BREAST CANCER AFTER MANTLE IRRADIATION FOR HODGKIN’S DISEASE: CORRELATION OF CLINICAL, PATHOLOGIC, AND MOLECULAR FEATURES INCLUDING LOSS OF HETEROZYGOSITY AT BRCA1 AND BRCA2

DAVID K. GAFFNEY, M.D., PH.D.,* JOHN HEMMERSMEIER, B.S.,* JOSEPH HOLDEN, M.D., PH.D.,† JAY MARSHALL, M.D.,‡ LYNN M. SMITH, M.D.,* VILIJA AVIZONIS, M.D.,‡ THAO TRAN,§ AND SUSAN L. NEUHAUSEN, PH.D.§

Departments of *Radiation Oncology, †Pathology, and §Medical Informatics, University of Utah, Salt Lake City, UT; ‡Department of Radiation Medicine, Latter Day Saints Hospital, Salt Lake City, UT

Purpose: Hodgkin’s disease patients who receive mantle irradiation have an age-dependent increased risk of developing breast cancer. To determine if genetic factors predispose these patients to develop breast cancer, we evaluated breast cancer specimens for loss of heterozygosity (LOH) at regions where BRCA1 and BRCA2, two breast cancer tumor suppressor genes, are located. We also evaluated whether breast cancers in patients who were previously treated with radiation have a more aggressive phenotype, and whether the clinical course differed from a sporadic group of breast cancer patients.

Methods and Materials: All females with Hodgkin’s disease who were subsequently diagnosed with breast cancer and for whom tissue blocks were available were included. Using a case–control design, case patients (previously treated with radiation therapy) were matched with sporadic breast cancer patients for age, breast cancer stage, and date of breast cancer diagnosis. After microdissection of tumor and normal tissue from paraffin-embedded tissue blocks, DNA was extracted and samples were examined for LOH at chromosomal segments encompassing BRCA1 and BRCA2. Breast cancer specimens were also evaluated in a blinded fashion for tumor grade and immunoreactivity to estrogen and progesterone receptors, p53, her2-neu, and topoisomerase II alpha. Comparisons were made between the case and control populations using χ2 analysis, and a paired Student’s t test. Survival differences were evaluated using a log–rank test.

Results: From January 1960 to December 1983, 917 patients were diagnosed with Hodgkin’s disease. Twelve patients were subsequently diagnosed with breast cancer and tissue blocks were available on 10 cases. No statistical difference was observed between the case and control populations for LOH at BRCA1 or BRCA2. In the Hodgkin’s disease group, LOH was observed in 30% of tumors at BRCA1 and 10% of tumors at BRCA2 vs. 10% and 0% of tumors in the control group at BRCA1 and BRCA2, respectively. Breast tumors from patients who received radiation therapy for Hodgkin’s disease displayed greater nuclear pleomorphism (p < 0.02), and an increase in topoisomerase II alpha expression (p < 0.05) vs. the control population. Five of 10 patients were pregnant at the time of their Hodgkin’s treatment, and those patients had a shorter time interval to the development of breast cancer compared with the patients who were not pregnant (12.4 years compared with 18.6 years). There was no significant difference in disease-free survival; however, overall survival was inferior in the population previously treated with radiation therapy for Hodgkin’s disease (p = 0.01). 80% of patients with a previous Hodgkin’s diagnosis died of breast cancer or treatment related effects vs. 30% in the control group.

Conclusion: We were unable to find statistical evidence for LOH at BRCA1 and BRCA2 in breast cancers from patients previously irradiated for Hodgkin’s disease. Breast cancer diagnosed after mantle irradiation may be more biologically aggressive based on the greater nuclear pleomorphism and increase in topoisomerase II alpha staining. This did not translate into a statistical difference in breast cancer disease-free survival; however, overall survival was significantly inferior in the Hodgkin’s disease patients. © 2001 Elsevier Science Inc.

Breast cancer, Hodgkin’s disease, BRCA1, BRCA2, Radiation, Carcinogenesis.

INTRODUCTION

Radiation is a well-described risk factor in breast carcinogenesis (1). A dose-dependent increase in the incidence of breast cancer in the contralateral breast has been described for women who undergo radiation at age less than 45 years and are followed for at least 10 years (2). Patients who are treated for Hodgkin’s disease have a marked increase in secondary malignancies (3–16). The risk of breast cancer after mantle irradiation is highly dependent on age at the
time of treatment. Females at the greatest risk are those exposed to irradiation at the time of puberty (4, 5, 9, 11). By the time Hodgkin’s patients reach 30 years of age, the relative risk for breast cancer approaches that of the normal population (4, 9). The Late Effects Study Group estimated a cumulative probability of breast cancer of 35% at 40 years of age in a large cohort of patients with a median age of 11 years at time of treatment for Hodgkin’s disease (8). Total radiation dose has been associated with an increased risk for breast carcinogenesis. Bhatia et al. reported on a series of pediatric Hodgkin’s disease patients, in which patients who received a higher dose of mantle radiation (median, 4000 cGy) had a higher risk for breast cancer compared to those who received lower radiation doses (median, 2000 cGy) (8).

In patients who had previously been treated for Hodgkin’s disease, Yahalom et al. described the more frequent development of breast cancer in the medial portion of the breast which receives a greater radiation dose compared with patients with sporadic breast cancer (3).

Previous studies have demonstrated that mutations in the breast cancer tumor suppressor genes, BRCA1 and BRCA2, increase the susceptibility to ionizing radiation (17, 18). BRCA2 mutant cells have increased radiation sensitivity and diminished capacity to repair double strand breaks (18, 19). Decreased expression of BRCA1 has been found to occur at the transition from carcinoma-in-situ to invasive breast cancer, and inhibition of BRCA1 expression with antisense oligonucleotides produces accelerated growth of normal and malignant mammary cells (20). The protein products of BRCA1 and BRCA2 have been shown to interact with the DNA repair protein rad51 (17, 18). Kinzler and Vogelstein have therefore suggested that these genes may be involved in the stability of the genome (21).

Germ-line mutations in BRCA1 and BRCA2 predispose carriers to early onset breast cancer. The majority of tumors from affected carriers demonstrate loss of heterozygosity (LOH) of the normal allele (22). The chromosomal regions of BRCA1 and BRCA2 display LOH in 25–56% of sporadic breast tumors, whereas somatic mutations of BRCA1 or BRCA2 in sporadic breast tumors is a rare event with a frequency of 0–9% (23–28). These data suggest separate pathways in breast carcinogenesis for sporadic tumors compared with those patients who harbor a germ-line mutation (28).

Little is known about the molecular pathogenesis of breast cancer in women treated with irradiation for Hodgkin’s disease. Various hypotheses include a genetic defect, which may predispose patients to multiple secondary malignancies and/or an immunologic defect from Hodgkin’s disease or its treatment may aid in the propagation of a malignant phenotype (1, 11). We hypothesized that somatic mutations in BRCA1 or BRCA2 may increase the risk for breast cancer after irradiation for Hodgkin’s disease due to the diminished capacity for altered cells to repair DNA double strand breaks. To further investigate this, we evaluated LOH at BRCA1 and BRCA2. We also examined the molecular phenotype of breast cancer in these patients compared with a control population matched for stage, age at diagnosis, and date of birth.

METHODS AND MATERIALS

Patient characteristics

All patients who were diagnosed with Hodgkin’s disease and underwent mantle irradiation and subsequently developed breast cancer for whom paraffin-embedded blocks were available were included in this study. From January 1960 to December 1983, 917 patients were diagnosed with Hodgkin’s disease at two referral hospitals (452 patients at Latter Day Saints [LDS] Hospital and 465 patients at the University of Utah Health Sciences Center). Twelve patients were identified who fulfilled the criteria, and tissue blocks were available in 10 cases. Each case was matched with a control from the same hospital within 2 years of date of birth, age at diagnosis of breast cancer within 2 years, and stage of breast cancer. The clinical course of the patients was obtained from the medical record. Institutional review board approval for this study was obtained at each hospital.

Immunohistochemistry

All slides were reviewed to confirm the diagnosis of breast cancer and assigned a modified Bloom–Richardson score (29). The grading of the tumors and the interpretation of immunohistochemical stains was performed in a blinded fashion by a pathologist with expertise in breast carcinomas. The source of the chemicals and antibodies used were previously described (30). Antibodies against p53 (clone D07) were obtained from DAYCO, Carpinteria, California. The c-erbB2 monoclonal antibody which recognizes the carboxy terminus of the protein was used to identify Her2-neu (Oncogene Science, Cambridge, MA). Immunohistochemical staining of histologic specimens has been previously described (30). Slides were deparaffinized and heated (except for Her2-neu, which does not require the heating step) in 10 millimolar sodium citrate (pH 6.0) for 30 min in a microwave oven. After cooling, immunohistochemical staining was performed with a secondary mouse anti-immunoglobulin linked to biotin following incubation with streptavidin linked to horseradish peroxidase. Color development was accomplished with diaminobenzidine as the chromogen. The dilutions of the antibody used in immunohistochemical staining were as follows: topoisomerase II alpha, 1:500; estrogen and progesterone receptors, 1:60; Her2-neu, 1:800; and p53, 1:80. Topoisomerase II alpha was expressed as an index or as a percentage of positive staining cells. At least 500 tumor cells were counted and the number of positive stain cells was determined. Evaluation of p53 expression was performed in a similar fashion. Neoplasms that contained greater than 20% p53 positivity were interpreted as positive for p53 missense mutation and those that contained 20% or less were interpreted as negative for a p53 mutation. This interpretation
was based on previous data indicating a high correlation between a missense mutation in the p53 gene and the observation of positive p53 staining in at least 20% of the tumor cells (31, 32). Tumor cells not containing p53 proteins due to either a deletion or a nonsense mutation would not be detected in our evaluation. Overexpression of Her2-neu was described by noting any distinct membrane staining of the tumor cells as described (33). Positive staining for Her2-neu is similar to 3+ staining commonly reported. Hormone receptor staining was interpreted as positive if nuclear staining was observed in greater than 20% of the cells and negative when 20% or less of the cells shows positive staining (30).

Loss of heterozygosity

LOH was performed as previously described (22). Samples of tumor and adjacent normal tissue were microdissected by the pathologist from surgical material previously embedded in paraffin blocks. Five-μm sections from one or more blocks from each case were placed on glass slides and stained with hematoxylin and eosin without coverslips for histologic evaluation. Small fragments of tissue with either tumor cells or normal cells were removed and placed into 0.2 mL buffer containing 10 mMTris-HCl (pH 8.3), 50 mM KCl, 2.5 mM MgCl2, 0.45% Tween 20, 0.5 mg/mL proteinase K, and 0.0025 mL 100 X BSA (22). Samples were incubated for 8 h at 55°C and then boiled for 10 min. Four μL were used in subsequent PCR reactions. In order from centromere to telomere, the polymorphic short tandem repeat markers (STRs) used for examining LOH on 17q at D17s1699, D17s171, and D17s310. PCR reactions were performed in a 10-μL volume with 35 ng of each oligonucleotide primer, 0.25 unit TaqI polymerase, 200 μM concentrations each of dGTP, dATP, and dTTP and 5 μM dCTP, with 0.5 μCi 32P, in a standard PCR buffer. Samples were amplified for 35 cycles of 5 s at 94°C, 5 s at 55°C, and 10 s at 72°C. Products were electrophoresed in 6% denaturing polyacrylamide gels. Alleles were detected after autoradiography by exposure to Kodak X-OMAT film for 1–24 h. LOH was scored as a decrease in intensity of one allele relative to the other as determined for comparison of paired tumor and normal DNAs. At least two assays were performed for each marker. LOH was defined as clear loss of one allele in multiple markers without retention of the intervening chromosomal segment in other microsatellite markers.

Statistics

Disease-free and overall survival of breast cancer patients and controls were analyzed by the Kaplan–Meier method (34). Differences between survival curves were determined by the log–rank test. A paired t test was used to evaluate for differences between cases and controls for tumor grade and immunohistochemical properties. χ2 was used to evaluate differences in LOH at the BRCA1 and BRCA2 loci between cases and controls. Statistics were performed with the use of Graph Pad Prism software (San Diego, Calif.).

RESULTS

Clinical characteristics of breast cancer patients after thoracic irradiation for Hodgkin’s disease

Hodgkin’s disease characteristics are described in Table 1. The 10 cases received treatment for Hodgkin’s disease between 1960 through 1983. Only the patient with Stage III disease received chemotherapy. Five of the 10 patients were pregnant at the time of their diagnosis of Hodgkin’s disease. The mean follow-up interval was 74 months for patients with Hodgkin’s disease and 81 months for control patients.

The breast cancer clinical characteristics of these same patients are shown in Table 2. Three patients had Stage I, 6 Stage II, and 1 Stage IV breast cancer. The patient with Stage IV disease had a neglected breast mass and presented with proptosis and widely metastatic osseous disease. A subareolar or medial location was present in 3 of 7 evaluable case patients and 2 of 10 control patients (not signifi-
cant by $\chi^2$). Additionally, 4 of the 10 patients developed a third malignancy: 2 patients with basal cell skin cancers, 1 with sarcoma of the scapula, and 1 with a contralateral, metachronous breast cancer. The patient who developed the sarcoma of the scapula also developed a follicular thyroid cancer. This patient is alive 11 years after her breast cancer diagnosis. One other patient developed 4 malignancies: Hodgkin’s disease, breast cancer, thyroid cancer, and skin cancer. This patient died of progressive cardiopulmonary failure.

The age of patients when their breast cancer was diagnosed ranged from 31 to 55 years. The latency period from treatment of Hodgkin’s disease to diagnosis of breast cancer was 6–29 years, with a mean of 15.5 years. The mean latency between Hodgkin’s disease, and breast cancer diagnosis was 12.4 years for the 5 patients who were pregnant compared, with 18.6 years for the 5 patients who were not pregnant at the time of their Hodgkin’s disease diagnosis ($p = 0.18$). The shortest latency period between Hodgkin’s disease and breast cancer was 6 years in a women who was 48 years old (Case 6) at the time of her Hodgkin’s diagnosis. The penultimate oldest Hodgkin’s diagnosis was 32 years of age. The 48-year-old patient was not pregnant at the time of her Hodgkin’s diagnosis. If she is removed from the analysis, the mean latency interval in the 4 nonpregnant patients was 21.7 years, which is significantly different from that of the patients who were pregnant at the time of their Hodgkin’s diagnosis ($p = 0.04$, unpaired $t$ test with Welch’s correction for unequal variances).

Pathobiologic results of breast cancers after thoracic irradiation for Hodgkin’s disease

Table 3 demonstrates the pathobiologic characteristics of the breast cancers. There was no overall difference between cases and controls in tumor grade. However, there was a higher extent of nuclear pleomorphism in the case population with six of the case patient’s tumors displaying Grade 3 nuclear pleomorphism compared with one of the controls ($p < 0.05$). In addition, the proliferative marker topoisomerase II alpha had a mean value of 51.9 in the case population vs. 27.3 in the control population ($p < 0.05$). LOH is shown in Fig. 1. Evaluation of LOH demonstrated 3 case patients had LOH at the region encompassing $BRCA1$, and 1 case patient had LOH at the $BRCA2$ region. One control patient had LOH at the $BRCA1$ region. In 30% (30/99) and 37% (35/93) of the evaluations for LOH at $BRCA1$ and $BRCA2$, respectively, the two alleles in the normal tissue were the same. Thus, the marker was uninformative in these instances, as loss can not be seen because of only one allele type present. For 17% (17/99) and 13% (12/93) of the markers for $BRCA1$ and $BRCA2$, respectively, there was insufficient tumor DNA, so that there were no LOH data.

### Table 2. Breast cancer clinical characteristics

<table>
<thead>
<tr>
<th>Patient (no.)</th>
<th>Age at breast cancer</th>
<th>Latency (years)</th>
<th>Breast cancer stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>T size (cm)</th>
<th>No. of positive lymph nodes</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>31</td>
<td>11</td>
<td>IIA</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0.8</td>
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<td>A</td>
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<tr>
<td>2.</td>
<td>42</td>
<td>12</td>
<td>I</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0.1</td>
<td>0</td>
<td>A</td>
</tr>
<tr>
<td>3.</td>
<td>45</td>
<td>13</td>
<td>IIB</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>4.5</td>
<td>11</td>
<td>D, Br ca</td>
</tr>
<tr>
<td>4.</td>
<td>35</td>
<td>22</td>
<td>IIA</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2.0</td>
<td>9</td>
<td>D, Lung</td>
</tr>
<tr>
<td>5.</td>
<td>55</td>
<td>29</td>
<td>IV</td>
<td>4d</td>
<td>3</td>
<td>1</td>
<td>ND</td>
<td>ND</td>
<td>D, Br ca</td>
</tr>
<tr>
<td>6.</td>
<td>54</td>
<td>6</td>
<td>I</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1.8</td>
<td>0</td>
<td>D, Br ca</td>
</tr>
<tr>
<td>7.</td>
<td>38</td>
<td>15</td>
<td>IIA</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>3.5</td>
<td>0</td>
<td>D, Br ca</td>
</tr>
<tr>
<td>8.</td>
<td>43</td>
<td>18</td>
<td>I</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0.7</td>
<td>0</td>
<td>D, Br ca</td>
</tr>
<tr>
<td>9.</td>
<td>34</td>
<td>11</td>
<td>IIA</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2.5</td>
<td>0</td>
<td>D, Heart</td>
</tr>
<tr>
<td>10.</td>
<td>40</td>
<td>18</td>
<td>IIA</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1.7</td>
<td>ND</td>
<td>D, Heart</td>
</tr>
</tbody>
</table>

*Abbreviations: No. = number; T = tumor; N = nodes; M = metastasis; A = alive; D = dead; Br ca = breast cancer.

### Table 3. Breast cancer pathological characteristics

<table>
<thead>
<tr>
<th></th>
<th>Cases no. (%)</th>
<th>Controls no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER</td>
<td>4 (40)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>PR</td>
<td>4 (40)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>P53</td>
<td>3 (30)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Her2-neu</td>
<td>1 (10)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0 (0)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>2</td>
<td>5 (55)</td>
<td>5 (55)</td>
</tr>
<tr>
<td>3</td>
<td>4 (44)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Tubule formation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2</td>
<td>0 (0)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>3</td>
<td>9 (100)</td>
<td>8 (89)</td>
</tr>
<tr>
<td>Nuclear pleomorphism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0 (0)</td>
<td>2 (22)</td>
</tr>
<tr>
<td>2</td>
<td>3 (33)</td>
<td>6 (67)</td>
</tr>
<tr>
<td>3</td>
<td>6 (67)</td>
<td>1 (11)*</td>
</tr>
<tr>
<td>Mitotic score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5 (55)</td>
<td>5 (55)</td>
</tr>
<tr>
<td>2</td>
<td>2 (22)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>3</td>
<td>2 (22)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Topic II index (mean)</td>
<td>51.9</td>
<td>27.3*</td>
</tr>
<tr>
<td>LOH of BRCA 1</td>
<td>3 (30)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>LOH of BRCA 2</td>
<td>1 (10)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

* $p < 0.05$; paired $t$ test evaluation was performed.
One case had microinvasive carcinoma only and therefore could not be scored for tumor grade.
LOH = loss of heterozygosity.
In Fig. 2, disease-free survival between the case study population and the control population is shown. The median disease-free survival time in the 10 case-study patients was 59 months, and the median survival in the control population has not been reached. There was no statistical difference in the survival curves by log–rank analysis. Overall survival is shown in Fig. 3. Breast cancer patients who received irradiation for Hodgkin’s disease had a significantly worse overall survival by log–rank test with a p value of 0.01. The median survival in the case-study population was 104 months vs. 145 months in the control population.

Overall, 8 of the case study patients died, compared with 3 of the control patients. Five of the case-study patients died of breast cancer and 3 died of radiation-induced cardiopulmonary failure. All 3 of the control patients died of breast cancer. Of the 2 patients who died of radiation-induced heart disease, 1 had congestive heart failure, mitral valve dysfunction, cardiomyopathy, coronary artery disease, and pericardial disease. The second patient had esophageal strictures and aortic, mitral, and tricuspid valve disease. She underwent aortic and mitral valve replacement and a tricuspid annuloplasty. Pathologic evaluation demonstrated fibrosis of the aortic and mitral valves. The patient died of congestive heart failure and respiratory failure. The third patient who died of treatment related effects was diagnosed with radiation pleuritis. This patient received 4069 cGy to a mantle field at age 13 years, and 22 years later, developed bilateral breast cancer. She had 9 involved axillary lymph nodes and underwent high-dose chemotherapy and stem cell rescue, and electron irradiation to the right chest wall with 6-MeV electrons. She developed shortness of breath and atypical chest pain. Right heart catheterization yielded pericardial constriction and pulmonary hypertension. She underwent a pericardiectomy and died 30 months later of progressive cardiopulmonary failure.

**DISCUSSION**

The etiology of increased breast cancer risk after irradiation for Hodgkin’s disease is unknown. We hypothesized
that genomic instability may be a central feature, and as such, an increase in LOH at BRCA1 or BRCA2 in breast tumors may be identified. Kinzler and Vogelstein have stated that BRCA1 and BRCA2 may function as a caretaker gene, characterized by multiple mutations required for tumor initiation, a low risk of mutation in sporadic tumors, and a relatively low incidence of cancer in affected carriers (21). In this study, there was no increased elevation of LOH from BRCA1 or BRCA2 compared with the control population. In previous studies, the prevalence of BRCA1 and BRCA2 loss of heterozygosity in sporadic breast cancer cases range from 25% to 56% (23, 24). This small series suggests that inactivation of BRCA1 or BRCA2 is not a required step in breast carcinogenesis after thoracic irradiation for Hodgkin’s disease. Given the small number of case patients (10), all statistical analyses reported should be interpreted cautiously.

It is uncertain if breast cancers from patients who had previously been treated for Hodgkin’s disease are biologically more aggressive compared with sporadic breast cancer. As performed in a blinded analysis by an experienced pathologist, breast cancers from patients who underwent thoracic irradiation demonstrated increased nuclear pleomorphism compared with a matched population. In addition, there was a significant increase in the proliferative marker topoisomerase II alpha. In a multivariate analysis of prognostic factors of 863 breast cancers, topoisomerase II alpha expression was found to have the greatest prognostic value on overall survival second only to nodal status (36). Topoisomerase II alpha is a proliferative marker that is expressed in G1, S, and G2 phases of the cell cycle. This study showed no significant difference between estrogen receptor positivity, progesterone receptor positivity, or p53 or Her2-neu expression in the cases vs. controls. In the series of 37 patients from Yahalom et al., they found no difference in nodal involvement, histologic type, grade, presence of lymphatic reaction, lymphatic invasion and prognosis compared with 935 primary breast cancers (3). Although our study demonstrated a greater proliferative index, as measured by topoisomerase II alpha expression, and greater nuclear pleomorphism compared with a matched control population, additional studies will be required to confirm whether patients who have been previously treated with radiation for Hodgkin’s disease have increased anaplasia of their breast neoplasms compared with sporadic controls.

Second malignancies have been demonstrated to be a significant cause of morbidity and mortality in patients who undergo mantle irradiation for Hodgkin’s disease. In the pediatric population, several reports indicate that after two decades of follow-up, late effects of treatment are the principle cause of mortality (8–13, 15, 16). This study demonstrates in a case–control design that, although breast cancer disease-free survival was not inferior, overall survival was significantly worse for the Hodgkin’s disease population than for the matched-control population. Earlier reports did not demonstrate decreased survival in patients with breast cancer who were previously treated for Hodgkin’s disease; however, more recent reports have documented diminished survival (3, 13). Factors that may influence whether diminished survival is detected include the size of the study, length of follow-up, and age at which the patients are treated for Hodgkin’s disease. Because the induction of breast cancer and radiation-induced heart disease after thoracic irradiation for Hodgkin’s disease is dose dependent, it is plausible that the rate of severe late effects will lessen in the future (1, 8, 37). Advances in the 1980s in the treatment of Hodgkin’s disease that were not practiced previously include lower total doses, decreased dose per fraction, treatment of all fields each day, lower cardiac doses, and use of divergent blocks (12). The still relatively short follow-up in these patients who receive radiotherapy at young ages is concerning, and highlights the importance of following these patients for life.

Several reports have documented the increased risk of a second malignancy after salvage treatment (7, 12). Because these events carry substantial morbidity and potential mortality, this highlights the importance of minimizing any recurrence of Hodgkin’s disease. Also of significant concern is morbidity and mortality secondary to radiation-induced heart disease in patients who require salvage treatment. The prevalence of bilateral breast cancers after treatment for Hodgkin’s disease in different series ranges from 21% to 29% (3, 8, 14). In this series, 2 of 10 patients developed a contralateral breast cancer.

In this report of 10 patients, 5 patients were pregnant at the time of their Hodgkin’s diagnosis. Patient 6 was 48 years old at the time of her Hodgkin’s disease diagnosis. It is plausible that her tumor was not radiation induced because her interval to breast cancer was only 6 years. If Patient 6 is deleted from the analysis, the mean latency interval in the 4 nonpregnant patients was 21.7 years, which is significantly longer than 12.4 years for the patients who were pregnant at the time of their Hodgkin’s diagnosis ($p = 0.04$, unpaired t test with Welch’s correction for unequal variances). It is not certain if a shorter latency period may determine a higher ultimate oncogenic transformation or a more aggressive phenotype. There was no significant correlation between the latency period and the proliferation marker, topoisomerase II alpha. The patients who were pregnant had a mean topoisomerase index of 51.4 compared with 43.8 from the patients who were not pregnant ($p = 0.66$). Additionally, the modified Bloom–Richardson grade was higher in the pregnant patients (mean ± SEM, 8.0 ± 0.7) than the patients who were not pregnant (mean ± SEM, 6.7 ± 0.5; $p = 0.19$). In women who received radiation therapy for postpartum mastitis, lactation or elevated prolactin levels were felt to increase the risk of breast carcinoma (35). The relative risk of breast cancer is highly age dependent after irradiation for Hodgkin’s disease with the highest risk for radiation at the time of puberty (4, 5, 9, 11, 15, 16). It is plausible that hormonally induced hypertrophy and/or hyperplasia of the breast whether at puberty or at pregnancy increases the susceptibility of epithelial breast
cells to radiation-induced damage. Larger studies will be needed to confirm this observation.

With contemporary therapy, the likelihood of cure of Hodgkin’s disease greatly exceeds the risk of late effects (12). Reduction in total doses and dose per fraction as practiced currently for thoracic irradiation of Hodgkin’s disease will likely result in reduced late effects. This study demonstrated that patients who underwent mantle irradiation for Hodgkin’s disease had a worse overall survival compared to a matched-control population. Breast cancers in patients who had been irradiated for Hodgkin’s disease were more proliferatively active, as demonstrated by topoisomerase II alpha expression, and they demonstrated greater nuclear pleomorphism. One-half of the patients who developed a breast cancer after thoracic irradiation for Hodgkin’s disease were pregnant, and a shorter latency period was identified for patients who were pregnant at the time of their Hodgkin’s disease diagnosis. Future studies involving analysis of gene expression between breast cancers in women who have previously been treated for Hodgkin’s disease compared with women with sporadic breast cancer may be also useful in elucidating the etiology of breast cancer after treatment for Hodgkin’s disease. Larger series and prospective studies are warranted to confirm and extend these observations.

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