American Journal of Epidemiology

Vol. 161, No. 4
Printed in U.S.A.
DOI: 10.1093/aje/kwi050

Increased Risk of Squamous Cell Esophageal Cancer after Adjuvant Radiation Therapy for Primary Breast Cancer

Lydia B. Zablotska[1], Amitabh Chak[2], Ananya Das[2], and Alfred I. Neugut[1,3,4]

[1] Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY.
[2] Division of Gastroenterology, Case Western Reserve University School of Medicine, Cleveland, OH.
[3] Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, NY.
[4] Herbert Irving Comprehensive Cancer Center, College of Physicians and Surgeons, Columbia University, New York, NY.

Received for publication June 18, 2004; accepted for publication September 10, 2004.

Prior studies have demonstrated that adjuvant radiation therapy following mastectomy for breast cancer increases the risk of second primary esophageal cancer after 10 years, but the risk following breast-conserving surgery (lumpectomy) has yet to be determined. The authors used 1973–2000 data from the population-based Surveillance, Epidemiology, and End Results Program and estimated relative risks of 2.83 (95% confidence interval: 1.35, 5.92) and 2.17 (95% confidence interval: 1.67, 4.02) for squamous cell esophageal cancer at 5–9 and ≥10 years, respectively, following postmastectomy radiation therapy. This increase was mainly due to tumors located in the upper and middle thirds of the esophagus. No significant increase in risk was found for adenocarcinoma following mastectomy or for any type of esophageal cancer following lumpectomy. In summary, postmastectomy radiation therapy moderately increases the risk of squamous cell esophageal cancer starting 5 years after exposure, which persists after 10 years, with no increase in the risk of adenocarcinoma. This finding appears to be a function of the portals used for postmastectomy radiation therapy, which do not expose the lowest third of the esophagus, where adenocarcinomas commonly arise.

breast neoplasms; esophageal neoplasms; mastectomy; mastectomy, segmental; neoplasms, second primary; radiotherapy; registries

Abbreviations: CI, confidence interval; RR, relative risk; SEER, Surveillance, Epidemiology, and End Results.

Esophageal cancer is the sixth most common malignancy worldwide (1) but is significantly less common in the United States. In the past, the vast majority of cases have been of squamous cell histology, but, in recent years in the United States, about 75 percent of esophageal malignancies are adenocarcinomas, primarily located in the lowest third (1). Both histologic types are associated with tobacco use, although squamous cell carcinoma has generally had a stronger association with cigarette smoking and alcohol consumption (2).

History of irradiation has been linked to an increased risk of esophageal carcinoma. The first reports that linked radiation therapy with cancer of the esophagus appeared in the early 1960s, when several case reports described cases of esophageal cancer after regional radiation treatment for primary cancers of the head, neck, and chest (3, 4). More recently, several reports described case series observed in various hospitals around the world (5–7).

Several studies investigated the relation between doses from radiation therapy for primary cancer and noncancer diseases and the subsequent risk of esophageal carcinoma (8–13). In general, risks were increased twofold but tended to decrease over time.

There is a particular interest in the consequences of radiation therapy for breast cancer because of the large number of women who receive such treatment each year. The standard treatment for invasive breast cancer in the United States includes high, concentrated doses of radiation to the chest field and to the lymph nodes (about 40–60 Gy total) (14). Initially, localized radiotherapy was combined with radical mastectomy, but, since the mid-1980s, many women undergo breast-conserving surgery (hereinafter referred to as

Correspondence to Dr. Alfred I. Neugut, Mailman School of Public Health, 722 West 168th Street, 7N-725, New York, NY 10032 (e-mail: ain1@columbia.edu).

lumpectomy) and whole-breast radiotherapy (15, 16). Women irradiated before the mid-1980s received higher radiation doses to the lungs, contralateral breast, thoracic bone, and esophagus than women treated with lumpectomy. Tissues and organs situated close to the radiation field received higher doses, on the order of 1–4 Gy (17), which have been previously shown to cause radiogenic damage (18).

In an earlier population-based, retrospective cohort study of 220,806 women in the Surveillance, Epidemiology, and End Results (SEER) Program diagnosed with nonmetastatic primary breast cancer between 1973 and 1993, we showed that the standardized incidence ratio of esophageal cancer after radiation therapy was 54 percent higher than in the general population (95 percent confidence interval (CI): 1.27, 1.84) (19). Risk increased with time, reaching a standardized incidence ratio of 5.42 (95 percent CI: 2.33, 10.68) for esophageal squamous cell carcinoma 10 years after radiotherapy.

Our analysis was limited by a relatively short follow-up period (1973–1993) and a small number of endpoints, which did not permit adequate subgroup analyses. At that time, lumpectomy and radiation therapy had not yet come into common use, and it was not possible to compare the effects of radiation therapy after mastectomy and lumpectomy. In the current study, we extended follow-up of the cohort with 8 additional years of data (1973–2000) to confirm and extend our earlier findings on postmastectomy radiation therapy and also to investigate the impact of postlumpectomy radiation therapy on second primary esophageal cancer. Separate analyses were performed to evaluate the relation between radiation therapy and the histologic type of esophageal cancer as well as the location of the second esophageal cancer in relation to the primary field of irradiation.

MATERIALS AND METHODS

The SEER Program of the US National Cancer Institute collects cancer data routinely from designated population-based cancer registries around the United States (20), representing an estimated 10–14 percent of the US population. For all cases diagnosed between 1973 and the end of 2000 in nine geographic areas, information was available on demographics; the anatomic site of all cancers; their morphology, histology, and laterality; and the length of follow-up, primary surgery, and whether radiation therapy was performed. The SEER database does not include detailed data on radiation therapy, that is, information on dose or treatment protocol (use of wedge compensators or half-beam block leads to various scattering patterns and absorbed doses of radiation) (21).

We identified all newly diagnosed cases of invasive nonmetastatic breast cancer registered in SEER between January 1, 1973, and December 31, 2000. We excluded cases diagnosed by autopsy or death certificate and those diagnosed without microscopic confirmation. In addition, we excluded breast cancer cases for whom type of surgery was unknown and those for whom radiation therapy was prescribed but it was unknown whether it was administered. The breast cancer was required to precede esophageal cancer in time. Using the SEER registry and a case number assigned to each patient (case numbers are not unique across registries), we linked the breast cancer and digestive cancer files to identify subjects with both breast cancer and esophageal cancer. We identified cases who developed a second or later primary esophageal cancer after an initial primary breast cancer during the 1973–2000 follow-up. Our cohort included only those subjects with nonmetastatic primary breast cancer because those with metastases have a short survival time and to exclude the possibility of misclassification of metastatic cancers as second primary cancers. Radiation therapy was dichotomized into "present" and "absent" and was treated as the main exposure of interest.

We defined cancers of the esophagus as those assigned *International Classification of Diseases*, Ninth Revision diagnostic codes 150.0–150.9 (22). Cancers occurring in the cervical, thoracic, and abdominal parts of the esophagus were included in the upper, middle, and lower third categories, respectively. Squamous cell cancers were defined as those with histology codes 807 and adenocarcinoma with codes 814 (23).

For each female patient with an initial invasive breast cancer, we calculated the time interval from 6 months after diagnosis until diagnosis of a new primary esophageal cancer, death, date last known to be alive, or cutoff date of December 31, 2000, whichever took place first. Cases of esophageal cancer occurring within 6 months of the primary breast cancer diagnosis were excluded to eliminate synchronous tumors.

We used the PROC PHREG procedure in the SAS statistical software package (SAS Institute, Inc., Cary, North Carolina) to estimate Cox regression models. Cox regression is a very robust, semiparametric method that easily incorporates time-dependent covariates, allows stratification, and is used for regression analysis of survival data (24). The maximum partial likelihood method was used to estimate the hazard for each woman and the 95 percent confidence interval around the estimate. The hazard ratio for indicator variables is interpreted as the ratio of the estimated hazard for those with a value of 1 to the estimated hazard for those with a value of 0 (controlling for all other covariates). All p values presented in this paper are two sided.

The hazard ratios directly comparing irradiated breast cancer cases with nonirradiated cases were calculated separately for the mastectomy and lumpectomy groups. These ratios were calculated by stratification on patient age and calendar period at the time of diagnosis of the primary breast cancer, registry, and time since diagnosis. These variables were included in the models in the form of intervals (age: <40, 40–49, 50–59, 60–69, 70–79, 80–89, and ≥90 years; calendar period at the time of diagnosis: 1973–1979, 1980–1984, 1985–1989, 1990–1994, and 1995–2000; and time since diagnosis: 6 months–4 years, 5–9 years, and ≥10 years, respectively). We calculated hazard ratios for esophageal cancer overall and separately for the two major histologic subtypes (squamous cell and adenocarcinoma). In addition, we calculated hazard ratios for esophageal cancers originating in the different parts of the esophagus (upper third, middle third, and lowest third) in the mastectomy group. The hazard rate for the nonirradiated cases was used as a reference category.

TABLE 1. Selected demographic characteristics of women who did and did not receive radiation treatment following nonmetastatic breast cancer, Surveillance, Epidemiology, and End Results Program database, nine geographic areas of the United States, 1973–2000

Characteristic	Mastectomy group			Lumpectomy group		
	No radiation	Radiation	Probability of the *t* test*	No radiation	Radiation	Probability of the *t* test*
No. (%)	156,517 (85.4)	26,665 (14.6)		15,322 (24.9)	46,120 (75.1)	
Age (years) at diagnosis (%)						
≤29	0.7	1.1		0.7	0.6	
30–39	6.2	9.1		5.5	6.9	
40–49	16.3	21.2		14.9	20.5	
50–59	20.9	25.9		19.0	23.7	
60–69	24.6	24.0		11.9	25.2	
70–79	20.9	14.8		20.4	18.4	
≥80	10.4	3.9		27.5	4.7	
Mean age (years) at diagnosis	61.2	56.8	<0.0001	66.3	58.5	<0.0001
Calendar period of diagnosis (%)						
1973–1979	24.0	39.1		0	0	
1980–1989	44.7	36.7		30.4	26.4	
1990–2000	31.3	24.3		69.6	73.6	
Mean year of diagnosis	1985	1983	<0.0001	1992	1992	
Laterality (%)						
Right breast	48.7	49.0		49.4	49.0	
Left breast	51.2	50.8		50.6	51.0	
Race (%)						
White	88.6	85.9		86.9	87.8	
Black	6.5	8.1		8.9	6.6	
Other, unknown	4.9	6.0		4.2	5.5	
Histologic stage (%)						
Localized	61.6	29.7		78.5	79.3	
Regional	38.4	70.3		21.5	20.7	

* Two-sided *t* test.

RESULTS

Demographic characteristics of the mastectomy and lumpectomy groups

There were 433,272 subjects with an initial diagnosis of primary breast cancer registered in the SEER database between 1973 and 2000. Of 289,604 women with invasive nonmetastatic breast cancer whose diagnoses were confirmed microscopically, we further excluded 39,899 (13.8 percent) with missing or unknown information for surgery type and 5,081 (1.8 percent) for radiation treatment. Thus, our cohort for analysis consisted of 244,624 women with nonmetastatic invasive breast cancer who had survived at least 6 months after initial diagnosis. This cohort was divided into the 183,182 women in the mastectomy group, 14.6 percent of whom received radiation therapy (table 1), and the 61,442 women treated with breast-conserving surgery (lumpectomy), 75.1 percent of whom received radiation therapy.

Table 1 compares those who received radiation therapy with those who did not in the two study groups regarding several important demographic characteristics. In both groups, women who received radiation therapy were significantly younger than those who did not. The majority of women in the mastectomy group were diagnosed around 1985, while those who underwent lumpectomy were diagnosed around 1992. There was a significant difference in age at diagnosis between women who received adjuvant radiation therapy and those who did not, in both the lumpectomy and mastectomy groups. Cases with regional spread of breast cancer were treated with radiation therapy more often than cases with localized cancers (70 percent vs. 30 percent) in the mastectomy group, but this pattern was reversed in the lumpectomy group. In the mastectomy group, the average follow-up times were 9.1 years in the irradiated group and 9.8 years in the nonirradiated group, with 35 and 136 esophageal cancers subsequently diagnosed in each group, respectively. In the lumpectomy group, the average follow-up times were 7.3 years in the irradiated group and 6.1 years in

TABLE 2. Hazard ratios and 95% confidence intervals for esophageal cancer due to radiation treatment after primary breast cancer, calculated for different survival intervals, Surveillance, Epidemiology, and End Results Program database, nine geographic areas of the United States, 1973–2000

Survival interval after breast cancer	After mastectomy and radiation treatment						After lumpectomy and radiation treatment					
	All		Squamous cell		Adenocarcinoma		All		Squamous cell		Adenocarcinoma	
	HR*	95% CI*	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
6 months–4 years	1.04	0.44, 2.46	1.11	0.43, 2.86	1.63	0.19, 13.74	0.95	0.31, 2.89	0.82	0.22, 3.09	—†	
5–9 years	2.86	1.50, 5.44	2.83	1.35, 5.92	1.65	0.20, 13.49	1.26	0.36, 4.43	1.22	0.26, 5.71	1.12	0.12, 10.29
≥10 years	1.81	1.03, 3.19	2.17	1.67, 4.02	1.34	0.29, 6.14	0.64	0.17, 2.37	0.61	0.12, 3.05	0.49	0.04, 5.47

* HR, hazard ratio; CI, confidence interval.
† No cases.

the nonirradiated group, with 38 and 10 esophageal cancers diagnosed in each group, respectively.

Risk of esophageal cancer by treatment group, histologic type, and follow-up interval

Table 2 presents the results of analysis of the risk of second primary esophageal cancer following mastectomy or lumpectomy and adjuvant radiation therapy for different survival times. In the mastectomy group, risks tended to increase 5 years after treatment for primary breast cancer and remained elevated after 10 years. The increase in risk was limited to squamous cell esophageal cancer (relative risk (RR) = 2.83, 95 percent CI: 1.35, 5.92 for those who survived 5–9 years after breast cancer), with no significant increase for adenocarcinoma (RR = 1.65, 95 percent CI: 0.20, 13.49). There was no indication of any increase in risk in the lumpectomy group as a whole or for any individual histologic subtype of esophageal cancer.

Differences in risk of esophageal cancer due to radiation therapy by location of the second primary tumor

Table 3 shows the main results of our analysis. It is evident that the risk of esophageal cancer was significantly increased in the mastectomy group after 5 years of follow-up. Irradiated women in the mastectomy group had a relative risk of 2.86 (95 percent CI: 1.50, 5.44) for developing esophageal cancer compared with nonirradiated women, controlling for age at diagnosis of the primary breast cancer and calendar time of initial diagnosis. This risk remained elevated with increased length of follow-up. Separate analysis of the mastectomy group for location of the second primary cancer showed that this increase was mainly for tumors located in the upper (cervical) and middle (thoracic) thirds of the esophagus, with risks of 9.09 (95 percent CI: 1.22, 67.74) and 2.54 (95 percent CI: 0.99, 6.50) in the survival interval 5–9 years after the initial breast cancer diagnosis, respectively. Risks remained increased 10 years after radiation therapy, although individual estimates were smaller and less stable because of small numbers. In contrast, the risk for the lowest (abdominal) third of the esophagus was only slightly increased 5–9 years after exposure (nonsignificant) and was not increased 10 years after the radiation therapy.

Distribution of esophageal cancers by treatment group, histologic type, and survival time

Table 4 shows that there were significantly more squamous cell esophageal cancer cases in the mastectomy and

TABLE 3. Hazard ratios and 95% confidence intervals for esophageal cancer following mastectomy and radiation treatment for primary breast cancer, by location of the esophageal cancer and calculated for different survival intervals,* Surveillance, Epidemiology, and End Results Program database, nine geographic areas of the United States, 1973–2000

Survival interval after breast cancer	Upper (cervical) third of esophagus†		Middle (thoracic) third of esophagus‡		Lowest (abdominal) third of esophagus§		Total	
	HR¶	95% CI¶	HR	95% CI	HR	95% CI	HR	95% CI
6 months–4 years	3.45	0.35, 34.50	1.53	0.52, 4.52	—#		1.04	0.44, 2.46
5–9 years	9.09	1.22, 67.74	2.54	0.99, 6.50	1.89	0.54, 6.64	2.86	1.50, 5.44
≥10 years	3.08	1.03, 9.22	1.83	0.66, 5.05	0.84	0.25, 2.82	1.81	1.03, 3.19

* Total number of cases with known localization of the second primary esophageal cancer following mastectomy = 153.
† Eight cases positive for radiation therapy (RT+) and 15 cases negative for RT (RT–).
‡ Fifteen cases RT+ and 54 cases RT–.
§ Six cases RT+ and 55 cases RT–.
¶ HR, hazard ratio; CI, confidence interval.
# No cases.

TABLE 4. Number of esophageal cancer cases after primary breast cancer, by treatment group and survival time, Surveillance, Epidemiology, and End Results Program database, nine geographic areas of the United States, 1973–2000

Survival interval after breast cancer	After mastectomy							After lumpectomy						
	All types	Squamous cell			Adenocarcinoma			All types	Squamous cell			Adenocarcinoma		
		All	RT* = 0	RT = 1	All	RT = 0	RT = 1		All	RT = 0	RT = 1	All	RT = 0	RT = 1
6 months–4 years	50	38	33	5	7	6	1	19	12	3	9	5	0	5
5–9 years	51	37	27	10	9	8	1	17	11	2	9	5	1	4
≥10 years	60	43	39	14	13	11	2	12	8	2	6	3	1	2
Total	171	128	99	29	29	25	4	48	31	7	24	13	2	11

* RT, radiation therapy.

lumpectomy groups (128 vs. 29 and 31 vs. 13, respectively) than esophageal adenocarcinomas. The preponderance of squamous cell esophageal cancers was also evident in the mastectomy group when the data were analyzed by location in the upper, middle, or lowest third of the esophagus (data not shown). In fact, 91 percent of cases of cancer located in the upper esophagus and 87 percent of cases of cancer located in the middle esophagus were squamous cell. In contrast, only 39 percent of cases of cancer in the lowest esophagus were squamous, while the majority (53 percent) were adenocarcinomas (figure 1).

DISCUSSION

We used the National Cancer Institute's population-based SEER database, which represents approximately 10–14 percent of the US population, to determine that there is a moderately increased risk of squamous cell esophageal cancer in patients treated with postmastectomy radiotherapy for primary breast cancer, confirming our earlier findings that radiation-induced squamous cell esophageal cancer develops after a substantial latency period (19). In the present study, the risk of radiation-induced cancer started to increase 5 years after the radiation therapy and remained increased with increased length of follow-up. We showed that second primary esophageal carcinomas in the field of irradiation were primarily squamous cell (88 percent of cancers of the upper and middle thirds of the esophagus). We did not observe an increase in the risk of squamous cell esophageal cancer in the lowest third of the esophagus, which is situated in the abdomen and would have received substantially lower doses of radiation than the upper and middle thirds of the esophagus. The risk of adenocarcinoma following postmastectomy radiation therapy was small and not statistically significant.

The current study also compared the effects of radiation therapy for primary breast cancer on the subsequent risk of esophageal cancer in patients treated with mastectomy and with breast-conserving surgery (lumpectomy). We did not observe an increase in the risk of radiation-induced esoph-

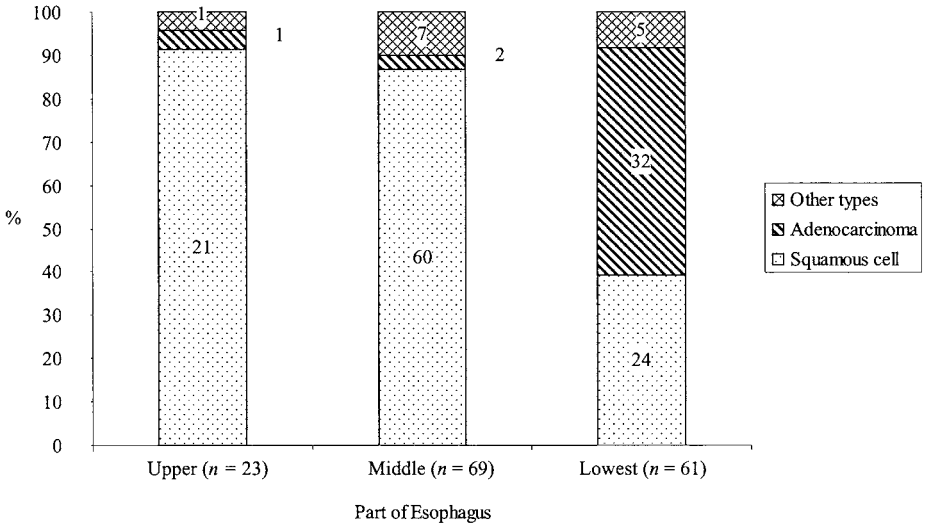

FIGURE 1. Distribution of histologic types of esophageal cancer after mastectomy and radiation therapy, by anatomic location, for cases with known localization of the tumor, Surveillance, Epidemiology, and End Results Program database, nine geographic areas of the United States, 1973–2000.

ageal cancer following lumpectomy plus radiation therapy in the group of patients who survived 5–9 years after radiation therapy, while we observed a threefold increase in risk in the postmastectomy group with similar follow-up time.

Our findings are supported by other studies. On the basis of data from the cohort of Japanese survivors of the atomic bombings of Hiroshima and Nagasaki, cancers of the esophagus have been conclusively linked to ionizing radiation exposure (25). Women who survived the atomic bombings had an estimated dose of 0.236 Sv to the esophagus and were observed to be at increased risk of esophageal cancer later in life (excess RR = 2.03 per Sv, 95 percent CI: 0.39, 5.31) (25). Recently updated information on mortality of atomic bomb survivors showed that excess relative risks continue to be significantly increased (18). Analysis of incidence in the same cohort showed a similar sized, but nonsignificant increase in risk for women (excess RR = 1.83 per Sv) (26).

Four cohorts have measured radiation doses and given estimates of incident esophageal cancer risk following radiation therapy. In general, excess relative risk estimates for esophageal cancer tended to be slightly lower than in the study of survivors of atomic bombings, but they were statistically compatible. In a study of ankylosing spondylitis patients, the mean dose to the area of the esophagus was 4.20 Gy for those receiving only one course of treatment and 5.55 Gy for all patients, while the mean dose to other organs was substantially lower (1.92 Gy) (8). Significant increases in risk were seen for cancer of the esophagus and other cancers located in the radiation field (standardized mortality ratio = 1.94, 95 percent CI: 1.53, 2.42; excess RR = 0.17 per Sv, 95 percent CI: 0.09, 0.25). After 25 years, the increase in risk of esophageal cancer did not diminish. Griem et al. (9) showed that patients who received radiation therapy for peptic ulcer were exposed on average to doses to the esophagus of 2.28 Gy and were at increased risk of subsequent esophageal cancer (RR = 1.14, 95 percent CI: 0.2, 5.7). Extended follow-up of the same cohort 11–62 years after therapy showed that the risks were no longer increased (RR = 0.97, 95 percent CI: 0.17, 5.45) (10).

In a large international study of survivors of cervical cancer, women treated with radiation therapy had a significantly increased risk of incident esophageal cancer compared with those who did not receive radiation therapy (standardized incidence ratio = 1.5, $p < 0.05$) (27). Another study of the incidence of second primary cancers after treatment for cervical cancer by Kleinerman et al. (28) was based on 13 population-based cancer registries in five countries. It showed a similarly increased risk of esophageal cancer among women treated with radiation therapy (standardized incidence ratio = 1.6, $p < 0.05$).

A US (Massachusetts) cohort study of patients with tuberculosis who received multiple chest x-ray fluoroscopies during the course of lung-collapse treatment showed that, following an average dose to the esophagus of 0.80 Gy, female patients had significantly higher esophageal cancer mortality than the general population (standardized mortality ratio = 2.3, $p < 0.05$ for women) (12). The risk was present mainly among 5-year survivors who received doses to the esophageal tissue of 0.5 Gy or more. On the basis of these data, Little (29) estimated an excess relative risk of 0.53 per Sv (95 percent CI: –0.22, 2.48) comparing irradiated and nonirradiated patients.

In the largest known study to date that analyzed the risks of esophageal cancer following breast cancer radiation therapy, we used data from the SEER database and showed that the risks of esophageal cancer after radiation therapy for primary breast cancer were significantly higher than would be expected based on the rates of esophageal cancer in the general population (19). A total of 116 cancers were observed in this large cohort of more than 220,000 women over a period of 21 years. The risk of second malignant esophageal tumors increased with time and remained increased after 10 years.

The current analysis was based on the 219 cases of second primary esophageal cancer observed over a period of 29 years. Women were exposed to radiation as a result of radiation therapy treatment for their primary breast cancers. Several studies have shown that the average dose given to patients undergoing radiation therapy following mastectomy is 50–55 Gy (30, 31). Inskip et al. (30) estimated that the mean absorbed dose is 15.2 Gy to the ipsilateral lung, 4.6 Gy to the contralateral lung, and 9.8 Gy to both lungs combined. Radiation therapy to the regional nodes adds to the radiation dose. Multiple studies report that the doses given in adjuvant radiation therapy following lumpectomy are similar in magnitude to the doses given to mastectomy patients (45–50 Gy to the entire breast with or without an additional 20–25 Gy to the tumor bed (32, 33)), but absorbed doses are much lower because of the physical barrier of the remaining breast tissue and new megavoltage treatments (34–36).

Several randomized studies that investigated the effectiveness of radiation therapy in preventing breast cancer recurrence had accurately measured radiation doses (16, 37). Overgaard et al. (37) in particular noted that internal mammary nodes in the four upper intercostal spaces were irradiated to prevent the recurrence of breast cancer. The current study shows that, as expected, the carcinogenic effect of radiation is limited to the upper and middle thirds of the esophagus, which receive much higher doses of radiation than the lowest third, which is situated in the abdomen. As a result, the increased risk is limited to squamous cell carcinoma since adenocarcinoma does not generally occur in the upper two thirds of the esophagus. Furthermore, this study shows that current methods of whole breast radiation therapy after lumpectomy produce considerably less radiation exposure to the esophagus and do not lead to an increase in the risk of esophageal cancer. Thus, we did not find an increased risk of esophageal cancer due to postlumpectomy radiation therapy based on the more than 10 years of follow-up since the widespread introduction of breast-conserving surgery in the mid-1980s.

The findings of this study are limited by the absence of information on cigarette smoking. A large SEER-based study showed that subjects with tobacco-related primary malignancies (lung cancer and head and neck cancer) had a much higher risk of developing second esophageal cancers (RR = 5.1 and RR = 38.8, respectively) (38). Estimated risks were stronger for squamous cell carcinoma than for adenocarcinoma and were stronger for women compared with men. We could not exclude confounding by smoking in our

data, but our analysis of the location of the esophageal cancers in this cohort shows that the risk of esophageal cancer was increased in only the upper and middle parts of the esophagus (close to the site of irradiation) and not in the lowest part (RR = 9.09 and RR = 2.54 vs. RR = 1.89, respectively, 5–9 years after radiation therapy and mastectomy). Thus, our findings are supportive of a true effect that cannot be explained by uncontrolled confounding by smoking.

Although we did not have information on alcohol consumption, which has been shown to be associated with esophageal cancer, it is unlikely that our results were confounded by this factor, as was shown above for smoking. We could not control for socioeconomic status, which affects diet and other related factors and has been shown to affect rates of esophageal cancer at the ecologic level (2). One other possibility is that obesity acted as a confounding variable. Obesity is a known risk factor for adenocarcinoma of the esophagus but not for squamous cell carcinoma. While obesity is unlikely to offer a complete explanation, a future study in which information on weight and height is available would be desirable.

In addition, we did not have individual patient information on the specific types of radiation therapy, associated doses, and compensation methods used during radiotherapy. Absence of information on the individual doses did not enable us to investigate the form of the dose-response relation and to estimate the size of the risk associated with the unit of exposure. It is possible, therefore, that we underestimated the importance of ionizing radiation in the form of radiation therapy to the subsequent risk of squamous cell esophageal cancer.

Several studies have raised the issue of completeness of radiation therapy information in the SEER database. Du et al. (39) used the linked Medicare-SEER database to compare information on radiation therapy for women with breast cancer who were older than age 65 years in 1992. These authors found that more than 18 percent of women identified from the Medicare database as receiving radiation therapy within 4 months of initial therapy for primary breast cancer were not identified as such by SEER and that 7 percent of those identified in SEER as receiving radiation therapy were not identified as such by Medicare. Some of the reasons for the discordance in the radiation therapy information cited were missing information from the outpatient settings and radiation therapy received in out-of-state medical facilities. The proportion of false-positive results was much higher among patients with breast-conserving surgery than among patients with mastectomy. If indeed present, this would bias our results; however, we do not believe that it would have altered our finding of no increased risk of radiation-induced lung cancer after lumpectomy and radiation therapy.

Analysis of the SEER data was further limited by its inability to trace patients who moved away from the registration area. However, this finding would be equally applicable to both study groups and would most likely have led to an underestimation of the effects of radiation therapy. We also did not have information on the use of chemotherapy, which may have an impact on esophageal cancer risk. Fifteen percent of subjects were excluded from analysis because no information was available about their surgery type and/or radiation therapy or, if prescribed, if it was performed. This problem could have biased our results in either direction, but, because exclusions applied equally to mastectomy and lumpectomy groups, it is unlikely that they would have changed our primary findings.

In summary, this study has shown that postmastectomy radiation therapy for breast cancer, as practiced in the 1970s and 1980s, increased the risk of subsequent squamous cell esophageal cancer. No increase was observed for adenocarcinoma, presumably reflecting the absence of irradiation of the distal third of the esophagus, where adenocarcinomas typically arise. In contrast, postlumpectomy radiation therapy produces much lower radiation exposure to the esophagus and, as expected, does not increase the risk of subsequent esophageal cancer. New squamous cell esophageal cancers in women who received adjuvant radiation therapy after mastectomy should be evaluated as a possible second primary esophageal cancer. Patients and physicians should be aware that the history of such treatment appears to carry a threefold increase in esophageal cancer risk 5–9 years after radiation therapy. The risks are significantly higher for cancers located in the upper and middle thirds of the esophagus.

Our data indicate that average survival after second primary esophageal cancer is very short (a little more than a year; median, 8 months). However, in our cohort, the incidence of esophageal cancer following breast cancer was low at 9.65 per 100,000 person-years of observation. In view of these data, we do not think that additional screening of women who underwent mastectomy is warranted. We conclude, therefore, that clinicians need to weigh a threefold increase in the relative risk of squamous cell esophageal carcinoma, with a very small increase in absolute risk, against the proven benefits of radiation therapy in terms of treating the primary breast cancer. In particular, the choice between mastectomy and lumpectomy should be carefully evaluated. In addition, special care should be exercised in advising breast cancer patients to quit smoking, because previous research has shown that smoking multiplies the effects of irradiation (35).

Further studies with more detailed information about radiation exposure, cigarette smoking, and alcohol exposure are needed to answer the question of the multiplicative effect of these exposures and to provide guidelines to physicians treating young women with breast cancer who smoke or drink.

ACKNOWLEDGMENTS

Dr. Neugut was supported by a K05 grant (CA89155) from the National Cancer Institute.

REFERENCES

1. Ribeiro U Jr, Posner MC, Safatle-Ribeiro AV, et al. Risk factors for squamous cell carcinoma of the oesophagus. Br J Surg 1996;83:1174–85.

2. Daly JM, Karnell LH, Menck HR. National Cancer Data Base report on esophageal carcinoma. Cancer 1996;78:1820–8.
3. Parker RG, Enstrom JE. Second primary cancers of the head and neck following treatment of initial primary head and neck cancers. Int J Radiat Oncol Biol Phys 1988;14:561–4.
4. Seydel HG. The risk of tumor induction in man following medical irradiation for malignant neoplasm. Cancer 1975;35:1641–5.
5. Goffman TE, McKeen EA, Curtis RE, et al. Esophageal carcinoma following irradiation for breast cancer. Cancer 1983;52: 1808–9.
6. Scholl B, Reis ED, Zouhair A, et al. Esophageal cancer as second primary tumor after breast cancer radiotherapy. Am J Surg 2001;182:476–80.
7. Micke O, Schafer U, Glashorster M, et al. Radiation-induced esophageal carcinoma 30 years after mediastinal irradiation: case report and review of the literature. Jpn J Clin Oncol 1999; 29:164–70.
8. Weiss HA, Darby SC, Doll R. Cancer mortality following x-ray treatment for ankylosing spondylitis. Int J Cancer 1994;59: 327–38.
9. Griem ML, Kleinerman RA, Boice JD Jr, et al. Cancer following radiotherapy for peptic ulcer. J Natl Cancer Inst 1994;86: 842–9.
10. Carr ZA, Kleinerman RA, Stovall M, et al. Malignant neoplasms after radiation therapy for peptic ulcer. Radiat Res 2002; 157:668–77.
11. Boice JD Jr, Preston D, Davis FG, et al. Frequent chest X-ray fluoroscopy and breast cancer incidence among tuberculosis patients in Massachusetts. Radiat Res 1991;125:214–22.
12. Davis FG, Boice JD Jr, Hrubec Z, et al. Cancer mortality in a radiation-exposed cohort of Massachusetts tuberculosis patients. Cancer Res 1989;49:6130–6.
13. Little MP, Boice JD Jr. Comparison of breast cancer incidence in the Massachusetts tuberculosis fluoroscopy cohort and in the Japanese atomic bomb survivors. Radiat Res 1999;151:218–24.
14. Curtis RE, Boice JD Jr, Stovall M, et al. Leukemia risk following radiotherapy for breast cancer. J Clin Oncol 1989;7:21–9.
15. Lichter AS, Lippman ME, Danforth DN Jr, et al. Mastectomy versus breast-conserving therapy in the treatment of stage I and II carcinoma of the breast: a randomized trial at the National Cancer Institute. J Clin Oncol 1992;10:976–83.
16. Fisher B, Anderson S, Redmond CK, et al. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. N Engl J Med 1995;333:1456–61.
17. Boice JD Jr, Harvey EB, Blettner M, et al. Cancer in the contralateral breast after radiotherapy for breast cancer. N Engl J Med 1992;326:781–5.
18. Preston DL, Shimizu Y, Pierce DA, et al. Studies of mortality of atomic bomb survivors. Report 13: solid cancer and noncancer disease mortality: 1950–1997. Radiat Res 2003;160:381–407.
19. Ahsan H, Neugut AI. Radiation therapy for breast cancer and increased risk for esophageal carcinoma. Ann Intern Med 1998; 128:114–17.
20. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) public-use data (1973–2000), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2003, based on the August 2002 submission.
21. Brenner DJ, Schiff PB, Zablotska LB. Adjuvant radiotherapy for DCIS. (Letter). Lancet 2000;355:2071; author reply 2072–3.
22. World Health Organization. International classification of diseases. Manual of the international statistical classification of diseases, injuries, and causes of death. Ninth Revision. Geneva, Switzerland: World Health Organization, 1977.
23. Percy C, Van Holten V, Muir CS, eds. International classification of diseases for oncology. 2nd ed. Geneva, Switzerland: World Health Organization, 1990.
24. Allison PD. Survival analysis using the SAS system: a practical guide. Cary, NC: SAS Institute, Inc, 1995.
25. Pierce DA, Shimizu Y, Preston DL, et al. Studies of the mortality of atomic bomb survivors. Report 12, part I. Cancer: 1950–1990. Radiat Res 1996;146:1–27.
26. Thompson DE, Mabuchi K, Ron E, et al. Cancer incidence in atomic bomb survivors. Part II: solid tumors, 1958–1987. Radiat Res 1994;137:S17–67.
27. Boice JD Jr, Day NE, Andersen A, et al. Second cancers following radiation treatment for cervical cancer. An international collaboration among cancer registries. J Natl Cancer Inst 1985; 74:955–75.
28. Kleinerman RA, Boice JD Jr, Storm HH, et al. Second primary cancer after treatment for cervical cancer. An international cancer registries study. Cancer 1995;76:442–52.
29. Little MP. Cancer after exposure to radiation in the course of treatment for benign and malignant disease. Lancet Oncol 2001;2:212–20.
30. Inskip PD, Stovall M, Flannery JT. Lung cancer risk and radiation dose among women treated for breast cancer. J Natl Cancer Inst 1994;86:983–8.
31. Das IJ, Cheng CW, Fein DA, et al. Patterns of dose variability in radiation prescription of breast cancer. Radiother Oncol 1997;44:83–9.
32. Vicini FA, Chen PY, Fraile M, et al. Low-dose-rate brachytherapy as the sole radiation modality in the management of patients with early-stage breast cancer treated with breast-conserving therapy: preliminary results of a pilot trial. Int J Radiat Oncol Biol Phys 1997;38:301–10.
33. Vicini F, Kini VR, Chen P, et al. Irradiation of the tumor bed alone after lumpectomy in selected patients with early-stage breast cancer treated with breast conserving therapy. J Surg Oncol 1999;70:33–40.
34. Inskip PD, Boice JD Jr. Radiotherapy-induced lung cancer among women who smoke. Cancer 1994;73:1541–3.
35. Neugut AI, Meadows AT, Robinson E. Multiple primary cancers. Philadelphia, PA: Lippincott Williams & Wilkins, 1999: 484.
36. Travis LB, Curtis RE, Inskip PD, et al. Re: Lung cancer risk and radiation dose among women treated for breast cancer. (Letter). J Natl Cancer Inst 1995;87:60–1.
37. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med 1997;337: 949–55.
38. Ahsan H, Neugut AI, Gammon MD. Association of adenocarcinoma and squamous cell carcinoma of the esophagus with tobacco-related and other malignancies. Cancer Epidemiol Biomarkers Prev 1997;6:779–82.
39. Du X, Freeman JL, Goodwin JS. Information on radiation treatment in patients with breast cancer: the advantages of the linked Medicare and SEER data. Surveillance, Epidemiology and End Results. J Clin Epidemiol 1999;52:463–70.