2. Gréen H, Soderkvist P, Rosenberg P, et al: Mdr-1 single nucleotide polymorphisms in ovarian cancer tissue: G2677T/A correlates with response to paclitaxel chemotherapy. Clin Cancer Res 12:854-859, 2006
3. Marsh S, King CR, McLeod HL, et al: ABCB1 2677G>T/A genotype and paclitaxel pharmacogenetics in ovarian cancer. Clin Cancer Res 12:4127, 2006
4. Gréen H, Peterson C, Soderkvist P: In Response. Clin Cancer Res 12:4127-4128, 2006
5. Marsh S, Van Booven DJ, McLeod HL: Global pharmacogenetics: Giving the genome to the masses. Pharmacogenomics 7:625-631, 2006
6. Engen RM, Marsh S, Van Booven DJ, et al: Ethnic differences in pharmacogenetically relevant genes. Curr Drug Targets 7:1641-1648, 2006
7. Garte S, Gaspari L, Alexandrie AK, et al: Metabolic gene polymorphism frequencies in control populations. Cancer Epidemiol Biomarkers Prev 10:1239-1248, 2001

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In Early-Stage Breast Cancer, the Estrogen Receptor Interacts With Correlation Between Human Epidermal Growth Factor Receptor 2 Status and Age at Diagnosis, Tumor Grade, and Lymph Node Involvement

To the Editor: Analyzing breast cancer patients' characteristics and tumor biology, Bartlett et al[1] identified significant interactions between human epidermal growth factor receptor 2 (HER-2) and estrogen receptor (ER) expression that correlate with tumor pathology and age. First, they show that the HER-2 status of breast cancer was predicted by ER expression only in patients older than age 40 years. Second, the HER-2 status of breast cancer was predicted by the lymph node status in ER-negative but not in ER-positive tumors. In ER-positive tumors, the HER-2 status was predicted by the tumor grade. Although the results are interesting, some issues deserve additional attention.

The authors claim to be the first to report that tumor ER expression affects the impact of HER-2 expression on classical pathologic features. We previously reported on the qualitative interaction between age and expression of HER-2 and steroid receptors.[2-4] Considering patients younger than 40 years, we described that the age-related decline in HER-2–positive breast cancers was restricted to the ER-positive, and especially the ER-positive progesterone receptor–positive subset. We have previously also shown that HER-2 is correlated with tumor grade in ER-positive and not in ER-negative patients.[5,6]

Data from Bartlett et al[1] on the higher risk for HER-2 expression with four or more positive lymph nodes as compared with negative lymph nodes in ER-negative and not in ER-positive patients prompted us to reanalyze our database for an interaction among HER-2, ER expression, tumor grade, and lymph node status, as was performed in this study. Our database contains 2,552 consecutive women with an invasive breast cancer primarily operated on at one center between January 2000 and December 2005. The importance of cross-checking their findings in our database is relevant, as they recognize their data are based on patients with an extremely high risk for relapse. In their series, 17.1% were younger than 40 years, 56.6% and 79.3% were the figures, respectively, for grade 3 and lymph node–positive tumors; 31.1% of all breast cancers were ER negative, and 23.6% were HER-2 positive. In our database only 7.0% of patients were younger than 40 years, and 41.0% and 38.4% were our figures, respectively, for grade 3 and lymph node-positive tumors; 15.4% of breast cancers in our institution were ER negative, and 11.6% had a HER-2–positive phenotype.

Table 1. Predicted Probability of HER-2 Positivity (in %) by Tumor Grade and ER Status

ER Status	Tumor Grade		
	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)
No. of patients	347	1,158	1,047
ER-positive, n = 2,158	1.2	4.3	18.1
ER-negative, n = 394	33.3	30.8	29.2

Abbreviations: HER-2, human epidermal growth factor receptor 2; ER, estrogen receptor.

All women had a classical lymph node dissection, mostly level I and II. After June 2003, the sentinel lymph node procedure was performed in patients with a cT1 tumor. An axillary lymph node dissection was only performed if the sentinel node was involved. Tumor grading was performed according to the Ellis and Elston grading system. Lymph nodes were examined by hematoxylin and eosin staining using three sections per node; sentinel lymph nodes and those from lobular breast cancers classified as negative on hematoxylin and eosin staining were additionally stained with epithelial markers. Expression of steroid and HER-2 was demonstrated by immunohistochemistry (IHC) according to the Envision method using the following primary monoclonal antibodies: NLC-ER-6F11 for ER and CB11 for HER-2 (Novocastra Laboratories, Newcastle-on-Tyne, United Kingdom). Since 2005, highly sensitive rabbit monoclonal antibodies were used for the assessment of ER expression (SP1; Labvision Corp, Fremont, CA). IHC staining was performed according to standard procedures for clinical purposes as previously described. For ER, any nuclear staining of invasive tumor cells was considered as positive. For HER-2, either strong expression by IHC (score 3+) or *HER2* gene amplification by fluorescent in situ hybridization was considered HER-2–positive.

In this updated analysis (Table 1), we can confirm our previous data[4] and the current data by Bartlett et al[1] showing an interaction of ER between HER-2 overexpression and tumor grade. In ER-positive breast cancers, HER-2 expression correlated with tumor grade. However, this was not the case in ER-negative tumors.

In our series, HER-2 was also related with nodal involvement (10.1% in lymph node–negative and 13.8% in lymph node–positive patients; $P = .0038$, χ^2). These figures were 21.1% in lymph node–negative and 24.2% in lymph node–positive patients in the series from Bartlett et al[1] of high-risk patients. Correlating these figures with ER status and tumor grade in our series (Table 2), HER-2 expression in ER-negative patients remained independent of tumor grade ($P = .7858$, Mantel-Haenszel χ^2). Although more women in the ER-negative "four or more lymph node" group were HER-2 positive, this figure was not significant ($P = .2894$, χ^2). However, in our series of ER-positive patients, HER-2 expression, which is mainly dependent

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Table 2. Predicted Probability of HER-2 Positivity (in %) by Tumor Grade, Nodal Status, and ER Status

Node Status	All (%)	ER-Positive (%)				ER-Negative (%)			
		All	Grade 1	Grade 2	Grade 3	All	Grade 1	Grade 2	Grade 3
No. of patients		2,158	344	1,106	708	394	3	52	339
0 nodes, n = 1,571	10.1	6.9	1.5	4.2	16.2	27.7	33.3	25.0	28.2
1-3 nodes, n = 679	12.4	9.3	0.0	4.7	17.8	29.7	0.0	38.5	28.4
≥ 4 nodes, n = 302	17.2	13.4	0.0	3.4	23.8	36.7	0.0	36.4	36.8

Abbreviations: HER-2, human epidermal growth factor receptor 2; ER, estrogen receptor.

on tumor grade ($P < .0001$, Mantel-Haenszel χ^2), was also related to the degree of lymph node involvement ($P = .0022$, χ^2).

Table 3 shows the proportion of breast cancers in our series that are lymph node–positive by ER and HER-2 status. Tumors with an ER-positive HER-2–positive phenotype were more likely lymph node–positive than tumors of any other ER/HER-2 status.

We agree with Bartlett et al[1] that the risk of nodal involvement among HER-2–positive breast cancers is associated with ER status. It would be interesting to see the frequencies of lymph node involvement per ER/HER-2 group in the article by Bartlett et al[1] because it now gives the impression that HER-2–positive breast cancers are more likely lymph node-positive if ER is absent than if ER is present. However, such differences may be related to the high-risk population they consider, because numbers in different HER-2 risk categories differ when comparing normal-risk with high-risk patients.

Table 3. Predicted Probability of Nodal Involvement (in %) by ER and HER-2 Expression

Expression	Probability
All cases	38.4
ER positive	38.5
HER-2 negative	37.5
HER-2 positive	49.1
ER negative	38.0
HER-2 negative	36.7
HER-2 positive	41.3

Abbreviations: HER-2, human epidermal growth factor receptor 2; ER, estrogen receptor.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

REFERENCES

1. Bartlett JMS, Ellis IO, Dowsett M, et al: Human epidermal growth factor receptor 2 status correlates with lymph node involvement in patients with estrogen receptor (ER)–negative, but with grade in those with ER-positive early-stage breast cancer suitable for cytotoxic chemotherapy. J Clin Oncol 25:4423-4430, 2007

2. Huang HJ, Neven P, Drijkoningen M, Paridaens R, Wildiers H, Van Limbergen E, et al: Association between HER-2/neu and the progesterone receptor in oestrogen-dependent breast cancer is age-related. Breast Cancer Res Treat 91:81-87, 2005

3. Huang HJ, Neven P, Drijkoningen M, Paridaens R, Wildiers H, Van Limbergen E, et al: Hormone receptors do not predict the HER2/neu status in all age groups of women with an operable breast cancer. Ann Oncol 11:1755-1761, 2005

4. Neven P, Van Calster B, Vanden Bempt I, et al: Age interacts with the expression of steroid and HER-2 receptors in operable invasive breast cancer. Breast Cancer Res Treat [epub ahead of print on August 9, 2007]

5. Huang HJ, Neven P, Drijkoningen M, Paridaens R, Wildiers H, Van Limbergen E, et al: Association between tumour characteristics and HER-2/neu by immunohistochemistry in 1362 women with primary operable breast cancer. J Clin Pathol 58:611-616, 2005

6. Van Calster B, Vanden Bempt I, Drijkoningen M, et al: Axillary lymph node status of operable breast cancers by combined steroid receptor and HER-2 status: Triple positive tumours are more likely lymph node positive. Breast Cancer Res Treat [epub ahead of print on February 9, 2008]

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In Reply: Thank you for the opportunity to respond to the letter by Neven et al regarding our recent article.[1] Our original observation,[2] presented at the June 2005 American Society of Clinical Oncology meeting, contemporaneously with reports by Huang et al,[3,4] showed that in estrogen receptor (ER)–positive tumors, histologic type, grade, and progesterone receptor status but not nodal status was associated with increasing frequency of human epidermal growth factor receptor 2 (HER-2) positivity. Simultaneously for ER-negative patients, we observed an association with nodal status but not grade. At that time we suggested a significant interaction between HER-2 and ER in determining disease spread or differentiation in breast cancer.[5] These observations were based on samples from both the United Kingdom Taxotere as Adjuvant Chemotherapy (TACT) and United Kingdom Tamoxifen versus Exemestane Adjuvant Multicenter (TEAM) trials analyzed within Bartlett's laboratory. The analyses were subsequently extended to the entire TACT patient cohort,[1] for whom a high quality of HER-2 testing has been achieved.[6] Data on the TEAM trial cohort will be analyzed separately. Confirmation of an interaction between HER-2 and increasing grade in ER-positive breast cancer by Neven et al adds to the evidence that this is a significant and potentially clinically important interaction. We apologize if we appeared to overlook this

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