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CLINICAL INVESTIGATION **Breast**

NONBREAST SECOND MALIGNANCIES AFTER TREATMENT OF PRIMARY BREAST CANCER

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Purpose: To determine the incidence and risk factors for nonbreast second malignancies (NBSMs) in women after treatment for primary breast cancer.

Methods and Materials: Between January 1985 and December 1995, a total of 1,084 breast cancer patients were analyzed for NBSMs. Detailed analysis was carried out for age, family history, disease stage, radiation therapy, chemotherapy, hormone therapy, other clinical/pathologic characteristics, and site of NBSMs. The Cox proportional hazard regression model was used to estimate the relative risk of NBSMs.

Results: Median follow-up was 12 years. In total, 33 cases of NBSMs were noted in 29 patients. The overall incidence of NBSM was 3%, and the median time for NBSMs was 7 years. The most common NBSMs were gynecologic (22 patients), gastrointestinal (4 patients), head and neck (3 patients), hematologic (2 patients), lung (1 patient), and thyroid (1 patient). The NBSMs rate at 12 years was 2.4% for both mastectomy and radiation therapy groups. In the subset of patients less than 45 years of age at the time of treatment, the NBSMs rate was 0.7% as compared with 4.6% in patients more than 45 years of age ($p = 0.001$). Statistically significant higher incidences of endometrial and ovarian cancer were seen in patients with hormonal therapy (5.2%) as compared with patients without hormonal therapy (1.8%, $p = 0.002$). Women with a family history of breast cancer had a higher incidence (6%) of endometrial and ovarian malignancy compared with women without such a history (2.1%, $p = 0.003$). Chemotherapy did not affect the risk of second malignancy.

Conclusion: The most common NBSMs in this study were gynecologic. Family history of breast cancer was a high risk factor for NBSMs. No risk of NBSMs with radiotherapy was observed.

Second malignancy, Breast cancer, Radiotherapy, Chemotherapy.

INTRODUCTION

Patients with carcinoma of the breast can now survive long enough to be prone to the development of nonbreast second malignancies (NBSMs). Risk factors responsible for such cancers may be genetic (family history), or they may be related to the environment, to behaviors such as alcohol consumption or smoking, or to treatment such as radiotherapy, chemotherapy, or hormone therapy (1, 2). Some NBSMs may be sporadic and thus manifest in a population of patients without a prior cancer diagnosis, and some may be linked to breast cancer diagnosis. It may be that the same environmental or genetic factors that predisposed the patient to primary breast cancer may have also contributed to the development of the NBSM. These factors have been studied thoroughly in regard to the development of primary cancers and should also be looked for in NBSMs. Therefore the purpose of our study was to determine the incidence and risk factors of NBSMs in patients of primary breast cancer treated with surgery, radiotherapy, chemotherapy, and hormonal therapy from a single institution.

METHODS AND MATERIALS

Between January 1985 and December 1995, the records of 1,084 breast cancer patients at the Post Graduate Institute of Medical Education and Research (Chandigarh, India) were analyzed for NBSMs. Eligible patients included women 25 to 76 years of age who underwent mastectomy or CBS (partial mastectomy, segmental mastectomy, lumpectomy, quadrantectomy, tylectomy, wedge resection, or excisional biopsy) after their first diagnosis of histologically confirmed breast cancer during this duration. In all the patients a detailed analysis was carried out with respect to age, family history, disease stage, radiation therapy technique, dose, the use of chemotherapy or hormone therapy, and other clinical and/or pathologic characteristics in December 2005. Family history of the cancer patient was obtained from medical records and family members. Breast cancer occurrence in the first-degree relatives was considered affirmative for family history of breast cancer. Second malignancies included all first cancers occurring after treatment of the primary breast cancer except basal cell or squamous cell carcinoma of the skin and carcinoma *in situ* of the cervix. Any patient identified as having developed NBSM was recorded as such. The site and date of diagnosis of

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NBSM was then confirmed on the basis of anatomic pathology reports. Clinical examinations were the source of incidence data. Clinical and pathologic features of the new lesions were compared with those of the initial breast primary to rule out metastatic lesions. The NBSMs were subdivided into soft tissue, lung, head-and-neck, gastrointestinal, gynecologic, genitourinary, or other site of origin.

Mastectomy was performed in 949 (87%) patients and 135 (13%) patients underwent CBS (Table 1). Postoperative radiation was given to 959 patients (88%) as 35 Gy/40 Gy/15 fractions over the course of 3 weeks. We follow the Manchester shorter fractionation schedule (3) of 35 Gy to the chest wall and 40 Gy to axilla and supraclavicular region. Axillary node–positive patients and some axillary lymph node–negative patients with T3 tumors or when axillary status unknown or when there was incomplete axillary dissection such patients were also given radiation to axilla and supraclavicular region. The anterior photon field was used to deliver radiation to the supraclavicular, infraclavicular, axillary, and internal mammary nodes. Two tangential opposed fields were used to irradiate the chest wall. The borders for chest wall radiotherapy were the anterior midline (medial), the mid-axillary line (laterally), the inframammary fold (inferior),, and the bottom of the head of the clavicle (superior). The supraclavicular, infraclavicular, and high axillary lymph nodes were treated with an anterior photon field; the inferior portion of this field was matched to the superior edge of the tangent fields. The head of the humerus was also shielded from the radiation beam. Internal mammary nodes were irradiated with a separate 12×6-cm field in 144 patients (13.5%). The dose delivered was 40 Gy in 15 fractions over 3 weeks. Treatment was given using ^{60}Co units or a 4-MV linear accelerator. Doses were prescribed at the mid point of the central axis.

Two chemotherapy regimens used. The first regimen, FAC, consisted of 5-fluorouracil 600 mg/m^2, adriamycin 50 mg/m^2, and cyclophosphamide 600 mg/m^2 and was administered to 131 patients (12%). The second regimen, CMF, consisted of cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, and 5-fluorouracil 600 mg/m^2 and was administered to 398 patients (37%). Tamoxifen was given to 735 (68%) patients irrespective of estrogen receptor/progesterone receptor status; the dosage was 20 mg daily for 5 years. The patients were followed at regular intervals and further tested only if they had symptoms or evidence of recurrent disease, contralateral breast cancer and any other cancer. All patients had a clinical examination twice a year for 5 years after the end of treatment, then annually with unilateral or bilateral mammography.

The Cox proportional hazard regression model was used to estimate the relative risk (RR) of NBSMs with adjustment for confounders, including age, family history, menopausal status, histologic type, RT, chemotherapy, and hormonal therapy. All tests for statistical significance were performed using the Chi-square method for categorical variables. All reported p values are two sided and are considered statistically significant at values of <0.05.

Table 1. Patient and treatment characteristics in study patients

Characteristic	No. of patients (%)
Age (y)	
≤45	548 (51)
>45	536 (49)
Menopausal status	
Premenopausal	547 (51)
Postmenopausal	537 (49)
Family history of breast cancer	
Positive	32 (3)
Negative	1052 (97)
Surgery	
TMAC	467 (43)
SM	294 (27)
MRM + AC	188 (17)
CBS	135 (13)
Histologic type	
Ductal	1009 (93)
Lobular	44 (4)
Medullary	22 (2)
Papillary	9 (1)
Radiotherapy	
Tangent	815 (75)
Tangent + Internal mammary	144 (13)
No	125 (12)
Chemotherapy	
CMF	398 (37)
FAC	131 (12)
Not received	555 (51)
Tamoxifen	
Yes	735 (68)
No	349 (32)

Abbreviations: CMF = cyclophosphamide, methotrexate, 5-fluorouracil; FAC, 5-Fluorouracil, adriamycin, cyclophosphamide; MRM + AC = modified radical mastectomy with axillary clearance; SM = simple mastectomy; TMAC = total mastectomy with axillary clearance.

RESULTS

The median follow-up was 12 years (up to December 2005). At the end of the study period, 15% of patients were lost to follow-up, 6% at 5 years and 9% at 10 years. Of 1,084 patients, 222 were dead and 764 were alive. Among the 1,084 patients, 29 developed NBSMs, with a total 33 NBSMs observed. The 12-year rate of any second malignancy was 5.3% and the NBSM rate was 3%. The median time for the development of NBSMs was 7 years. The most common NBSMs were gynecologic (22 patients), followed by gastrointestinal (4 patients), head and neck (3 patients), hematologic (2 patients), thyroid (1 patient), and lung (1 patient) (Table 2). Of 1,084 patients, 32 (3%) had positive family history of breast cancer. Among the 29 patients with NBSMs, 7 (24%) patients had a family history of breast cancer. All (100%) developed NBSMs, 3 (43%) patients in the ovary, 2 (28.5%) patients endometrial and gastrointestinal (28.5%) in the cecum respectively. Three patients developed triple malignancies. All 3 patients had bilateral breast malignancies with carcinomas of cecum, ovary, and endometrium respectively, as well as a positive family history of breast cancer.

The NBSM rate at 12 years was 2.4% for both mastectomy and RT groups (p = 0.4). In the subset of patients aged 45 years or less at the time of treatment, the NBSM rate at 12 years was 0.7% as compared with 4.6% in patients aged more than 45 years (p = 0.001). Patients older than 45 years had higher chances of developing ovarian (RR = 2.03; 95% CI = 1.02–8.09; p = 0.027) and endometrial cancers (RR = 3.06; 95% CI = 1.09–12.12; p = 0.023), and patients 45 years or less had a high risk of developing cervical cancer. Six patients developed cervical cancer; and all 45 years of age or less. The median time to the development of cervical cancer