

## ASYMMETRIES IN BREAST CANCER LATERALIZATION AND BOTH AXILLARY LYMPH NODE NUMBER AND METASTATIC INVOLVEMENT

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### ABSTRACT

*Previous studies have demonstrated right or left lateralization of some paired organ cancers and left-sided asymmetry of different lymph nodes. We investigated left-right asymmetry lateralization of breast cancer and distribution of involved/ non-involved axillary lymph nodes following metastatic invasion in patients with breast cancer. One hundred and sixty five women who underwent axillary lymphadenectomy during the study period were included. Right or left axillary nodal regions were removed and sent for pathologic examination. Lymph nodes were palpatorily identified, isolated from fat tissue, counted and macroscopically examined. Pathological examination was performed on formalin fixed specimens. We found left-sided lateralization for breast cancer in this study group. Both total number as well as the number of axillary lymph nodes involved by metastatic breast cancer cells were higher on right side in patients with breast cancer on the right side. Although the mechanism is not known, and further investigation is needed, this phenomenon may be the result of stronger cell-mediated immune activity in the left sides of humans.*

**Keywords:** breast cancer, breast cancer asymmetry, lateralization, lymph node, metastasis

Previous studies have shown a right or left lateralization of paired organ cancers including studies with breast cancer demonstrating higher frequently on the left side than on the right side in females (1-8). This is in contrast to the right-sided lateralization of the head-neck (9), lung (10), kidney (11) and testis (12) cancers. In a large study of a UK cohort involving over a quarter of a million cancer patients, right-sided lateralization was reported for lung, testis, ovarian and kidney cancers while breast cancer demonstrated left-side lateralization (8). In this study, the incidence ratios (left/right) were 0.88 for male lung cancer, 0.86 for female lung cancers, 0.87 for testis cancer, 0.99 for ovarian cancer, 0.86 for ovarian germ cell cancer, 0.96 for male kidney cancer, 0.94 for female kidney cancer, and 1.07 for breast cancer.

Data from human and animal studies have suggested that lymphoid organs have an anatomical asymmetry along the right-left axis in which right-sided lymph nodes are more numerous than left-sided ones (13-15). In patients with gynecologic malignancies, a left-right asymmetry in pelvic lymph node distribution with right-side prevalence for the number of lymph nodes has been reported (16-18). In addition, two recent studies examining left-right asymmetry in pelvic lymph node involvement by metastatic invasion of endometrial, cervical and ovarian cancer found right-side prevalence (17,18).

Because axillary lymphadenectomy is a well-established and widely used procedure for staging and therapeutic decision-making in breast cancers, we aimed (1) to investigate if there is a possible lateralization for breast cancers, (2) to reexamine left–right asymmetry in the distribution of involved and non-involved axillary lymph nodes in patients with breast cancer.

### *MATERIALS AND METHODS*

Patients who underwent systematic axillary lymphadenectomy between January 2000 and May 2007 were identified from the oncologic database of Oncology Department of Medical Faculty, Ataturk University. One hundred and sixty five women were identified, contacted for informed consent, and were included in the study. Details were collected on demography, tumor stage, surgical procedures, lymph node count, metastatic lymph nodes, intra- and post-operative complications, and hospital stay.

During operation, right or left axillary nodal packets were removed and sent for pathologic examination. Lymph nodes were palpatorily identified and isolated from fat tissue, counted and macroscopically examined. Nodes were embedded in paraffin and 5  $\mu$ m sections were cut and stained with hematoxylin and eosin. All specimens were analyzed by one pathologist.

For statistical evaluation, unpaired T-tests (SPSS 11.0 for Windows) were used to test two-sample differences, and tests for two proportions from one group (Microsta program) for hypothesis testing was applied.

### *RESULTS*

Mean patients age was  $48.17 \pm 10.95$ . Of 165 patients, 71 (43%) had right breast cancer and 94 (57%) had left breast cancer ( $z=2.45$ ,  $p<0.01$ ). Menopausal status was determined in 151 patients with 83 (55%) pre-menopausal and 68 (45%) post-menopausal. Among the

83 pre-menopausal patients, 34 (41%) had right breast cancer and 49 (59%) had left breast cancer ( $p<0.05$ ). Among the 68 post-menopausal patients, 33 (49%) had right and 35 (51%) had left side breast cancer. Mean number of dissected lymph nodes was  $12.49 \pm 6.0$  for patients with right-sided breast cancer, and  $10.46 \pm 4.8$  for the left-sided breast cancer patients ( $t=2.33$ ,  $p=0.05$ ). Mean number of axillary lymph nodes with metastases was  $4.76 \pm 5.9$  and  $2.83 \pm 4.0$  for right breast and left breast cancer patients, respectively ( $t=2.37$ ,  $p<0.05$ ).

### *DISCUSSION*

We found a significant left-sided lateralization for breast cancer in the present study which was consistent with analyses performed in previous studies (1-8). In terms of lateralization, breast cancer demonstrates left-side lateralization compared to other paired organ cancers associated with the right sided lateralization (8-12). It has been reported that the breast cancer first occurred more often in the left breast in patients with asynchronous bilateral disease, and patients with simultaneous bilateral disease usually had a larger tumor on the left (2). Because differences in breast size were considered a contributing factor, relative breast volumes were computed from the mammograms of 174 healthy women, and 55% were found to have a larger left breast (2). It has been suggested that the asymmetry of breast carcinoma reflects differences in the sensitivity of the mammary glands to hormonal stimulation, resulting in unequal volumes of tissue at risk to develop carcinoma (2).

In the present study, the menopausal status of patients was important. There was a statistically significant left-sided lateralization in the pre-menopausal patients but not in the post-menopausal patients. This result suggests the possible role of estrogen hormone in the reversed lateralization of breast cancer in comparison to other paired organ cancers. The structural asymmetries of human brain

can also be related to handedness (19,20). Sandson et al. (21) reported the reversed cerebral asymmetry in women with breast cancer. The frontal lobe was wider in the right side of right-handed controls, but it was wider in the left side of the right-handed patients with breast cancer. The occipital lobe was wider in the left side of right-handed controls, but it was wider in the right side of the right-handed patients with breast cancer. They suggest that an intrauterine influence, possibly estrogen hormone (22), could predispose to breast cancer in adulthood based on Geschwind and Galaburda's (23) proposal that variations in intrauterine hormone concentrations can result in atypical cerebral asymmetry.

In the present study, the numbers of axillary lymph nodes were significantly higher in the right side of patients with breast cancer on the right side compared to the left side of patients with breast cancer on the left side. These results are consistent with the recent studies (16-18). In addition, a right-sided prevalence of the external and common iliac lymph nodes was found in 54% of 152 autopsy examinations of individuals who died from causes other than lymphatic organ disorders (13), and modified pelvic lymphadenectomies on 30 cadavers showed that both external iliac and obturator nodes were more prevalent on the right side than on the left (24). Moreover, a right-left asymmetry in nodal distribution with a lateral right prevalence has been reported in a variety of nodal groups (14). A study focusing on lymph nodes found that left-sided axillary lymph nodes were fewer in number but larger in size than the right-sided ones in women with breast cancer (15).

The numbers of axillary lymph nodes involved by metastatic cancer cells were also significantly higher on the right side of patients with breast cancer on the right side compared to the left side of patients with breast cancer on the left side. Borekci et al (17) reported that the numbers of involved external iliac, and hypogastric+obturator

lymph nodes by metastatic cancer cells were significantly higher on the right side than on the left side in patients with endometrial, cervical and ovarian cancers. Also, Dane et al (18) reported right-sided lateralization for ovarian cancer with the number of external iliac and hypogastric+obturator lymph nodes increased on the right in patients with ovarian cancer on the right side and almost equal numbers on the right and left sides in patients with ovarian cancer in their left side. The numbers of lymph nodes involved by metastatic cancer cells were also higher on right side in patients with ovarian cancer of either the right and left sides. These asymmetries in lymph node involvement may result from functional immune asymmetry. Cell-mediated immune hypersensitivity is thought to be stronger in the left side both in human (25) and mice (26). The stronger cell-mediated immune activity in the left sides may be associated with the blocking of the metastatic invasion of cancer cells from gynecologic malignancies in the left body side.

Li et al (27) reported that 14 of 91 patients with ovarian cancer visibly confined to one ovary had positive lymph nodal metastases, and isolated ipsilateral lymph nodal metastases occurred in five patients and isolated contralateral lymph nodal metastases in three patients.

Morphological, biochemical, physiological, and pathological asymmetries at different levels of the neuroendocrine system have been reviewed (28). There are functional asymmetries of adrenal glands (29) and phenotypic and functional characteristics of the cells from lymphoid organs (30). It has even been reported that there is asymmetrical function of a bilateral immune organ, the thymus (31).

Cell mediated hypersensitivity differences between right and left body sides using the tuberculin test with 22 male and 36 healthy female high school students was investigated and the results demonstrated a higher response in the left compared to the right (25). Correspondingly, a similar study in mice using the sheep erythrocytes instead of

tuberculin, replicated this result with higher delayed type hypersensitivity (cell mediated immune hypersensitivity) reaction in the left paw of both left- and right-pawed animals (26). It has also been reported that the intensity of the delayed type hypersensitivity reaction to sheep red blood cells in the front paws of mice depends not only on whether the antigen is injected into the left or right paw but also on the motor asymmetry of the hemispheres. While comparing the delayed type hypersensitivity reaction in the back left and right paw of mice, it was shown that in both right- and left-pawed mice, it was much more pronounced in the left paw than in the right one. They suggested that the intensity of delayed type hypersensitivity reaction in mice may be dependent on the functional asymmetry of regional lymph nodes (32).

In humans, a more frequent appearance of herpes zoster infection was found on the left body side of women, and cell mediated immune hypersensitivity was lower on the involved side than on the noninvolved side of the body in patients with herpes zoster infection (33,34). It has also been reported that there was left-sided lateralization of all immune reactions and diseases in a single left-handed female subject (35).

As a general conclusion, we found a left-sided lateralization of breast cancer and an asymmetry (more on the right side) for numbers of involved or non-involved axillary lymph nodes. A possible mechanism for greater involvement on the right side may be the reported stronger cell-mediated immune activity found in the left side of humans (25). This observation will require further studies for validation.

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