Original Study

Axillary Lymph Node Involvement in Women With Breast Cancer: Does It Depend on Age?

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Abstract

Introduction: Despite the reduced aggressiveness of breast cancer with older age, elderly patients are diagnosed with larger and more advanced tumors compared with younger patients. We studied the specific relationship between lymph node (LN) involvement and age. **Patients and Methods:** Data were analyzed on 12,152 consecutive breast cancer patients who were operated on between 1995 and 2006 in a single institution. Cubic spline logistic models were used. **Results:** LN involvement was present in 5409 patients (44.5%). Median age was 52 years; median tumor diameter was 1.7 cm; 83.4% had positive estrogen receptors; and 15.3% had human epidermal growth factor receptor (HER)2/*neu* overexpression. At the univariate analysis, the probability of LN involvement decreased with increasing age up to approximately 65 years, but it increased thereafter. However, when investigating the relationship in pT strata, after adjusting for other prognostic factors, we observed no increase of LN involvement probability in elderly patients. **Conclusion:** Increasing risk of LN involvement in the elderly can be explained by delayed diagnosis in this age group. Lack of systematic screening programs for this subpopulation and tendency of the elderly to wait longer before consulting a physician might be blamed. Aging per se does not increase the risk of LN involvement.

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Introduction

Breast carcinoma is the most common tumor among women in most of the developed world. The incidence rates of breast cancer increase with age: approximately 50% of breast carcinomas occur in women ≥ 65 years, and > 30% in women ≥ 70 years.[1]

Despite the reduced aggressiveness of breast cancer with older age, elderly patients are diagnosed with larger and more advanced tumors compared with younger patients.[2-4] Regarding the specific relationship between age and lymph node (LN) involvement and its biologic meaning, there have been conflicting observations: some studies suggested a monotone decreasing risk of LN involvement with increasing age,[5-8] some showed no effect of age,[9,10] and others showed an increased risk in elderly patients.[11,12] With the aim of studying this relationship, we extracted data from our breast cancer database on 12,152 consecutive breast cancer patients operated on between 1995 and 2006 at the European Institute of Oncology (IEO) in Milan, Italy. This study represents the largest series on this subject.

Patients and Methods

From January 1995 to December 2006, 16,027 women were operated on for primary breast cancer at the IEO in Milan. We excluded patients with synchronous distant metastases, bilateral or recurrent tumor, previous cancer, and those receiving primary medical treatment. We then decided to include only patients with complete information on the axillary LN status and with pT1-pT4 tumors. A total of 12,152 patients are included in the current study.

All cases were prospectively entered into the IEO breast cancer database and discussed at the weekly multidisciplinary meeting, which is attended by breast surgery, medical oncology, radiotherapy, and pathology specialists and which results in a proposal for postoperative adjuvant treatments.

Statistical Methods

The relationship between clinical and biologic variables and LN involvement was first evaluated in a univariate analysis using the χ^2 test.

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The functional form of the relationship between age and probability of LN involvement was evaluated fitting univariate and multivariable restricted cubic spline logistic regression models.[13] Cubic splines are smoothly joined, piecewise polynomials of third order. Polynomials are fitted within categories, the extremes of which are defined by knots. Restrictions are placed on the resulting curve to ensure a smooth appearance at the knot points. In our data, 5 knots were specified in the univariate model at ages 35, 45, 55, 60, and 75 years, and 3 knots were specified in the multivariable model at ages 35, 50, and 70 years. Other numbers and knot positions were examined, and the curves were similar. Departure from linearity was evaluated using the Wald test.[14] All statistical analyses were performed using R software (The R Development Core Team 2004; Free Software Foundation, Boston, MA) and SAS software (SAS Institute, Inc., Cary, NC). All reported *P* values were 2-sided.

Results

The main characteristics of the population are shown in Table 1. The median age was 52 years (range, 17-91 years). LN involvement was observed in 5409 patients (44.5%): 1 LN was involved in 2103 patients (17.3%); from 2 to 4 LNs in 1446 patients (11.9%); and ≥ 5 LNs in 1860 patients (15.3%). Furthermore, 78% of the carcinomas were ductal and 10.4% were lobular; 65.1% were pT1; median tumor diameter was 1.7 cm; 83.4% had positive estrogen receptors; and 15.3% had human epidermal growth factor receptor (HER)2/*neu* overexpression. Out of 6743 patients with pN0 tumors, 4882 (72.4%) underwent sentinel node biopsy without axillary dissection.

All features analyzed in Table 1 were strongly associated with LN involvement, except for estrogen receptor status. The association with progesterone receptor was borderline significant. Notably, the probability of LN involvement decreases with age, but it increases slightly in the elderly. This result was confirmed when smoothed functions were used at a univariate level (Figure 1A): the probability of LN involvement decreases with age up to approximately 65 years, but it increases slightly thereafter. Unsurprisingly, we obtained a similar trend for tumor size (Figure 1B): the probability of observing a tumor diameter > 2 cm decreases with age up to approximately 65 years, but it increases thereafter.

Given the high correlation between tumor size and LN involvement, we excluded bias attributable to the confounding effect of tumor size on the relationship between age and LN involvement by setting up a spline logistic regression model stratified by pT, adjusting for tumor size (in mm), estrogen and progesterone receptor status, Ki-67, HER2/*neu*, and vascular invasion (Figure 2). We observed a monotone decreasing probability of LN involvement with increasing age in patients with pT1 tumors (n = 7917). While the linear effect of age was statistically significant, the nonlinear effect was not (ie, we observed a statistically significant decreasing probability of LN involvement with increasing age, in a linear fashion). Regarding tumors staged as pT2 (n = 3753) and pT3/pT4 (n = 482), we observed higher probability of LN involvement compared with pT1 tumors, but we did not detect any statistically significant relationship between age and LN involvement.

Table 1 Patient Characteristics and Stratification for Axillary Lymph Node Status

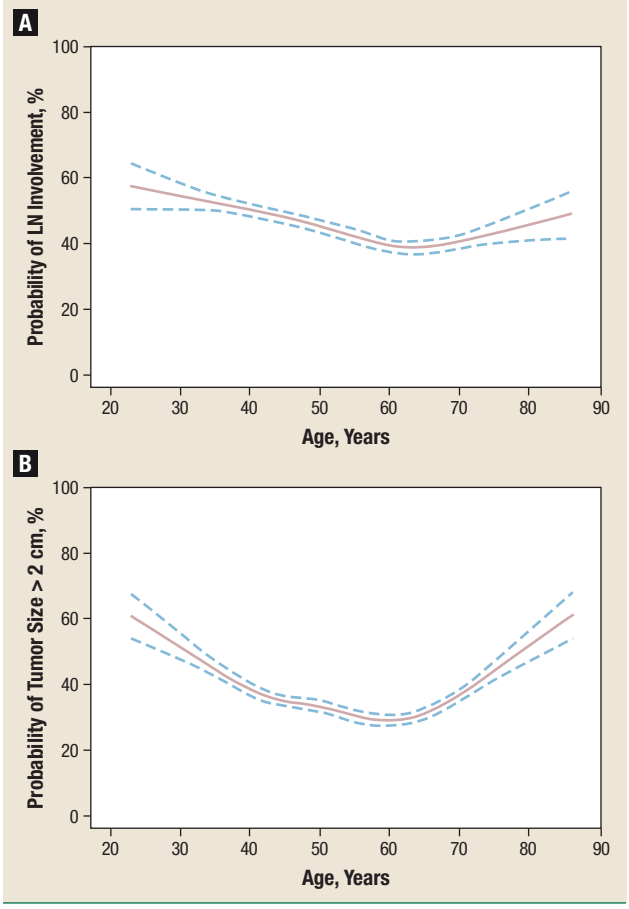
Characteristic	Total, n (%)	Positive Axillary Lymph Node, n (%)	Univariate *P* Value[a]
Number of Patients	12,152	5409 (44.5)	
Age			
< 35 years	525 (4.3)	275 (52.4)	< .001
35-49 years	4526 (37.2)	2216 (49)	
50-64 years	4902 (40.3)	2039 (41.6)	
65-74 years	1878 (15.5)	736 (39.2)	
≥ 75 years	321 (2.6)	143 (44.6)	
pT			
pT1	7917 (65.1)	2683 (33.9)	< .001
pT2	3753 (30.9)	2334 (62.2)	
pT3	410 (3.4)	329 (80.2)	
pT4	72 (0.6)	63 (87.5)	
Histotype			
Ductal	9477 (78)	4382 (46.2)	< .001 (.007)[b]
Lobular	1268 (10.4)	535 (42.2)	
Mixed	428 (3.5)	280 (49.6)	
Other	979 (8.1)	979 (28.6)	
Estrogen Receptors			
Negative	1997 (16.6)	857 (42.9)	.101
Positive	10,006 (83.4)	4494 (44.9)	
Progesterone Receptors			
Negative	4223 (35.2)	1832 (43.4)	.049
Positive	7774 (64.8)	3518 (45.3)	
Grading			
Grade 1	2243 (19.5)	581 (25.9)	< .001
Grade 2	5369 (46.6)	2482 (46.2)	
Grade 3	3899 (33.9)	2068 (53)	
Ki-67			
< 20%	5839 (49.0)	2183 (37.4)	< .001
≥ 20%	6087 (51)	3136 (51.5)	
HER2/*neu*			
Overexpressed	1595 (15.3)	825 (51.7)	< .001
Not overexpressed	8851 (84.7)	3712 (41.9)	
Vascular Invasion			
Present	3258 (27)	2483 (76.2)	< .001
Absent	8808 (73)	2887 (32.8)	

In some cases, the sum does not add up to the total because of missing values.
[a]Associations between axillary lymph node status and other clinicopathologic features are tested using the χ^2 test.
[b]Only ductal and lobular histotypes are compared.

Discussion

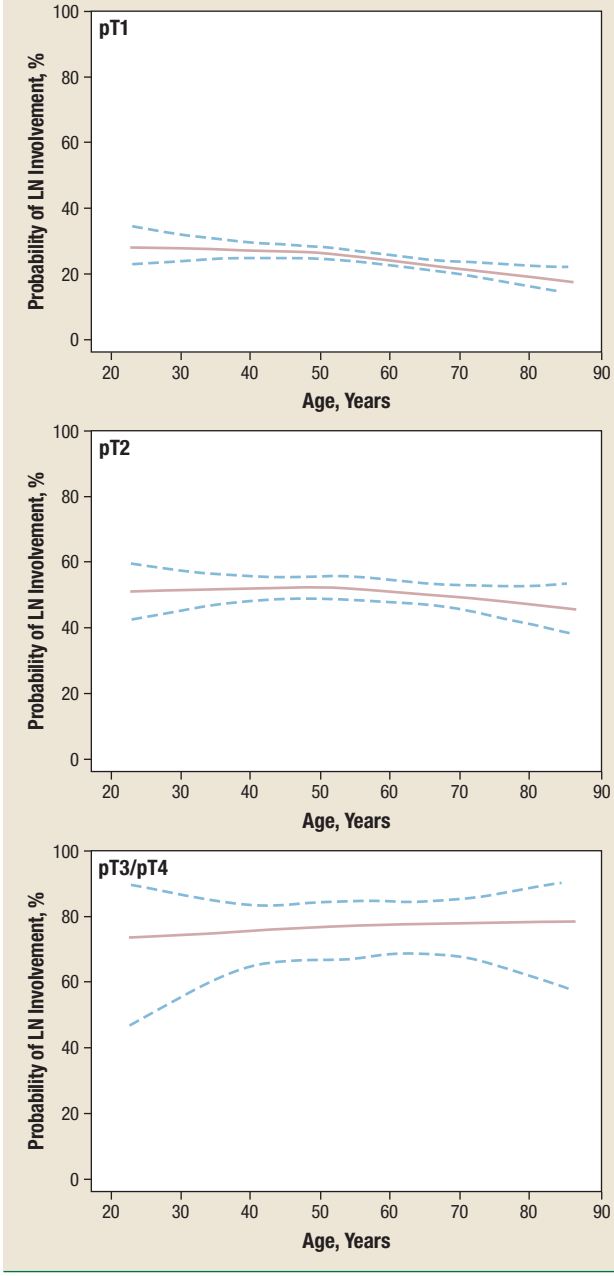
This study investigated the relation between LN involvement and age in a monoinstitutional series of 12,152 breast cancer patients. Univariate analysis showed that the probability of LN involvement decreased with age up to approximately 65 years, but it increased slightly thereafter. However, we observed no increase of

Figure 1 Relationship Between Age and Probability of (A) Lymph Node Involvement and (B) Tumor Size Greater Than 2 cm



The relationship is modeled by a cubic spline (continuous line) with 5 knots, unadjusted for other prognostic factors. Model-based 95% confidence interval is reported (dashed lines).
Abbreviation: LN = lymph node

Figure 2 Relationship Between Age and Probability of Lymph Node Involvement, Stratified by pT Status



The relationship is modeled by a cubic spline (continuous line) with 3 knots. Model-based 95% confidence interval is reported (dashed lines). The model is adjusted for tumor size (in mm); estrogen and progesterone receptor status; degree of Ki-67 expression; HER2/*neu*; and vascular invasion. Predicted probabilities are computed with covariates set to median values.
Abbreviation: LN = lymph node

LN involvement probability in the elderly patients at the multivariable analysis stratified by pT, suggesting that advancing age does not increase the risk of LN involvement by itself.

Interestingly, a recent study by Wildiers et al[11] observed that the probability of LN involvement decreases with age but increases after age 70, even after adjusting for tumor size and other factors. This result was based on a series of 2227 patients who underwent operation in a single institution between 2000 and 2005. Their series and ours were similar in terms of patient characteristics, but the statistical analyses used were not. We investigated the relationship in pT stage strata using nonparametric smooth functions, whereas Wildiers et al applied a linear piecewise function with a break at age 70 to the entire set of patients, on the basis of the results of their univariate analysis. To explain their observations, they hypothesized that the nonlinear relationship between LN involvement and age could reflect the alteration of immune defense mechanisms in elderly individuals, resulting in a decreased defense against nodal invasion.

In contrast to these findings, we observed no increase of LN involvement probability in elderly patients. On the contrary, we observed a monotone decreasing probability of LN involvement with increasing age in patients with pT1 tumors and no effect of age for larger tumors. The monotone decreasing trend in pT1 tumors might reflect the reduced aggressiveness and proliferative rate of breast cancers with increasing age[10,15] still present even after adjusting for receptor status, Ki-67, HER2/*neu*, and vascular invasion. This trend was not observed in larger tumors, suggesting an interactive effect of

size and age on the risk of LN involvement. One possible explanation of this interaction could be the following: There is general consensus that LN involvement is the product of biologic aggressiveness and chronological age of the disease.[16] Assuming that tumors have more indolent histologies in the elderly,[10,15] we must suppose that, on average, older people have older tumors for any given dimension; ie, a pT2 tumor of an old woman is older than a pT2 tumor of a younger woman. Moreover, the bigger the tumor, the greater the difference in tumor chronological age between young and old patients. Therefore, the benefit deriving from the indolent histologies in the elderly could be eroded by the longer chronological age of the tumor, in a proportional fashion with respect to tumor size.

Despite the tendency of older patients to wait longer before consulting a physician[3] and the established reduced mortality from breast cancer among screened persons in their 50s and 60s,[17] the benefit of breast cancer screening programs in elderly patients is controversial.[18] First of all, screening mammography studies have always limited their accrual to individuals younger than 75 years,[4,18] (69 years in Italy[19]) so that the impact of mammography is not clear in older individuals. Second, since breast cancer is more indolent in elderly women and given their decreased life expectancy, the problems of overdiagnosis and overtreatment become critical.[20-22] Therefore, characteristics of individual patients that go beyond age should be the driving factors in screening decisions, such as preferences of the patient, health status, benefits, and harms of the test.

The large number of patients in this cohort gives strength to the results of the current study, as we could perform a detailed and powerful statistical analysis and supply firm evidence on the controversial relationship between age, LN involvement, and other tumor characteristics. Regarding the limitations of the study, besides the classic issues of any observational study, it is important to notice that 4882 of the 6743 patients with pN0 tumors (72.4%) underwent sentinel node biopsy without axillary dissection, and it is estimated that 4%-7% of those patients might have undetected positive axillary nodes.[23] This could have slightly biased the results.

Conclusion

We strongly believe that the increase in risk of LN involvement in the elderly, observed in the clinical practice, is simply due to delayed diagnosis in this age group. Lack of systematic breast cancer screening programs for this subpopulation and tendency of the elderly to wait longer before consulting a physician might be blamed. We observed no increase of LN involvement probability in elderly patients in the multivariable analysis stratified by pT, suggesting that aging per se does not increase the risk of LN involvement.

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Disclosures

The authors have no relevant relationships to disclose.

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