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Incidence of radiation induced sarcoma attributable to radiotherapy in adults: A retrospective cohort study in the SEER cancer registries across 17 primary tumor sites

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Abstract

Background: Previous studies have noted the incidence of radiation-induced sarcomas (RIS) but have not investigated the relative risk (RR) of developing RIS based on primary tumor organ disease site. By examining data from the Surveillance, Epidemiology, and End Results (SEER) database, we hypothesized that breast cancer would have a higher incidence of RIS compared to seventeen other primary cancer sites.

Methods: This was a retrospective cohort study that examined patients from SEER registries between 1973 and 2013. We included patients aged 18 years or older who were diagnosed with cancer and those diagnosed with a cancer who subsequently developed a sarcoma. We excluded patients with missing information on initial radiotherapy treatment or stage. RIS was defined as those who developed a secondary sarcoma near the site of their original malignancy and after a 24-month latency period.

Results: Our patients had a mean age of 60 years and follow up time of 9.2 years. Breast cancer comprised the majority with 693,701(36.8%) patients of which 161 (0.02%) had a secondary

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CRediT authorship contribution statement

Anson Snow: Investigation, Project administration, Data curation, Writing - original draft. **Alexander Ring:** Writing - review & editing, Visualization. **Lucas Struycken:** Data curation. **Wendy Mack:** Formal analysis, Data curation. **Melissa Koç:** Formal analysis, Data curation. **Julie E. Lang:** Conceptualization, Writing - review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

None.

sarcoma. Of the 359 patients with secondary sarcomas, 242 (67.4%) had RIS. Breast cancer had the highest number of RIS patients at 126 compared to all combined non-breast cancer sites at 116. The RR of RIS in breast cancer versus 19 other primary cancer sites was 1.21 (CI: 1.01–1.45, $p < 0.03$, adjusted for age at primary diagnosis, gender, and latency).

Conclusions: Our study demonstrated that breast cancer has a higher risk of developing RIS compared to other solid cancers.

Keywords

Radiation-induced sarcoma; Secondary sarcoma; Breast cancer; SEER; Surveillance; Epidemiology; and end results; Radiotherapy; Radiation therapy

1. Introduction

Radiation-induced sarcoma (RIS) is a rare iatrogenic malignancy occurring after radiotherapy that carries a poor prognosis with a 5-year overall-free survival rates ranging as low as 32% to as high as 58% compared to sporadic soft tissue sarcomas [1,2]. RIS are hard to treat as they occur in previously treated areas and are difficult to resect [3]. The diagnosis of a RIS is usually clinical and based on three guiding principles that have not significantly changed since the late 1940s: 1) Antecedent history of radiation exposure before development of sarcoma, 2) Development of sarcoma in or near the field or radiation, and 3) Sarcoma diagnosis confirmed by histology, which differs from the primary cancer [4].

Previous studies have investigated the incidence of all secondary cancers due to radiotherapy using data from the Surveillance, Epidemiology, and End Results Program (SEER) and have noted that less than 10% of secondary cancers may be due to radiation therapy. However, incidence of RIS in a contemporary population-based cohort has not been noted [5]. Interestingly, upon review of RIS cases, a majority are found in breast cancer patients [2,6]. In the United States, it is estimated that 252,710 women in 2017 will be diagnosed with invasive breast cancer [7]. Approximately half of these patients will receive radiation therapy during their treatment for stage I-IV breast cancer [8]. We hypothesized that breast cancer would have a higher incidence of RIS compared to seventeen other primary cancer sites in a large series spanning forty years.

2. Methods

2.1. Data Source

This study was approved by the institutional review board of the University of Southern California (#HS-14–00512). Patients were obtained from the SEER*Stat Databases specifically using Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2015 Sub (1973–2013, version April 2016). The index record selected to obtain specific data sets for each primary cancer were: Age at Diagnosis. Age recode with <1 year olds = '15–19 years','20–24 years','25–29 years','30–34 years','35–39 years ','40–44 years','45–49 years','50–54 years','55–59 years ','60–64 years','65–69 years','70–74 years','75–79 years','80–84 years'; Race, Sex, Year Dx, Registry, County, Year of diagnosis} = '1973–2013'; Multiple Primary Fields, Sequence number} = '1st of 2 or more primaries';

Site and Morphology, Primary Site - labeled; Cause of Death (COD) and Follow-up, Survival months = 24–491; Stage - LRD (Summary and Historic), SEER historic stage A = 'In situ', Localized', 'Regional'; and Site and Morphology, Site recode ICD-O-3/WHO 2008. To obtain secondary sarcomas we selected the above index record in addition to selecting the following: Multiple Primary Fields. Sequence number = '2nd of 2 or more primaries'; Site and Morphology. Primary Site - labeled = 'C49.4-Conn, subcutaneous, other soft tis: abdomen','C49.5-Conn, subcutaneous, other soft tis: pelvis'; and Site and Morphology. Site recode ICD-O-3/WHO 2008} = 'Soft Tissue including Heart'.

2.2. Study cohort

The present analysis was limited to adult patients aged 18 or older who were diagnosed with a first solid cancer reported in the SEER registry between January 1, 1973-December 31, 2013. Nineteen primary cancer sites routinely treated with radiotherapy were included: abdomen, anal, brain, breast, cervical, eye, head, larynx, lung, nonHodgkin lymphoma (NHL), pelvis, pharynx, prostate, rectal, salivary, testicular, thorax, thyroid, and uterine. Patients with only local or regional SEER historic stage were included. Exclusion of missing, unstaged, and distant staged cancers eliminated all NHL cases from our analytical cohort. Since the Ann Arbor Staging criteria are used to stage NHL, it was difficult to make comparisons to solid cancers which utilize a different staging system. For brain malignancies, only primary sites frontal lobe, parietal lobe, temporal lobe, occipital lobe, cerebellum, and brain stem were included in the analysis; the staging for these tumors was treated as localized. Patients were further classified according to whether or not they received any radiation sequence with surgery or radiation therapy, including external beam, radioactive implants, radioisotopes, NOS method, combination radiotherapy, or other. Patients with unknown or missing data for radiation therapy were excluded.

Secondary sarcoma data were collected only for patients in the first course of treatment for their first malignancy. Patients whose second malignancy was less than 24 months from their primary cancer (as determined by survival months) were excluded from the present analysis. The lag time to developing RIS is debated to be as early as six months post-radiation to as long as five years [4,9]. For our study, we chose to have a latency of 2 years for the development of RIS as several studies have used this criterion [2,10–13]. Although sarcomas developing within six months of radiation therapy have been reported, they are extremely rare [14].

Inclusion criteria for secondary sarcoma were: 1) patients aged 18 years or older; 2) diagnosis of a first primary invasive solid cancer defined by the International Classification of Diseases for Oncology 3rd Edition (ICD-O-3) codes; 3) diagnosis of a second primary soft tissue sarcoma defined by ICD-O-3 codes; 4) occurrence of secondary sarcoma around primary tumor site defined by ICD-O-3 codes 5) SEER historic stage A (in situ, localized, and regional); 6) follow-up survival of greater than 24 months; 7) year of diagnosis between 1973–2013. Exclusion criteria were: 1) incomplete staging; 2) missing information on initial treatment with radiotherapy.

2.3. Statistical analysis

Basic descriptive statistics were used to summarize the data. Results were reported as proportions or means for categorical or numerical data, respectively, by both primary cancer site and by radiotherapy vs. no radiotherapy. Differences in patient characteristics between the radiotherapy vs. no radiotherapy groups were calculated by chi-squared test or Fisher's exact test, as appropriate. The follow-up time for the incidence of secondary sarcoma was calculated by subtracting the survival months from the second cancer from the survival months of the primary cancer. For patients who had more than two cancers, data from only the second cancer was used to avoid potential bias or lack of attributability.

Due to the low number of secondary sarcomas observed and taking into consideration the primary research objective, primary cancer sites were further classified into breast vs. "non-breast" in order to have sufficient statistical power for calculation of appropriate relative risks (RR). The analytical cohort was further restricted to patients who developed a secondary sarcoma; based on the selection methods for secondary sarcoma from the SEER registry, patients who received radiation therapy for their primary cancer and later developed a secondary sarcoma (after 24 months) were classified as having RIS in the present analysis. Differences in the proportion of observed sarcomas in the RIS vs. no RIS groups were compared by Fisher's exact test, stratified by both primary cancer sites and by breast vs. non-breast primary site groups.

A modified multivariate Poisson regression analysis using robust error variance was conducted to estimate the RR and 95% confidence interval (CI) of RIS as these are rare events within a large population and accounts for bias of different treatments over time. Results are reported by both primary cancer site and by breast vs. non-breast primary site groups. Variables found to be significantly different between RIS groups in the univariate analyses using Fisher's exact test were included in a multivariable model evaluating the RR of RIS in patients initially treated with RT for breast cancer (compared to other cancers combined), adjusted for any confounding variables.

A two-sided p-value <0.05 was considered significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

3. Results

3.1. Patients characteristics

A total of 2,031,963 patients were identified for analysis through SEER. We excluded 9567 patients with unstaged primary brain cancers, and 2900 patients did not meet the age criteria (18 years or older). We excluded 18,282 patients with distant, unstaged, or missing SEER historic stage, and 39,956 patients were excluded for unknown or missing radiation therapy. Patients with a secondary cancer occurring within 24 months of their primary diagnosis were additionally excluded from the final analytical sample, yielding a total of 1,884,469 patients meeting inclusion/exclusion criteria. Fig. 1 depicts a detailed flow chart for the analytical cohort selection process.

Among the 1,884,469 patients meeting our inclusion/exclusion criteria, only 359 (0.02%) were diagnosed with a second sarcoma (Table 1). Of those 359 patients with secondary sarcoma, 242 (0.01%) fit the criteria for radiation-induced sarcoma. The mean age at diagnosis for a primary cancer was 60 years and the average follow-up time was approximately 9.4 years. Approximately 43.0% of the study cohort received radiotherapy (Table 1). Patients who did and did not receive radiotherapy had comparable patient and cancer characteristics (Table 2).

3.2. Radiation induced sarcoma characteristics

In comparing patients with secondary sarcoma in RIS versus no RIS groups (Table 3), no significant differences were observed in terms of year of first diagnosis, race, or cancer stage. However, there were several differences. Patents with RIS were more likely to be between the ages of 45–74 years of age at first diagnosis (33.5% vs. 29.9% for ages 45–59, 42.6% vs. 33.3% for ages 60–74, and 8.3% vs. 17.1% first diagnosed over age 75; $p = 0.04$). Females were more likely to develop RIS (71.1% vs. 53.0%; $p < 0.001$), and patients with RIS tended to have a greater latency period (74.8% vs. 59.8% with a latency period ≥5 years; $p = 0.02$).

3.3. Frequency of radiation induced sarcoma

An overall RIS rate of 0.02% was observed for breast cancer patients (Table 1). Comparing individual non-breast cancer sites, the RR of RIS was increased for anal, brain, larynx, and pharyngeal cancer sites compared to breast cancer, while the RR of RIS was decreased for uterine cancer compared to breast cancer. No patients who had a primary cancer of the eye later developed a secondary sarcoma. However, these RR values have limited interpretation given the small number of RIS events within each primary cancer group, excluding breast cancer. All results are detailed in Table 4 and 5.

4. Discussion

Elucidating risk factors for the development of RIS has historically been difficult given its rare occurrence. Also, RIS tumors are aneuploid and have complex genomics making it a challenging disease to understand [15]. Our group has previously evaluated evidence-based practices for RIS and found no prospective, randomized trials on RIS of the breast. Thus high-quality evidence on RIS is lacking [16]. The SEER database is advantageous to studying RIS as it contains a large cancer population with well-documented follow-up times [17,18]. Our study used the most recent version of SEER to determine if breast cancer patients had an increased risk for RIS. We found that the RR of developing RIS in breast cancer, after adjusting for differences in age at primary diagnosis, gender, and latency, was 1.21 (95% CI: 1.01–1.45) times that of the risk for non-breast cancers. Prior studies have found a slightly higher RR for developing sarcomas in breast cancer patients. For example, a study examining 13,490 patients in the Swedish Cancer Registry had an RR of 2.2 (CI 95% 1.3–3.4) for the development of secondary soft tissue sarcoma in breast cancer patients [19]. Another study found that the RR of developing angiosarcoma in breast cancer patients after radiation therapy was 15.9 (95% CI, 6.6–38.1) and for developing other sarcomas, it was 2.2 (95% CI 1.4–3.3) [20]. The lower RR found in our study may be due to more stringent

inclusion criteria as only secondary sarcomas found in the area of the primary tumor were included. In addition, if we were to stratify sarcomas into angiosarcomas versus other soft tissue sarcomas, we may have found a larger RR for angiosarcomas.

Overall our study found the incidence of RIS was 0.02% in breast cancer patients. Prior investigations estimated the incidence of RIS to be 0.03–0.2%, but there are some estimates as high as 0.8% [21,22]. Several studies have examined the rates of RIS specifically in breast cancer. Taghian et al. found the cumulative incidence of RIS in breast cancer to be 0.2% at 10 years, 0.43% at 20 years, and 0.78% at 30 years [23]. Kirova et al. reviewed 16,705 breast cancer patients and found the cumulative RIS incidence to be 0.07% at 5 years, 0.27% at 10 years, and 0.48% at 15 years [24]. Yap et al. investigated the SEER database from 1973 to 1997 and found the incidence of RIS in breast cancer to be 0.09% at 15 years post-diagnosis [25]. In comparison to Yap et al., we included data from 1973 to 2013 and found a lower RIS incidence than that previous analysis of SEER data. Two explanations could account for our lower RIS incidence. First, many RIS studies collected data from academic centers, which may inherently have a bias towards accumulating rare cases. Secondly, radiation therapy has changed significantly since the 1990s. Before the advent of computed tomography simulation and the incorporation of imaging from magnetic resonance imaging and positron emission tomography, radiation therapy lacked precise modeling to guide therapy [26]. We propose that our analysis, including recent data 15 years beyond the results published by Yap et al., captured the effect of new techniques for superior radiation delivery and dosing, which have improved patient safety and radiation toxicity [27].

While many studies do not comment on RR, they have calculated standardized incidence ratios (SIR). Barrington et al. examined an older version of the SEER database for RIS among solid tumors. They found that ovarian cancers had the highest SIR of radiation-induced soft tissue sarcoma at 6.25, followed by brain and CNS cancers at 3.66, lung and bronchus cancers at 3.44, and finally breast at 2.67. For radiation-induced bone sarcomas in solid tumor cancers, those with the highest SIR values from highest to lowest were in ovarian, brain and CNS, oral cavity and pharynx, cervix uteri, rectum and anus, and thyroid [17]. Interestingly, we noticed that anal, brain, larynx and pharynx had increased RR of RIS when compared to breast cancer in our study, while prostate and uterine cancers had decreased RR of RIS compared to breast cancer. However, these values should be interpreted with caution as the absolute number of RIS events for these cancers was low and therefore, may not have clinical significance.

Breast cancer patients who developed RIS had an average survival of rate of 36% at 5-years after their diagnosis [24]. Thus, it is essential to understand the biological mechanisms behind the development of RIS. Prior breast cancer treatment with and without radiation therapy is associated with higher rates of soft tissue sarcomas; however, a concrete mechanism for sarcoma development is unknown [28,29]. One proposed mechanism for radiation carcinogenesis involves: 1) A direct ionizing radiation event leading to the release of reactive oxygen species, 2) radiation-induced bystander events (cells not directly hit by radiation) that lead to the release of inflammatory mediators, 3) Decrease in DNA repair and cell cycle checkpoint from inflammatory mediators, and 4) Cell death and a primary instability event that leads to carcinogenesis [30]. Lymphedema, a common complication of

cancer, has been linked as a possible risk factor in the development of sarcomas [31,32]. The evidence for lymphedema as a risk factor is inconclusive. One study found that upper extremity edema was the only risk factor linked to the development of angiosarcoma (AS) [19], whereas another found the risk of soft tissues sarcomas including AS increased with higher radiation dose and not edema [33]. Particularly interesting is that chronic lymphedema can cause chronic inflammation [34], which has been thought to affect different stages of cancer development [35,36]. Surgical treatment of breast cancer often involves axillary lymph node dissection for node positive disease as is the case for head and neck cancers. We found similar rates of RIS (larynx = 0.01%, pharynx = 0.04%, salivary = 0.04%, compared to breast = 0.02%). However, the numbers of RIS for all other cancer sites were too low to compare all individual groups. Another potential explanation for higher rate of RIS in breast cancer patients could be age. Women who commonly get breast cancer are menopausal at the median age of diagnosis. Several studies showed that estrogen signaling affects cellular response to ionizing radiation and tissue injury [37–39]. An obvious assumption would be that cancers with higher doses of radiation should have a higher number of RIS (i.e. lung or head and neck) which we did not see in our analysis. Thus, radiation dose may not matter that much as a driving factor for RIS development in breast cancer as the typical Gy dose is 40, whereas the other had doses of 50–60 Gy. However, our data was taken from the 1970s to the present time. Radiation doses and technique have changed significantly, and SEER does not report these variables with fine detail, therefore it was not possible to test for this assumption.

Thus, the development of RIS in breast cancer is likely multifactorial with radiation and treatments causing lymphedema all playing a role at increasing patients' risk for soft tissue sarcomas.

There were several limitations to this study regarding the use of the SEER database. First, SEER does not record information about germline mutations. Several hereditary cancer syndromes (i.e. Li-Fraumeni, retinoblastoma, Nijmegen breakage syndrome) and defects in DNA-repair mechanisms (e.g. BRCA1) have been suggested to play a role in the pathogenesis of RIS [40–43]. While RB1 and TP53 alterations have been found to be higher in RIS than in sporadic sarcomas [44,45], germline p53-mutations appear to be overall rare in most sarcomas [46]. Kadouri et al. found that BRCA or p53 mutations ultimately did not increase the risk of RIS and concluded they should not be considered in risk stratification of breast cancer patients receiving radiation therapy [47]. Although data on the genetics of RIS exist, this line of research is in its early stages [48]. Hence, to our knowledge studies on RIS did not include mutations to distinguish these lesion from other secondary sarcomas [20,49,50]. Given that the strength of a SEER analysis is the large population, the limitation is that variables not tracked by SEER such as genetic testing cannot be controlled for in this analysis. However, the vast majority of RIS patients would not be expected to carry a deleterious gene mutation in a tumor suppressor gene based on what is currently known from the population genetics of RIS. Therefore, the impact of germline mutations on this data analysis is unlikely to change the main study results reporting on the incidence rates for each histology. As we enter an age of precision medicine, future investigations may determine genetic risk factors for RIS in breast cancer. The incidence rate of RIS in breast

cancer patients in our study was 0.02%, which does not indicate an over-abundance of RIS cases as would be expected if attribution bias was a significant problem.

Another limitation is that SEER does not provide data on radiation dosing or subsequent radiation therapy which is important as studies suggest rates of RIS in adults increase with higher doses of radiation [17]. Specifically, in breast cancer patients, those who received radiotherapy of greater than 14 Gy had a higher risk of developing a sarcoma [33]. SEER does not provide data on radiation fields, but if the data were available, there is likely considerable variation in techniques over time given changing methodologies for radiation therapy delivery [51]. In addition, SEER only lists whether a patient received chemotherapy during their first cancer diagnosis but does not provide chemotherapy regiments or list subsequent chemotherapy treatments after the primary diagnosis.

We found that the RR for RIS was higher in anal, brain, cervical, larynx and pharynx. A potential explanation could be the fact that chemoradiotherapy is frequently used in the treatment of these cancers and often as the first line of therapy [52–55]. The combination of radiation and chemotherapy together has been demonstrated to result in higher cumulative toxicity leading to an increase in the rate of secondary malignancies, including RIS [56–60]. Platinum-based compounds and alkylating agents have been associated with secondary cancers, although not specifically as carcinogens in sarcomas [61,62]. Another contributing factor could be that higher cumulative radiation doses correlate with higher rates of secondary cancers. Kuttesch et al. did not observe any secondary sarcomas in patients receiving less than 48 Gy [63], while Rubino et al. observed that a 30.6 higher risk for sarcomas for doses greater than 44 Gy compared to doses of less than 15 Gy [33]. For most cancers with a higher RR for RIS in our analysis (i.e. anal, brain, cervical, head and neck) radiation doses are > 45 Gy and may exceed 80 Gy. Schonfeld et al. found that increase incidence of secondary soft tissue sarcoma was highest for breast cancer as primary cancer in young adulthood cancer survivors [64]. Although they did not focus on RIS, they found the highest incidence rate after chemoradiotherapy compared to radiation or chemotherapy alone, acknowledging limited availability of detailed information as data available through SEER regarding drugs, doses, schedules (initial treatment only) and overlap with radiotherapy is limited. Furthermore, radiations doses, techniques and treatment modalities have changed substantially for all cancer types.

Lastly, given our small numbers of secondary sarcomas for non-breast cancers, it is difficult to conclude the importance or compare the RR of RIS for other primary cancer sites. SEER also does not provide detailed information about the site of cancers so our study may underestimate the incidence of RIS as we included secondary sarcomas found at the site of primary cancer based upon SEER documentation. Our study confirms that breast cancer patients are more likely to

Our study confirms that breast cancer patients are more likely to develop RIS compared to most non-breast cancers (excluding NHL). Using SEER data from 45 years of follow-up, including current data of the past 15 years not included in previous studies, we found a lower incidence rate which we attributed to technical and safety advances in radiation therapy. Further studies need to confirm our finding and delineate other RIS risk factors to better

stratify those receiving radiation therapy, especially patients with breast cancer, to decrease rates of these deadly cancers.

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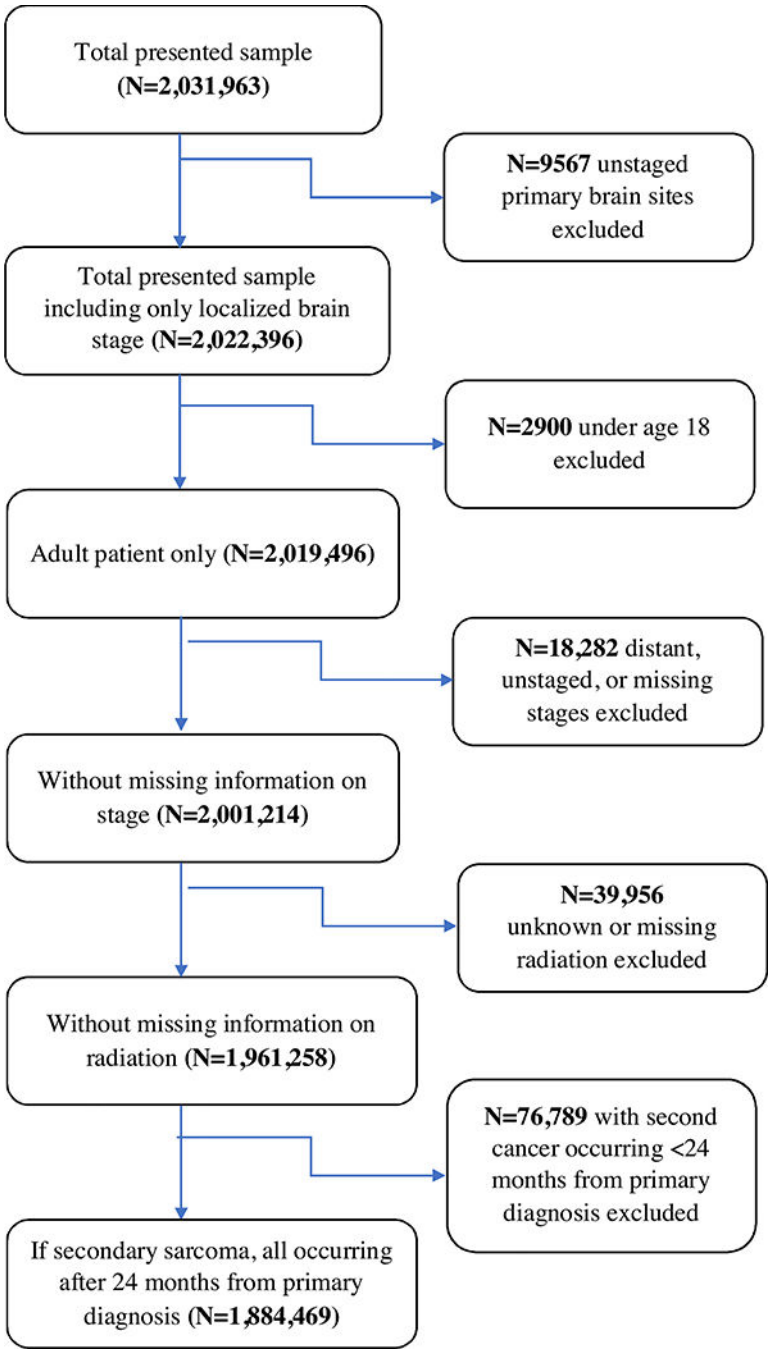

Fig. 1.
Study cohort.

Table 1

Descriptive statistics of study population stratified by primary cancer site *(n* = 1,884,469).

1st cancer site	Total n	Secondary sarcoma	RT		RIS	Follow-up time, *yr*	Age at diagnosis, *yr*	Female Gender	Race			Stage	
			Yes	No					White	Black	Other[a]	Local	Regional
Abdomen	1403	4 (0.29%)	23.1%	76.9%	1 (0.07%)	8.1	53.1	52.7%	78.2%	13.0%	8.8%	68.4%	31.6%
Anal	10,606	3 (0.03%)	75.1%	24.9%	3 (0.03%)	8.3	58.7	62.1%	86.8%	9.8%	3.4%	63.8%	36.2%
Brain	17,617	2 (0.01%)	64.4%	35.6%	2 (0.01%)	7.8	42.6	43.5%	88.2%	5.6%	6.2%	100.0%	0
Breast	693,701	161 (0.02%)	47.3%	52.8%	126 (0.02%)	10.2	58.6	99.4%	83.8%	8.8%	7.4%	66.2%	33.8%
Cervical	48,824	17 (0.03%)	46.5%	53.5%	15 (0.03%)	12.3	47.1	100.0%	77.4%	12.8%	9.8%	67.3%	32.7%
Eye	6852	0	45.0%	55.0%	–	9.6	58.6	44.9%	96.7%	1.4%	1.9%	91.8%	8.2%
Head	1469	8 (0.54%)	33.4%	66.6%	3 (0.20%)	10.3	55.7	31.9%	85.9%	7.5%	6.6%	72.4%	27.6%
Larynx	22,125	3 (0.01%)	76.0%	24.0%	3 (0.01%)	11.3	61.7	18.3%	84.5%	11.9%	3.6%	64.9%	35.1%
Lung	109,858	9 (0.01%)	30.4%	69.6%	3 (0.003%)	6.3	65.3	51.0%	84.3%	9.6%	6.1%	53.2%	46.8%
Pelvis	2109	10 (0.47%)	40.5%	59.5%	6 (0.28%)	9.1	53.3	46.0%	82.1%	12.0%	5.9%	73.2%	26.8%
Pharynx	9085	4 (0.04%)	88.3%	11.7%	4 (0.04%)	8.6	57.5	26.3%	69.6%	10.5%	19.9%	19.8%	80.2%
Prostate [b]	594,271	75 (0.01%)	39.3%	60.7%	44 (0.007%)	7.9	65.7	0	80.8%	14.1%	5.0%	–	100.0%
Rectal	77,296	22 (0.03%)	42.3%	57.7%	14 (0.02%)	8.8	61.8	42.5%	82.1%	8.4%	9.5%	62.8%	37.2%
Salivary	9353	6 (0.06%)	52.5%	47.5%	4 (0.04%)	10.6	55.4	48.4%	82.1%	9.1%	8.8%	65.1%	34.9%
Testicular	33,387	5 (0.01%)	40.4%	59.6%	2 (0.006%)	13.1	34.8	0	93.5%	2.4%	4.1%	78.6%	21.4%
Thorax	1484	2 (0.13%)	41.9%	58.1%	1 (0.07%)	10.2	52.4	39.2%	82.6%	10.2%	7.3%	69.3%	30.7%
Thyroid	106,381	6 (0.01%)	47.8%	52.2%	1 (0.0009%)	10.4	46.5	77.9%	83.0%	6.2%	10.9%	65.1%	34.9%
Uterine	138,648	22 (0.02%)	29.7%	70.3%	10 (0.007%)	11.6	60.5	100.0%	87.3%	5.8%	6.9%	85.3%	14.7%
Total	**1,884,469**	**359** (0.02%)	43.0%	57.0%	**242** (0.01%)	**9.4**	**60.0**	57.3%	**83.1**%	**10.1**%	**6.8**%	46.2%	53.8%

[a]Other includes American Indian/Alaskan Native, Asian/Pacific Islander.

[b]Local/regional stages combined, accounting for 31.5% of total stages.

[a]By Chi-squared or Fisher's exact test, as appropriate.

Table 2

Descriptive statistics of study population stratified by radiotherapy (*n* = 1,884,469).

	Radiotherapy		No radiotherapy		*p*-value
	n	**%**	***n***	**%**	
Total	809,879	43.0%	1,074,590	57.0%	–
Secondary sarcoma	242	0.03%	117	0.01%	<0.001
Age at first diagnosis, yr					
18–44	109,778	13.6%	139,365	13.0%	
45–59	250,317	30.9%	339,011	31.6%	<0.001
60–74	344,198	42.5%	437,789	40.7%	
75+	105,586	13.0%	158,425	14.7%	
Year of first diagnosis					
1973–1998	198,715	24.5%	330,866	30.8%	
1999–2003	219,079	27.1%	253,002	23.5%	<0.001
2004– 2007	195,714	24.2%	234,668	21.8%	
2008–2011	196,371	24.3%	256,054	23.8%	
Female gender	477,563	59.0%	602,036	56.0%	<0.001
Race					
White	665,435	82.6%	885,342	83.5%	
Black	83,098	10.3%	105,649	10.0%	<0.001
Other	57,059	7.1%	69,836	6.6%	
Stage					
Local	348,742	43.0%	521,821	48.6%	<0.001
Regional	461,137	57.0%	552,769	51.4%	

Table 3

Descriptive statistics of final analytical cohort stratified by radiotherapy *(n* = 359).

	RIS		No RIS		p-value [a]
	n	%	n	%	
Total	242	67.4%	117	32.6%	–
Age at first diagnosis, yr					
18–44	38	15.7%	23	19.7%	0.04
45–59	81	33.5%	35	29.9%	
60–74	103	42.6%	39	33.3%	
75+	20	8.3%	20	17.1%	
Year of first diagnosis					
1973–1998	94	38.8%	40	34.2%	0.08
1999–2003	97	40.1%	38	32.5%	
2004–2007	36	14.9%	30	25.6%	
2008–2011	15	6.2%	9	7.7%	
Latency, *yr*					
2– 4	61	25.2%	47	40.2%	0.02
5– 9	118	48.8%	44	37.6%	
10–14	43	17.8%	14	12.0%	
15+	20	8.3%	12	10.3%	
Female gender	172	71.1%	62	53.0%	<0.001
Race					
White	201	83.1%	87	74.4%	0.15
Black	22	9.1%	16	13.7%	
Other	19	7.9%	14	12.0%	
Stage					
Local	112	46.3%	65	55.6%	0.12
Regional	130	53.7%	52	44.4%	

[a] By Fisher's exact test.

Table 4

Proportion of secondary sarcoma stratified by primary cancer site and radiotherapy.

	1st cancer Site	Total Secondary Sarcoma	Secondary Sarcoma		*p*-value[a]
			RT	No RT	
By cancer site	**Abdomen**	4	1 (25.0%)	3 (75.0%)	>0.99
	Anal	3	3 (100.0%)	0	>0.99
	Brain	2	2 (100.0%)	0	0.54
	Breast	161	126 (78.3%)	35 (21.7%)	<0.001
	Cervical	17	15 (88.2%)	2 (11.8%)	<0.001
	Eye	0	–	–	–
	Head	8	3 (37.5%)	5 (62.5%)	>0.99
	Larynx	3	3 (100.0%)	0	>0.99
	Lung	9	3 (33.3%)	6 (66.7%)	>0.99
	Pelvis	10	6 (60.0%)	4 (40.0%)	0.33
	Pharynx	4	4 (100.0%	0	>0.99
	Prostate [b]	75	44 (5.7%)	31 (41.3%)	<0.001
	Rectal	22	14 (63.6%)	8 (36.4%)	0.05
	Salivary	6	4 (66.7%)	2 (33.3%)	0.69
	Testicular	5	2 (40.0%)	3 (60.0%)	>0.99
	Thorax	2	1 (50.0%)	1 (50.0%)	>0.99
	Thyroid	6	1 (16.7%)	5 (83.3%)	0.22
	Uterine	22	10 (45.5%)	12 (54.6%)	0.16
	All non-breast	198	116 (58.6%)	82 (41.4%)	

[a]By Fisher's exact test comparing the incidence of secondary sarcoma by radiation therapy.

Table 5

Relative risk of RIS by primary cancer site (n = 359).

	Primary cancer site	Total *n*	% RIS	Relative risk (95% CI)	p-value
By cancer site	Breast	161	78.3%	*ref*	*ref*
	Abdomen	4	25.0%	0.32 (0.06, 1.75)	0.19
	Anal	3	100.0%	1.28 (1.18, 1.39)	<0.001
	Brain	2	100.0%	1.28 (1.18, 1.39)	<0.001
	Cervical	17	88.2%	1.13 (0.93, 1.37)	0.22
	Head	8	37.5%	0.48 (0.20, 1.18)	0.11
	Larynx	3	100.0%	1.28 (1.18, 1.39)	<0.001
	Lung	9	33.3%	0.43 (0.17, 1.08)	0.07
	Pelvis	10	60.0%	0.77 (0.46, 1.28)	0.31
	Pharynx	4	100.0%	1.28 (1.18, 1.39)	<0.001
	Prostate	75	58.7%	0.75 (0.61, 0.92)	0.01
	Rectal	22	63.6%	0.81 (0.59, 1.13)	0.21
	Salivary	6	66.7%	0.85 (0.48, 1.51)	0.58
	Testicular	5	40.0%	0.51 (0.17, 1.50)	0.22
	Thorax	2	50.0%	0.64 (0.16, 2.56)	0.53
	Thyroid	6	16.7%	0.21 (0.04, 1.28)	0.09
	Uterine	22	45.5%	0.58 (0.36, 0.92)	0.02

[a]Model adjusted for age at primary diagnosis, gender, and latency.