Proportion of second cancers attributable to radiotherapy treatment in adults: a cohort study in the US SEER cancer registries

Amy Berrington de Gonzalez, Rochelle E Curtis, Stephen F Kry, Ethel Gilbert, Stephanie Lamart, Christine D Berg, Marilyn Stovall, Elaine Ron*  

Summary

Background Improvements in cancer survival have made the long-term risks from treatments more important, including the risk of developing a second cancer after radiotherapy. We aimed to estimate the proportion of second cancers attributable to radiotherapy in adults with data from the US Surveillance, Epidemiology and End Results (SEER) cancer registries.

Methods We used nine of the SEER registries to systematically analyse 15 cancer sites that are routinely treated with radiotherapy (oral and pharynx, salivary gland, rectum, anus, larynx, lung, soft tissue, female breast, cervix, endometrium, prostate, testes, eye and orbit, brain and CNS, and thyroid). The cohort we studied was composed of patients aged 20 years or older who were diagnosed with a first primary invasive solid cancer reported in the SEER registries between Jan 1, 1973, and Dec 31, 2002. Relative risks (RRs) for second cancer in patients treated with radiotherapy versus patients not treated with radiotherapy were estimated with Poisson regression adjusted for age, stage, and other potential confounders.

Findings 647 672 cancer patients who were 5-year survivors were followed up for a mean 12 years (SD 4-5, range 5–34); 60 271 (9%) developed a second solid cancer. For each of the first cancer sites the RR of developing a second cancer associated with radiotherapy exceeded 1, and varied from 1·08 (95% CI 0·79–1·46) after cancers of the eye and orbit to 1·43 (1·13–1·84) after cancer of the testes. In general, the RR was highest for organs that typically received greater than 5 Gy, decreased with increasing age at diagnosis, and increased with time since diagnosis. We estimated a total of 3266 (2862–3670) excess second solid cancers that could be related to radiotherapy, that is 8% (7–9) of the total in all radiotherapy patients (≥1 year survivors) and five excess cancers per 1000 patients treated with radiotherapy by 15 years after diagnosis.

Interpretation A relatively small proportion of second cancers are related to radiotherapy in adults, suggesting that most are due to other factors, such as lifestyle or genetics.

Funding US National Cancer Institute.

Introduction Radiotherapy reduces the risk of cancer recurrence, promotes tumour control, and improves survival.1 However, with improved survival, the long-term risks from radiotherapy—including the risk of developing a second cancer—become more important. Subsequent malignancies in cancer survivors now constitute 18% of all cancer diagnoses in the US Surveillance, Epidemiology and End Results (SEER) cancer registries, making them the third most common cancer diagnosis. Compared with the general population, cancer survivors have an approximately 14% higher rate of cancer.2 These greater risks are probably the result of a combination of shared lifestyle and genetic factors, as well as the treatment for the first cancer. Although many studies have shown an association between radiotherapy and the risk of developing a second cancer, it is not known what proportion of second cancers might be related to radiotherapy. In two recent studies3,4 we used the SEER cancer registries to develop some of the first estimates of the attributable risk for specific first cancers, and we concluded that about 5–6% of second solid cancers after breast cancer3 and 11% after endometrial cancer3 might be related to radiotherapy. Here, we extend this assessment to do a comprehensive and systematic analysis of all first solid cancer sites in adults that are routinely treated with radiotherapy with data from the SEER registries. The large population covered by these registries, combined with more than three decades of follow-up, enables long-term detailed assessment of the patterns of risk after radiotherapy.

Methods

Population and follow-up The cohort was composed of patients aged 20 years or older who were diagnosed with a first primary invasive solid cancer reported to one of nine SEER registries (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco–Oakland, Seattle–Puget Sound, and Utah) between Jan 1, 1973, and Dec 31, 2002. We included 15 solid-cancer sites that are routinely treated with radiotherapy (oral and pharynx, salivary...
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between radiation exposure and solid-cancer induction,\(^3\) we excluded patients who survived less than 5 years from the analysis. This restriction also ensured that we eliminated any surveillance bias that might result if patients who received radiotherapy were monitored more intensively than other patients in the first 5 years. The follow-up time (person-years at risk) for second

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Table 1: Descriptive statistics of the 5-year cancer survivors by site of first cancer

<table>
<thead>
<tr>
<th>Site of First Cancer</th>
<th>Number of Patients Treated with Radiotherapy (%)</th>
<th>Number of Patients Not Treated with Radiotherapy (%)</th>
<th>Mean Follow-up (years)</th>
<th>Mean Age at Diagnosis (years)</th>
<th>Proportion of Patients Treated with Radiotherapy by Stage</th>
<th>Proportion of Patients Treated with Radiotherapy by Year of Diagnosis</th>
<th>Proportion of Patients Treated with Radiotherapy by Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral/pharynx*</td>
<td>9714 (58%)</td>
<td>7012 (42%)</td>
<td>10.8</td>
<td>11.9</td>
<td>57 (58%)</td>
<td>58% (62%)</td>
<td>46% (55%)</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>1542 (48%)</td>
<td>1660 (52%)</td>
<td>12.3</td>
<td>15.0</td>
<td>55 (51)</td>
<td>44% (47%)</td>
<td>56% (53%)</td>
</tr>
<tr>
<td>Rectum†</td>
<td>9234 (28%)</td>
<td>24317 (72%)</td>
<td>10.6</td>
<td>12.1</td>
<td>61 (63)</td>
<td>39% (31%)</td>
<td>24% (21%)</td>
</tr>
<tr>
<td>Anus</td>
<td>1618 (66%)</td>
<td>816 (34%)</td>
<td>10.9</td>
<td>12.7</td>
<td>58 (59)</td>
<td>68% (65%)</td>
<td>62% (67%)</td>
</tr>
<tr>
<td>Larynx</td>
<td>931 (74%)</td>
<td>3124 (26%)</td>
<td>11.8</td>
<td>13.1</td>
<td>61 (60)</td>
<td>71% (73%)</td>
<td>77% (75%)</td>
</tr>
<tr>
<td>Lung (non-small cell)</td>
<td>7218 (23%)</td>
<td>27775 (77%)</td>
<td>9.5</td>
<td>11.0</td>
<td>61 (62)</td>
<td>27% (27%)</td>
<td>18% (21%)</td>
</tr>
<tr>
<td>Soft tissue (non-limbs)</td>
<td>746 (33%)</td>
<td>15141 (67%)</td>
<td>12.0</td>
<td>13.8</td>
<td>51 (51)</td>
<td>32% (33%)</td>
<td>34% (32%)</td>
</tr>
<tr>
<td>Female breast</td>
<td>90613 (40%)</td>
<td>137911 (60%)</td>
<td>11.0</td>
<td>13.2</td>
<td>57 (59)</td>
<td>42% (43%)</td>
<td>37% (32%)</td>
</tr>
<tr>
<td>Cervix†</td>
<td>7779 (40%)</td>
<td>11494 (60%)</td>
<td>14.7</td>
<td>16.8</td>
<td>52 (42)</td>
<td>25% (53%)</td>
<td>66% (62%)</td>
</tr>
<tr>
<td>Endometrium†</td>
<td>19618 (36%)</td>
<td>34559 (64%)</td>
<td>14.8</td>
<td>14.1</td>
<td>62 (60)</td>
<td>24% (34%)</td>
<td>39% (38%)</td>
</tr>
<tr>
<td>Prostate§</td>
<td>76362 (28%)</td>
<td>123800 (62%)</td>
<td>9.4</td>
<td>10.1</td>
<td>68 (66)</td>
<td>28% (40%)</td>
<td>43% (42%)</td>
</tr>
<tr>
<td>Testes (seminomas)</td>
<td>6420 (79%)</td>
<td>17212 (21%)</td>
<td>15.8</td>
<td>14.2</td>
<td>37 (37)</td>
<td>79% (80%)</td>
<td>70% (78%)</td>
</tr>
<tr>
<td>Eye/orbit</td>
<td>556 (26%)</td>
<td>15810 (74%)</td>
<td>10.8</td>
<td>13.4</td>
<td>56 (56)</td>
<td>25% (28%)</td>
<td>22% (25%)</td>
</tr>
<tr>
<td>Brain/CNS¶</td>
<td>4075 (61%)</td>
<td>25153 (39%)</td>
<td>12.1</td>
<td>12.3</td>
<td>40 (42)</td>
<td>64% (59%)</td>
<td>50% (54%)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>10904 (39%)</td>
<td>16821 (61%)</td>
<td>12.7</td>
<td>16.3</td>
<td>44 (44)</td>
<td>40% (38%)</td>
<td>37% (34%)</td>
</tr>
</tbody>
</table>

RT=radiotherapy. *Lip excluded as fewer than 20% of patients received radiotherapy. †Age-groups 60–74 years and 75–79 years were combined because of small numbers. ‡44% of cancer staging is unknown. §Age-groups <45 years and 45–59 years were combined because of small numbers; local and regional stages combined. ¶No stage data available.

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Figure 1: Relative risk of second solid cancer for radiotherapy versus no radiotherapy by site of first cancer

Relative risk (RR) adjusted for sex, attained age, and attained year through the use of external rates and additionally adjusted for stage, age at diagnosis, and year of diagnosis through stratification. For salivary gland, cervix, endometrial, prostate, and thyroid cancers second cancers of the same site were excluded because standard treatment usually involves surgical removal of the affected organ or because of second cancer coding rules (prostate).
cancers for each individual began 5 years after the date of diagnosis of the first cancer and ended at the date of diagnosis of any second malignant cancer, last known vital status, death, or the end of study (Dec 31, 2007), whichever was first. Patients were censored at age 85 years since there is evidence of under-ascertainment of second primary cancers after that age in SEER. We excluded patients with missing information on radiotherapy or stage, unless the first primary was prostate, brain, or lung cancer, because stage information was often unavailable for these cancers during the study period. We excluded haematological cancers from both the first and second cancer sites because of potential confounding by chemotherapy, details of which were not available. For similar reasons we also excluded non-seminoma testicular cancers and small-cell lung cancers. Soft-tissue sarcomas in extremities were excluded because radiotherapy for these cancers would be unlikely to result in second solid cancers. Our study did not need ethics committee approval because the data are publicly available.

Treatment information
SEER cancer registries collect information on the first course of treatment. Patients were classified according to whether or not they had received radiotherapy as part of their initial cancer treatment and the type of radiotherapy given: external beam, brachytherapy, or combination therapy (external beam and brachytherapy).

Classification of second cancers
To provide sufficient statistical power for risk estimation, our analyses were done for all second solid cancers combined. Furthermore, for the first cancer sites with at least 1000 second cancers, the typical radiation doses delivered to each second cancer site were estimated with standard radiotherapy protocols from the period of study. The distance of the second cancer site from the border of the primary radiotherapy field was then used to categorise the second cancer sites into broad groups: <3 cm, high-dose (>5 Gy); 3–10 cm, medium-dose (1–5 Gy); and >10 cm, low-dose (<1 Gy). Dose groups for thyroid cancer were based on treatment with iodine-131, and we assumed an administered activity of 7·4 GBq. The second cancer dose groupings for the nine eligible first cancer sites are given in the webappendix (pp 1–15).

Statistical analysis
We used Poisson regression analysis to estimate the relative risk (RR) and 95% CIs of second solid cancer in patients who received radiotherapy compared with those who did not receive radiotherapy. These risks were adjusted for potential confounding factors: stage, age at and year of first cancer diagnosis, and additionally adjusted for calendar period and attained age by use of the expected number of second cancers in the general population as an offset. We assessed effect modification of the risk associated with radiotherapy by age at first cancer diagnosis, time since first diagnosis, and year of diagnosis. This analysis was restricted to the outcome of high-dose second cancer sites to maximise the power to detect differences. We also did a sensitivity analysis in which we restricted the analysis to the subgroup of patients who were surgically...
treated for their first cancer. All analyses were done with Epicure Amfit (version 1.8).

We estimated the number of excess second cancers related to radiotherapy by taking the number of second cancers in those treated with radiotherapy minus the estimated number of cancers in these patients if they had not received radiotherapy (estimated from the Poisson regression models). Although the analysis of excess cancers was restricted to patients who had survived for 5 years or longer (to eliminate potential surveillance bias in the early period of follow-up), the overarching goal of our study was to estimate the proportion of second solid cancers related to radiotherapy in all cancer survivors. Therefore, we expressed this excess as a proportion of the total number of second cancers in all cancer survivors (defined as ≥1 year survivors). We calculated the number of second cancers in patients that survived 1 year or longer with the SEER cancer registries database, applying the same exclusions as defined above for patients that survived 5 years or longer. This approach assumes that the number of radiation-related solid cancers in the first 5 years is zero.

To estimate the cumulative excess risk by 15 years after diagnosis we estimated the excess number of cases that happened were diagnosed by 15 years and divided this by the total number of patients who received radiotherapy (defined as ≥1 year survivors). The overall excess and attributable risks were then estimated by summing across all 15 first cancer sites.

Role of the funding source
The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
There were 647,672 adult cancer patients who survived for 5 years or longer in the cohort, followed up for a mean 12 years (SD 4–5, range 5–34). The proportion of patients who received radiotherapy as part of their initial cancer treatment varied from 23% for non-small-cell lung cancer to 79% for testicular seminomas (table 1). Patterns of radiotherapy varied across the first cancer sites, but receipt of radiotherapy was slightly less common in the oldest patients (age 75–79 years) for most first cancer sites and for localised stage disease, and was more common in recent years. The main exceptions to these patterns were cervical and endometrial cancer, for which radiotherapy was more common in older women (≥60 years) and for more advanced stage disease and was less common in recent years.

During the follow-up period (1978–2007), 60,271 (9%) of the 5-year survivors developed a second solid cancer. For each of the first cancer sites the RR of developing a second solid cancer associated with radiotherapy was greater than 1, and for most first cancer sites the increased risk was statistically significant (figure 1). The adjusted RR for radiotherapy varied from 1.08 (95% CI 0.79–1.46) after cancers of eye and orbit to 1.43 (1.31–1.54) after testicular seminoma. Adjustment for stage at diagnosis, age at diagnosis, and year of diagnosis of the first cancer had a small effect on the RR estimates, generally reducing the risks (webappendix pp 1–15). Restricting the cohort to patients treated with surgery did not change the RRs by more than 10% except for cancers of the eye and orbit, which were based on very small numbers (webappendix p 16). When we assessed the RRs associated with radiotherapy treatment for the group of second cancers that were related to smoking we found that these risks were often higher than the risks for second cancers not related to smoking, suggesting possible confounding by smoking (webappendix p 17).

<table>
<thead>
<tr>
<th>Diagnosed age</th>
<th>Diagnosed age</th>
<th>Diagnosed age</th>
<th>Diagnosed age</th>
<th>p-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral/pharynx</td>
<td>0.70 (0.49 to 0.99)</td>
<td>1.18 (0.93 to 1.53)</td>
<td>1.14 (0.99 to 1.33)</td>
<td>1.27 (0.63 to 2.58)</td>
</tr>
<tr>
<td>Rectum*</td>
<td>1.09 (0.48 to 2.27)</td>
<td>1.00 (0.78 to 1.27)</td>
<td>1.19 (1.00 to 1.42)</td>
<td>1.61 (0.91 to 2.72)</td>
</tr>
<tr>
<td>Larynx†</td>
<td>1.04 (0.46 to 2.57)</td>
<td>1.52 (1.07 to 2.21)</td>
<td>1.17 (0.76 to 1.83)</td>
<td>-</td>
</tr>
<tr>
<td>Lung (non-small cell)</td>
<td>1.42 (0.93 to 2.12)</td>
<td>1.29 (1.11 to 1.50)</td>
<td>1.20 (1.03 to 1.38)</td>
<td>1.14 (0.58 to 2.11)</td>
</tr>
<tr>
<td>Female breast</td>
<td>1.83 (1.46 to 2.29)</td>
<td>1.45 (1.29 to 1.62)</td>
<td>1.15 (1.03 to 1.28)</td>
<td>1.03 (0.63 to 1.66)</td>
</tr>
<tr>
<td>Cervix (external beam)*†</td>
<td>3.25 (2.21 to 4.79)</td>
<td>1.48 (1.06 to 2.08)</td>
<td>1.15 (0.76 to 1.75)</td>
<td>-</td>
</tr>
<tr>
<td>Endometrium (external beam)*</td>
<td>3.25 (2.08 to 5.04)</td>
<td>1.65 (1.37 to 1.98)</td>
<td>1.72 (1.47 to 2.03)</td>
<td>0.92 (0.46 to 1.74)</td>
</tr>
<tr>
<td>Prostate (external beam)*†</td>
<td>1.85 (1.52 to 2.22)</td>
<td>1.48 (1.38 to 1.58)</td>
<td>1.15 (0.96 to 1.37)</td>
<td>0.0007/0</td>
</tr>
<tr>
<td>Thyroid†</td>
<td>1.34 (0.69 to 2.52)</td>
<td>1.08 (0.57 to 2.03)</td>
<td>0.78 (0.39 to 1.57)</td>
<td>-</td>
</tr>
</tbody>
</table>

Data are relative risk (RR; 95% CI) unless otherwise stated. RR adjusted for sex, attained age, and attained year through the use of external rates and additionally adjusted for stage, age at diagnosis, and year of diagnosis through stratification. For endometrial and prostate cancer the group treated with external beam radiotherapy includes patients treated with internal beam and brachytherapy. *Second cancers of the same site were excluded because standard treatment usually involves surgical removal of the affected organ or because of second cancer coding rules (prostate). †Highest age-group of 60 years or older used because of small numbers. No second cancers recorded in the youngest age-group.

Table 2: Relative risk of second solid cancer at high-dose sites for radiotherapy versus no radiotherapy by age at diagnosis of the first cancer and first cancer site.
For six of the nine first cancer sites for which we did grouped dose–response analyses, the RR for radiotherapy was higher for the group of second cancer sites that typically receive a high dose (>5 Gy) than for the sites that typically receive moderate or low radiation doses (≤5 Gy; figure 2). The RR for the high-dose second cancer sites varied from 1.03 (95% CI 0.71–1.47) after cancer of the thyroid to 1.78 (1.42–2.16) after cancer of the cervix. For cancer of the female breast, endometrium, and prostate there was a highly significant trend across the dose groups (figure 2). There was also a possible, but not significant, increasing trend for laryngeal and cervical cancer. For the remaining sites the patterns of risk were less consistent. Results for each individual second cancer site and each dose group are given in the webappendix (pp 1–15).

We assessed effect modification by age and year of diagnosis and time since diagnosis for second solid-cancer sites that typically receive high doses of radiation (>5 Gy). The RRs associated with radiotherapy decreased significantly with increasing age at diagnosis for second cancers after cancers of the breast, cervix, endometrium, and prostate (table 2). The RRs increased significantly with increasing year since diagnosis after cancer of the lung, breast, cervix, endometrium, and prostate (table 3). The RRs decreased with increasing year of diagnosis for second cancers after breast cancer (p<0.0001) and endometrial cancer (p=0.064), but for the other sites there were no clear patterns (webappendix p 18). Because all of these time variables are probably related, these patterns should be interpreted with some caution.

There were an estimated 3266 (95% CI 2862–3670) excess second solid cancers that could be related to radiotherapy in the 5-year survivors in our analysis; more than half of these were in breast and prostate cancer survivors (table 4). If we assume that there were no excess radiation-related solid cancers in the first 5 years of follow-up, we estimate that 8% (95% CI 7–9) of the 42 294 second solid cancers diagnosed in patients that survived longer than 1 year could be related to radiotherapy (table 4). This proportion was lowest for patients initially treated for cancers of the eye and orbit and highest for those initially treated for testicular seminoma (table 4). For every 1000 patients treated with radiotherapy we estimated three excess cancers by 10 years after first cancer diagnosis, and five excess cancers by 15 years (data not shown).

In the nine first cancer sites for which we assessed risk by broad dose groups, 1541 (54%) of 2876 estimated excess radiation-related cancers were in the high-dose group (>5 Gy) compared with 10 535 (28%) of 38 099 second cancers overall (data not shown). By contrast, 839 (29%) of 2876 excess cancers were in the low-dose group compared with 18 601 (49%) of 38 099 second cancers overall. To assess the potential effect of bias in the low-dose group we also estimated the attributable risk for these nine first cancers excluding the low-dose group excess, this decreased the estimate from 7% (95% CI 6–8) to 5% (4–6). For the high-dose cancer sites, 566 (37%) of the excess cases were in patients irradiated at ages 45–59 years and 812 (51%) in patients treated aged 60–74 years.

**Discussion**

Our results suggest that about 8% (95% CI 7–9) of second solid cancers might be related to radiotherapy treatment for the first cancer. This figure varied according to first cancer diagnosis, and five excess cancers by 15 years (data not shown).
in the previous study, because of the small number of cancers after breast cancer were related to radiotherapy or the cumulative absolute risk (panel). Our results were generally consistent with the existing evidence, where it was available. None of the previous studies had combined data from multiple first cancer sites.

**Interpretation**

Our results suggest that a small proportion of second cancers (<10%) in adult cancer survivors are probably related to radiotherapy, which suggests that most are due to other factors, such as lifestyle or genetics. These findings can be used by physicians and patients to put the risk of radiation-related cancer into perspective when compared with the probable benefits of the treatment. Studies of the second-cancer risks from newer radiotherapy treatments such as intensity-modulated radiotherapy, however, are still needed.

Although there have been many studies of second cancers after treatment with radiotherapy, our systematic review did not find an existing study that estimated the proportion of second cancers overall that might be related to radiotherapy or the cumulative absolute risk (panel). We previously estimated that 5–6% of second solid cancers after breast cancer were related to radiotherapy in the SEER cancer registries. With published results from the pooled analysis of randomised radiotherapy trials for breast cancer we estimated a similar attributable risk (8%). which suggests that our estimate was not subject to strong confounding. In an earlier analysis of cancer registry data for patients with cervical cancer, Boice and colleagues estimated an attributable risk of 5%, which is substantially smaller than our estimate (table 4). One possible reason for this difference was the use of the general population as the comparison group in the previous study, because of the small number of patients who did not receive radiotherapy during the study period. Also, only cancers that were thought to be radiation inducible were included in the excess, for example rectal cancers were excluded in the previous study but they are now thought to be radiation inducible and were included in our analysis. In an earlier study of prostate cancer radiotherapy using SEER registries, Brenner and colleagues estimated that there were three excess cancers per 1000 patients in all survivors, which is similar to our overall estimate of five cancers per 1000 patients.

Previous studies have estimated the dose–response relation for specific second solid cancers after radiotherapy based on individual treatment records. One such study of cervical cancer treatment reported a positive dose–response relation for second cancers of the bladder, rectum, and bone, and all female genital cancers combined after radiotherapy for cervical cancer. In patients with breast cancer, dose–response relations have also been reported for lung, bone, connective tissue, and contralateral breast cancers after radiotherapy, and for stomach cancer after testicular cancer and Hodgkin’s lymphoma. Although site-specific risks were not the focus of our study, the patterns of risks were generally consistent with these previous reports (webappendix pp 1–15). There is also evidence from registry-based studies with fewer details on the radiotherapy treatment (yes or no, external beam or brachytherapy) and hospital series. These studies include several analyses of SEER registries that focused on a single first cancer. Our results were broadly consistent with those in previous studies, which reported that those treated with radiotherapy have a small (RR 1·1–1·4) increased risk of a second cancer overall compared with those who did not receive radiotherapy (webappendix p 19).

One of the strengths of our study is the systematic approach that we used to assess all first cancer sites, which enabled us to compare risks across first cancer sites and assess common patterns of risk. The large sample size and long-term follow-up are also key strengths of the SEER registries for assessing the late effects of radiotherapy, along with comprehensive coding rules for second cancers, which have changed little over time. We assessed the plausibility that the associations were causal by assessing the dose response across groups of second-cancer sites and the relation with age at exposure and latency. Mostly these followed the expected patterns—ie, higher RRs for sites typically exposed to higher doses, for younger ages at exposure, and with longer time since diagnosis. Our dose–response analysis, however, was necessarily crude and sites were probably misclassified since we did not have individual treatment data on the radiotherapy fields used.

The main limitation of the SEER data, like any observational study of treatment effects, is the lack of treatment randomisation and therefore the potential for confounding. Confounding would happen if factors...
related to radiotherapy use were also related to the risk of second cancer. We used a number of approaches to try to minimise this and other potential biases. We excluded the first 5 years of follow-up from the analyses to reduce the potential effect of surveillance bias. We adjusted all analyses for probable confounding factors that were available such as stage, age at diagnosis, year of diagnosis, attained calendar period, and attained age. For some cancer sites, receipt of radiotherapy rather than surgery might be associated with risk factors for second cancers like smoking if these risk factors are contraindications for surgery. It was reassuring, therefore, that the results from our analysis restricted to patients who had had cancer-related surgery were similar to those for all patients (webappendix p 16). In general, the RRs were higher for second cancer sites that are smoking related.6 Lack of data on smoking and other treatments, including chemotherapy and hormonal therapy, means that there is probably some residual confounding. The level of confounding might vary across the first cancer sites because factors that determine receipt of radiotherapy vary by cancer site, and could have resulted in either overestimation or underestimation of the risks related to radiotherapy.

Our results are for patients treated in the USA over the past 30 years, and radiotherapy techniques have changed during this period. For most sites, however, we did not find strong evidence of trends in the risks over time (webappendix p 18). An unavoidable limitation of studying the late effects of radiotherapy is that we could not include the most recent changes in practice. In particular, since all the patients were treated before 2003 the effect of the widespread introduction of intensity-modulated radiotherapy (IMRT) could not be assessed. There is concern that IMRT might actually increase second-cancer risks because of the greater volume of tissue that receives low-level radiation exposure,5 and it will be important to study this directly in the future. Nevertheless, we estimate that by 15 years of follow-up the absolute risks for adults are typically in the future. Nevertheless, we estimate that by 15 years of follow-up the absolute risks for adults are typically in the future. Nevertheless, we estimate that by 15 years of follow-up the absolute risks for adults are typically in the future. Nevertheless, we estimate that by 15 years of follow-up the absolute risks for adults are typically in the future. Nevertheless, we estimate that by 15 years of follow-up the absolute risks for adults are typically in the future. Nevertheless, we estimate that by 15 years of follow-up the absolute risks for adults are typically in the future.

Contributors
AAbDg and ER conceived the study. SFK, SL, and MS did the radiation dosimetry. AAbDg, REC, and EG were responsible for data management and statistical analyses. All authors were responsible for the interpretation of the data. AAbDg wrote the report and all authors reviewed and edited the report.

Conflicts of interest
The authors declared no conflicts of interest.

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