

Lymphoid Infiltration as a Prognostic Variable for Early-Onset Breast Carcinomas¹

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ABSTRACT

Infiltration by lymphoid cells is a common feature of many human tumors, including breast carcinomas, and the degree of infiltration has been suggested to be a measure of the host immune response. Our analyses in a series of 1919 cases of primary ductal and lobular infiltrating breast carcinomas from women with a long-term follow-up revealed: (a) a 16-17% frequency of infiltrated tumors independent of the patient's age at diagnosis; and (b) a strong positive correlation between survival rates and the presence of lymphocytes at the tumor site in patients less than 40 years of age ($P = 0.0002$) but no association with prognosis in patients 40 years of age or older. Multivariate analysis indicated that lymphoid infiltration is independent of other conventional prognostic factors such as nodal status and tumor size in predicting survival. Thus, a possible immune response against the tumor seems to be relevant only in women with early-onset tumors. Because the immune system is functionally maximum in younger years, declining with age, this finding might reflect a difference in the efficiency of the immune system. Alternatively, the biology of these tumors might differ, leading to a difference in immunogenicity.

INTRODUCTION

Although notable improvements have occurred in the last two decades with mammography for early diagnosis and the introduction of adjuvant postsurgical therapy, breast cancer remains one of the major causes of death in women. Histological and immunohistochemical examinations have shown that breast

carcinomas, like many other human tumors, can be infiltrated by lymphoid cells. Breast tumors seem to be immunogenic based on evidence in experimental models, and in human tumors, the degree of infiltration has been suggested to be a measure of the host immune response (1, 2). However, perhaps because the evaluation criteria for tumor infiltrates are not sufficiently standardized to yield reliable and reproducible results in different institutions, the prognostic significance of lymphoid infiltrate at the tumor site and the relative importance of these infiltrates as an indicator of host immune status remain controversial (3-8). Because the immune system is functionally maximum in younger years, declining with age (9-11), lymphoid infiltration may have a different prognostic significance depending upon the age of the patient at diagnosis. We investigated this hypothesis in a series of 1919 cases of primary ductal and lobular infiltrating breast carcinomas from patients with a long-term follow-up.

PATIENTS AND METHODS

A series of 1919 patients operated on during a period from 1968 to 1979 in our institute for primary ductal, lobular, or mixed breast carcinoma were considered. About 40% of the node-positive patients received adjuvant chemotherapy after surgery, whereas all of the node-negative patients did not receive any postsurgical treatment. All patients were treated with chemotherapy or hormonal therapy at the time of relapse.

The diameter of the primary tumor and the axillary nodal status were obtained from histopathological reports. H&E-stained histological slides of each patient included in the retrospective study were reviewed by pathologists for diagnostic reassessment of histotype and graded according to Bloom and Richardson. Lymphoid infiltration was evaluated morphologically on H&E-stained slides selected by the pathologists as most representative of the case. Infiltrates were scored as positive when a dense or moderate cellular infiltration in the stroma surrounding the tumor nests inside the tumor mass was present and were scored as negative when only occasional inflammatory cells were found.

Patients were grouped according to age at diagnosis (group 1, <40 years; group 2, 40-49 years; group 3, ≥ 50 years) and compared for overall survival from the date of surgery as a function of lymphoid infiltration. Only breast cancer deaths were considered as events. The median follow-up was 18 years, during which 886 cases of death from breast cancer were registered. The log-rank method was used to statistically analyze the differences in survival. Multifactorial analysis was carried out using the Cox regression model.

RESULTS

Analysis of the frequency of lymphocyte-infiltrated tumors revealed no significant differences among the three age groups of patients (16, 17, and 16% in group 1, 2, and 3, respectively).

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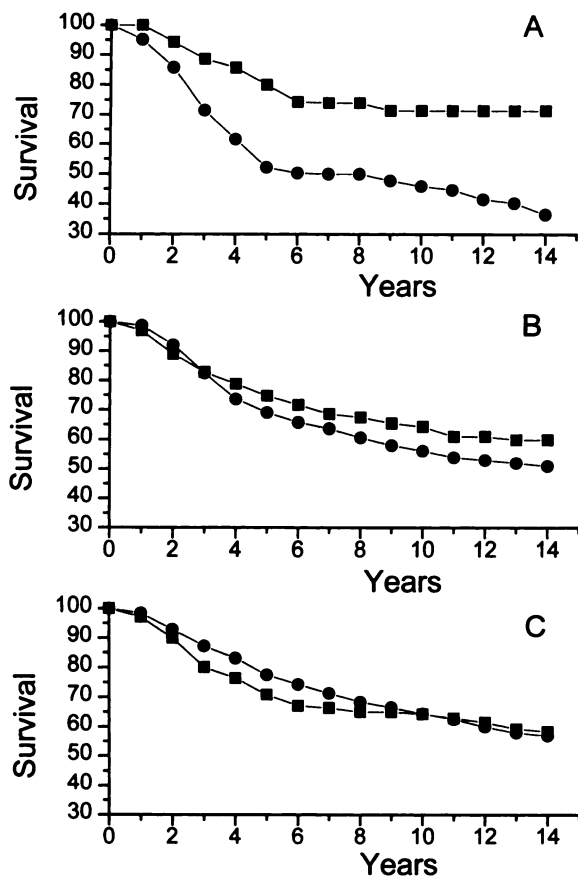


Fig. 1 Impact of lymphoid infiltration on survival in breast cancer patients under 40 years of age (A), 40–49 years of age (B), and 50 years of age or older (C). ■, lymphoid infiltrate-positive cases (A, 35 cases; B, 100 cases; and C, 174 cases); ●, lymphoid infiltrate-negative cases (A, 164 cases; B, 445 cases; and C, 1001 cases).

Survival curves of the 1919 patients divided according to the lymphocytic infiltration overlapped (data not shown). However, analysis within individual age groups revealed a strong positive correlation ($P = 0.0002$) between survival and lymphocytic infiltration at the tumor site in patients less than 40 years of age, a weak association ($P = 0.07$) of infiltration and survival in patients 40–49 years of age, and no association ($P = 0.45$) in patients 50 years of age or older (Fig. 1).

To verify the dependence of the prognostic significance of lymphoid infiltration on other conventional prognostic factors, subgroups of patients diagnosed before 40 years of age were considered according to nodal status, tumor size, and grading. In all of these subgroups, lymphoid infiltration remained a statistically significant prognostic factor for 5-, 10- and 15-year survival (Table 1). Multivariate analysis considering lymphocytic infiltration together with nodal status and tumor size in patients grouped according to age at diagnosis (Table 2) indicated no difference among the three groups in the relative risk associated with nodal positivity and large tumor size, although P was increased in older patients due to differences in the number of cases included in the three groups. By contrast, lymphoid infiltration was significantly associated with prognostic

Table 1 Impact of lymphoid infiltration on survival in early onset breast carcinomas grouped according to conventional prognostic factors

| Group ^a | Lymphoid infiltration | No. of cases | % survival | | | P |
|--------------------|-----------------------|--------------|------------|-------|-------|-------|
| | | | 5-yr | 10-yr | 15-yr | |
| N- | + | 16 | 94 | 88 | 87 | 0.02 |
| N- | - | 57 | 70 | 61 | 54 | |
| N+ | + | 18 | 85 | 61 | 61 | 0.005 |
| N+ | - | 99 | 44 | 33 | 21 | |
| T1 | + | 18 | 89 | 78 | 78 | 0.01 |
| T1 | - | 75 | 61 | 51 | 40 | |
| T2 and T3 | + | 12 | 83 | 67 | 58 | 0.04 |
| T2 and T3 | - | 67 | 45 | 31 | 26 | |
| Grade I and II | + | 13 | 92 | 77 | 77 | 0.03 |
| Grade I and II | - | 82 | 66 | 55 | 41 | |
| Grade III | + | 20 | 75 | 60 | 65 | 0.001 |
| Grade III | - | 60 | 43 | 26 | 21 | |

^a N-, node-negative; N+, node positive. Parameters are not known for node status in 9 cases, tumor size in 27 cases, and grade in 24 cases.

Table 2 Multivariate analysis of the association between survival and nodal status, tumor size, and lymphoid infiltration according to patient age at diagnosis

| Covariate | Patient age (yrs) | | | | | |
|-----------------------|-------------------|----------------------|--------------------|----------------------|------------------|----------------------|
| | <40 ^a | | 40–49 ^b | | >49 ^c | |
| | RR ^d | P ^e | RR | P | RR | P |
| Nodal status | | | | | | |
| - | 1.00 | 2.9×10^{-4} | 1.00 | 2.1×10^{-7} | 1.00 | 1.0×10^{-8} |
| + | 2.32 | | 2.22 | | 2.00 | |
| Tumor size | | | | | | |
| ≤2 | 1.00 | 0.06 | 1.00 | 3×10^{-4} | 1.00 | 2.8×10^{-6} |
| >2 | 1.47 | | 1.64 | | 1.61 | |
| Lymphoid infiltration | | | | | | |
| - | 1.00 | 1.0×10^{-3} | 1.00 | 0.09 | 1.00 | 0.11 |
| + | 2.86 | | 1.35 | | 1.25 | |

^a n = 199.

^b n = 545.

^c n = 1175.

^d RR, relative risk.

^e From one-degree of freedom Cox test.

sis in patients under 40 years of age, with a relative risk of 2.86 independent of the nodal status and the tumor size, whereas no such association was found in older patients.

DISCUSSION

Our data indicate that a possible immune response against the tumor is relevant only in women with early-onset breast tumors. This finding might underlie the discordant data reported regarding the prognostic relevance of lymphoid infiltration in breast carcinomas (3–8). Indeed, depending on the number of young (less than 40 years of age) patients included in the different series, the final conclusions may change considerably.

The fact that lymphocyte infiltration has a prognostic impact only when observed in tumors from young patients might reflect a difference in the biology of these tumors, leading to a difference in immunogenicity. In this context, tumors arising in

young patients were more frequently reported to be positive for expression of *c-erbB-2* and/or p53 oncoproteins (12) that seem to be immunogenic (13, 14). Some of the cases of early-onset tumors with lymphocytic infiltration are likely to be of familial origin and thus might display a peculiar biology and immunogenicity (15, 16). Alternatively, the immune system may be more easily stimulated by tumor antigens in younger patients. However, the finding that the frequency of infiltrated tumors is independent of the age at diagnosis suggests that the defect in older patients is not at the recognition level but instead at the effector level, often leading to an anergic infiltrate with no impact on tumor growth. The immune system has long been known to decline with age, leading to the replacement of virgin T cells by memory T cells and to the accumulation of cells with signal transduction defects (17). The production of interleukin 2 is also decreased, as well as the proliferative response to mitogens (17). Therefore, the immunogenicity of newly presented antigens may be impaired in older patients. The phenotypic characterization of the cells infiltrating the tumors in young and older patients may help us to understand the difference in responsiveness.

From a technical viewpoint, immunohistochemical staining of the infiltrating cells might be developed as a quantitative tool to help standardize the scoring system.

From a clinical perspective, our data suggest that this new criterion not only provides prognostic information for early-onset breast carcinomas, but that it also allows the selection of candidate patients for active immunotherapy because they are immunologically responsive.

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