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HIGH MAMMOGRAPHIC BREAST DENSITY IS INDEPENDENT PREDICTOR OF LOCAL BUT NOT DISTANT RECURRENCE AFTER LUMPECTOMY AND RADIOTHERAPY FOR INVASIVE BREAST CANCER

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Purpose: Biologically meaningful predictors for locoregional recurrence (LRR) in patients undergoing breast-conserving surgery (BCS) and radiotherapy (RT) are lacking. Tissue components, including extracellular matrix, could confer resistance to ionizing radiation. Fibroglandular and extracellular matrix components of breast tissue relative to adipose tissue can be quantified by the mammographic breast density (MBD), the proportion of dense area relative to the total breast area on mammography. We hypothesized that the MBD might be a predictor of LRR after BCS and RT for invasive breast cancer.
Methods and Materials: We conducted a nested case-control study of 136 women with invasive breast cancer who had undergone BCS and RT and had had the MBD ascertained before, or at, diagnosis. Women with known recurrence were matched to women without recurrence by year of diagnosis. The median follow-up was 7.7 years. The percentage of MBD was measured using a computer-based threshold method.
Results: Patients with a high MBD (≥75% density) vs. low (≤25%) were at increased risk of LRR (hazard ratio, 4.30; 95% confidence interval, 0.88–021.0; $p = 0.071$) but not distant recurrence. In addition, we found a complete inverse correlation between high MBD and obesity (body mass index, ≥30 kg/m^2). In a multivariate Cox proportional hazards model, patients with MBD in the greatest quartile were at significantly greater risk of LRR (hazard ratio, 6.6; 95% confidence interval, 1.6–27.7; $p = 0.01$). Obesity without a high MBD also independently predicted for LRR (hazard ratio, 19.3; 95% confidence interval, 4.5–81.7; $p < 0.001$).
Conclusion: The results of our study have shown that a high MBD and obesity are significant independent predictors of LRR after BCS and RT for invasive breast cancer. Additional studies are warranted to validate these findings. **© 2009 Elsevier Inc.**

Breast cancer, Lumpectomy, Radiotherapy, Locoregional recurrence, Mammographic breast density, Obesity, Body mass index.

INTRODUCTION

Radiotherapy (RT) reduces the risk of locoregional recurrence (LRR) by approximately two thirds after lumpectomy for invasive breast cancer (1). However, LRR remains a significant problem months and years after treatment, and robust predictors for identifying patients at increased risk are lacking. Ionizing radiation is known to act on residual cancer cells; however, increasing evidence has indicated that it has important effects on the tumor microenvironment and that the extracellular matrix (ECM) might mediate resistance to treatment (2). The physiologic effects of RT on breast stroma could contribute significantly to reducing or increasing the risk of LRR.

Normal breast tissue is composed of an epithelial cell compartment separated from fibroadipose stroma and ECM regulated by a complex hormonal milieu. Breast tissue that represents mammographic density is thought to be nonadipose fibroglandular tissue whose nature and specific composition is an area of active investigation (3–5). Mammographic breast density (MBD) is one of the strongest known risk factors for the development of breast cancer (6), and the percentage of MBD correlates strongly with risk. Conversely, obesity, which has previously been reported to be associated with a poor prognosis after breast cancer treatment (7, 8), is associated with lower relative amounts of fibroglandular tissue and MBD (9).

We hypothesized that patients with a high MBD represent a subset that might have a biologically and clinically distinct response to RT compared with women with a low MBD. We

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report the results of a nested case-control study that considered the factors, including breast density and obesity, associated with local only or any recurrence after treatment of predominantly early-stage invasive breast cancer.

METHODS AND MATERIALS

Patient population

The institutional review board of the University of California approved this study. The 136 women in this study were a subset of a larger case-control study of women with breast cancer who had developed recurrence and a random sample of women who had not (controls) from the same retrospective cohort of women with breast cancer (10). All women had undergone breast-conserving surgery (BCS) and RT at the University of California, San Francisco, or California Pacific Medical Center for early-stage invasive breast cancer between 1982 and 1998. The MBD was ascertained from a mammogram of the contralateral breast at diagnosis, before treatment. Recurrences were categorized as locoregional (ipsilateral breast, axillary, or supraclavicular nodes) or distant. The controls were interviewed every 18 months to determine disease status and to inquire when they had had their last mammography examination. The population characteristics are listed in Table 1. The median follow-up was 7.7 years.

Case-control selection

In the original larger case-control study (10), patients with known recurrence were matched by year of diagnosis and disease stage to controls. All patients with recurrence with an original diagnosis of an invasive tumor between 1982 and 1998, inclusive, and who had had MBD measurements were included in the study. The original matching consisted of 2 controls for each patient, and a request was made to obtain the original diagnostic mammogram for each patient. All available mammograms were digitized to obtain the mammographic density scores. The present study drew, from the original matched case-control set, those whose local treatment consisted of lumpectomy and RT alone, and all patients had MBD scores from their original diagnostic mammogram. Ten matched sets were formed, using the year of original diagnosis as the indexing variable. We found too few matches by stage and by year; therefore, this criterion was relaxed for the present study. Also, with the passage of time and continued follow-up, some of the original controls developed recurrence. These controls with late recurrence were not included in the present study.

MBD measurements and clinical characteristics

All patients had the MBD measured using a validated computer-based threshold method, as described previously (10, 11). Each craniocaudal screening view of the breast without cancer was first digitized on a Lumisys LumiScan 200 radiographic films digitizer (Kodak, Rochester, NY; 12-bit dynamic range, 100-mm pixel size). This semiautomated, computer-assisted method involves dividing the mammographic image into a distribution of gray values, with darker regions indicative of fat tissue and lighter regions representing dense tissue. The method is based on the interactive selection of two thresholds in the image of a digitized mammogram. One threshold separates the breast image from the background (breast area), and the other identifies the regions that represent radiographically dense tissue (mammographic density). The percentage of MBD was determined by measuring the total area of the breast and number of pixels outlined in the dense regions using dedicated computer software (11). A single radiologist trained in assessing MBD with the University of California, San Francisco, Mammography Density Workstation read all study films.

Women were interviewed within 1 year of their breast cancer diagnosis to determine demographics, breast cancer risk factors, including self-reported height and weight, and adjuvant treatments. Tumor characteristics, including tumor size, axillary node status, tumor grade, and hormone receptor status, were obtained from the hospital tumor registries.

Statistical analysis

We analyzed several factors for an association with LRR, distant recurrence, or any recurrence (Table 1). The variables included in the univariate analysis were age, stage according to the American Joint Committee on Cancer (6th edition), tumor size, number of positive axillary nodes, tumor grade, estrogen receptor status, progesterone receptor status, race/ethnicity, adjuvant chemotherapy, adjuvant hormonal therapy, body mass index (BMI), and MBD. We used a Cox proportional hazard model stratified by year of diagnosis to estimate the hazard ratios (HRs) for recurrence (Table 2). The time at risk was measured separately for each type of recurrence and was equal to the interval to recurrence if a recurrence of the specified type had developed; when no recurrence of the specified type was present, the time at risk was considered equal to the length of follow-up. Patients were considered at risk of a specified type of recurrence even if they had already developed recurrence of a different type. For example, when the failure type was distant recurrence, calculation of the survival time ignored the presence of local or contralateral recurrence. We chose a Cox model for the analyses to account for follow-up time, because some controls had less follow-up time than patients in the matched sets. The factors were first tested univariately, using the stratified Cox model. Those that were significant at $p < 0.10$ were then included in a multivariate model and then removed, one by one, by eliminating each with the greatest p value and retesting with the remaining factors. This was continued until only factors with $p < 0.05$ remained in the multivariate model. Stepwise backward elimination eliminated all predictors except for BMI and MBD. A more detailed analysis of BMI and MBD indicated that these two factors could be used to identify three predictive groups (see Table 3).

RESULTS

In the entire group, at a median follow-up of 7.7 years, 19 LRRs (14%) and 25 distant recurrences (18%) had developed. Of the LRRs, 16 were in-breast and 3 were regional/nodal. (These recurrence rates might be greater than what would be expected in the population of all patients with invasive breast cancer, because only a subset of nonrecurring controls was included in this study.)

On univariate analysis, several factors were significantly associated ($p < 0.05$) with LRR only, including age, tumor grade, hormonal therapy, and obesity (BMI $\geq$30 kg/m^2; Table 1). We found that patients in the greatest MBD quartile (defined as having a percentage of MBD of $\geq$75%) had the greatest HR for LRR relative to those in the lowest quartile (HR, 4.30; 95% confidence interval [CI], 0.88–21.0; p = 0.071). The HR was modestly elevated for those in the middle quartiles (Table 2).

To determine which factors were independently associated with LRR, we performed a stepwise elimination logistic regression analysis of those factors that were significant on