A Retrospective Cohort Analysis of Second Breast Cancer Risk for Primary Breast Cancer Patients With an Assessment of the Effect of Radiation Therapy [1,2]

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ABSTRACT—Second breast cancer experience was examined for 27,175 primary breast cancer patients diagnosed in the State of Connecticut during 1935-75 with follow-up for second breast cancers through 1980. The overall ratio of observed to expected second breast cancers was 3.2. Relative risk was found to be inversely related to age at diagnosis and directly related to stage of the first breast cancer. The overall risk of second breast cancers was 711 per 100,000 person-years at risk. Risk of second breast cancers showed a similar relationship to age and stage as relative risk and was also directly related to calendar period of diagnosis of the first breast cancer. Some interactions were observed because patients less than 45 years old at diagnosis with positive nodes had elevated risks and relative risks in the early followup period, whereas less of an effect of stage on relative risk and risk was seen for older patients. The effect of the use of adjunctive radiation therapy on second breast cancer risk was also assessed by the ratio of the risk of second breast cancers for those patients who received both surgery and radiation to the risk of those patients who only received surgery being estimated for patients diagnosed during 1935-59 and for patients diagnosed during 1960-75. For both cohorts relative risks of 1.2-1.4 were found for the 5-year period immediately following diagnosis, likely resulting from the uncontrolled effect of stage in the analysis. Elevated long-term relative risks were not found for patients diagnosed during 1935-59. A long-term marginally statistically significant relative risk of 1.4 (≥10 yr after diagnosis) was found for patients diagnosed during 1960-75. The data do not indicate an overall pattern of relative risks consistent with an effect on long-term second breast cancer risk of radiation exposure to the opposite breast incurred during adjunctive radiation therapy for a first breast cancer. —JNCI 1983; 70:797-804.

The study of multiple primary cancers has substantial potential for providing useful information on cancer etiology and carcinogenic mechanisms. The finding that patients with a first primary cancer of a particular site are at an elevated risk of cancer of some other site (or the same site) is of interest because it may suggest a common etiology for both the first and subsequent cancers or possibly some biologic predisposition to certain kinds of cancer. In addition, a second cancer could result from treatments such as chemotherapy or radiotherapy administered for a first cancer.

The focus of this analysis is on the occurrence of second breast cancers in patients with an initial breast cancer. The association of such factors as age and stage of the first cancer with second breast cancer risk is described. An attempt is also made to quantify the effect on second breast cancer risk of an average dose of radiation to the remaining breast from adjunctive radiotherapy. This is of particular importance because of the current interest in the use of radiation therapy as an adjunct to less radical breast surgery, or as the only therapy, for a substantial number of breast cancer patients (1). Many breast cancer patients and particularly those with minimal disease have a good prognosis, making the quantification of any long-term deleterious effects of radiation or other therapies of particular concern.

PREVIOUS RESEARCH

There have been many studies of the occurrence of subsequent cancers for patients with various first cancers. Some studies have included an assessment of second breast cancer risk following a first breast cancer and have indicated that second breast cancers occur from two to six times as frequently as would be expected (2-8). The relative risk of second breast cancers has been found to be larger for younger first breast cancer patients than for older patients (3, 4, 7). The risk of second breast cancers has also been shown to be negatively associated with age at diagnosis of the first cancer; i.e., younger first breast cancer patients have a higher risk than older patients (7).

We could find only one study in the literature of the effect on second breast cancer risk (9) of adjunctive radiation therapy in the treatment of a first breast cancer. Data on a total of only 1,489 patients were analyzed, and not surprisingly no association was found of second breast cancer risk with the use of adjunctive radiotherapy for the first breast cancer. There has, however, been speculation, both pro and con, on the effects of adjunctive radiation therapy on second breast cancer risk based on the exposure of the remaining breast to radiation (*10,11*). Although there is to date little

ABBREVIATIONS USED: CTR=Connecticut Tumor Registry; IDR=incidence density ratio(s); S=surgery; SEER= Surveillance, Epidemiology, and End Results; SIR=standardized incidence ratio(s); S&R=S plus adjunctive radiation.

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TABLE 1.—*SIR (relative risks) for second breast cancers*

Age, yr	Total	Negative nodes				
		Total negative nodes	Length of follow-up			
			0–4 yr	5–9 yr	10–14 yr	≥15 yr
Total	3.2 (1,544/480.6)	2.8 (885/316.6)	3.0 (383/128.7)	3.1 (261/84.5)	2.5 (120/48.5)	2.2 (121/54.9)
						1935–
Total	2.9 (655/223.4)	2.6 (391/148.8)	3.2 (131/40.6)	3.1 (102/32.5)	2.2 (60/26.9)	2.0 (98/48.8)
<45	4.9 (218/44.7)	3.9 (127/32.7)	7.9 (38/4.8)	5.8 (32/5.5)	3.7 (23/5.9)	2.1 (34/16.5)
45–54	3.2 (196/61.9)	2.8 (112/39.3)	5.5 (42/7.7)	3.6 (26/7.3)	1.5 (11/7.3)	1.9 (33/17.0)
≥55	2.1 (241/116.8)	2.0 (152/76.8)	1.8 (51/28.1)	2.2 (44/19.7)	1.9 (26/13.7)	2.0 (31/15.3)
						1960–
Total	3.5 (889/257.2)	2.9 (494/167.8)	2.9 (252/88.1)	3.1 (159/52.0)	2.8 (60/21.6)	3.8 (23/6.1)
<45	7.0 (212/30.4)	5.3 (105/19.8)	6.8 (50/7.3)	5.1 (35/6.9)	2.9 (12/4.1)	5.3 (8/1.5)
45–54	3.9 (258/65.7)	3.1 (124/40.4)	2.7 (52/19.5)	3.7 (48/12.9)	3.0 (18/6.0)	3.0 (6/2.0)
≥55	2.6 (419/161.1)	2.5 (265/107.6)	2.4 (150/61.3)	2.4 (76/32.2)	2.6 (30/11.5)	3.5 (9/2.6)

[a] Values are relative risks (observed No./expected No.).
[b] Patients with distant metastases are not included.

evidence to document the long-term effects of possible radiation exposure of the remaining breast incurred during adjunctive radiation therapy for a first breast cancer, there is evidence that radiotherapy for acute (12) and chronic (13) breast conditions significantly increases the risk of subsequent breast cancer.

There are unknown factors, however, that complicate speculation about the effect on second breast cancer risk of radiotherapy for a first breast cancer. The dose to the opposite breast is not well established and would likely vary according to the procedures and type of equipment used and the areas irradiated. Another important factor is that patients with a first breast cancer may represent a subgroup of women whose breast tissue is particularly prone to carcinogenesis and, therefore, the effects of radiation on the remaining breast might be different (greater) than would otherwise be expected.

DESCRIPTION OF DATA

The ideal setting for doing multiple cancer studies is within a defined population in which the occurrence of cancer is monitored. Such a population is that of the State of Connecticut where the diagnoses of nearly all cancers have been routinely reported to the CTR spanning the time from 1935 to the present. Follow-up of all cancer patients for survival and the diagnosis of subsequent primary cancers is also done by the CTR.

The CTR is one of nine population-based tumor registries that participate in the SEER Program of the National Cancer Institute. The other tumor registries in the SEER Program have not been in existence as long as the CTR, but they do afford the potential of doing multiple primary cancer studies in the future.

Data on 34,922 invasive primary breast cancers diagnosed in women as a first cancer in the State of Connecticut during 1935-75 were available for analysis. The following exclusions were made to the patient group in the order given: unknown age (32); tumor sequence errors, interrecord errors, or unknown follow-up (4); first cancer diagnosed from death certificate or autopsy report (2,054); no follow-up available (58); at least one other primary cancer including breast cancer diagnosed within 2 months of first breast cancer (261); distant metastasis (2,570); unstaged (1,815); and surgery not done (953). Surgery as used here refers to surgery done for the purpose of removing the primary tumor. After these exclusions, 27,175 patients were available for analysis. Limiting the analysis to those patients whose first breast cancer was surgically removed and who had less than distant involvement should have resulted in the analysis of patients who were clinically free of disease subsequent to treatment of their first cancer and, therefore, problems associated with the diagnosis of second primary breast cancers were hopefully minimized.

The second breast cancer experience for eligible patients was assessed through 1980. A second breast cancer was counted only if it was invasive, and it may have been diagnosed when the patient was a nonresident of the state. For the 27,175 patients included in the study, 1,544 invasive second breast cancers were diagnosed. This number included second breast cancers diagnosed on the basis of either a death certificate or an autopsy report.

The pathologic diagnosis of second cancers was done by the various hospital pathologists in the State; it probably resulted in variation in the criteria applied to the diagnosis of second breast tumors. This is a potential problem because the remaining breast is a common metastatic site of a first breast cancer, and the problems of the pathologist in diagnosing a new primary cancer in the remaining breast are well documented (14, 15). In this regard, however, the first and second breast cancers were histologically confirmed for 97.0% of the 1,544 patients who had at least 2 breast tumors. For those 25,521 patients who had only 1 breast tumor. the histologic confirmation rate was 99.6%. The high histologic confirmation rates were largely due to only inclusion of patients in the study who had surgery for the purpose of removing their first breast cancer.

Data on stage of disease at diagnosis and treatment are routinely collected by the CTR. With the use of the stage classification as coded since 1935, it was possible to classify

by calendar period, age, stage, and length of follow-up[a]

Total positive nodes	Positive nodes[b]			
	Length of follow-up			
	0–4 yr	5–9 yr	10–14 yr	≥15 yr
4.0 (659/164.0)	4.9 (408/83.4)	3.3 (134/40.5)	3.4 (70/20.8)	2.4 (47/19.3)
59				
3.5 (264/74.6)	4.8 (140/29.4)	2.8 (46/16.3)	3.1 (36/11.8)	2.5 (42/17.1)
7.6 (91/12.0)	16.1 (53/3.3)	5.0 (13/2.6)	3.8 (9/2.4)	4.3 (16/3.7)
3.7 (84/22.6)	6.5 (45/6.9)	2.5 (11/4.4)	3.7 (14/3.8)	1.9 (14/7.5)
2.2 (89/40.0)	2.2 (42/19.2)	2.4 (22/9.3)	2.3 (13/5.6)	2.0 (12/5.9)
75				
4.4 (395/89.4)	5.0 (268/54.0)	3.6 (88/24.2)	3.8 (34/9.0)	2.3 (5/2.2)
10.1 (107/10.6)	14.8 (74/5.0)	5.6 (19/3.4)	7.6 (13/1.7)	2.0 (1/0.5)
5.3 (134/25.3)	6.7 (96/14.4)	3.6 (26/7.2)	3.1 (9/2.9)	3.8 (3/0.8)
2.9 (154/53.5)	2.8 (98/34.6)	3.2 (43/13.6)	2.7 (12/4.4)	1.1 (1/0.9)

the patients into the following groups: no ipsilateral axillary lymph node metastases, ipsilateral axillary lymph node metastases but no distant metastases, distant metastases, and unknown stage. Data on treatment were limited to that initially given for the purpose of controlling the primary cancer. Treatments administered may have included any one or a combination of the following: surgery, radiotherapy, chemotherapy, hormones, and endocrine radiation and/or endocrine surgery. The areas irradiated, doses of radiation, and the names of drugs were not included in the CTR data base.

STATISTICAL METHODS

One statistic used in the analysis was the SIR or relative risk, which as used here is the ratio of the observed and expected numbers of second breast cancers. The expected number of second breast cancers that should occur in a defined cohort of first breast cancer patients was obtained by application of appropriate age, sex, and calendar year specific breast cancer incidence rates to the person-years at risk (16, 17). Person-years at risk for each patient were the time from diagnosis of the first breast cancer to the date of diagnosis of any second cancer or date of death. Date of last follow-up was used if neither of the latter two events occurred. The primary objective in computation of the SIR was to examine patterns of relative risk by age, stage, length of follow-up, and calendar period.

Incidence densities were also calculated to assess risk patterns. An incidence density is the number of second breast cancers diagnosed subsequent to diagnosis of the first cancer divided by the person-years at risk which accrued (18). The use of incidence densities facilitated the comparison of risks for specific patient groups as well as the utilization of appropriate multivariate procedures. The statistic generally used for comparison purposes is the IDR, i.e., relative risk, which is the ratio of the incidence densities for the 2 patient groups being compared.

RESULTS

Epidemiology

It is of interest from both an epidemiologic and a clinical viewpoint to examine the second breast cancer experience for those patients included in the study in regard to relative risk (SIR) and risk (incidence density) patterns. Table 1 presents SIR by age (<45, 45-54, or >=55 yr), stage of disease (negative nodes or positive nodes, excluding patients with distant metastases), length of follow-up (<5, 5-9, 10-14, or >=15 yr), and calendar period of diagnosis (1935-59 or 1960-75). The relative risks are particularly high overall in the less than 45-year age group—4.9 (1935-59) and 7.0 (1960-75). Those patients in the age group less than 45 years old with positive nodes had relative risks of 7.6 (1935-59) and 10.1 (1960-75) compared to 3.9 (1935-59) and 5.3 (1960-75) for those patients with negative nodes. It can be seen, however, that the relative risks are substantially higher during the 0 to 4-year follow-up period for those patients less than 45 years old at diagnosis of their first breast cancer and who had positive nodes than for the corresponding patients with negative nodes. The effects of node status and length of follow-up on relative risk gradually decrease with increasing age at diagnosis. The relative risks for the total groups in the later calendar period tend to be a little larger than the corresponding relative risks for the 1935–59 calendar period. This elevated risk appears, however, to be a result primarily of differential follow-up because the corresponding relative risks by length of follow-up appear to be quite similar for the two calendar periods. This observation suggests that whatever caused the increase in the first breast cancer risk during the period of study had a similar effect on the second breast cancer risk. The age-adjusted incidence rate for female breast cancer increased from 53 per 100,000 during 1935-39 to 84 per 100,000 during 1970-74 in Connecticut.

Some comment on the magnitude of the relative risks is appropriate. It is important to realize that if the risk factors for primary breast cancer are also operative for the risk of second breast cancers and if the two events occur independently, then it is not surprising that the relative risks are greater than 1.0. Elevated relative risks would occur simply because the distribution of first breast cancer patients over breast cancer risk factors would be skewed toward those patients at higher risk, and these risk factors are not taken into account in the calculation of the expected number of second breast cancers. The strong relationship of relative

TABLE 2.—*Incidence densities (second breast cancers per 100,000 person-years at risk) by calendar period, age, stage, and length of follow-up*[a]

Age, yr	Total	Negative nodes			Positive nodes		
		Total negative nodes	Length of follow-up		Total positive nodes	Length of follow-up	
			0–9 yr	≥10 yr		0–9 yr	≥10 yr
Total	711 (1,544)	637 (885)	650 (644)	603 (241)	843 (659)	881 (542)	702 (117)
1935–59							
Total	601 (655)	560 (391)	582 (233)	532 (158)	674 (264)	696 (186)	626 (78)
<45	696 (218)	604 (127)	695 (70)	521 (57)	882 (91)	1,076 (66)	597 (25)
45–54	609 (196)	569 (112)	682 (68)	453 (44)	673 (84)	712 (56)	606 (28)
≥55	530 (241)	523 (152)	475 (95)	628 (57)	544 (89)	503 (64)	685 (25)
1960–75							
Total	822 (889)	714 (494)	697 (411)	811 (83)	1,013 (395)	1,024 (356)	923 (39)
<45	1,005 (212)	778 (105)	793 (85)	723 (20)	1,406 (107)	1,428 (93)	1,273 (14)
45–54	811 (258)	637 (124)	619 (100)	729 (24)	1,083 (134)	1,125 (122)	786 (12)
≥55	758 (419)	731 (265)	705 (226)	935 (39)	810 (154)	810 (141)	812 (13)

[a] Values are incidence densities (No. of second breast cancers).

risk of second breast cancers to age suggest that the effects of some second breast cancer risk factors may be related to age at diagnosis and stage of the first cancer. Additional data would be required to determine the relationship beteen first and second breast cancer risk factors.

The overall risk of second breast cancers was 711 per 100,000 person-years at risk. Examination of table 2 indicates that the risk of second breast cancers is inversely related to age and directly related to stage of the first cancer during the first 9 years after diagnosis for both calendar periods. For the period 10 years or more after diagnosis, the effect of age and stage on risk appears to be less than during the first 9 years. Also, for each of the two follow-up periods subsequent to diagnosis of the first breast cancer, the corresponding risks of second breast cancers for the various age and stage categories are greater in the later calendar period.

Effect of Adjunctive Radiation

For purposes of this analysis, patients were classified as before by age, stage, length of follow-up, and calendar period of diagnosis as well as by whether or not they had only S or only S&R as their primary treatment. Patients who had other treatments in combination with either S or S&R were excluded. The two calendar periods utilized in the analysis roughly correspond to the use of orthovoltage equipment in administering radiation therapy (1935-59) and to the use of higher voltage equipment (1960-75) (Goldenberg I: Personal communication).

The S group consisted of 19,034 patients, and the S&R group, of 6,690 patients. Table 3 provides information on number of patients, average ages, and average years of follow-up for the various patient subgroups. The average age of the patients within each age and stage category of the S group is very similar to that for the corresponding category in the S&R group. Of interest, however, is the consistently shorter average follow-up for each category in the S&R group as compared to the corresponding category in the S group. This phenomenon suggests that differences

TABLE 3.—*Number of patients, average age at diagnosis of the primary breast cancer, and average years of follow-up for the various cohorts of patients included in the analysis*

Cohort	1935–59			1960–75		
	No. of patients	Average age, yr	Average yr of follow-up	No. of patients	Average age, yr	Average yr of follow-up
S only						
Negative nodes						
<45	1,052	38.7	16.7	1,115	39.2	9.5
45–54	1,087	49.2	15.6	1,797	49.3	8.8
≥55	2,674	67.5	9.7	4,487	69.1	6.9
Positive nodes						
<45	638	39.0	8.4	421	39.5	6.5
45–54	948	49.4	8.2	803	49.8	6.6
≥55	2,068	66.1	6.0	1,944	67.9	5.4
S&R						
Negative nodes						
<45	191	38.5	13.3	217	38.8	7.4
45–54	166	49.6	12.9	369	49.5	7.5
≥55	355	65.5	8.8	714	67.0	6.4
Positive nodes						
<45	392	38.5	8.5	520	39.2	5.8
45–54	502	49.4	7.6	947	49.7	5.7
≥55	751	64.1	5.2	1,566	64.9	4.9

in stage of disease between the 2 treatment groups remained after the patients were classified on the basis of node status.

Estimates of radiation dose to the opposite breast were not made. The dichotomous classification of the patients with respect to treatment implied that the effect of an average dose to the remaining breast was being estimated. At a later date more details on individual radiation treatments may be obtained to supplement this analysis.

That radiation causes breast cancer has been established (19). In considering the effects of radiation on the risk of subsequent cancer in the remaining breast for first breast cancer patients, it is possible that radiation could have acted as a promoter of second breast cancers in addition to being a causative agent; however, radiation has not been found to promote the occurrence of *first* breast cancer (19).

Table 4 presents relative risks (IDR), i.e., the ratio of the incidence density of second breast cancers for the S&R group to that of the S group, by calendar period, age, stage, and length of follow-up. The numerators of each of the two incidence densities for each ratio are also given as some measure of the power for detection of significant departures of the relative risk from 1.0. No discernible pattern in relative risk by age, stage, calendar period, or length of follow-up appears, but the relative risks tend to be greater than 1.0.

As an aid in data summarization, age-adjusted relative risks were calculated independently by stage, calendar period, and interval of follow-up. The multivariate logistic model was used for this purpose and can be defined as log $[P/(1-P)] = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3$, where P is the probability of a second breast cancer within some specified follow-up period (incidence density); the X's are regressor variables defined as $X_1 = 1$ (age 45–54) and $X_1 = 0$ (otherwise), $X_2 = 1$ (age ≥ 55) and $X_2 = 0$ (otherwise), and $X_3 = 1$ (S&R) and $X_3 = 0$ (otherwise); and the β's are coefficients to be estimated from the data. By the regressor variables being defined in this way, i.e., 0 or 1 for the absence or presence of a factor, the quantity exp (β_j) can be interpreted as the ratio of two incidence densities (presence divided by the absence of the factor associated with the variable X_j). Therefore, for X_3 (treatment), $\exp(\beta_3)$ would be an estimate of the ratio of the incidence density for the S&R group to that of the S group adjusted for the other regressor variables if no interactions with treatment are specified in the model. A discussion of logistic models that relates to the analysis done here can be found in (20).

Age-adjusted estimates of relative risk by stage, calendar period, and length of follow-up are given in table 5. For each of the four stage-calendar-period categories, the relative risk is elevated to at least 1.2 during the first follow-up period, and these elevated relative risks are likely due to a confounding effect of stage. The relative risks for 10 years or more of follow-up for those patients diagnosed during 1935-59 are not indicative of any excess long-term risk of second breast cancers associated with the use of radiation therapy for either stage category. For those patients alive 10 years or more after diagnosis and diagnosed during 1960-75, the relative risk for those patients with negative nodes is 1.3 (one-sided $P = 0.25$); for those patients with positive nodes, the relative risk is 1.6 (one-sided $P = 0.11$). A relative risk adjusted for both age and stage was calculated for the 10-

TABLE 4.—*Relative risks (S&R group to that of S group) by time period, stage, age, and length of follow-up*[a]

Age, yr	Grand total	Negative nodes: Total negative nodes	Negative nodes: Length of follow-up 0–4 yr	5–9 yr	10–14 yr	≥15 yr	Positive nodes: Total positive nodes	Positive nodes: Length of follow-up 0–4 yr	5–9 yr	10–14 yr	≥15 yr
					1935–59						
Total	1.2 (128/494)	1.1 (46/331)	1.4 (21/105)	1.0 (11/86)	0.9 (6/52)	0.8 (8/88)	1.2 (82/163)	1.5 (50/81)	0.7 (9/32)	1.2 (12/23)	0.9 (11/27)
<45	1.1 (43/155)	1.2 (17/101)	1.6 (7/27)	0.8 (3/27)	1.8 (4/17)	0.8 (3/30)	0.8 (26/54)	1.0 (17/29)	1.0 (4/7)	0.5 (2/6)	0.4 (3/12)
45–54	1.3 (44/142)	1.2 (14/94)	1.8 (8/33)	2.1 (5/19)	0.8 (1/10)	0.0 (0/32)	1.3 (30/48)	1.5 (19/25)	0.2 (1/8)	1.5 (6/8)	1.3 (4/7)
≥55	1.1 (41/197)	0.9 (15/136)	1.0 (6/45)	0.6 (3/40)	0.3 (1/25)	1.8 (5/26)	1.3 (26/61)	1.5 (14/27)	0.8 (4/17)	1.5 (4/9)	1.9 (4/8)
					1960–75						
Total	1.4 (265/569)	1.2 (73/402)	1.2 (40/203)	1.2 (24/131)	1.5 (8/47)	0.6 (1/21)	1.3 (192/167)	1.4 (139/108)	1.0 (37/42)	2.0 (16/12)	0.0 (0/5)
<45	1.7 (68/116)	1.5 (18/78)	1.3 (9/37)	2.0 (7/24)	1.9 (2/10)	0.0 (0/7)	1.2 (50/38)	1.3 (38/24)	0.6 (6/9)	1.9 (6/4)	0.0 (0/1)
45–54	1.3 (82/159)	0.9 (16/103)	0.7 (6/42)	1.0 (7/41)	1.0 (2/15)	2.0 (1/5)	1.2 (66/56)	1.1 (50/41)	1.5 (13/9)	1.3 (3/3)	0.0 (0/3)
≥55	1.3 (115/294)	1.2 (39/221)	1.3 (25/124)	1.0 (10/66)	1.7 (4/22)	0.0 (0/9)	1.4 (76/73)	1.5 (51/43)	1.0 (18/24)	2.6 (7/5)	0.0 (0/1)

[a] Values are relative risks (No. of second breast cancers in S&R group/No. of second breast cancers in S group).

TABLE 5.—*Age-adjusted relative risks by calendar period, stage, and length of follow-up*[a]

Calendar period	Negative nodes				Positive nodes			
	0–4 yr	5–9 yr	10–14 yr	≥15 yr	0–4 yr	5–9 yr	10–14 yr	≥15 yr
1935–59	1.4 (1.0, 2.1)	1.0 (0.6, 1.7)	0.9 (0.5, 1.9)	0.8 (0.4, 1.4)[b]	1.3 (1.0, 1.8)	0.7 (0.4, 1.3)	1.2 (0.6, 2.1)	0.9 (0.5, 1.6)[b]
1960–75	1.2 (0.9, 1.5)	1.2 (0.8, 1.7)	1.3 (0.7, 2.3)[c]		1.3 (1.1, 1.6)	1.0 (0.7, 1.5)	1.6 (0.9, 2.8)[c]	

[a] Values are relative risks (90% confidence limits). Lengths of follow-up are shown under negative and positive nodes.
[b] Evidence of an interaction between treatment and age ($P < 0.10$) suggests that relative risk for treatment was not constant over age.
[c] This cell represents ≥10 yr.

year or more follow-up period and was found to be 1.4 (one-sided $P = 0.07$).

The age-adjusted relative risks for treatment were estimated under the assumption of a constant relative risk over the 3 age groups. A test of this assumption based on score statistics (Brown C: Personal communication) was performed for each age-adjusted relative risk. For some of the age-adjusted relative risks, there was evidence of an interaction between treatment and age; i.e., the associated P-value for the test of an interaction between treatment and a specific age group was less than or equal to 0.1. It does not appear that consideration of the interactions changes any inference to be made from table 5. No evidence of interactions was found for the relative risks in the later calendar period.

Although the relative risks were not statistically significant, it is of some interest to estimate for those patients diagnosed in the later calendar period the absolute excess risk, i.e., the difference between the risk in the S&R group and that in the S group, associated with the relative risks of 1.3 (negative nodes) and 1.6 (positive nodes) for the 10-year or more follow-up period. With the use of established procedures (21), this was done by multiplication of the incidence density of the appropriate S group in the 10-year or more follow-up period by the age-adjusted relative risk minus 1.0. For the negative-node patients the absolute excess risk was found to be on the order of 200 second breast cancers per 100,000 person-years at risk, and, similarly, for positive-node patients the absolute excess risk was found to be 500. The statistical significance of these estimated absolute excess risks is the same as that associated with the age-adjusted relative risks used in their computation. The corresponding incidence densities for the S group 10 years or more after diagnosis for the later calender period were 789 (negative nodes) and 778 (positive nodes) per 100,000 person-years at risk.

Certain factors must be considered in the interpretation of these observations. Because of criteria generally utilized in selecting a patient for radiation therapy, it is likely that the group of patients with positive nodes who received radiation therapy had more advanced disease, i.e., larger tumors or more positive nodes, for example, than those patients with positive nodes who did not receive radiation therapy. This possibility is indicated to some degree as previously mentioned by a shorter average follow-up in the S&R group as compared to the follow-up in the S group within the various stage, age, and calendar-period categories (table 3). Table 2 indicates that the incidence density of second breast cancers is shown to be related to node status during the first 10 years after diagnosis of the primary cancer, particularly for patients younger than 55 years at diagnosis for the later calendar period. For the 10-year or more follow-up period, the relationship to stage does not appear to be important except for those patients younger than 45 years old and diagnosed during 1960-75.

Although the possibility cannot be ruled out that uncontrolled effects of stage contributed to the somewhat elevated long-term relative risks given in table 5 for patients diagnosed during 1960-75, it is likely that stage was not an important factor in this regard for the following reasons: First, the effect of negative versus positive nodes on the long-term risk of second breast cancers is likely greater than are the effects of differences in stage (extent of disease) by treatment category within the node-negative group and correspondingly within the node-positive group. In that regard, the ratio of the incidence density in table 2 for all patients with positive nodes diagnosed during 1960-75 10 years or more after diagnosis to that for the corresponding patients with negative nodes is 1.1, suggesting that any uncontrolled effect of stage was not a major factor regarding the long-term relative risks for these patients in table 5. Second, the relative risks given in table 4 do not appear to be related to age, and only two of the age-adjusted relative risks given in table 5 were found to be associated with an age-treatment interaction; they were for patients diagnosed during 1935-59. The incidence densities given in table 2 suggest that if stage was influencing the relative risks for treatment, then the younger women should have had higher relative risks (table 4); this situation would have resulted in age-treatment interactions. Third, in calculation of the relative risk of 1.4 for the 10-year or more follow-up period adjusted for both age and stage, neither of these two factors had regression coefficients that even approached statistical significance. Finally, the relative risks in table 5 are elevated in the first follow-up period and then decrease and remain constant (earlier calendar period) or increase 10 years or more after diagnosis (later calendar period). This later calendar-period pattern is not consistent with a decreasing effect of stage on risk during follow-up (table 2). The long-term relative risks for those patients diagnosed during 1935-59 were not elevated, suggesting that an uncontrolled effect of stage did not influence these relative risks. Taken in total. the previous discussion suggests that the elevated long-term relative risks for the later calendar period may well be due to chance but are not likely due to an uncontrolled effect of stage.

Another factor deserving mention in interpreting the relative risks given in table 5 is the likelihood that radiation was used in treatment of disease recurrence in both treatment categories. It is unlikely, however, that patients with

recurrent disease would have survived long enough subsequent to a recurrence such that any second breast cancers caused by radiation therapy for recurrences would have been a confounding factor in this analysis.

DISCUSSION

The observations made regarding the epidemiology of second breast cancers indicate that age at diagnosis, stage, calendar period of diagnosis of the first cancer, and length of follow-up were found to be important factors regarding risk of a second breast cancer (incidence density). The same factors, with the exception of calendar period, were found to affect relative risk (SIR). Prior and Waterhouse (7) made the same observations regarding the negative association between age at diagnosis of a first breast cancer and the risk and relative risk of second breast cancers. They speculated that younger breast cancer patients may represent a genetically more susceptible subgroup of the population. Fraumeni (22) also has made the observation that multiple primary cancers tend to arise at an earlier than usual age, possibly because of genetic predisposition.

The finding of an effect of stage of the first cancer on second breast cancer risk may not be surprising because the originally unaffected breast is a common metastatic site. However, the reasons for the apparent interaction between age and stage of the first breast cancer on second breast cancer risk are not clear (table 2). It would not seem likely that differences in intensity of follow-up by age or problems with diagnosis could explain the substantial differences in risk and relative risk between the older and younger patients who had node involvement associated with their first cancers. It is possible, however, that node involvement for younger first breast cancer patients is somehow related to genetic predisposition.

It is of interest to compare the relative risks (SIR) bv age for these data with those obtained by Prior and Waterhouse (7) in a study of 22,000 first breast cancer patients diagnosed during 1936-64 and registered in the population-based Birmingham Regional Cancer Registry (England). After exclusion of simultaneous tumors, the reported relative risks (SIR) by age were 5.3 (<45 yr), 3.0 (45-59), and 1.0 (≥60), with 2.4 overall. For the data presented here, the relative risks by age for those patients diagnosed during 1935-59 were 4.9 (<45 yr), 3.2 (45-54), and 2.1 (≥55), with 2.9 overall (table 1). There is possibly some difference for the older patients, but otherwise the relative risks are quite similar.

Our findings concerning the effects of adjunctive radiation therapy on second breast cancer risk are not consistent for the two calendar-year cohorts of first breast cancer patients analyzed; however, a marginally statistically significant long-term relative risk (≥10 yr after diagnosis) of 1.4 was observed for patients diagnosed during the 1960-75 calendar period. It is of some interest to speculate on the dose to the opposite breast that would account for a relative risk of this magnitude. The best estimate of the percent increase in relative risk per rad for women over the age of 20 years at the time of exposure is 0.42% per rad (23). Thus a relative risk of 1.4 would be associated with an average dose to the opposite breast for all patients who received adjunctive radiation therapy of about 100 rad, and this appears to be within the range of possible exposure (24) with the assumption that radiation affects the long-term risk of second breast cancers in the same way as it affects the risk of first breast cancers.

The observations concerning treatment effects, particularly for those patients diagnosed in the later calendar period, could possibly be further refined by an appropriately designed case-control study in which additional information could be collected on stage of the first breast cancer, type of radiation equipment and procedures used, areas irradiated, and dosages of radiation given. With such information, estimates of the dose of radiation received by the remaining breast might be possible for individual patients. Such a study might provide additional insight into the effect on the long-term risk for a second breast cancer resulting from radiation dose received by the opposite breast during adjunctive radiation therapy for a first breast cancer.

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