VOLUME 30 · NUMBER 21 · JULY 20 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Clinically Used Breast Cancer Markers Such As Estrogen Receptor, Progesterone Receptor, and Human Epidermal Growth Factor Receptor 2 Are Unstable Throughout Tumor Progression

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Submitted May 31, 2011; accepted March 27, 2012; published online ahead of print at www.jco.org on June 18, 2012.

Supported by grants from the Swedish Research Council, Gösta Miltons Donationsfond, Karolinska Institutet Foundations, FOU Värmlands Läns Landsting, Swedish Cancer Society, Cancer Society in Stockholm, The King Gustaf V Jubilee Fund, Swedish Breast Cancer Association, and Märit and Hans Rausing's Initiative Against Breast Cancer.

L.S.L. and E.K. contributed equally to this work.

Presented at the 46th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 4-8, 2010; the 33rd Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 8-12, 2010; and the 2011 European Multidisciplinary Cancer Congress, Stockholm. Sweden, September 23-27, 2011.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/12/3021-2601/$20.00

DOI: 10.1200/JCO.2011.37.2482

ABSTRACT

Purpose
To investigate whether hormonal receptors and human epidermal growth factor receptor 2 (HER2) change throughout tumor progression, because this may alter patient management.

Patients and Methods
The study cohort included female patients with breast cancer in the Stockholm health care region who relapsed from January 1, 1997, to December 31, 2007. Either biochemical or immunohistochemical (IHC)/immunocytochemical (ICC) methods were used to determine estrogen receptor (ER), progesterone receptor (PR), and HER2 status, which was then confirmed by fluorescent in situ hybridization for IHC/ICC 2+ and 3+ status.

Results
ER (459 patients), PR (430 patients), and HER2 (104 patients) from both primary tumor and relapse were assessed, revealing a change in 32.4% (McNemar's test $P < .001$), 40.7% ($P < .001$), and 14.5% ($P = .44$) of patients, respectively. Assessment of ER (119 patients), PR (116 patients), and HER2 (32 patients) with multiple (from two to six) consecutive relapses showed an alteration in 33.6%, 32.0%, and 15.7% of patients, respectively. A statistically significant differential overall survival related to intraindividual ER and PR status in primary tumor and relapse (log-rank $P < .001$) was noted. In addition, women with ER-positive primary tumors that changed to ER-negative tumors had a significant 48% increased risk of death (hazard ratio, 1.48; 95% CI, 1.08 to 2.05) compared with women with stable ER-positive tumors.

Conclusion
Patients with breast cancer experience altered hormone receptor and HER2 status throughout tumor progression, possibly influenced by adjuvant therapies, which significantly influences survival. Hence, marker investigations at relapse may potentially improve patient management and survival.

J Clin Oncol 30:2601-2608. © 2012 by American Society of Clinical Oncology

INTRODUCTION

Despite achievements in the use of different adjuvant therapies, 20% or more of women with early-stage breast cancer will later develop metastatic disease.[1-3] Clinically used primary breast cancer markers such as estrogen receptor (ER) status, progesterone receptor (PR) status, and human epidermal growth factor receptor 2 (HER2), are usually used to help make decisions about therapy in the metastatic setting. Previous smaller studies[4-17] reveal lack of stability of the hormonal and/or HER2 markers during tumor progression. Indeed, most studies, except for a few with limited numbers of patients,[17] have been restricted to intraindividual comparisons of primary tumor and relapse, whereas it would be biologically and clinically relevant to contrast clinically used markers throughout tumor progression by assessing intraindividual marker status in multiple consecutive relapses. If therapy-predictive markers continue to change throughout tumor progression, then investigating metastatic lesions via biopsy would provide additional important information on the nature of the radiologically verified lesions, including marker expression, which would enable better management of patients with metastatic disease.

In this study, we aimed to assess intraindividual ER, PR, and HER2 status throughout tumor progression by contrasting primary tumor and relapse

and by comparing intraindividual marker status in consecutive relapses in a large and representative cohort of women diagnosed with breast cancer relapse.

PATIENTS AND METHODS

At Radiumhemmet, Karolinska University Hospital, the clinical routine during the last decade has been to morphologically confirm clinical and/or radiologic suspicion of a breast cancer relapse. By using the population-based Stockholm-Gotland Breast Cancer Registry established in 1976, we identified (by using a unique 12-digit number assigned to each individual living in Sweden) a total of 1,010 females diagnosed with a local or systemic breast cancer relapse from January 1,1997, to December 31, 2007. Patients underwent surgery at (or their cancers were reported from) the Karolinska University Hospital, St. Göran's Hospital, or Sophiahemmet, all located in the Stockholm region. The majority of biopsies were taken at Radiumhemmet, Karolinska University Hospital. The predefined exclusion criterion was advanced disease at the time of primary breast cancer diagnosis. Patients with synchronous bilateral breast cancer (as defined by the Stockholm-Gotland Breast Cancer Registry) were excluded.

ER and PR status were assessed by monoclonal antibody–based biochemical methods (Abbott Laboratories, Abbott Park, IL), with a threshold ≥ 0.05 fmol/μg DNA classified as receptor positive, by immunohistochemistry (IHC; BenchMark automated system; Ventana Medical Systems, Tucson, AZ; with commercially available antibodies) or by immunocytochemistry (ICC; Abbott Laboratories and Dako, Carpinteria, CA; with commercially available antibodies); both IHC and ICC with a threshold ≥ 10% were classified as receptor positive.

Antigen retrieval and staining procedures were performed according to manufacturer's instructions.[18] Positive controls were run with each batch. Using appropriate negative and positive controls is of utmost importance in interpreting immunocytologic stains. At Karolinska University Hospital and other laboratories that process large numbers of immunostainings, daily controls are provided indirectly by slides from other patients. To be reliable, this system requires a high volume of immunostainings and single samples are not run separately (standard procedure at Karolinska University Hospital).[19]

At Radiumhemmet, Karolinska University Hospital, alcohol-based fixate has not been used for fine-needle aspiration (FNA) samples because early tests suggested that this method may be suboptimal. Instead, FNA samples were air-dried and fixed in buffered formalin.[19,20]

HER2 status was assessed by using IHC/ICC analyses (or directly by fluorescent in situ hybridization) with three antibodies: CB11 (Ventana Medical Systems), A485 (Dako), and Ab-17 (Neomarkers; Lab Vision, Fremont, CA), from 2000 to March 2005. After March 2005, IHC analyses were run with two antibodies: CB11 (Ventana and Novocastra Leica, Wetzlar, Germany) and A485. The internal control consisted of four breast cancer cell lines; BT474 (3+), MDA453 (2+), RT4 (1+), and 5637 (0), with the protein staining of the membrane set at four levels (0, 1+, 2+, and 3+). IHC/ICC was classified as positive at the 3+ protein level, according to the Swedish Breast Cancer Group recommendation; fluorescent in situ hybridization (with a cutoff level of two copies per cell) was performed in a majority of samples if the IHC/ICC protein level was 2+ or 3+.

ER, PR, and HER2 status was manually collected from pathology reports, and information on adjuvant therapies was obtained from the Stockholm-Gotland Breast Cancer Registry or from patient records. The ethical committee at Karolinska Institutet approved this study.

Statistical Methods

Intraindividual ER, PR, and HER2 status was assessed for several relapses in a portion of individuals in the cohort. Thus, to perform survival analyses as well as intraindividual primary tumor and relapse comparison of ER, PR, and HER2 status (Table 1), the earliest diagnosed relapse (from primary breast cancer diagnosis) with assessed ER, PR, or HER2 status was selected. The difference in intraindividual ER, PR, and HER2 status in primary tumor and relapse was investigated by using McNemar's test; the association between intraindividual ER status and adjuvant therapy was investigated by using Fisher's exact test.

Table 1. Intraindividual ER, PR, and HER2 Status Throughout Tumor Progression

Hormonal and HER2 Status	ER*		PR*		HER2†	
	No.	%	No.	%	No.	%
Primary tumor and relapse						
Local and systemic relapse						
Primary positive/relapse positive	216	47.1	109	25.4	20	19.2
Primary positive/relapse negative	113	24.6	142	33.0	9	8.7
Primary negative/relapse positive	36	7.8	33	7.7	6	5.8
Primary negative/relapse negative	94	20.5	146	33.9	69	66.3
Total	459	100.0	430	100.0	104	100.0
Local relapse						
Primary positive/relapse positive	82	55.8	50	37.6	4	21.1
Primary positive/relapse negative	24	16.3	36	27.1	3	15.8
Primary negative/relapse positive	10	6.8	7	5.2	2	10.5
Primary negative/relapse negative	31	21.1	40	30.1	10	52.6
Total	147	100.0	133	100.0	19	100.0
Systemic relapse						
Primary positive/relapse positive	134	43.0	59	19.9	16	18.8
Primary positive/relapse negative	89	28.5	106	35.7	6	7.1
Primary negative/relapse positive	26	8.3	26	8.7	4	4.7
Primary negative/relapse negative	63	20.2	106	35.7	59	69.4
Total	312	100.0	297	100.0	85	100.0
Multiple relapses‡						
Local and systemic relapse						
Relapse positive/relapse positive	43	36.1	15	12.9	3	9.4
Relapse positive/relapse negative	19	16.0	25	21.6	3	9.4
Relapse negative/relapse positive	15	12.6	8	6.9	2	6.2
Relapse negative/relapse negative	36	30.3	64	55.1	24	75.0
Unstable§	6	5.0	4	3.5	0	0.0
Total	119	100.0	116	100.0	32	100.0

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

*Cutoff value of 0.05 fmol/μg DNA for monoclonal antibody–based biochemical methods and 10% cutoff for immunohistochemical/immunocytochemical (IHC/ICC) methods.

†Analyzed by using IHC/ICC (or by fluorescent in situ hybridization [FISH] directly); a majority were confirmed by FISH for IHC/ICC 2+ and 3+.

‡From two to six consecutive relapses assessed.

§Tumor marker status altering between positive and negative throughout tumor progression (consecutive intraindividual relapses) was labeled unstable.

The Kaplan-Meier method was used to perform univariate analysis of overall survival from diagnosis of either primary breast cancer or of relapse until death (including both breast cancer–specific death and other) or until the end of study follow-up (December 31, 2007), according to intraindividual ER and PR status in primary tumor and relapse, respectively.

The risk of death in relation to ER status in primary tumor and relapse was modeled by using a multivariable Cox proportional hazard model. The proportional hazard assumption for the main exposure variable was assessed by using Schoenfeld's test statistics.[21] No statistically significant deviation was noted for the main exposure as studied. An arbitrary level of 5% statistical significance (two-tailed) was used.

RESULTS

A flow chart of the cohort with assessment of ER, PR, and HER2 status in primary tumor and relapse is presented in Figure 1. A summary of the primary tumor characteristics stratified by ER, PR, and HER2 status is presented in Appendix Table A1 (online only), and the

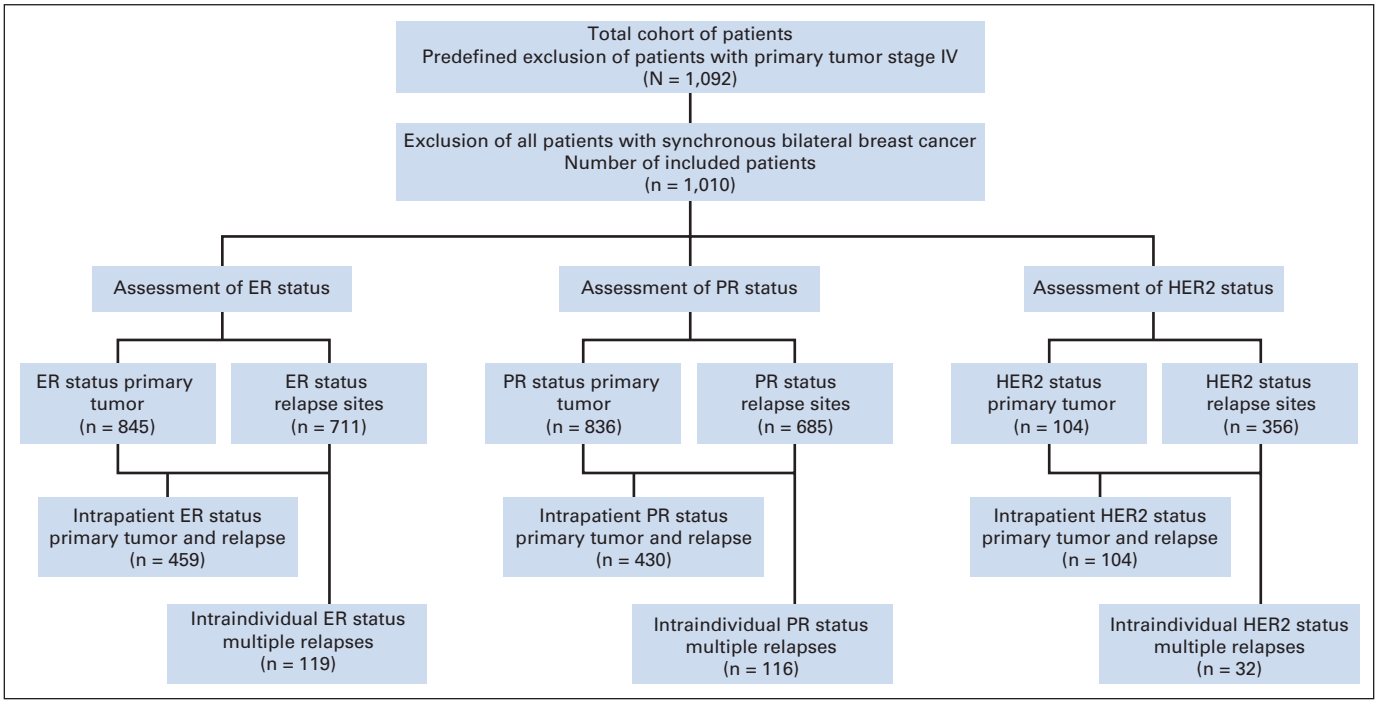

Fig 1. Flow chart of the cohort with assessment of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status in primary tumor and relapse.

biopsy-verified sites of relapse stratified by ER, PR, and HER2 status are presented in Appendix Table A2 (online only).

Intraindividual Primary Tumor and Relapse

ER status of both primary tumor and one (or more) relapse(s) was assessed in 459 patients, PR status in 430 patients, and HER2 status in 104 patients (Table 1). In summary, for ER, PR, and HER2, 32.4% (McNemar's test $P < .001$), 40.7% (McNemar's test $P < .001$), and 14.5% (McNemar's test $P = .44$) of patients, respectively, had altered marker status. ER and PR status changed from positive in primary tumor to negative in relapse in 24.6% and 33.0% of the patients, whereas ER and PR status changed from negative to positive in 7.8% and 7.7% of the relapse sites, respectively. Further, in 15 (14.5%) of 104 patients, HER2 status changed between primary tumor and relapse.

In our study, a threshold $\geq$ 10% (recommended by the European guidelines[22]) was classified as receptor positive for IHC and ICC; previous studies from Karolinska have shown that less than 1% of tumors have an ER expression level ranging between 1% and 9%.[18,23] Reassuringly, the discordance rates were similar when contrasting a 1% and 10% cutoff (Appendix Table A3, online only).

In Table 2, the intraindividual ER status in primary tumor and relapse was stratified into either adjuvant hormonal therapy or chemotherapy both in combination or no treatment. The proportion of patients losing ER was highest in the group treated with hormonal therapy alone and in hormonal therapy combined with chemotherapy, lower in the group treated with chemotherapy alone, and lowest in the group that received no treatment ($P < .001$, Fisher's exact test contrasting intraindividual ER status among the treatment groups). Few patients who gained ER received hormonal therapy; on the contrary, in the chemotherapy alone and no treatment groups, the proportion was three times as high (13%).

The pattern of intraindividual HER2 status in primary tumor and relapse reflected a trend of worsening tumor characteristics in agreement with ER (intraindividual primary tumor and relapse) groups (Appendix Table A4, online only). To summarize, in the stable ER-positive group, 87% of patients had stable HER2-negative status between primary tumor and relapse. In the group that gained ER at relapse, 71% of patients had stable HER2-negative status. In comparison, in the group that lost ER at relapse and in the stable ER-negative group, only approximately 50% of patients had stable HER2-negative disease.

In Figure 2, patients categorized by intraindividual ER status (in primary tumor and in first diagnosed site of relapse) were stratified according to relapse-free survival at $\leq$ 2, 5, and 10 years in addition to site of relapse.

In our cohort, approximately half the patients with ER-negative primary tumors who gained ER at relapse received hormonal therapy and 24 of 104 patients received trastuzumab in the relapse setting.

Multiple Relapses

Intraindividual ER, PR, and HER2 status in multiple (from two to six) consecutive relapses (from different sites in the majority of patients) was assessed in 119, 116, and 32 patients, respectively (Table 1). Interestingly, all three markers were unstable in similar proportions in the relapse setting. For ER, 33.6% of patients had discordant ER status between different relapses, whereas 36.1% had stable positive marker status and 30.3% had stable negative marker status. For PR, 32.0% of patients had altered PR status, with a majority of the change (21.6%) being from PR positive to PR negative. HER2 status changed in 15.7% of patients between consecutive relapses with similar proportions of change from negative to positive and from positive to negative. Given that the relapse sites ranged from two to six sites per individual, a statistical test was not performed. In approximately half

Table 2. Adjuvant HT and CT Stratified by Intraindividual ER Status in Primary Tumor and Relapse

ER Status*	No.	%
Total No. of patients	459	100.0
Adjuvant HT positive/adjuvant CT positive†		
Primary positive/relapse positive	55	55.6
Primary positive/relapse negative	34	34.3
Primary negative/relapse positive	4	4.0
Primary negative/relapse negative	6	6.1
Total	99	100.0
HT positive/CT negative†		
Primary positive/relapse positive	99	61.1
Primary positive/relapse negative	47	29.0
Primary negative/relapse positive	7	4.3
Primary negative/relapse negative	9	5.6
Total	162	100.0
HT negative/CT positive†		
Primary positive/relapse positive	25	22.5
Primary positive/relapse negative	22	19.8
Primary negative/relapse positive	14	12.6
Primary negative/relapse negative	50	45.1
Total	111	100.0
HT negative/CT negative†		
Primary positive/relapse positive	37	42.5
Primary positive/relapse negative	10	11.5
Primary negative/relapse positive	11	12.7
Primary negative/relapse negative	29	33.3
Total	87	100.0

Abbreviations: ER, estrogen receptor; CT, chemotherapy; HT, hormonal therapy.
*Cutoff value of 0.05 fmol/μg DNA for monoclonal antibody–based biochemical methods and 10% cutoff for immunohistochemical/immunocytochemical methods.
†$P < .001$ for Fisher's exact test contrasting intraindividual ER status between the treatment groups.

the patients with data on three or more consecutive relapse sites, the change to discordant marker status occurred on second progression, whereas half the patients showed change at a relapse site that was assessed later.

Hormonal Measurement Methods

The distribution of hormonal measurement methods comparing intraindividual primary tumor and relapse is presented in Appendix Table A5 (online only). Subgroup analysis (concordant or discordant measurement methods) was performed to investigate potential systematic differences in ER assessment due to discordant methods of hormonal receptor determination. Reassuringly, these results showed similar intraindividual ER discordance proportions for the comparison of concordant and discordant methods for ER determination (ER positive to ER negative, 26.0% *v* 23.5%; ER negative to ER positive, 7.2% *v* 8.4%; Appendix Table A6, online only).

Survival Analyses

We performed univariate Kaplan-Meier analyses of intraindividual ER (Fig 3) and PR status (Appendix Fig A1, online only) in primary tumor and in relapse. All analyses showed statistically significant differential overall survival by intraindividual ER and PR status in primary tumor and relapse (follow-up from primary breast cancer diagnosis to death or censoring, as well as follow-up from breast cancer relapse diagnosis to death or censoring analyzing all sites of relapse, in addition to subanalyses that included systemic relapses only).

To further test the difference in survival by intraindividual ER status in primary tumor and relapse, a multivariate Cox proportional hazards model was used, adjusting for potential confounders on survival such as age and calendar year of primary breast cancer diagnosis, relapse diagnosis, PR, tumor stage, adjuvant hormonal therapy, and adjuvant chemotherapy. In the Cox proportional hazards survival model from primary breast cancer diagnosis to death or censoring at end of follow-up, patients with ER status that changed from positive to negative had a statistically significantly increased hazard ratio (HR) for death, including both local and systemic relapses (HR 1.48; 95% CI, 1.08 to 2.05) and systemic relapses only (HR, 1.62; 95% CI, 1.12 to 2.34) compared with stable ER-positive patients (Table 3). The increased HR for death was similar and statistically significant when modeling the follow-up from relapse diagnosis to death or censoring (Table 3). A statistically significant trend of increasing risk of death by intraindividual ER status in primary tumor and relapse was seen in all analyses (Table 3).

DISCUSSION

Our study demonstrates instability in clinically used markers throughout tumor progression. One in three patients with breast cancer experience alteration of hormone receptor status, and 15% of patients experience a change in HER2 status during tumor progression. The importance of changed receptor status is underlined by the fact that a statistically significant differential survival was noted in women that was related to intraindividual ER and PR status in primary tumor and relapse. Our findings broaden the understanding of tumor dissemination by clarifying the instability of clinically used tumor markers throughout tumor progression (and in the advanced setting) inferring both biologic and therapeutic implications.

ER, PR, and HER2 are lost and gained in a considerable proportion of patients throughout tumor progression. Importantly, patients with ER-positive disease at relapse have better prognosis than ER-negative patients, independent of the ER status of the primary tumor. In contrast, PR status for the primary tumor rather than PR status at relapse seems to have an impact on patient survival. Interestingly, the intraindividual ER groups reflect a trend of worsening tumor characteristics by means of HER2 status. One third of patients receiving hormonal therapy lost ER expression at relapse, whereas only one of 10 untreated patients showed altered ER status. A small proportion of patients who gained ER received hormonal therapy; on the contrary, in the chemotherapy alone and no treatment groups, the proportion was three times as high.

The clinical implication of this instability is important, whereas loss of ER and HER2 generally means resistance to endocrine therapy and trastuzumab, respectively; thus, these patients would benefit from a change in therapy. However, in ER-positive patients, PR status has not been found to be predictive of tamoxifen response.[3] Equally, gain of ER and HER2 in the relapse setting would introduce additional choices of therapies, potentially leading to tumor response and prolonged survival in some patients. Since tumor instability is seen not only between the primary and relapse setting but also throughout tumor progression, this dynamic will make clinical decisions more difficult and will bring forward the potential need for taking biopsies

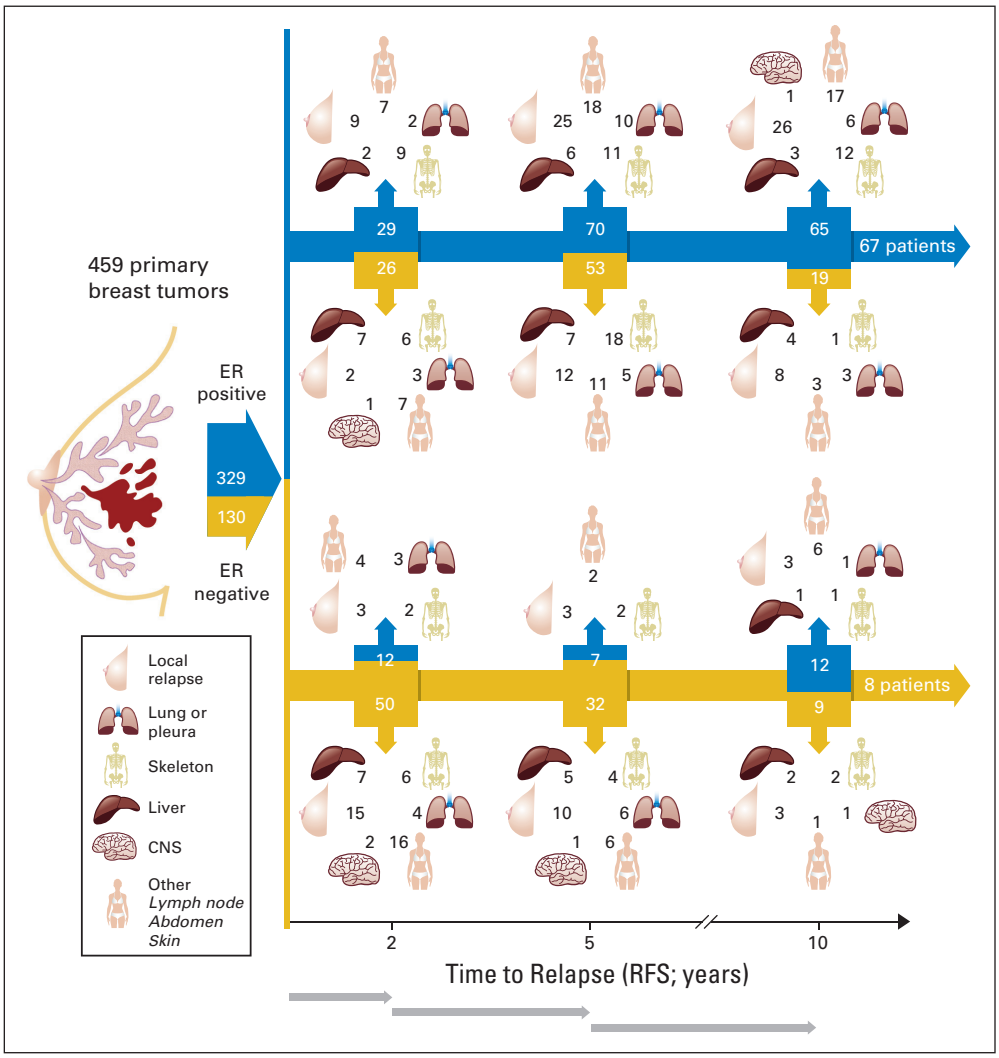

Fig 2. Patients by intraindividual estrogen receptor (ER) status (in primary tumor and first diagnosed site of relapse) were stratified according to relapse-free survival (RFS) at ≤ 2, 5, and 10 years. The sites of relapse were grouped into local relapse (ipsilateral breast), skeleton, lung and pleura combined, liver, CNS, or other (mainly defined as lymph node, abdomen, or skin).

in a consecutive manner in the advanced setting to optimize treatment decision making for the patient.

There are several likely explanations for our findings. It has been shown that primary breast tumors demonstrate intratumor heterogeneity with various metastatic capacities.[24-26] Inherent host and tumor biologic factors may also be involved in the clonal expansion and metastatic spread of cells with specific characteristics.[27] The microenvironment in the blood circulation and in other organs has the potential to influence this clonal selection.[25,26] Adjuvant therapies may also influence these processes,[28] with the net result of clonal expansion of metastatic tumors with characteristics different from those of the primary tumors.

One limitation of this study is its retrospective nature. However, the Department of Pathology and Cytology at Karolinska University Hospital has participated in various quality assurance programs for hormonal receptors and HER2 over the years, and a subsample of 58 tumors (20 paired primary tumor and relapse samples from the same patient, nine primary tumors, and nine relapses) from this cohort was reanalyzed. All but four of the reanalyzed samples corresponded closely to the original ER determination. Worth noting is that one of the four samples was rescored to be exactly 10% (the cutoff for ER positivity) compared with less than 10% as in the original ER assessment. In addition, smaller prospective studies[4,13,14] verify the lack of stability of all three receptors. Conversely, the retrospective design of this study enabled the definition of a large and representative cohort of women diagnosed with a breast cancer relapse. Indeed, it is possible that the change in receptor status could be due to methodologic shortcomings. But this seems unlikely, given that our results are based on both biochemical receptor determinations and IHC/ICC, which resulted in similar discordance rates, irrespective of the intraindividual methods being concordant or discordant; previous studies from Karolinska also revealed a high concordance value.[18] Interestingly, patients also gained and lost hormonal receptor expression in the relapse setting, with a majority of receptor determinations done by IHC/ICC. Finally, intraindividual receptor status is significantly associated with a differential survival in both univariate and multivariate analyses, with a significant trend toward worsening survival by loss of ER, which strongly indicates that the observed receptor changes are reflections of true biologic alterations.

FNA biopsy has the advantage of being easy to perform with minimal risk of complications, whereas core-needle biopsy allows the possibility of obtaining sections for further analyses. Several reports[29-32] have been published in the cytology arena documenting the reliability of

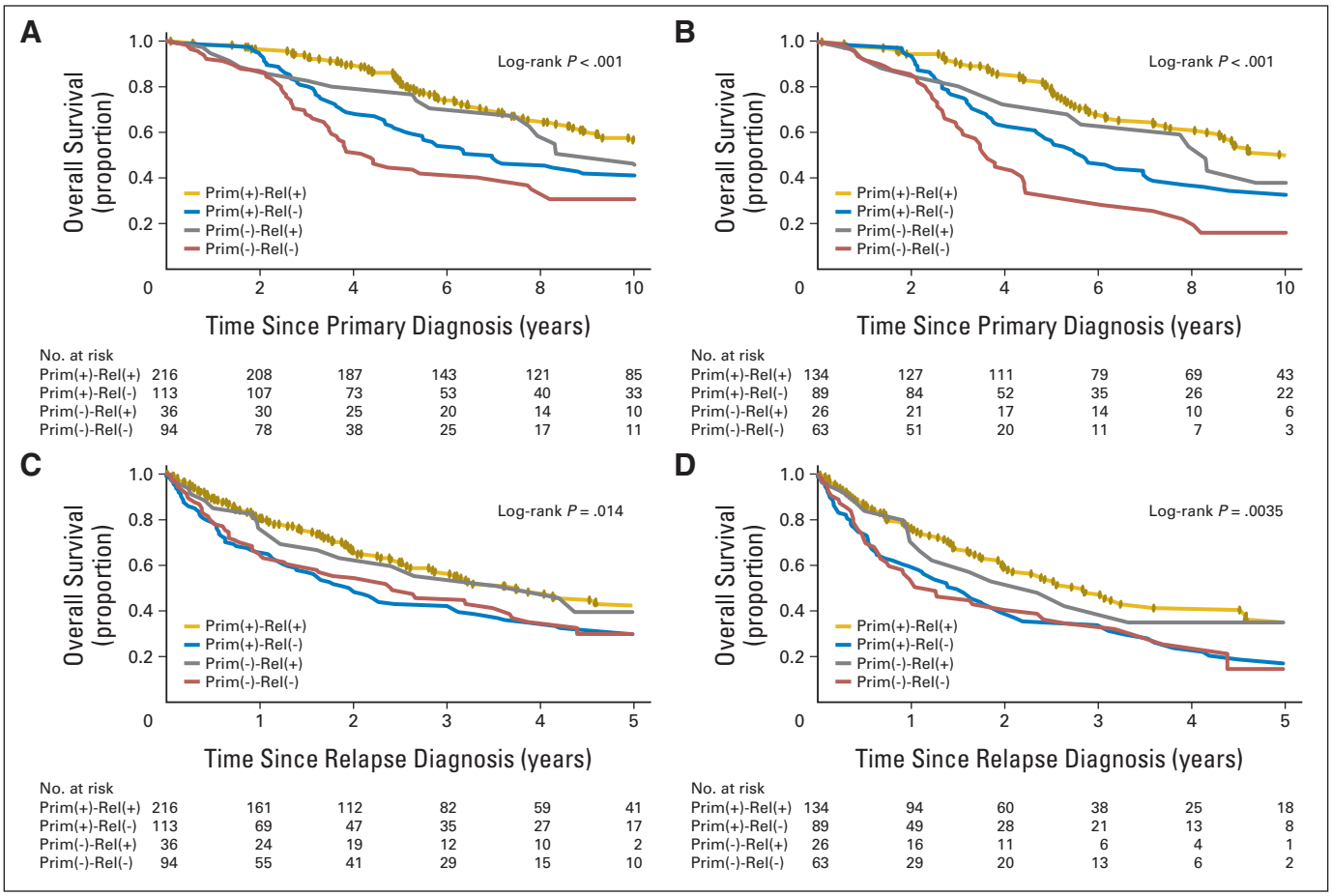

Fig 3. Kaplan-Meier survival curves in women diagnosed with breast cancer. Overall survival from the time of primary (Prim) breast cancer diagnosis to death or censoring contrasting intraindividual estrogen receptor status in primary tumor and relapse (Rel) with (A) both local and systemic relapses included and with (B) only systemic relapses included. Overall survival from the time of breast cancer relapse diagnosis to death or censoring contrasting intraindividual estrogen receptor status in primary tumor and relapse with (C) both local and systemic relapses included and with (D) only systemic relapses included.

evaluating FNA material in the assessment of ER; the concordance rate is around 90% between ICC and IHC, but both techniques have the potential shortcoming that they may result in a false-negative result. Therefore, special attention and expertise are vital for minimizing this issue.[19,33]

Despite observations revealing hormone receptor and HER2 instability during tumor progression, management of patients with metastatic breast cancer is frequently based on primary tumor characteristics. For a portion of patients, biopsy verifications will be

Table 3. Risk of Death in Patients With Breast Cancer, Depending on Intraindividual ER Status in Primary Tumor and Relapse

ER Status	No. of Patients	Overall Deaths	OS* Adjusted HR‡	OS* 95% CI	Trend Test P	Trend Test χ^2	OS† Adjusted HR‡	OS† 95% CI	Trend Test P	Trend Test χ^2
Local and systemic relapse					.020	5.38			.025	5.02
Primary positive/relapse positive	216	109	1.0 (Ref.)				1.0 (Ref.)			
Primary positive/relapse negative	113	75	1.48	1.08 to 2.05			1.46	1.06 to 2.01		
Primary negative/relapse positive	36	17	1.07	0.61 to 1.89			0.99	0.56 to 1.76		
Primary negative/relapse negative	94	54	1.14	0.74 to 1.76			1.00	0.65 to 1.55		
Total	459	255								
Systemic relapse					.016	5.84			.034	4.51
Primary positive/relapse positive	134	73	1.0 (Ref.)				1.0 (Ref.)			
Primary positive/relapse negative	89	67	1.62	1.12 to 2.34			1.51	1.05 to 2.17		
Primary negative/relapse positive	26	14	1.12	0.59 to 2.13			1.01	0.53 to 1.93		
Primary negative/relapse negative	63	42	1.30	0.77 to 2.21			1.16	0.68 to 1.97		
Total	312	196								

Abbreviations: ER, estrogen receptor; HR, hazard ratio; OS, overall survival; Ref., reference.
*From breast cancer diagnosis to death or censoring.
†From breast cancer relapse to death or censoring.
‡Adjusted for age and calendar year of primary breast cancer diagnosis, relapse diagnosis, progesterone receptor status, tumor stage, hormonal treatment, and chemotherapy.

important and may change management options. An obvious advantage of morphologic confirmation of a breast cancer relapse is that it identifies patients with benign lesions or other primary cancers, which is of major importance if these patients can be spared unnecessary and sometimes incorrect therapies.[14]

Our data are of clinical importance, because we, in a large representative cohort of women diagnosed with a local or systemic breast cancer relapse, demonstrate that the alterations in hormone receptor and HER2 status contrasting intraindividual primary tumors and relapse have statistically significant prognostic implications. Furthermore, our study found instability in ER, PR, and HER2 status between intraindividual consecutive relapses. Given that the therapy-predictive markers alter in clinically significant frequencies during tumor progression, biopsies should be taken as a routine procedure because they will have important implications for further therapy management. Our data, together with those of others, should lead to practice change at many institutions.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Jonas Bergh, Bayer Pharmaceuticals (C) **Stock Ownership:** None **Honoraria:** Jonas Bergh, AstraZeneca, Bayer Pharmaceuticals **Research Funding:** Jonas Bergh, sanofi-aventis, Amgen, Merck, Roche **Expert Testimony:** None **Other Remuneration:** None

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Data analysis and interpretation: Linda Sofie Lindström, Eva Karlsson, Jonas Bergh
Manuscript writing: All authors
Final approval of manuscript: All authors

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