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Second malignancy in young early-stage breast cancer patients with modern radiotherapy

A long-term population-based study (A STROBE-compliant study)

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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 staging 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 650,000 survivors of early-stage breast cancer are at risk for treatment-related late effects.[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.[2] Several reports have suggested increasing rates of second malignant neoplasm being related to hereditary predisposition,[3–5] young age,[4,6] radiation exposure,[7] and increased surveillance.[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.[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.[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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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.[13] 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-IIIA [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 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.[14] 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).[11,12]

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

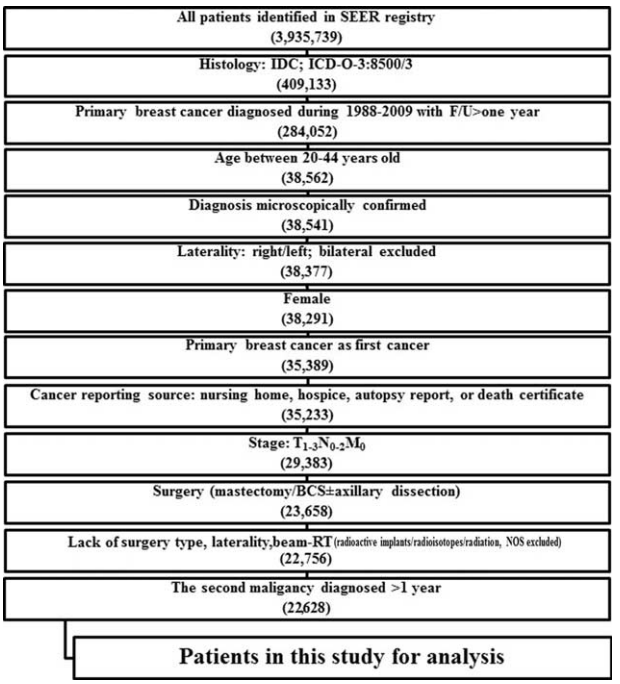

Figure 1. Flow chart of patient selection. BCS = breast-conserving surgery, F/U = follow-up, IDC = invasive ductal carcinoma, NOS = not otherwise specified, RT = radiation therapy, SEER = Surveillance, Epidemiology, and End Results.

(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"). Since the extent of the radiation fields (eg, +/− regional nodes) is traditionally based on the extent of surgery and the tumor stage, these items were used as surrogates for the likely extent of the radiation field.

2.3. Statistical analysis

SEER*Stat version 8.0.4 software was used. SEER Registry data from 1988 to 2009 was used since the data necessary for our analysis are complete and continuous for these years.

The cases of second malignancy for each cancer site categorized by estimated mean organ dose during breast RT were analyzed.

For each age between 20 and 44 years, CIs of all second malignancies, second primary contralateral breast cancers, non-breast second malignancies, and high-dose site second malignancies were calculated as well as in different subgroups decided by surgery type, axillary lymph node status, and AD, except for the subgroup of patients without AD and coded as pN0, given the deficiency of the full examination (Fig. 2). Competing risks including deaths from all causes in all CI analyses, and non-breast secondary malignancy in second primary contralateral breast cancer analysis, or second primary contralateral breast cancer in

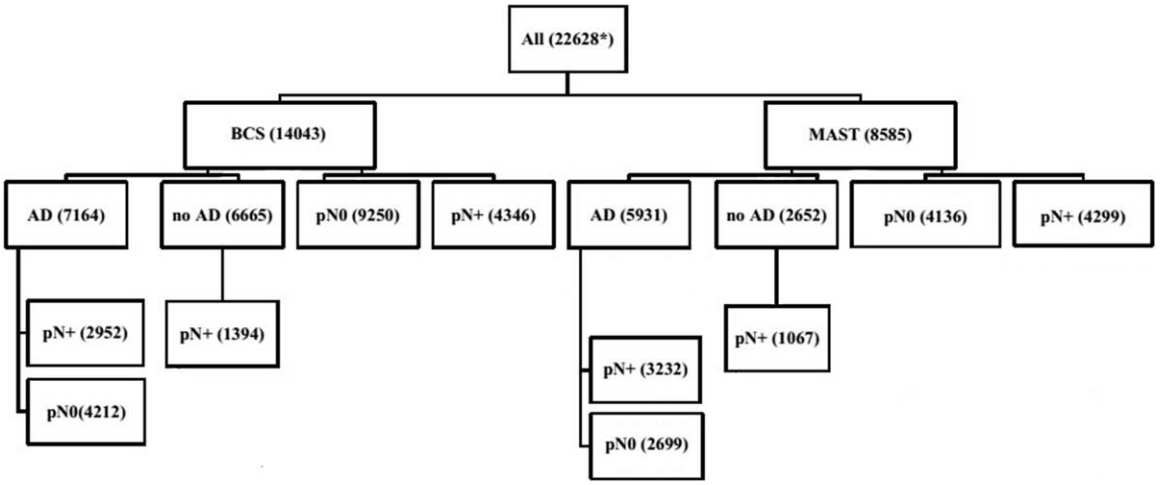

Figure 2. Subgroups dichotomized by surgery type (breast-conserving surgery [BCS] or mastectomy), axillary lymph node pathological status (pN+/pN0), and axillary dissection (with or without). *Number in parentheses indicates patient number of this group. Numbers added up not the same as upper level was due to missing data.

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 survivals (ie, 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.[15] 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-

Table 1

Patient demographics.

Characteristic	No of pts	%	RT	%	Non-RT	%	BCS RT	%	BCS non-RT	%	Mast RT	%	Mast non-RT	%
All	22,628	100	13,655	100	8973	100	11,501	100	2542	100	2154	100	6431	100
Age														
20–29	818	3.61	468	3.43	350	3.90	380	3.30	123	4.84	88	4.09	227	3.53
30–39	9026	39.89	5291	38.75	3735	41.62	4298	37.37	1015	39.93	993	46.10	2720	42.30
40–44	12,784	56.50	7896	57.82	4888	54.47	6823	59.33	1404	55.23	1073	49.81	3484	54.18
Year of diagnosis														
1988–1999	12,459	55.06	6637	48.60	5822	64.88	5593	48.63	1122	44.14	1044	48.47	4700	73.08
2000–2009	10,169	44.94	7018	51.40	3151	35.12	5908	51.37	1420	55.86	1110	51.53	1731	26.92
T stage														
T1	13,386	59.16	8435	61.77	4951	55.18	7841	68.18	1593	62.67	594	27.58	3358	52.22
T2	8107	35.83	4540	33.25	3567	39.75	3464	30.12	880	34.62	1076	49.95	2687	41.78
T3	1135	5.02	680	4.98	455	5.07	196	1.70	69	2.71	484	22.47	386	6.00
N stage														
pN0	13,386	59.16	8343	61.10	5043	56.20	7854	68.29	1396	54.92	489	22.70	3647	56.71
pN+	8645	38.20	5046	36.95	3599	40.11	3432	29.84	914	35.96	1614	74.93	2685	41.75
1–2(+)	5224	23.09	3025	22.15	2199	24.51	2418	21.02	608	23.92	607	28.18	1591	24.74
3(+)	1099	4.86	625	4.58	474	5.28	384	3.34	101	3.97	241	11.19	373	5.80
≥4(+)	2237	9.89	1348	9.87	889	9.91	604	5.25	193	7.59	744	34.54	696	10.82
Unknown (+) number	85	0.38	48	0.35	37	0.41	26	0.23	12	0.47	22	1.02	25	0.39
NA	597	2.64	266	1.95	331	3.69	215	1.87	232	9.13	51	2.37	99	1.54
Surgery type														
BCS	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	8905	77.43	1906	74.98	1567	72.75	4859	75.56
Asian	2459	10.87	1500	10.98	959	10.69	1181	10.27	193	7.59	319	14.81	766	11.91
Black	2678	11.83	1531	11.21	1147	12.78	1276	11.09	401	15.77	255	11.84	746	11.60
Other or unknown	254	1.12	152	1.11	102	1.14	139	1.21	42	1.65	13	0.60	60	0.93
Marital status at diagnosis														
Married	14,990	66.25	9023	66.08	5967	66.50	7534	65.51	1566	61.61	1489	69.13	4401	68.43
Single	4516	19.96	2740	20.07	1776	19.79	2345	20.39	603	23.72	395	18.34	1173	18.24
Divorced/separated /widowed	2611	11.54	1627	11.92	984	10.97	1399	12.16	278	10.94	228	10.58	706	10.98
NA	511	2.26	265	1.94	246	2.74	223	1.94	95	3.74	42	1.95	151	2.35
Axillary dissection														
Yes	13,095	57.87	7440	54.49	5655	63.02	5970	51.91	1194	46.97	1470	68.25	4461	69.37
No	9317	41.17	6110	44.75	3207	35.74	5426	47.18	1239	48.74	684	31.75	1968	30.60
NA	216	0.95	105	0.77	111	1.24	105	0.91	109	4.29	0	0.00	2	0.03
Laterality of primary breast cancer														
Left	11,504	50.84	6893	50.48	4611	51.39	5822	50.62	1283	50.47	1071	49.72	3328	51.75
Right	11,124	49.16	6762	49.52	4362	48.61	5679	49.38	1259	49.53	1083	50.28	3103	48.25
Location of primary														
Central/subareolar	1019	4.50	531	3.89	488	5.44	425	3.70	100	3.93	106	4.92	388	6.03
Upper outer quadrant	8778	38.79	5573	40.81	3205	35.72	4815	41.87	1000	39.34	758	35.19	2205	34.29
Lower outer quadrant	1601	7.08	1010	7.40	591	6.59	866	7.53	194	7.63	144	6.69	397	6.17
Axillary tail	269	1.19	195	1.43	74	0.82	180	1.57	34	1.34	15	0.70	40	0.62
Upper inner quadrant	2526	11.16	1639	12.00	887	9.89	1465	12.74	257	10.11	174	8.08	630	9.80
Lower inner quadrant	1149	5.08	689	5.05	460	5.13	607	5.28	143	5.63	82	3.81	317	4.93
Overlapping lesion	4666	20.62	2747	20.12	1919	21.39	2287	19.89	488	19.20	460	21.36	1431	22.25
NA	2620	11.58	1271	9.31	1349	15.03	856	7.44	326	12.82	415	19.27	1023	15.91
ER status														
Positive	12,318	54.44	8026	58.78	4292	47.83	6814	59.25	1322	52.01	1212	56.27	2970	46.18
Negative	6531	28.86	4062	29.75	2469	27.52	3375	29.35	794	31.24	687	31.89	1675	26.05
Borderline*	169	0.75	84	0.62	85	0.95	70	0.61	17	0.67	14	0.65	68	1.06
NA	3610	15.95	1483	10.86	2127	23.70	1242	10.80	409	16.09	241	11.19	1718	26.71
PR status														
Positive	11,588	51.21	7576	55.48	4012	44.71	6470	56.26	1240	48.78	1106	51.35	2772	43.10
Negative	7055	31.18	4386	32.12	2669	29.74	3610	31.39	856	33.67	776	36.03	1813	28.19
Borderline*	195	0.86	102	0.75	93	1.04	83	0.72	27	1.06	19	0.88	66	1.03
NA	3790	16.75	1591	11.65	2199	24.51	1338	11.63	419	16.48	253	11.75	1780	27.68
ER+/PR+	10,701	47.29	7067	51.75	3634	40.50	6044	52.55	1136	44.69	1023	47.49	2498	38.84
ER−/PR−	5610	24.79	3531	25.86	2079	23.17	2926	25.44	685	26.95	605	28.09	1394	21.68
ER+/PR− or ER−/PR+	2188	9.67	1293	9.47	895	9.97	1052	9.15	262	10.31	265	12.30	712	11.07

BCS = breast-conserving 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]

Table 2

Second malignancy cancer type in RT and non-RT groups.

Dose grouping, Gy*	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)
	All non-breast secondary malignancy	664	100.0	2.9	378	2.8	286	3.2
High (≥1)	Esophagus	3	0.45	0.01	1	0.01	2	0.02
	Thymus	2	0.3	0.01	1	0.01	1	0.01
	Lung	84	12.6	0.4	52	0.4	32	0.3
	Bone	55	8.3	0.2	31	0.2	24	0.3
	Soft tissue	23	3.5	0.1	17	0.1	6	0.1
	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
	Liver/gall bladder	2	0.3	0.01	2	0.01	0	0
	Larynx	3	0.45	0.01	2	0.01	1	0.01
	Thyroid	49	7.4	0.2	27	0.2	22	0.3
	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
	Salivary gland	9	1.3	0.04	5	0.04	4	0.04
	Colon	45	6.8	0.2	20	0.15	25	0.3
	Rectum and anus	21	3.2	0.1	11	0.1	10	0.1
	Pancreas	17	2.6	0.1	8	0.05	9	0.1
	Melanoma of the skin	59	8.9	0.3	36	0.25	23	0.3
	Cervix uteri	9	1.3	0.04	5	0.04	4	0.04
	Ovary	88	13.3	0.4	41	0.3	47	0.5
	Endometrial	93	14.0	0.4	51	0.4	42	0.5
	Other female genital	10	1.5	0.04	7	0.05	3	0.03
	Bladder	9	1.3	0.04	8	0.05	1	0.01
	Kidney	16	2.4	0.07	10	0.1	6	0.1
	Brain	10	1.5	0.04	8	0.05	2	0.02
	Eye	4	0.6	0.02	3	0.02	1	0.01
	Nasal cavity	1	0.2	0.004	0	0	1	0.01
	Other sites	30	4.5	0.1	17	0.1	13	0.1
	Subtotal	432	65.1	1.9	236	1.7	196	2.2
Dose grouping, Gy‡	**Cancer site**	**Case**	**% of all cases (831)**	**% of all pts (22,628)**	**RT**	**% of RT pts (13,655)**	**Non-RT**	**% of non-RT pts (8973)**
	Contralateral breast	831	100	3.7	459	3.3	372	4.2
1.8–2.0 (0.2–8.0)	Inner quadrants/overlapping lesions	272	32.7	1.2	152	1.1	120	1.3
1.0–1.2 (0.1–4.2)	Central portion	34	4.1	0.2	17	0.1	17	0.2
0.7–0.8 (0.1–2.7)	Outer quadrants/axillary tail	362	43.6	1.6	194	1.4	168	1.9
	Unknown	163	19.6	0.7	96	0.7	67	0.8

Pts = patients, RT = radiation therapy.

* RT dose grouping received by cancer sites based on data from Berrington de Gonzalez et al.[11]

† Number in parentheses indicates the denominator.

‡ RT dose grouping received by contralateral breast cancer sites based on data from Stovall et al.[12]

like actuarial incidence reference of second malignancy risks for each subgroup.

Second malignancy risk typically decreases with age at exposure.[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.[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.[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),[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.[7,25] Moreover, as the age at exposure increases, the importance of promotional process in carcinogenesis increases as well.[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[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-

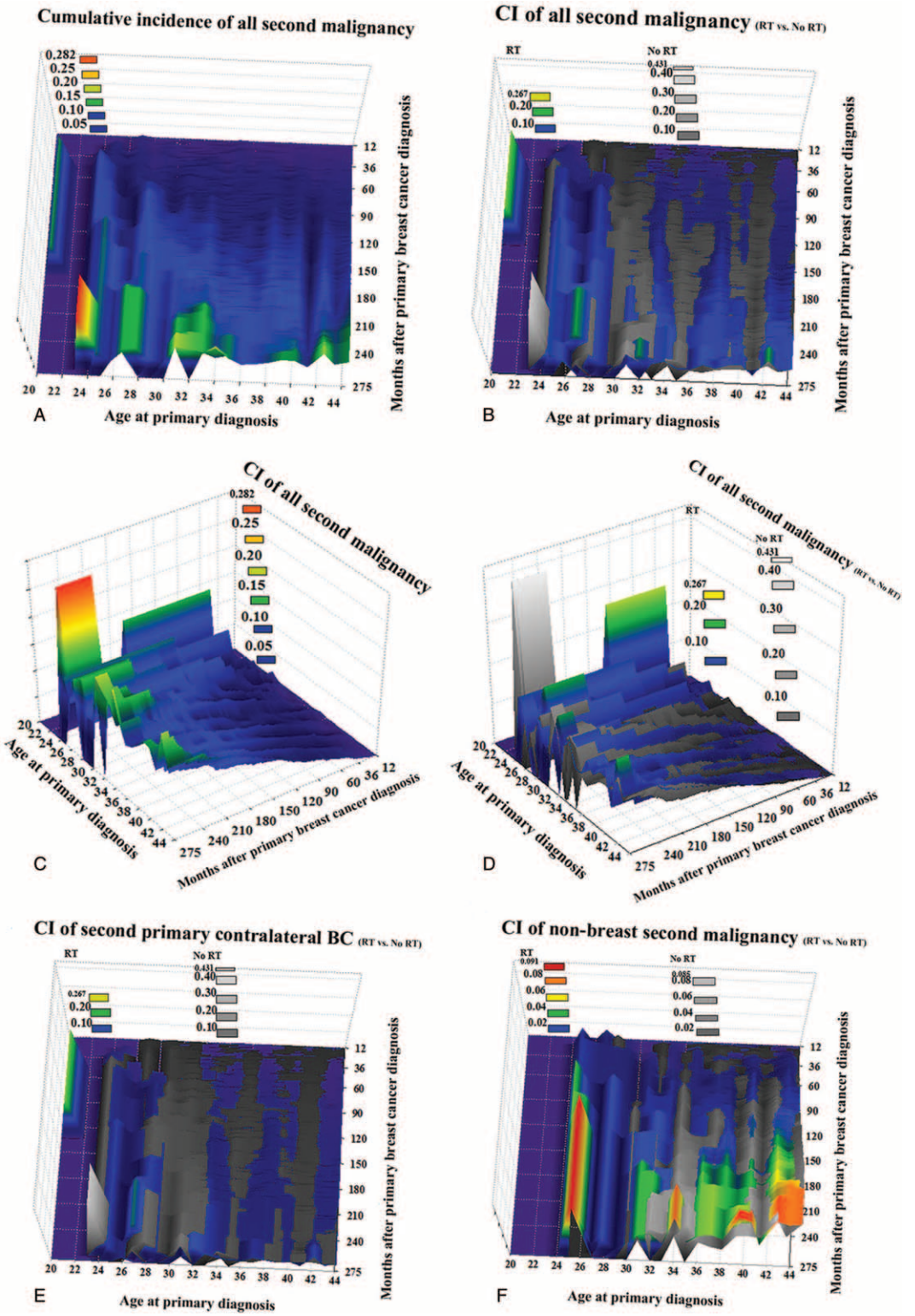

Figure 3. CI of all second malignancy in RT and non-RT groups in the whole group. (A, C) CI of all second malignancies and its relationship with age at primary diagnosis and time since initial diagnosis in the whole group, in 2 different angles of view. (B, D–F) second malignancies (including second 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.

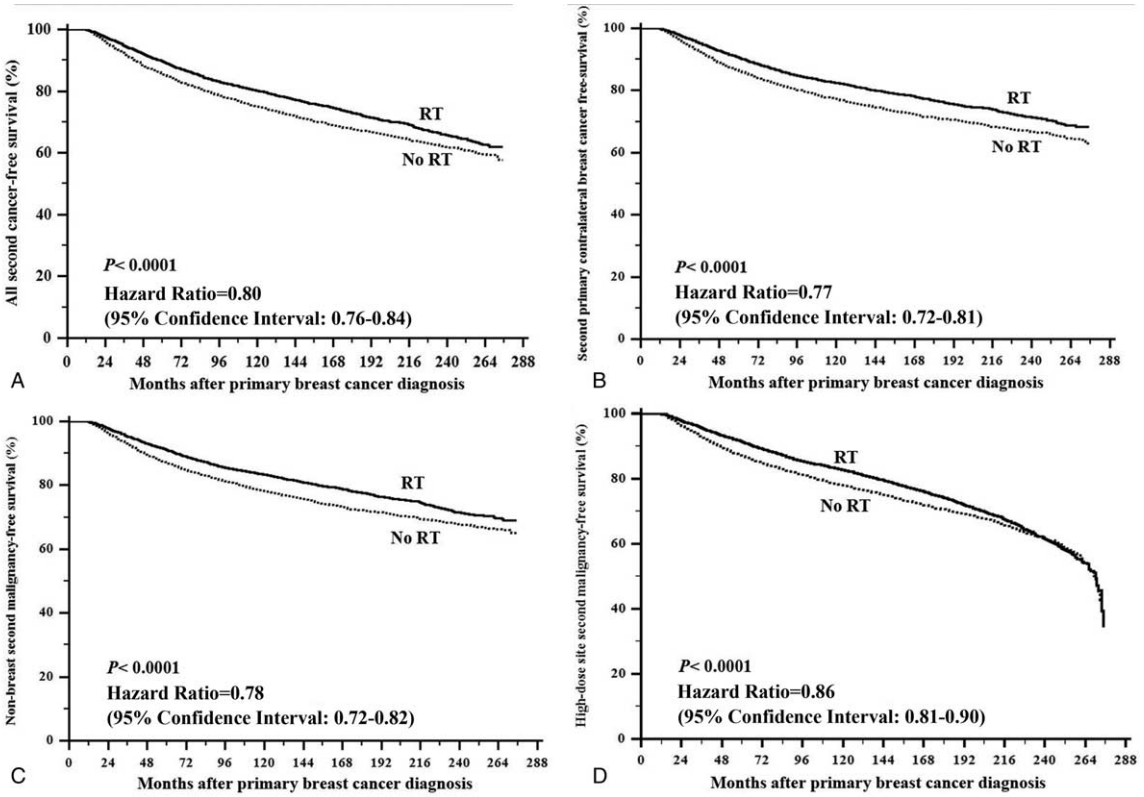

Figure 4. Comparison of second malignancies-free survivals between RT and non-RT groups in the whole group.

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

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-penetrance, and available data are mainly about DNA repair gene polymorphisms and genetic mutations, which are typically very rare.[23]

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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