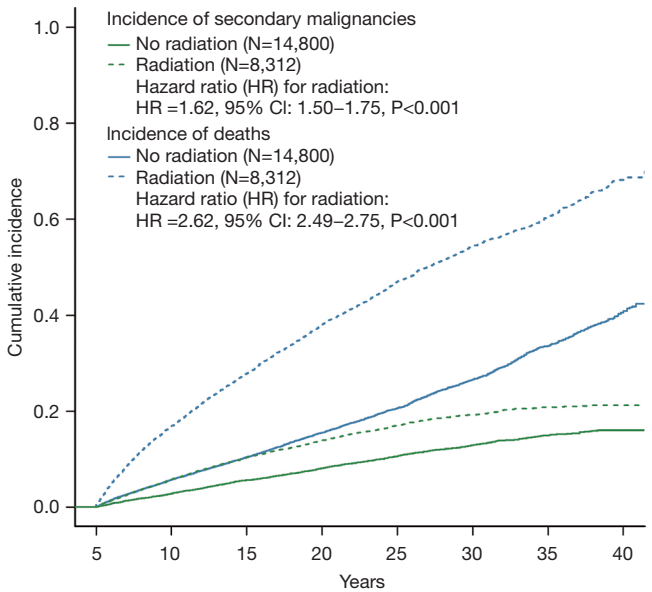

Figure 2 Cumulative incidence for the overall risk of second malignancies and death reported by age-adjusted competing-risk analysis.

radiotherapy =2:1), 10,270 patients were included in the PSM-adjusted competing-risk analysis (*Table 2*). Patients receiving radiotherapy had a significantly higher risk of developing a second cancer in the colon, rectum, and anus (HR: 1.43; 95% CI: 1.09–1.87; P=0.01); lung and bronchus (HR: 1.41; 95% CI: 1.13–1.76; P=0.002); corpus uteri (HR: 3.71; 95% CI: 1.71–8.06; P<0.001); ovary (HR: 2.79; 95% CI: 1.38–5.64; P=0.004); and urinary bladder (HR: 2.18; 95% CI: 1.35–3.54; P=0.002). However, radiotherapy significantly lowered the risk of a second cancer in the female breast (HR: 0.67; 95% CI: 0.52–0.86; P=0.002).

Discussion

This comprehensive, population-based study analyzed how radiotherapy affected the occurrence of second malignancies. The combined results from the unadjusted analysis and PSM-adjusted competing-risk analyses indicate that radiotherapy significantly increased the occurrence of a second cancer in the colon, rectum, and anus; lung and bronchus; corpus uteri; ovary; and urinary bladder; while a significant decrease in the risk of breast cancer was observed.

With the improvements in cancer prognoses in recent years, the occurrence of second malignancies is drawing increasingly more attention. Radiotherapy is an effective treatment modality for a variety of cancers. However, along with genetics, lifestyle, and chemotherapy, radiotherapy is considered a potential factor involved in increasing the risk of second malignancies (7). This is especially the case with cervical cancer. According to recent studies, the 5-year survival of all stages was up to 62.8% for all races in the United States between 2001 and 2009 (11). It has been estimated that half of cervical patients receive radiotherapy (12). Whether or not radiotherapy can lead to an increased risk of a second cancer has generated much concern. A systematic review and meta-analysis conducted in 2018 found an increased risk of rectal cancer after pelvic radiation for the treatment of cervical cancer [relative risk (RR) 1.61; 95% CI: 1.10–2.35] (13). This finding was consistent with our results and those found in a number of previous studies (5,14-17). It is generally believed that second cancers tend to occur in sites that have received radiation, so pelvic organs such as the rectum, corpus uteri, ovary, and urinary bladder could be more predisposed to second malignancies.

Our study found that lung cancer was the most common second malignancy in cervical cancer patients receiving radiotherapy and that radiotherapy significantly increased its risk (HR: 1.41; 95% CI: 1.13–1.76; P=0.002), which has been confirmed by other studies (4,6). Notably, lung cancer has also been identified as the most common second cancer in survivors of bladder cancer; both bladder cancer and lung cancer are associated with smoking, which might cause somatic mutations (4). Even though the lung receives

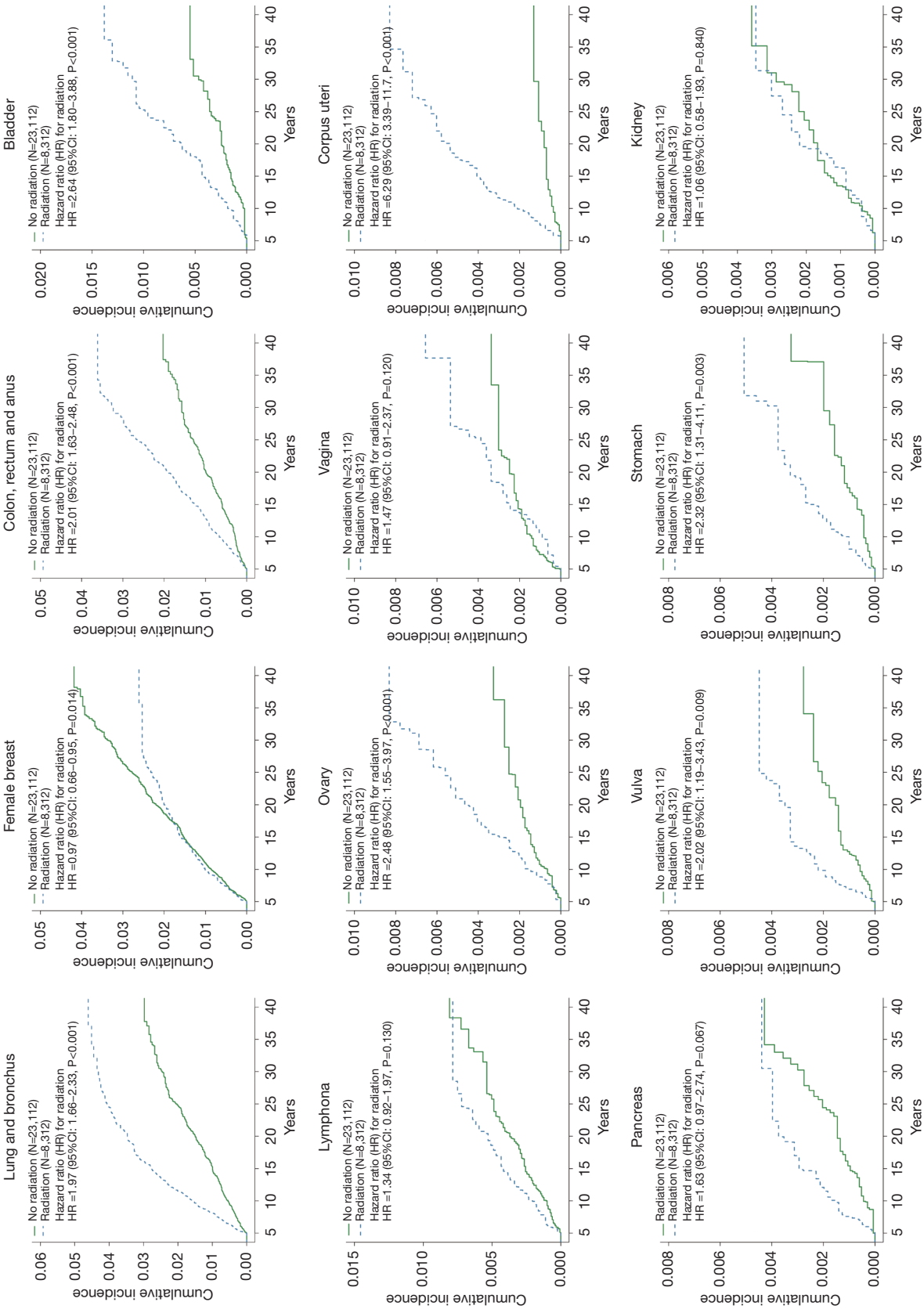

Figure 3 Cumulative incidence for the 12 most common sites of second malignancies among patients with or without radiotherapy.

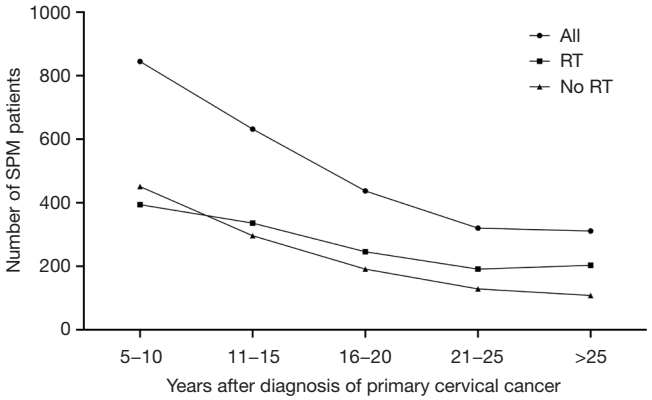

Figure 4 Changes in trends of the incidence of second primary malignancy (SPM) over years after diagnosis of first primary cervical cancer. RT, radiotherapy.

only a very small amount of radiation in the treatment of cervical cancer, smoking and radiation have been found to reinforce each other with respect to the development of subsequent cancers (18). A study by Arnold *et al.* found that cervical cancer patients who smoked and were receiving radiotherapy had an increased risk of a second tumor at smoking-related sites [incidence rate ratio (IRR): 1.6; 95% CI: 1.2–2.3] (19). Unfortunately, one of the limitations of using the SEER database is that patient characteristics, such as smoking history, are unknown. However, previous population-based studies have provided evidence that smoking is associated with poor survival (20) and a higher risk of second malignancies (19,21,22) in cervical cancer patients. As a result, the necessity of smoking cessation should be emphasized in cervical cancer patients, especially those receiving radiotherapy.

Human papillomavirus (HPV) infection is acknowledged as the main cause of cervical cancer and is also involved in the occurrence of second cancers. HPV-related sites include the cervix uteri, vulva, vagina, anus, and oropharynx (23). In this study, there was increased risk of a second cancer in the vulva (HR: 1.80; 95% CI: 0.93–3.49), vagina (HR: 1.37; 95% CI: 0.74–2.55), and oropharynx (HR: 2.02; 95% CI: 0.85–4.80) among cervical cancer patients. However, the risk of a second tumor in the cervix uteri (HR: 0.76; 95% CI: 0.28–2.02) was lower in cervical cancer patients than in the general population. The reasons for this remain to be further explored. According to a previous study, the risk of HPV-related second cancer varied by age and was especially high among cervical cancer survivors older than 70 years (19). This finding emphasizes the need for increasing patient education and enhanced screening in the future.

After analyzing changes in trends of the incidence of second malignancies over time, we found that incidence declined as survival time increased, which was observed in both the RT group and the no-RT group (*Figure 4*). The incidence rates were highest in the first 5 years (5–10 years since diagnosis of primary cervical cancer). However, the RT group started to show more second malignancies as time progressed (10–15 years after the diagnosis), which might indicate a long-term effect of radiotherapy on the incidence of second malignancies.

There are some limitations that should be addressed. First, the SEER database does not contain detailed patient information, such as smoking status, HPV infection status, or other environmental risk factors. Thus, this study was unable to analyze how these factors affect the occurrence of cervical cancer and related secondary malignancies. Second, this study did not consider other factors in the use of radiotherapy that could affect the occurrence of second malignancies. For example, intensity modulated radiotherapy (IMRT), a type of conformal radiotherapy, has been reported to be associated with increased risk of second cancer (24). The radiation dose might also affect this risk. These factors remain to be further investigated.

Conclusions

Radiotherapy appears to increase the risk of second cancers among cervical cancer patients. Our study found that those who underwent radiotherapy had a significantly higher risk of developing a second cancer in the colon, rectum, and anus; lung and bronchus; corpus uteri; ovary; and urinary bladder. Interestingly, radiotherapy seemed to be a protective factor for breast cancer in cervical cancer patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/atm-21-1393

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-1393). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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