Second malignancy in young early-stage breast cancer patients with modern radiotherapy
A long-term population-based study (A STROBE-compliant study)
Liyi Xie, MD, PhD\textsuperscript{a,b,*}, Chen Lin, MD\textsuperscript{c}, Huan Zhang, MD\textsuperscript{d}, Xuhui Bao, MD, PhD\textsuperscript{e}

Abstract
Second cancer is a leading cause of death in long-term survivors of younger early-stage breast cancer patients. To date, relationship of age, receipt of radiotherapy (RT), and estimated doses received by target organs have not yet been well elucidated. Using Surveillance, Epidemiology, and End Results database, patients aged 20 to 44, diagnosed with a first primary staged I–IIIA ipsilateral breast invasive ductal carcinoma, underwent surgery during 1988 to 2009 were identified, and those with a second malignancy at ≥1-year follow-up were analyzed to calculate cumulative incidences (CIs) of second malignancy in whole group and each subgroup. Subgroups were dichotomized by surgery type, axillary dissection, and axillary lymph node status. With a median follow-up of 11.8 years, 22,628 women including 1495 patients (6.6%) developing second malignancies (3.7% contralateral breast cancer, 2.9% non-breast second malignancies, and 0.7% high-dose site second malignancies) were identified. Three-dimensional coordinate systems with age at primary diagnosis, time after primary breast cancer diagnosis, and CI of second malignancy as 3 axes, for endpoints including all second malignancy, second primary contralateral breast cancer, and non-breast second malignancy were presented, along with the risk in RT and non-RT groups in overall group and subgroups. Five-, 10-, 15-, and 20-year all second malignancy-free survivals in RT and non-RT groups were 89.5% versus 85.4%, 80.1% versus 75.0%, 72.9% versus 67.9%, and 65.6% versus 61.8% (P < .0001). From the large national dataset, a broad visualized overview of second malignancy risk, including second contralateral breast cancer and non-breast second cancer, suggests generally beneficial therapeutic ratio for radiotherapy in young women with early-stage breast cancer.

Abbreviations: AD = axillary dissection, BCS = breast-conserving surgery, CI = cumulative incidence, NOS = not otherwise specified, RT = radiation therapy, SEER = Surveillance, Epidemiology, and End Results.

Keywords: early-stage breast cancer, long-term second malignancy, young women

1. Introduction
There is increasing recognition and concern for treatment-associated long-term side effects in cancer survivors. In the United States, more than 630,000 survivors of early-stage breast cancer are at risk for treatment-related late effects.\textsuperscript{[1]} Second primary malignant neoplasms (eg, in the contralateral breast or non-breast sites) are now among the leading causes of death in long-term survivors of breast cancer.\textsuperscript{[2]} Several reports have suggested increasing rates of second malignant neoplasm being related to hereditary predisposition,\textsuperscript{[3–5]} young age,\textsuperscript{[4,6]} radiation exposure,\textsuperscript{[7]} and increased surveillance.\textsuperscript{[8]}

Over the last several decades, there have been continued efforts to minimize irradiation of normal tissues through, for example, reducing prescription doses, and reducing irradiated volumes.\textsuperscript{[9,10]} However, the impact radiation therapy (RT) in recent eras on the risk of second malignant neoplasms, especially in younger patients, has not been broadly described. Further, there is increasing recognition that the carcinogenic effects of RT are dose dependent, and Berrington de Gonzalez et al suggested classifying organs into 3 subgroups based on differences in their received doses. For the typical patient prescribed to receive a total dose of 50 (Gy), organs receiving a mean dose >1 (Gy) are suggested to be classified as high risk, 0.5 to 0.99 (Gy) as medium risk, and <0.5 (Gy) as low risk.\textsuperscript{[11,12]}

The aims of the current study are to leverage population-based cancer registries to broadly describe the cumulative incidence (CI) and survival related to second malignancy in long-term survivors of women treated with and without RT for early-stage breast cancer at younger age considering surgical extent, axillary lymph node status, and estimated mean organ dose.

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\textsuperscript{a} Department of Radiation Oncology, Fudan University Shanghai Cancer Center, \textsuperscript{b} Department of Oncology, Fudan University Shanghai Cancer Center, \textsuperscript{c} Department of Medical Oncology, Zhejiang Cancer Hospital, Hangzhou, Zhejiang, \textsuperscript{d} Department of Internal Medicine, Shanghai Changzheng Hospital, Shanghai, China, \textsuperscript{e} Department of Surgery, Duke University Medical Center, Durham, NC, USA.

Correspondence: Liyi Xie, Department of Radiation Oncology, Fudan University Shanghai Cancer Center, 270 Dong An Road, Shanghai 200032, China (e-mail: xley@fudan.edu.cn).

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2. Methods

2.1. Data source

The incidence and survival data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute from the years between 1988 and 2009 were analyzed. The SEER Registries reflect around 10% of the population of the United States and thus the resultant findings should be broadly generalizable. SEER 9 Registries were used specifically due to their continuous active coverage of the study observation period. The data released by the SEER database do not require informed patient consent. Our study had already been approved by the Ethical Committee and Institutional Review Board of Fudan University Shanghai Cancer Centre (FUSCC). The methods were performed in accordance with the approved guidelines.

2.2. Patient population

Analysis was limited to women diagnosed at young age (20–44 years) with early-stage breast cancer (stage I-IIA [T1-3N0-2M0], American Joint Committee on Cancer [AJCC] 6th Edition) with ipsilateral (right or left) microscopically confirmed invasive ductal carcinoma (ICD-O-3 coded as “8500/3”) as their first primary breast cancer between 1988 and 2009 who underwent curative surgery. In this analysis, the designation of “young/younger patients” and the “20 to 44” age range was arbitrary, and was selected based on common clinical practice, although its definition is mostly consistent with what is found in literature.

All patients had complete information regarding the receipt of radiotherapy. Patients were scored as having RT (coded as “beam radiation,” but excluded those with “radioactive implants,” “radioisotopes,” or “radiation, not otherwise specified [NOS]”) or non-RT (coded as “none” or “refused”). Individuals with reporting sources such as “nursing/convalescent home/hospice,” “autopsy only,” “death certificate only,” or “other hospital outpatient units/surgery centers” were excluded because these patients would not have been likely to receive cancer-directed therapy. Patient exclusion workflow is shown in Fig. 1.

Any de novo primary malignancy diagnosed more than 1 year after the primary invasive ductal carcinoma diagnosis was designated as a “second malignancy.” Even though RT-related second malignancy is unlikely to occur in 5 years after primary diagnosis, the CI among all younger survivors (defined here as >1 year) is the most relevant summary statistic as a broad overview for all younger breast cancer survivors. Analyzed endpoints of second malignancy included the following categories: all second malignancies (including both second primary contralateral breast cancer and non-breast second malignancies), second primary contralateral breast cancer, and non-breast second malignancies (including hematological malignancies). Second malignancy risks based on estimated mean organ dose were also analyzed. High-dose sites were defined as those organs estimated to have received more than 1 (Gy) of mean dose during breast RT (measured with thermoluminescent dosimeters by previous report under the condition of 50 [Gy] tumor dose and an X-ray energy of 6 MV), medium-dose sites were 0.5 to 0.99 (Gy), and low-dose sites were <0.5 (Gy).

Parameters for dichotomization were: surgery types (breast-conserving surgery [BCS] or mastectomy), axillary lymph node pathological status (pN+ or pN0), and axillary dissection (AD) (with or without). Surgeries were considered as either BCS (including those coded as “partial mastectomy,” “lumpectomy or excisional biopsy,” or “segmental mastectomy”) or mastectomy (coded as “subcutaneous mastectomy,” “total [simple] mastectomy, without removal of uninvolved contralateral breast,” “modified radical mastectomy without removal of uninvolved contralateral breast,” “radical mastectomy without removal of uninvolved contralateral breast,” and “extended radical mastectomy without removal of uninvolved contralateral breast”), but excluding cases coded as “mastectomy, NOS,” “surgery, NOS,” and “unknown if surgery performed; death certificate only.” No patients were found to have the elective removal of the uninvolved contralateral breast in the current study. In this study, AD was defined as having ≥10 regional lymph nodes examined by the pathologist (coded as “regional nodes examined”)

### Figure 1. Flow chart of patient selection. BCS = breast-conserving surgery, F/U = follow-up, IDC = invasive ductal carcinoma, NOS = not otherwise specified, RT = radiation therapy, SEER = Surveillance, Epidemiology, and End Results.

### Patients in this study for analysis

| All patients identified in SEER registry            | 1,935,739 |
|---------------------------------------------------|-----------|
| Histology: IDC: ICD-O-3:85003                     | 669,332   |
| Primary breast cancer diagnosed during 1988-2009 with F/U one year | 284,952 |
| Age between 20-44 years old                      | 36,562    |
| Diagnosis microscopically confirmed              | 63,540    |
| Laterality: right/both, bilateral excluded        | 36,377    |
| Follow up                                       | 36,293    |
| Primary breast cancer as first cancer             | 27,200    |
| Cancer reporting source: nursing home, hospice, autopsy report, or death certificate | 35,233 |
| Stage: T1–N0–Mx                                  | 23,383    |
| Surgery (mastectomy BC/axillary dissection)      | 23,650    |
| Lack of surgery type, laterality breast RT        | 22,756    |

The second malignancy diagnosed >1 year (23,283)
non-breast second malignancy analysis, respectively. Gray test was used to calculate the CIs in the whole group and in subgroups.

Event-free survival was measured from the date of the primary breast cancer diagnosis until the date of second malignancy, death, or the last follow-up. Actuarial event-free survival (i.e., freedom from all forms of second malignancy including second primary contralateral breast cancers and non-breast second malignancies) were calculated using the Kaplan–Meier method. The log-rank test was used to compare the event-free survival curves between RT and non-RT patients in the whole group and in subgroups.

All analyses were performed using PASW Statistics 18.0 (SPSS Inc, Chicago, IL) and R software (version 3.2.5; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient demographics and tumor characteristics

A total of 3,935,739 patients were identified in the SEER registry, of which 22,628 were analyzed in our study. Patient and tumor characteristics at the time of the primary breast cancer diagnosis, grouped by patient and treatment parameters, are outlined in Table 1. There were 1495 patients (6.6%) developing second malignancies (including 831 [3.7%] second primary contralateral breast cancer, 664 [2.9%] non-breast second malignancies, and 167 [0.7%] high-dose site second malignancies). The median and mean age at the diagnosis of primary breast cancer was 40 and 39.1 years, respectively. Group subdivision is shown in Fig. 2. Overall, 14,043 (62.1%) patients received BCS and 8585 (37.9%) patients received mastectomy; 13,095 (57.9%) patients underwent AD and 9317 (41.2%) did not; 8645 (38.2%) patients were axillary pN+, while 13,386 (59.2%) were pN0. The follow-up time among surviving patients ranged from a minimum of 1 year to a maximum of 22.9 years (275 months), with a median of 11.8 years (95% confidence interval: 11.6–11.9 years).

3.2. Analysis of second malignancies in RT and non-RT group

Cases of non-breast second malignancy and second contralateral breast cancer types, as well as those for RT and non-RT groups, were listed in Table 2. Both were subdivided into 3 categories, based on estimated mean organ dose reported in a previous study.[16] CI curves for every single age between 20 and 44 were generated as a mesh (or 2 meshes for RT and non-RT groups) in a 3-dimensional coordinate systems with age at primary diagnosis, time after primary breast cancer diagnosis, and CI of second malignancy as 3 axes, for endpoints including all second malignancy, second primary contralateral breast cancer, and non-breast second malignancy (Fig. 3A, C). Same coordinates are established for all subgroups (Supplemental Figs. 1–16, http://links.lww.com/MD/C221).

In both RT and non-RT group, all second malignancies, second primary contralateral breast cancers, or non-breast second malignancies are shown in Fig. 3B, D, E, F, and corresponding results for BCS group are shown in Supplemental Figs. 1–8, http://links.lww.com/MD/C221; and corresponding results for mastectomy group are shown in Supplemental Figs. 9–16, http://links.lww.com/MD/C221.

3.3. Second malignancy-free survivals

Long-term second malignancy-free survivals in the whole group and in subgroups are shown in Supplemental Table 1, http://links.lww.com/MD/C221 and Fig. 4. Five-, 10-, 15-, and 20-year all second malignancy-free survivals in RT and non-RT groups were 89.5% versus 85.4%, 80.1% versus 75.0%, 72.9% versus 67.9%, and 65.6% versus 61.8% (P < .0001). The findings were similar for high-dose site second malignancy-free survivals.

4. Discussion

This study provides a detailed three-dimensional profile of long-term second malignancy risks for each age in young (20–44) early-stage breast cancer patients who did or did not receive RT in different settings of treatment, and meanwhile considering quantitative estimates of radiation doses delivered to the organs involved in breast RT. The risk of second malignancy has been discussed by several previous studies, and the risk reported in the current analysis is consistent with others.[17–19] Aside from risk prediction, this study offers practicing physicians a look-up table-
| Characteristic         | No of pts | RT  | Non-RT | BCS RT | Mast RT | Mast non-RT |
|-----------------------|-----------|-----|--------|--------|---------|-------------|
| All                   | 22,628    | 100 | 100    | 100    | 100     | 100         |
| Age                   |           |     |        |        |         |             |
| 20–29                 | 818       | 3.61| 468    | 3.43   | 350     | 4.00        |
| 30–39                 | 9026      | 39.89| 5291| 38.75 | 3735    | 41.62       |
| 40–44                 | 12,784    | 56.50| 7896| 57.82 | 4888    | 54.47       |
| Year of diagnosis     |           |     |        |        |         |             |
| 1988–1999             | 12,459    | 55.06| 6637| 48.60 | 5822    | 64.88       |
| 2000–2009             | 10,169    | 49.44| 7018| 51.40 | 3151    | 53.12       |
| T stage               |           |     |        |        |         |             |
| T1                    | 13,386    | 59.16| 8435| 61.77 | 4951    | 55.18       |
| T2                    | 8107      | 35.83| 4540| 33.25 | 3567    | 39.75       |
| T3                    | 1135      | 5.02| 680   | 4.98  | 455     | 5.07        |
| N stage               |           |     |        |        |         |             |
| pN0                   | 13,386    | 59.16| 8343| 61.10 | 5043    | 56.20       |
| pN+                   | 8665      | 38.20| 5046| 36.95 | 3599    | 40.11       |
| 1–2(+)                | 5224      | 23.09| 3025| 22.15 | 2199    | 24.51       |
| 3(+)                  | 1099      | 4.86| 625   | 4.58  | 474     | 5.26        |
| ≥4(+)                 | 2237      | 9.89| 1348| 9.87  | 889     | 9.91        |
| Unknown (+) number    | 85        | 0.38| 48    | 0.35  | 37      | 0.41        |
| NA                    | 597       | 2.64| 266   | 1.95  | 331     | 3.69        |
| Surgery type          |           |     |        |        |         |             |
| Mastectomy            | 14,043    | 62.06| 11,501| 84.23 | 2542    | 28.33       |
| Mastectomy            | 8585      | 37.94| 2154| 15.77 | 6431    | 71.67       |
| Race                  |           |     |        |        |         |             |
| White                 | 17,237    | 76.18| 10,472| 76.69 | 6765    | 75.39       |
| Asian                 | 2459      | 10.87| 1500| 10.98 | 959     | 10.69       |
| Black                 | 2676      | 11.83| 1531| 11.21 | 1147    | 12.78       |
| Other or unknown      | 254       | 1.12| 152   | 1.11  | 102     | 1.14        |
| Marital status at diagnosis |   |     |        |        |         |             |
| Married               | 14,990    | 66.25| 9023| 66.08 | 5967    | 66.50       |
| Single                | 4516      | 19.96| 2740| 20.07 | 1776    | 19.79       |
| Divorced/separated /widowed | 2611 | 11.54| 1627| 11.92 | 984     | 10.97       |
| NA                    | 511       | 2.26| 265   | 1.94  | 246     | 2.74        |
| Laterality of primary breast cancer |   |     |        |        |         |             |
| Left                  | 11,504    | 50.84| 6893| 50.48 | 4611    | 51.39       |
| Right                 | 11,124    | 49.16| 6762| 49.52 | 4681    | 51.67       |
| Location of primary   |           |     |        |        |         |             |
| Central/subareolar    | 1019      | 4.50| 531   | 3.89  | 488     | 5.44        |
| Upper outer quadrant  | 8778      | 38.79| 5573| 40.81 | 3205    | 35.72       |
| Lower outer quadrant  | 1601      | 7.08| 1010| 7.40  | 591     | 6.59        |
| Axillary tail         | 269       | 1.19| 195   | 1.43  | 74      | 0.82        |
| Upper inner quadrant  | 2526      | 11.16| 1639| 12.00 | 887     | 9.89        |
| Lower inner quadrant  | 1149      | 5.08| 689   | 5.05  | 460     | 5.13        |
| Overlapping lesion    | 4666      | 20.62| 2747| 20.12 | 1919    | 21.39       |
| NA                    | 2620      | 11.58| 1271| 9.31  | 1194    | 15.03       |
| ER status             |           |     |        |        |         |             |
| Positive              | 12,318    | 54.44| 8026| 58.78 | 4292    | 47.83       |
| Negative              | 6531      | 28.86| 4062| 29.75 | 2469    | 27.52       |
| Borderline           | 169       | 0.75| 84    | 0.62  | 85      | 0.95        |
| NA                    | 3610      | 15.95| 1483| 10.86 | 2127    | 23.70       |
| PR status             |           |     |        |        |         |             |
| Positive              | 11,588    | 51.21| 7576| 55.48 | 4012    | 44.71       |
| Negative              | 7055      | 31.18| 4386| 32.12 | 2699    | 29.74       |
| Borderline           | 195       | 0.86| 102   | 0.75  | 93      | 1.04        |
| NA                    | 3790      | 16.75| 1591| 11.65 | 2199    | 24.51       |
| ER+/PR+               | 10,701    | 47.29| 7067| 51.75 | 3634    | 40.50       |
| ER+/PR               | 5610      | 24.79| 3531| 25.86 | 2079    | 23.17       |
| ER+/PR−               | 2188      | 9.67| 1203| 9.47  | 895     | 9.97        |

BSC = breast-consenting surgery, ER = estrogen receptor, IHC = immunohistochemistry, mast = mastectomy, NA = not available, No. of pts = number of patients, pN+ = axillary lymph-node pathologically positive, pN0 = axillary lymph-node pathologically negative, PR = progesterone receptor, RT = radiation therapy.

Borderline ER+/PR+ positive cancers is defined as having 1% to 10% positivity by IHC.\[15\]
Second malignancy risk typically decreases with age at exposure.\cite{20,21} According to data on atomic bomb survivors, the risk of developing a second malignancy decreased from about 15% per unit dose equivalent (Sv\(^{-1}\)) for those exposed at less than 10 years old to around 1% (Sv\(^{-1}\)) for more than 60 years old.\cite{22} Generally, patients around the age of 20, an age span included in this study, are considered to be at high risk for radiation-related second malignancy.\cite{8,23} Meanwhile, the decrease of association between RT-related cancer risk with adulthood age is not linearly continuous. Another prominent timing for RT-exposed carcinogenesis is around middle age (around 40 years old),\cite{24} which is also included in the current analysis. Since a number of dormant tumors may revive around middle age, exposure to radiation during this age can cause tumor proliferation.\cite{7,25} Moreover, as the age at exposure increases, the importance of promotional process in carcinogenesis increases as well.\cite{24} In the current study, a higher risk of non-breast second malignancy in RT group all over the follow-up duration was observed in patients aged 43 to 44 years with pN+ and underwent mastectomy, and somehow higher risk in RT group also seen in those 38 years with pN0 and mastectomy. The higher risk with RT may not be as accurate as in these small ranges of age group, yet the effect of radiation on second malignancy and middle age may warrant further investigation.

In the modern radiotherapy era, orthovoltage radiation has been replaced by the less carcinogenic megavoltage therapy\cite{10}; whereas 2-dimensional RT has been replaced by more accurate 3-dimensional conformal RT and intensity-modulated RT. These are pillar treatment techniques serving the era in the current study that can push treatment dose to high curative doses with less normal tissue injury. It is unclear so far how the modern technique and radiation treatment schema will affect the long-term outcomes of patients.

| Dose grouping, Gy\(^{-1}\) | Cancer site | Case | % of all cases (664) | % of all pts (22,628) | RT | % of RT pts (13,655) | Non-RT | % of non-RT pts (8973) |
|---------------------------|-------------|------|----------------------|----------------------|----|----------------------|--------|----------------------|
| High (\(\geq 1\))        | All non-breast secondary malignancy | 664  | 100.0                | 2.0                  | 378 | 2.8                  | 286    | 3.2                  |
| High (\(\geq 1\))        | Esophagus   | 3    | 0.45                 | 0.01                 | 1   | 0.01                 | 2      | 0.02                 |
| High (\(\geq 1\))        | Thymus      | 2    | 0.3                  | 0.01                 | 1   | 0.01                 | 1      | 0.01                 |
| High (\(\geq 1\))        | Lung        | 84   | 12.6                 | 0.4                  | 52  | 0.4                  | 32     | 0.3                  |
| High (\(\geq 1\))        | Bone        | 55   | 8.3                  | 0.2                  | 31  | 0.2                  | 24     | 0.3                  |
| High (\(\geq 1\))        | Soft tissue | 23   | 3.5                  | 0.1                  | 17  | 0.1                  | 6      | 0.1                  |
| High (\(\geq 1\))        | Subtotal    | 167  | 25.2                 | 0.7                  | 102 | 0.75                 | 65     | 0.7                  |
| Medium (0.5–0.99)         | Stomach/intestine | 11  | 1.6                  | 0.05                 | 9   | 0.07                 | 2      | 0.02                 |
| Medium (0.5–0.99)         | Liver/gall bladder | 2   | 3.0                  | 0.01                 | 2   | 0.01                 | 0      | 0                    |
| Medium (0.5–0.99)         | Larynx      | 3    | 0.45                 | 0.01                 | 2   | 0.01                 | 1      | 0.01                 |
| Medium (0.5–0.99)         | Thyroid     | 49   | 7.4                  | 0.2                  | 27  | 0.2                  | 22     | 0.3                  |
| Medium (0.5–0.99)         | Subtotal    | 65   | 9.8                  | 0.3                  | 40  | 0.3                  | 25     | 0.3                  |
| Low (<0.5)                | Oral cavity | 11   | 1.6                  | 0.05                 | 6   | 0.04                 | 5      | 0.05                 |
| Low (<0.5)                | Salivary gland | 1   | 3.0                  | 0.04                 | 5   | 0.04                 | 4      | 0.04                 |
| Low (<0.5)                | Colon       | 45   | 6.8                  | 0.2                  | 20  | 0.15                 | 25     | 0.3                  |
| Low (<0.5)                | Rectum and anus | 21  | 3.2                  | 0.1                  | 11  | 0.1                  | 10     | 0.1                  |
| Low (<0.5)                | Pancreas    | 17   | 2.6                  | 0.1                  | 8   | 0.05                 | 9      | 0.1                  |
| Low (<0.5)                | Melanoma of the skin | 59  | 8.9                  | 0.3                  | 36  | 0.25                 | 23     | 0.3                  |
| Low (<0.5)                | Cervix uteri | 9   | 1.3                  | 0.04                 | 5   | 0.04                 | 4      | 0.04                 |
| Low (<0.5)                | Ovary       | 88   | 13.3                 | 0.4                  | 41  | 0.3                  | 47     | 0.5                  |
| Low (<0.5)                | Endometrioid | 93  | 14.0                 | 0.4                  | 51  | 0.4                  | 42     | 0.5                  |
| Low (<0.5)                | Other female genital | 10  | 1.5                  | 0.04                 | 7   | 0.05                 | 3      | 0.03                 |
| Low (<0.5)                | Bladder     | 9    | 1.3                  | 0.04                 | 8   | 0.05                 | 1      | 0.01                 |
| Low (<0.5)                | Kidney      | 16   | 2.4                  | 0.07                 | 10  | 0.1                  | 6      | 0.1                  |
| Low (<0.5)                | Brain       | 10   | 1.5                  | 0.04                 | 8   | 0.05                 | 2      | 0.02                 |
| Low (<0.5)                | Eye         | 4    | 6.0                  | 0.02                 | 3   | 0.02                 | 1      | 0.01                 |
| Low (<0.5)                | Nasal cavity | 1   | 0.2                  | 0.004                | 0   | 0                    | 1      | 0.01                 |
| Low (<0.5)                | Other sites | 30   | 4.5                  | 0.1                  | 17  | 0.1                  | 13     | 0.1                  |
| Low (<0.5)                | Subtotal    | 432  | 65.1                 | 1.9                  | 236 | 1.7                  | 196    | 2.2                  |

\(\text{Pts} = \text{patients}, \text{RT} = \text{radiation therapy}\).\(^\dagger\) RT dose grouping received by cancer sites based on data from Berrington de Gonzalez et al.\cite{11}\(^\ddagger\) Number in parentheses indicates the denominator.\(^\S\) RT dose grouping received by contralateral breast cancer sites based on data from Stovall et al.\cite{12}
Figure 3. CI of all second malignancy in RT and non-RT groups in the whole group. (A, C) CI of all second malignancies and its relationship with age at primary diagnosis and time since initial diagnosis in the whole group, in 2 different angles of view. (B, D–F) second malignancies (including second primary contralateral breast cancer and non-breast second malignancy) in RT and non-RT groups in the whole group. Colored mesh indicates RT group and grayscale mesh indicates non-RT group. B and D indicate CI of all second malignancies in the whole group, in 2 different angles of view. BC = breast cancer, CI = cumulative incidence, RT = radiation therapy.
term risk of radiation-associated second cancer in young patients. Decreases of cancer risk by cell-killing (sterilization), which generally overcomes the transforming potential induced by radiation, reducing the malignant transformation of exposed cells, is postulated in high therapeutic dose.\[7\] However, intensity-modulated RT has been criticized for out-of-field dose from collimator scatter and head leakage even though absolute dose increment is measured to be tiny.\[26\] And in low-dose area, a consistent linear relationship between radiation exposure dose of 0.1 to 2 (Sv) and fatal cancer risk was reported.\[27\] More recently, a slight yet significant upward curvature was observed in this part of the dose-response curve, and this may be related to nontargeted effects, in which the cancer risk increases when the susceptible target size expands from one single cell to part of or the whole tissue.\[21\] In the current analyses, second cancer risk in RT and non-RT group was comparable (Table 2), this was similar for high- and low-dose organs. As shown in Supplemental Table 1, http://links.lww.com/MD/C221, RT did not affect high-dose site second-malignancy-free survival rates. Moreover, RT generally benefits second malignancy-free survival in these women at younger age.

Although this may be the first large population study to investigate the second cancer risk in young early-stage breast cancer survivors combining age and radiation dose, various strengths and weaknesses should be considered regarding the results of the current study. SEER serves as a population-based database containing a large number of patients ensuring no selection biases and long-term follow-ups for the current study, but a degree of data entry incompleteness, variations in data reporting, and a lack of information on treatment may need to be taken into consideration (eg, lack of smoking data, which influence the incidence of secondary lung cancer; and lack of family history data, which influence the incidence of contralateral second cancer; and the limited median follow-up time). Considering these caveats, no comparison was done between RT and non-RT group, so as to provide a relatively objective overview of the risk in both groups, and the small age subgroups (every single age) made it hard to analyze the significance and interpret the results. Nevertheless, under the discretion of physician, the patients receiving radiation usually have a more advanced stage of the disease than those who do not receive RT. Furthermore, even in prospective setting, most existing RT treatment planning systems do not provide accurate out-of-field far-off-target dose calculations, and peridose calculation has methodological limitations.\[28,29\] Therefore, whole-body dose calculations and risk assessments for conventional and advanced RTs are still a challenge for most studies.\[7,12,28\] As for systemic therapies, an increase of non-breast second malignancy by tamoxifen was indicated in previous data, and an increase of second malignancy induced by chemotherapy was also suggested by several studies.\[30,31\] The 1998 survey showed in stage I–II BCT patients, 36% and 55.8% received chemotherapy and tamoxifen, respectively, which represented a significant rise compared to 24% in the 1993 survey and 25.5% in 1989.\[32\] The large patient population in the current study can be helpful to settle the selection bias from information incompleteness. Genetic susceptibility is another important component unaccounted for in the SEER database. However, it is challenging to investigate the role that genes play regarding RT in breast cancer etiology even in prospective studies. It will require a larger population with RT exposure of a dose span for satisfying statistical power to discern the effect between RT and gene. Other issues to be

**Figure 4.** Comparison of second malignancies-free survivals between RT and non-RT groups in the whole group.
considered in this kind of studies include, for instance, accurate breast dose estimations, biospecimens for DNA extraction, and the control group selection. Recent studies are focusing on DNA repair genes with low-penetration, and available data are mainly about DNA repair gene polymorphisms and genetic mutations, which are typically very rare.[25]

5. Conclusion

In summary, findings of the current study indicate that with a broad visualized overview of all types of second malignancy, radiotherapy generally provides beneficial therapeutic ratio in young women with early-stage breast cancer. Caution is still necessary for young patients with more clinician and patient awareness and surveillance. Further studies on accurate dose measurement, whole-body risk assessment, and genetic target identification are needed to better dissect the role of radiotherapy in the treatment-related second malignancy.

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Author contributions

Conceptualization: Liyi Xie.

Formal analysis: Liyi Xie, Chen Lin, Huan Zhang.

Funding acquisition: Liyi Xie.

Investigation: Liyi Xie, Huan Zhang.

Methodology: Liyi Xie, Chen Lin, Huan Zhang, Xuhui Bao.

Project administration: Xuhui Bao.

Resources: Chen Lin.

Software: Chen Lin, Huan Zhang.

Supervision: Liyi Xie.

Validation: Chen Lin, Huan Zhang, Xuhui Bao.

Writing – original draft: Liyi Xie, Chen Lin, Huan Zhang.

Writing – review & editing: Liyi Xie, Chen Lin, Huan Zhang, Xuhui Bao.

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