## Title

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Scientific Article

# Association between Long-Term Second Malignancy Risk and Radiation: A Comprehensive Analysis of the Entire Surveillance, Epidemiology, and End Results Database (1973-2014)

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**Abstract**

**Purpose:** Second malignancies (SMs) after radiation therapy are rare but serious sequelae of treatment. This study investigates whether radiation therapy use is associated with changes in baseline SM risk.

**Methods and Materials:** We extracted all patients with cancer, with or without SM, in the Surveillance, Epidemiology, and End Results database from 1973 to 2014. Cumulative incidence of SM for patients stratified by radiation therapy status was calculated using a competing risk model, both for the entire cohort and for subgroups based on the primary tumor's anatomic location.

**Results:** We identified 2,872,063 patients with cancer, including 761,289 patients who received radiation therapy and 2,110,774 who did not. The SM rate at 20 years for patients receiving radiation therapy versus no radiation therapy was 21.4% versus 18.8%. The relative risk for SM associated with radiation therapy for the overall group was 1.138 at 20 years. The relative risks for SM associated with radiation therapy to malignancies arising from central nervous system and orbits, head and neck, thorax, abdomen, and pelvis at 20 years were 0.704, 1.011, 0.559, 0.646, and 1.106 for men and 0.792, 1.298, 1.265, 0.780, and 0.988 for women, respectively.

**Conclusions:** The association between SM and radiation therapy varies with both sex and disease anatomic location, with the largest increase in SM seen in females irradiated to the head and neck

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region. Overall, the absolute change in SM rates associated with radiation therapy remains small, with differences in various clinical contexts.


## Introduction

Radiation exposure is a known precipitant of malignancy, as determined by data from the Japanese atomic bomb survivors[1] and from individuals with occupational radiation exposure.[2] Similarly, previous studies of long-term cancer survivors have also determined that radiation therapy (RT) is associated with increased risk of second malignancy (SM).[3] Increased incidence or risk for SM has been reported in pediatric,[4] gynecologic,[5–8] breast,[9–13] prostate,[14–16] and hematologic[17–20] malignancies treated with RT. Despite the strong evidence for radiation-induced malignancy, existing literature has not been able to accurately quantify the SM risk associated with RT, which is presumed to be low and with an indolent time course. Throughout the past decade, cancer survival has significantly improved, attributed to both early diagnosis and more effective treatment regimens, exemplified by aggressive utilization of definitive therapies including RT. Prolonged cancer survival also increases the awareness of SMs, which are among the most devastating late sequelae of RT and can take many years to develop after treatment.

In this study, we attempted to estimate the relative risk of SM for patients who received RT compared with those who did not, using the entire Surveillance, Epidemiology, and End Results (SEER) database, which provides a large cohort size with decades-long follow-up. Our SM analysis used a competing risk model, accounting for all-cause mortality (ACM) as a competing risk event for SM. Given the inherent variation in individual anatomy and dose distribution, we combined all subsequent malignancies after the first malignancy diagnosis as SMs to provide a more accurate reference for the overall risk of SM after RT. Finally, we grouped the primary disease sites using an anatomically meaningful schema consisting of central nervous system (CNS) and orbits, head and neck, thorax, and abdomen and pelvis.

## Methods and Materials

### Patient population

This study was reviewed and approved by the institutional review board at our institution. For this study, the entire SEER database was used, which included patients with malignancies diagnosed between January 1, 1973 and December 31, 2014. Patients were excluded if they (1) were not in active follow-up, (2) had unknown RT status, or (3) received chemotherapy. Although this study intends to restrict the study population to patients who received no chemotherapy and to stratify the analysis according to RT status, it is possible that some patients who were recorded as having received no chemotherapy or no RT may have received either treatment owing to an inherent underascertainment issue associated with the SEER database.

Previous studies have concluded that hematopoietic SMs develop with a latency period of 2 years after radiation exposure[21] and solid SM are presumed to take longer to present, which compelled several previous studies to use a threshold of 5 years.[14,22–27] For this study, we excluded all cases with consecutive malignancies that occurred within 2 years of each other because the design of this study is to be inclusive of all possible SM, including both hematopoietic and solid malignancies. Extracted variables include age at diagnosis, sex, year of diagnosis, race, and RT status.

### Statistical methodology and analysis

To account for ACM as a competing risk for SM, cumulative incidences of SM and ACM were computed via a competing risk model. This was done for the entire SEER database and subsequently repeated for subgroups based on sex, age, and anatomic primary disease sites, defined as CNS and orbits, head and neck, thorax, abdomen, and pelvis. The distributions of the cumulative incidence of SMs for cohorts stratified based on RT status were evaluated via a k-sample test described by Gray et al,[28] which compared the weighted average of the hazards of the subdistribution for SM. Patients who were alive at last follow-up were censored. All statistical analyses were carried out using R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) with 2-sided testing and a statistical significance threshold of .05.

## Results

### Patient characteristics for the SEER cohort

The patient characteristics stratified by anatomic disease sites are shown in Table 1. A total of 2,872,063 patients from the SEER database who matched the

**Table 1** Patient characteristics

| | Abdomen | CNS and orbit | Head and neck | Pelvis | Thorax | *P* value |
|---|---|---|---|---|---|---|
| n | 416,452 | 35,907 | 184,632 | 1,420,338 | 814,734 | |
| Age (y, median [IQR]) | 67.00 [57.00, 76.00] | 40.00 [21.00, 57.00] | 56.00 [45.00, 67.00] | 66.00 [57.00, 73.00] | 63.00 [53.00, 73.00] | <.001 |
| Sex, male/female (%) | 218,642/197,810 (52.5/47.5) | 19,542/16,365 (54.4/45.6) | 94,399/90,233 (51.1/48.9) | 1,071,149/349,189 (75.4/24.6) | 73,665/741,069 (9.0/91.0) | <.001 |
| Race (%) | | | | | | <.001 |
| White | 338,143 (81.2) | 31,148 (86.7) | 155,123 (84.0) | 1,171,227 (82.5) | 686,258 (84.2) | |
| Black | 42,974 (10.3) | 2388 (6.7) | 14,122 (7.6) | 149,007 (10.5) | 67,596 (8.3) | |
| Asian/Pacific Islander | 2530 (0.6) | 237 (0.7) | 883 (0.5) | 5433 (0.4) | 3169 (0.4) | |
| Other unspecified | 30,022 (7.2) | 1675 (4.7) | 12,444 (6.7) | 69,899 (4.9) | 53,190 (6.5) | |
| Unknown | 2783 (0.7) | 459 (1.3) | 2060 (1.1) | 24,772 (1.7) | 4521 (0.6) | |
| Radiation, no/yes (%) | 410,452/6000 (98.6/1.4) | 22,436/13,471 (62.5/37.5) | 122,430/62,202 (66.3/33.7) | 1,035,560/384,778 (72.9/27.1) | 519,896/294,838 (63.8/36.2) | <.001 |
| SEER Registry (%) | | | | | | <.001 |
| San Francisco-Oakland | 34,856 (8.4) | 3023 (8.4) | 16,893 (9.1) | 118,818 (8.4) | 74,781 (9.2) | |
| Connecticut | 41,121 (9.9) | 3037 (8.5) | 17,417 (9.4) | 115,635 (8.1) | 79,305 (9.7) | |
| Metropolitan Detroit | 39,474 (9.5) | 2888 (8.0) | 17,569 (9.5) | 137,425 (9.7) | 79,713 (9.8) | |
| Hawaii | 11,872 (2.9) | 761 (2.1) | 5016 (2.7) | 30,480 (2.1) | 20,552 (2.5) | |
| Iowa | 32,778 (7.9) | 2821 (7.9) | 14,307 (7.7) | 97,991 (6.9) | 56,147 (6.9) | |
| New Mexico | 12,388 (3.0) | 1261 (3.5) | 6990 (3.8) | 45,244 (3.2) | 23,169 (2.8) | |
| Seattle (Puget Sound) | 29,592 (7.1) | 3267 (9.1) | 14,330 (7.8) | 118,370 (8.3) | 65,971 (8.1) | |
| Utah | 11,327 (2.7) | 1929 (5.4) | 7320 (4.0) | 51,227 (3.6) | 22,811 (2.8) | |
| Metropolitan Atlanta | 16,201 (3.9) | 1735 (4.8) | 8139 (4.4) | 59,552 (4.2) | 37,079 (4.6) | |
| Alaska | 618 (0.1) | 37 (0.1) | 155 (0.1) | 742 (0.1) | 763 (0.1) | |
| San Jose-Monterey | 9446 (2.3) | 934 (2.6) | 3805 (2.1) | 37,160 (2.6) | 20,755 (2.5) | |
| Los Angeles | 39,799 (9.6) | 3258 (9.1) | 15,782 (8.5) | 140,366 (9.9) | 75,582 (9.3) | |
| Rural Georgia | 654 (0.2) | 44 (0.1) | 293 (0.2) | 2373 (0.2) | 1247 (0.2) | |
| Greater California | 52,401 (12.6) | 4575 (12.7) | 21,255 (11.5) | 187,209 (13.2) | 107,961 (13.3) | |
| Kentucky | 16,559 (4.0) | 1321 (3.7) | 6727 (3.6) | 48,541 (3.4) | 27,907 (3.4) | |
| Louisiana | 16,655 (4.0) | 1028 (2.9) | 6518 (3.5) | 52,029 (3.7) | 25,914 (3.2) | |
| New Jersey | 32,691 (7.8) | 2533 (7.1) | 14,790 (8.0) | 11,6078 (8.2) | 61,789 (7.6) | |
| Greater Georgia | 18,020 (4.3) | 1455 (4.1) | 7326 (4.0) | 61,098 (4.3) | 33,288 (4.1) | |
| Marital status (%) | | | | | | <.001 |
| Single (never married) | 45,837 (11.0) | 14,241 (39.7) | 28,521 (15.4) | 152,755 (10.8) | 86,919 (10.7) | |
| Married | 243,841 (58.6) | 15,987 (44.5) | 111,847 (60.6) | 917,527 (64.6) | 457,773 (56.2) | |
| Separated | 5335 (1.3) | 256 (0.7) | 2059 (1.1) | 13,310 (0.9) | 9140 (1.1) | |
| Divorced | 28,769 (6.9) | 1890 (5.3) | 14,371 (7.8) | 89,958 (6.3) | 73,150 (9.0) | |
| Widowed | 72,265 (17.4) | 1659 (4.6) | 15,267 (8.3) | 123,927 (8.7) | 152,960 (18.8) | |
| Unmarried or domestic partner | 82 (0.0) | 6 (0.0) | 42 (0.0) | 308 (0.0) | 172 (0.0) | |
| Unknown | 20,323 (4.9) | 1868 (5.2) | 12,525 (6.8) | 122,553 (8.6) | 34,620 (4.2) | |
| Diagnosis year (%) | | | | | | <.001 |
| 1973-1980 | 33,196 (8.0) | 3104 (8.6) | 20,213 (10.9) | 93,134 (6.6) | 62,778 (7.7) | |
| 1981-1990 | 57,914 (13.9) | 5014 (14.0) | 27,208 (14.7) | 150,038 (10.6) | 106,554 (13.1) | |
| 1991-2000 | 86,342 (20.7) | 8589 (23.9) | 38,076 (20.6) | 344,694 (24.3) | 190,433 (23.4) | |
| 2001-2010 | 199,033 (47.8) | 16,329 (45.5) | 80,587 (43.6) | 702,089 (49.4) | 377,164 (46.3) | |
| 2010-2014 | 39,967 (9.6) | 2871 (8.0) | 18,548 (10.0) | 130,383 (9.2) | 77,805 (9.5) | |
| Vital status (%) | | | | | | <.001 |
| Alive at last contact | 186,199 (44.7) | 20,948 (58.3) | 101,160 (54.8) | 779,685 (54.9) | 425,184 (52.2) | |
| SM | 55,103 (13.2) | 2625 (7.3) | 30,901 (16.7) | 176,096 (12.4) | 113,552 (13.9) | |
| ACM | 175,150 (42.1) | 12,334 (34.3) | 52,571 (28.5) | 464,557 (32.7) | 275,998 (33.9) | |

*Abbreviations:* ACM = all cause mortality; CNS = central nervous system; IQR = interquartile ratio; SEER = Surveillance, Epidemiology, and End Results; SM = secondary malignancy.

previously described selection criteria were extracted for SM analysis. This cohort consisted of 35,907 cases of malignancies in CNS and orbits, 184,632 in head and neck, 814,734 in thorax, 416,452 in abdomen, and 1,420,338 in pelvis. Excluding patients who were reported as alive at last contact, ACM is significantly more likely as an outcome compared with SM, representing 34%, 28%, 34%, 42%, and 33% of the cohorts compared with 7%, 17%, 14%, 13%, and 12% for SM, for CNS and orbits, head and neck, thorax, abdomen, and pelvis, respectively. The median follow-up is 7.4 years for the entire study cohort and 7.1 and 7.8 years for male and females, respectively.

## Cumulative incidence of SMs

The cumulative incidences of SM for the entire SEER cohort stratified by RT status is shown in Figure 1 along with the $P$ value for the distribution of the cumulative incidence of SM. The plot shows statistically significant higher SM for the RT cohort compared with the no-RT cohort ($P < .001$). The SM rates at 20 years after initial diagnosis for patients receiving RT versus no RT were 21.4% versus 18.8%. The SM rates at 40 years after initial diagnosis for patients receiving RT versus no RT were 27.4% versus 24.2%. The relative risk for SM associated with RT for the overall group was 1.138 and 1.132 at 20 and 40 years, respectively.

## Subgroup cumulative incidence of SM by sex

Given that males and females have difference predilections for malignancies at each anatomic disease site, we repeated the calculation of cumulative incidence of SMs for males (N = 1,477,397) and for females (N = 1,394,666) separately, with the cumulative incidence plots shown in Figure 2. For all primary malignancies combined, males demonstrated no difference in SMs between RT and no-RT cohorts ($P = 1.000$), whereas females demonstrated a statistically significant increase in SMs with RT ($P < .001$).

## Subgroup cumulative incidence of SM by sex and by anatomic disease sites

The subgroup cumulative incidence plots for SM and ACM by anatomic disease sites are shown in Figures 3 and 4 for males and females, respectively. For males, patients who received RT had statistically significant lower cumulative incidence of SM for CNS and orbits ($P < .001$), head and neck ($P = .05$), thorax ($P < .001$), and abdomen ($P < .001$) primaries and higher cumulative incidence of SM for pelvis ($P < .001$) primaries. For females, RT resulted in a statistically significant lower cumulative incidence of SM for CNS and orbits ($P = .003$), abdomen ($P = .001$), and pelvis ($P = .007$) primaries and a higher cumulative incidence of SM for head and neck ($P < .001$) and thorax ($P < .001$) primaries. The relative risks for SM associated with RT to primary malignancies arising from CNS and orbits, head and neck, thorax, abdomen, and pelvis at 20 years were 0.704, 1.011, 0.559, 0.646, and 1.106 for men and 0.792, 1.298, 1.265, 0.780, and 0.988 for women. For men, the 20-year actuarial rate of SMs without RT was 0.126 (95% confidence interval [CI], 0.117-0.134), 0.274 (0.269-0.279), 0.220 (0.216-0.224), 0.224 (0.221-0.226), and 0.189 (0.188-0.191) for CNS and orbits, head and neck, thorax, abdomen, and pelvis, respectively, and 0.088 (0.081-0.097), 0.276 (0.271-0.282), 0.123 (0.117-0.128), 0.145 (0.132-0.158), and 0.209 (0.207-0.211) for with RT. For women, the 20-year actuarial rate of SMs without RT was 0.102 (0.094-0.111), 0.169 (0.165-0.173), 0.190 (0.188-0.191), 0.159 (0.157-0.161), and 0.169 (0.167-0.171) for CNS and orbits, head and neck, thorax, abdomen, and pelvis and 0.080 (0.072-0.088), 0.218 (0.211-0.225), 0.240 (0.237-0.242), 0.126 (0.111-0.141), and 0.167 (0.164-0.171) with RT.

## Subgroup cumulative incidence of SM by age group

Given that age at diagnosis may affect the incidence of SM, we repeated the calculation of cumulative incidence of SM for patients with age $\leq$18, 19 to 40, 41 to 60 and $\geq$61 years separately, with the cumulative incidence plots shown in Figure 5. For all primary malignancies combined, patients whose primary malignancy was diagnosed at $\leq$18 years of age demonstrated a statistically significant increase in SM with RT ($P < .001$), and those whose primary malignancy was diagnosed at 41 to 60 years of age demonstrated a statistically significant decrease in SM with RT ($P < .001$).

# Discussion

To study SM, a large population size is needed given the low incidence of SM, as is a careful choice of proper statistical methodologies. Because SM is such a rare event, prospective studies are impractical, and retrospective (single and multiple institutions) studies often lack the sample size to achieve statistical significance. Therefore, a large population-based database such as the SEER database provides the best context to elucidate the risk of SM.

With respect to statistical methodology, given the overall low incidence of SM among patients with cancer, mortality events represent a much more likely outcome compared with SM and thus compete with SM. Any disparity in mortality can thus significantly confound the

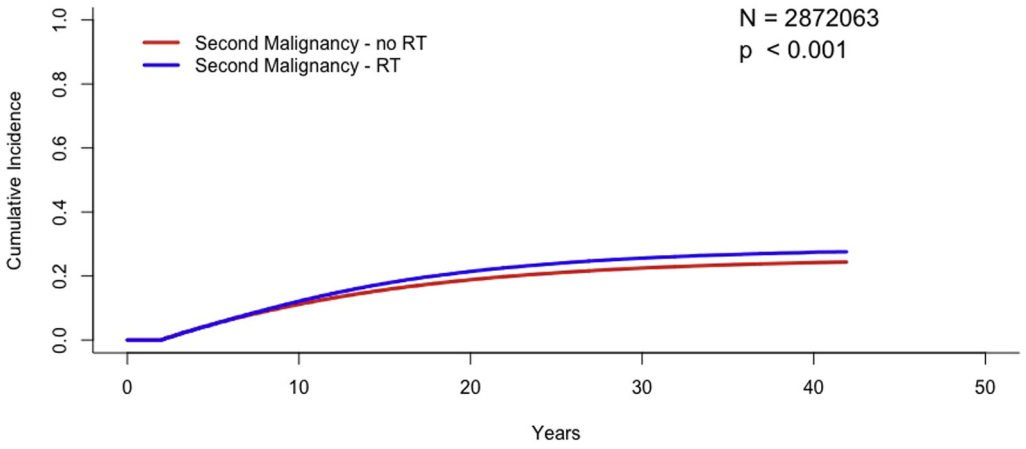


**Figure 1** Cumulative incidence of second malignancies in the entire Surveillance, Epidemiology, and End Results database cohort.

outcome of SM analysis. This is especially important when studying radiation-induced SM, given that RT has historically been recommended to patients who are deemed inoperable secondary to comorbidities, thus increasing their risk of overall mortality. The most common statistical methods for SM analysis consist of standard incidence ratio and Cox proportional hazards regression. However, neither methods can account for ACM as a competing risk event for the SM, and as a result they may inflate the incidence SM with higher baseline ACM.[14] Furthermore, patients with cancer are likely enriched for behavioral, environmental, and genetic factors that affect their likelihood of cancer compared with the noncancer population. In addition, standard incidence ratio only allows for investigation of specific type of SM, not the sum of all SMs. This is important considering that SM development depends both on dose and anatomy. Therefore, although patients may have varying risks of different types of SM, the summation of all SMs may provide a better estimate of the true incidence of SM from RT.

Thus, there is a clear need for a statistical method that can counteract the effect of ACM on the estimation of SM risk. Satagopan et al proposed that in the analysis of SM, an ACM event precludes the onset of SM and thus should be treated as a competing risk event instead of a censored event.[29] A competing risk model has previously been used in a SEER study of SM associated with EBRT for prostate cancer,[14] as well as in patients who received brachytherapy in a Dutch single-institution series.[30]

With an overall cohort size of >2.8 million patients, we have concluded that RT is indeed associated with a significant relative increase in SM ($P < .001$) compared with patients who received no RT, starting after the first decade after diagnosis and stabilizing after the second decade, as shown in Figure 1. When the cumulative incidence of SM in patients who received RT and those who did not was separately evaluated for males and females, only females showed a statistically significant increase in SM with RT ($P < .001$), as shown in Figure 2. On further stratification by anatomic disease sites, males who received RT had a statistically significant lower cumulative incidence of SM for CNS and orbits, head and neck, thorax, and abdomen and a higher cumulative incidence of SM for pelvis. Females who received RT had a statistically significant lower cumulative incidence of SM for CNS and orbits, abdomen, and pelvis and a higher cumulative incidence of SM for head and neck and thorax. Therefore, the results of our study, powered by the largest patient population to date, indicate that the relationship between RT and SM is highly complex and varies by sexes, age group, and

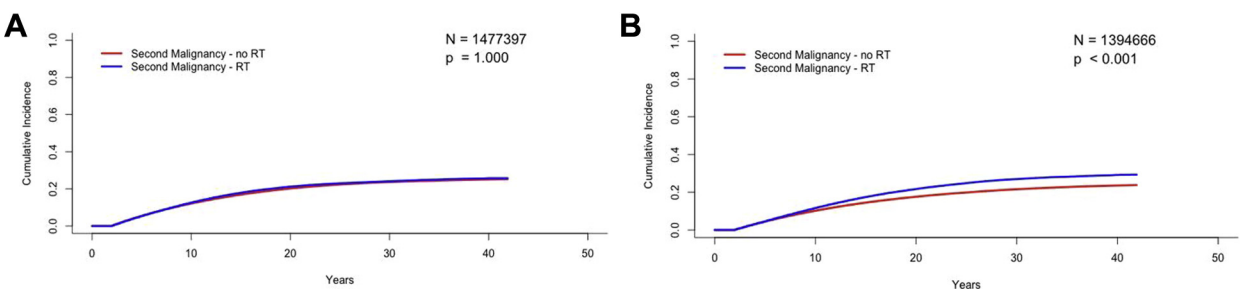


**Figure 2** Cumulative incidence of second malignancies in males (A) and females (B).

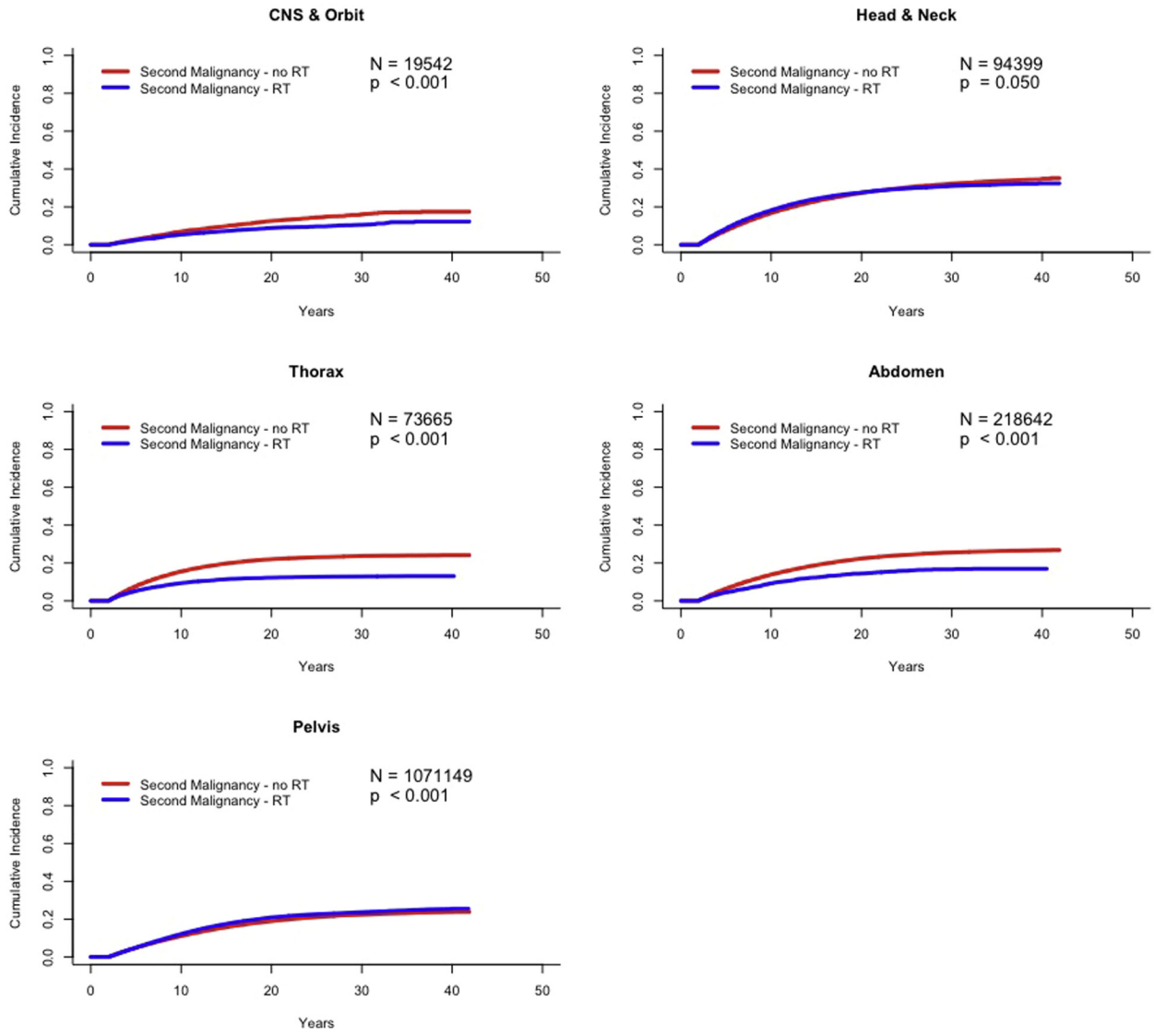


**Figure 3** Cumulative incidence of second malignancies by anatomic site of the primary for males.

anatomic disease site. However, even for anatomic disease sites with significant difference in SM between the RT and no-RT cohorts, the absolute difference remains low relative to ACM. Given the goal to assess the occurrence of SM after RT, we did not analyze and categorize the different types of SM. It is possible that some are not true SM. The pathogenesis, treatment, and prognosis of these different SM types should be the subject of independent evaluations.

The exact mechanism leading to radiation-induced SM is a topic of active debate. Radiation dose perceived by normal tissue during RT consists of primary radiation within each beam path, as well as secondary radiation outside of the beam path. Part of the secondary radiation is due to scatter within the patient and collimator, and part is due to leakage from the treatment machine.[31,32] More importantly, SMs attributed to secondary radiation in out-of-field organs such as lungs, esophagus, and stomach may be significantly modified by environmental and lifestyle factors, and thus they can present with a plethora of histologies for each anatomic disease site. In addition to the uncertainties associated with the location and histology of SM, the relationship between radiation dose and SM risk is also an area of active research. Throughout the years, multiple models have been proposed to estimate SM risk with respect to radiation dose. All models agree that for relatively low radiation dose exposure up to several gray, the SM risk increases in a linear relationship with radiation dose.[33] The rationale behind this is that low dose radiation may be insufficient to achieve cell kill and thereby allows cells to survive with sublethal damage that induces malignant transformation. It is important to note that this linear model is based on the assumption of a single whole-body exposure, as in the case of atomic bomb explosion; therefore, some allowances need to be made for fractionated RT.[34] For radiation exposure at

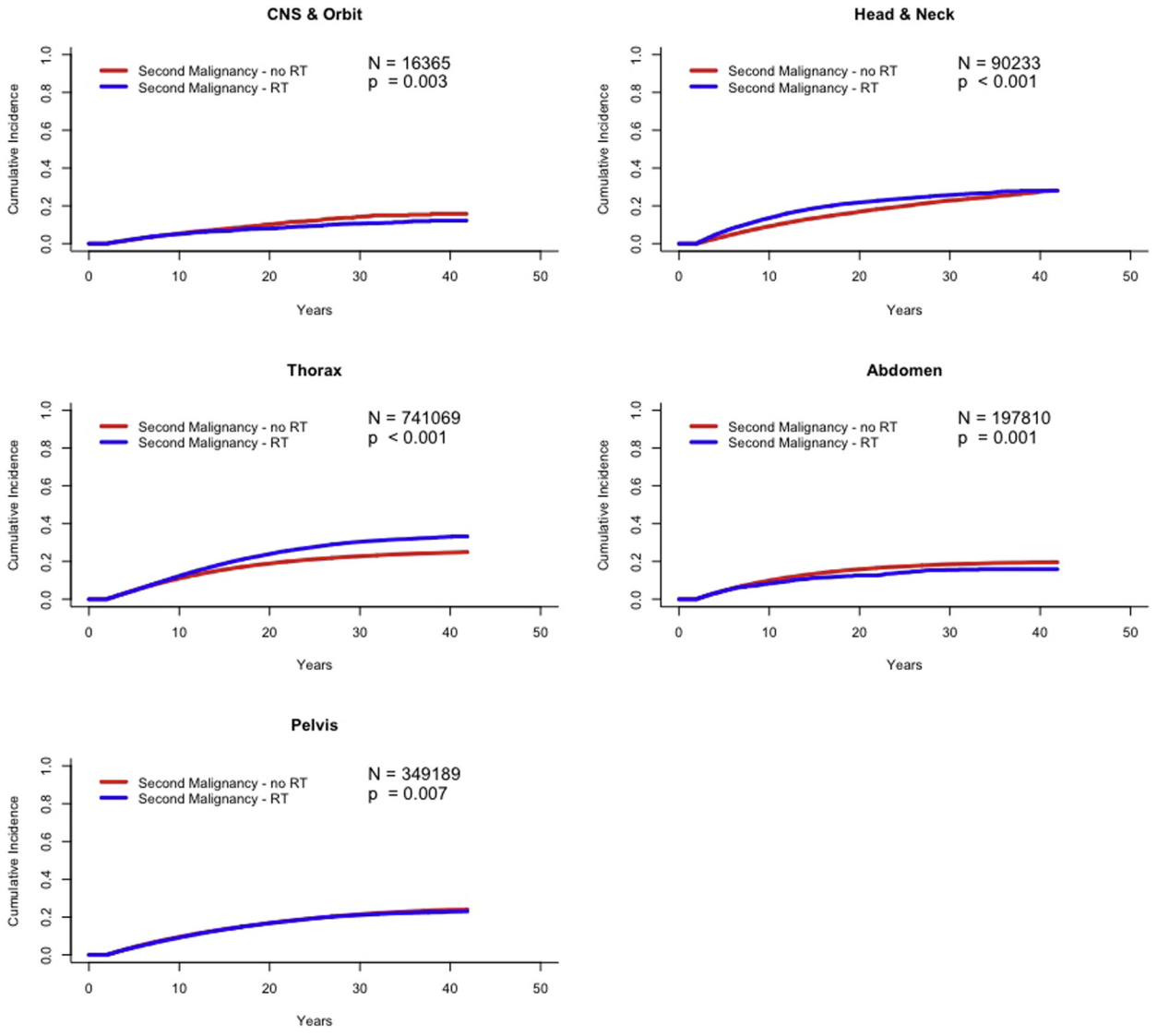


**Figure 4** Cumulative incidence of second malignancies by anatomic site of the primary for females.

higher dose past the initial 4 Gy, 3 dose-response models have been proposed. The linear-no-threshold model continues the earlier linear relationship between SM and dose,[35] the linear-plateau model achieves a plateau at a higher dose, and the linear exponential model demonstrates decreased SM at higher dose due to a presumed increase in cell sterilization. Together, the uncertainties surrounding the location and histology of SM, combined with the lack of understanding of its relationship with radiation dose, make our decision to use the broadest definition for SM not only justified, but also necessary to provide the most accurate estimation of its risk.

To the best of our knowledge, our study is the largest to look at the issue of SM after RT. This is the first investigation of RT-induced SM using the SEER database in its entirety along with a competing risk model capable of accounting for ACM as a competing risk event for SM. The analysis was carried out according to an all-inclusive definition of SM that departs from the traditional narrow definition of in-field SM. This was done to capture all SM event and thus render the analysis resilient to variations in individual anatomy and RT dose distribution. Instead, for part of the analysis, we grouped the primary disease sites by anatomic groups of RT delivery site. Chemotherapy use was removed as a major confounding factor for this analysis, although one could make the argument that chemotherapy is an intrinsic part of therapy for patients with cancer and thus its use should be included for the analysis to reflect reality in these patients. The analysis including chemotherapy patients will be the subject of a separate study.

The observation of RT significantly reducing the cumulative incidence of SM at some anatomic disease sites is especially interesting. Several theories may explain this intriguing phenomenon. First, both primary

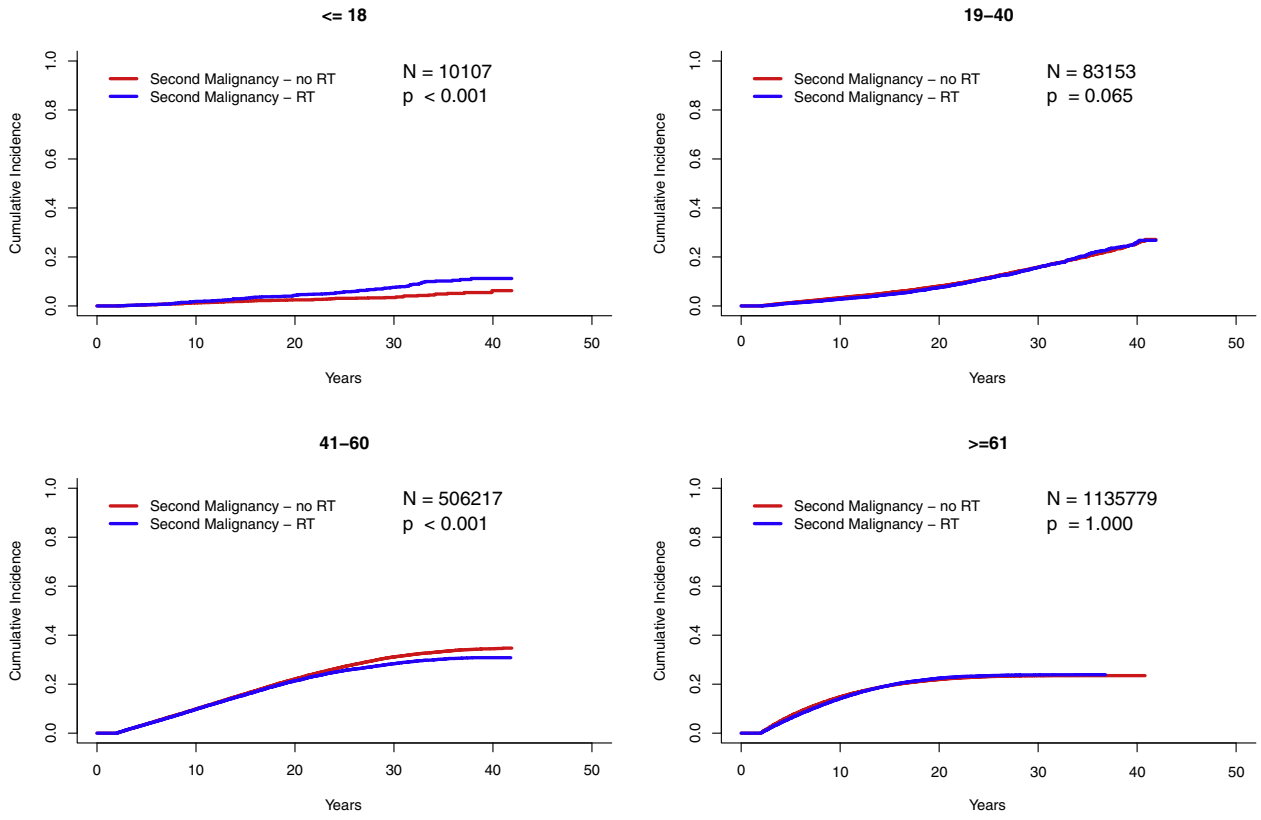


**Figure 5** Cumulative incidence of second malignancies by age group.

radiation to the primary disease site and secondary radiation to out-of-field organs may end up sterilizing occult synchronous malignancies and premalignant tissues. In addition to radiation's role in direct tumor kill, there is also evidence to suggest that radiation can induce strong antitumor immunity via a mechanism called immunogenic cell death,[36–38] which may have a systemic effect on the patient and reduce the risk of future malignancies. Finally, patients who did not receive RT may have eventually developed late metastases or recurrences that were mistaken for SM.

In terms of limitations, the SEER database only records treatment received as the first course of treatment; therefore, we cannot ascertain whether patients who initially received no RT had later salvage RT for recurrence. However, this is likely to be uncommon given the historical low utilization of RT in the salvage setting, which, when compounded by the already rare nature of SM, makes it unlikely to significantly confound our analysis. In addition, underascertainment of the receipt of RT in the SEER database has been previously established, which led to the eventual designation of the RT variable as an experimental variable.[39] However, the underascertainment of the RT variable biases toward the null hypothesis and in fact makes the statistically significant findings in this study even more significant. At the same time, the variation in underascertainment of RT utilization across different anatomic disease sites may affect the relative risk of SM associated with RT. Our study also excluded patients who received chemotherapy as the first course of treatment because chemotherapy can also induce SM. A study comparing SEER chemotherapy data with SEER-Medicare data has determined that SEER chemotherapy data have an overall sensitivity of approximately 68%, which translates into an overall positive predictive value of >85%.[40] However, it is unlikely that the underreporting of chemotherapy affects the cohorts stratified based on RT status differently. Because our analysis design focuses on anatomic disease site rather than specific cancer diagnosis, we were not able to balance clinical covariates such as stage, histology, and other patient-specific factors that may contribute to baseline SM rate. Finally, the SEER database does not record RT dose, fractionation, or the extent of RT field; therefore, it is impossible to determine the dose distribution for patients who received RT. This is somewhat remedied by the fact that we used an all-inclusive definition of SM, and we relied on the large population size of the SEER database to average the variations in RT field and dose. In addition, by relying on actual retrospective data for our analysis, we have concluded there is a significantly lower absolute risk for SM compared with computed risk using equivalent total mean body dose and the atomic bomb survival data,[41]

which further accentuates the divide between actual and perceived SM risk associated with RT.

Another factor that may alter SM incidence is RT technique, which in recent years has focused on minimizing radiation dose to normal tissues via image guidance, improved precision in beam delivery, and particle therapy. The effect of this evolution is both interesting and pertinent; however, the study of it will have to wait for additional years in follow-up to ensure adequate comparison.

## Conclusions

Our study shows that RT tends to be associated with a statistically significant increase in the cumulative incidence of SM at some anatomic disease sites, although it can result in statistically significant decrease in the cumulative incidence of SM at other anatomic disease sites, with significant variation based on age and sex. Despite this, the absolute change in SM associated with RT remains small. In the decision-making process to use RT as part of the initial treatment regimen, concerns about SM should be modulated because the pathogenesis is likely multifactorial and the potential benefits of RT will remain high relative to its risk for inducing SM.

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