

Genomic Instability and Prognosis in Breast Carcinomas

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Abstract

Background: We recently reported that DNA content of breast adenocarcinomas, cytometrically assessed by diploid (D), tetraploid (T), and aneuploid (A) categories, can be further divided into genomically stable and unstable subtypes by means of the stemline scatter index (SSI). The aim of the present study was to survey the clinical correlates and the prognostic value of the SSI in a consecutive series of 890 breast cancer patients.

Results: Genomically stable subtype had a significantly better survival compared with the unstable subtype within each ploidy category: D ($P = 0.04$), T ($P = 0.008$), and A ($P = 0.004$). By contrast, no statistically significant difference in survival was observed between the D, T, and A categories within the stable ($P = 0.23$) and unstable subtypes ($P = 0.12$). Among A tumors, the unstable subtype tended to be larger,

more frequently estrogen- and progesterone-receptor negative, and to be of higher grade compared with the stable subtype. Stable D tumors tended to have lower grade than the unstable subtype, but among the D and T tumors, genomic instability was not associated with receptor status. Within the Elston grade 3, lymph node-positive or estrogen receptor-positive subgroups, patients with stable tumors had significantly better survival compared with unstable tumors ($P = 0.01$, 0.002 , and $7.2E-5$, respectively).

Conclusions: The SSI contributes supplementary biological and clinical information in addition to ploidy information alone. Objective classification of breast adenocarcinomas into stable and unstable subtypes is a useful prognostic indicator independent of established clinical factors. (Cancer Epidemiol Biomarkers Prev 2006;15(9):1630–5)

Introduction

Chromosomal aberrations, comprising numerical changes of certain chromosomes or segments of chromosomes, are found in most breast adenocarcinomas (1, 2). Convincing evidence has also been obtained that the degree of karyotypic disturbance, generally called aneuploidy, correlates with clinical tumor aggressiveness (3, 4). Breast carcinomas with a stemline close to 46 chromosomes, i.e. minor chromosomal or DNA content deviations, present a significantly lower malignant potential than tumors with stemlines clearly deviating from 46 chromosomes (5–9).

There is evidence that nuclear DNA content values, usually determined by quantitative flow or image DNA cytometry, correlate with the number and type of chromosomal aberrations and the probability of progression to higher degrees of chromosomal disturbance (2, 10), which, in turn, leads to increasing tumor aggressiveness.

A drawback of traditional ploidy analysis is the subjective judgment of DNA content values, impeding the reproducibility of this method (6). In addition, there is more information in the DNA histograms than stemline position and estimation of S-phase fraction. We recently introduced an objective DNA-histogram evaluation, based on three quantities to capture nonmodal DNA content values, i.e. the coefficient of variation of the tumor stemline, the S-phase fraction, and the G₂-exceeding rate (11). The sum of these variables, termed stemline scatter index (SSI), enables us to

further divide aneuploid (A), diploid (D), and tetraploid (T) breast carcinomas into genomically stable and unstable subtypes. Separating genomically stable and unstable tumors using SSI has already been tested in a limited number of breast adenocarcinomas (11).

The aim of the present study was to investigate the clinical correlates and prognostic value of the SSI in a well-characterized consecutive series of 890 breast cancer patients.

Materials and Methods

Patients and Tumor Characteristics. Biopsies from 1,276 patients with primary breast adenocarcinomas were investigated. The patients underwent surgery in eight different hospitals within the Stockholm county between January 1990 and April 1993. The study was approved by the local ethical committee. None of the patients received any type of therapeutic treatment before surgery. From each tumor sample, imprints were taken for image cytometric DNA content determination, and 4 μm histologic sections were prepared for histopathologic assessment. To obtain a homogenous cohort for the follow-up study, we excluded each patient to whom at least one of the following criteria applied: (a) bilateral breast cancer, (b) noninvasive tumors, (c) other malignant tumors diagnosed before or during the follow-up time, (d) not primary operated, or (e) no longer registered as resident of Stockholm county.

After the selection process, the group studied comprised 890 remaining cases. All patients were under the standard protocol of the breast cancer treatment program of the Oncology Center Stockholm. Accordingly, all patients received total or partial mastectomy and, in addition, local radiation, antiestrogen, or cytostatic adjuvant treatment, depending on tumor size, lymph node, and estrogen receptor (ER) status and age. The histopathologic characteristics, tumor size, lymph node status, and malignancy grade (Elston grade) are documented in Table 1. During the study period, the frequency of surgical

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lymph node examination and the method used for histologic malignancy grading varied among the hospitals in the Stockholm county; this explains the relatively high percentages of nodal status and Elston grade which were not determined. However, within the genomically stable and unstable groups, missing status was not associated with survival (data not shown), so our results were not likely to be confounded by the missing data.

DNA Image Cytometry. Image cytometry was done on imprints taken from the biopsies and Feulgen stained to measure the nuclear DNA content of the tumor cells. The staining, the internal standardization and the tumor cell selection were based on previously described methods (6). All DNA values were calculated in relation to a corresponding staining control, which obtained the value 2c, denoting the diploid DNA content. On average, we measured 350 morphologically selected cells per taken imprint. The cell population of each specimen was characterized according to two principles based on nuclear DNA content measurements.

We divided the tumors into three ploidy categories: D stemline (1.8c-2.2c), and no cells exceeding 5c; T stemline (3.8c-4.2c) and <5% of the cells exceeding 5c; A stemline with one or more peaks outside the diploid or tetraploid region (6, 12). Furthermore, we measured the SSI of the 890 breast lesions, a measure of the percentage of tumor cells with nonmodal DNA content values, or of the degree of scattering of DNA histograms (11). The SSI is the sum of the percentage of cells with DNA content values in the S-phase region (S phase), plus the percentage of cells with DNA content values exceeding twice the modal value plus 1c (G_2 exceeding rate, or G_2 Exc), plus the coefficient of variation (CV) of the respective tumor stemline ($SSI = S \text{ phase} + G_2 \text{ Exc} + CV$). All cytometric measurements were done without knowledge of patient outcome.

We used an optimal cutoff value of SSI (8.8%; ref. 11) to differentiate between all lesions showing significantly scattered DNA histograms ($SSI > 8.8\%$) and those with insignificantly scattered ones ($SSI \leq 8.8\%$). Breast lesions with an $SSI \leq 8.8\%$ were termed genomically stable, and those with an $SSI > 8.8\%$ were termed genomically unstable. In short, genomically unstable tumors have high cell-to-cell variability in DNA content, whereas genomically stable tumors have low variability. Tumors with SSI values near the boundary value of

Table 2. Ploidy determination and SSI calculation

	All	Genomically stable	Genomically unstable
Aneuploid	524	78 (15%)	446 (85%)
Diploid	287	177 (62%)	110 (38%)
Tetraploid	79	41 (52%)	38 (48%)
All	890	296 (33%)	594 (67%)

8.8% are of uncertain status with respect to genomic stability. However, only ~5% of the tumors analyzed in this study had SSI values between 8.5% and 9.5%.

Statistical Analysis. Survival time was determined from the date of diagnosis until death or last follow-up date. The average follow-up time for the cohort of 890 breast cancer patients was 8.9 years. Breast cancer-specific mortality was our primary outcome. We also analyzed distant metastasis-free survival and overall death, but these results are not shown because they did not significantly differ from the cause-specific survival. For cause-specific event, the survival time was censored at other events or last follow-up date. Survival curves were computed using the standard Kaplan-Meier product limit estimator and were compared using log-rank statistics. To investigate the independent prognosis value of genomic instability, we analyzed subgroups defined by Elston grades 2 and 3, lymph node metastasis, and ER status. Elston grade 1 was not analyzed because there were too few individuals. A full multivariate model was not feasible because there was too much missing data when all the variables were analyzed jointly. For two-group comparisons, all *P* values are two sided. All data analyses, including the unpaired Student's *t* test, χ^2 test, and survival analysis, were done using the R statistical package.⁴

Results

DNA Image Analysis. Image cytometric measurements of 890 biopsies of primary breast carcinomas resulted in 524 A, 287 D, and 79 T tumors (Table 2). We determined 78 tumors to be of type A and genomically stable (Ags) and 446 Agu tumors. Furthermore, we measured 177 Dgs, 110 Dgu, 41 Tgs, and 38 Tgu specimens. Fifteen percent of all A carcinomas belonged to the Ags subgroup, 62% of the D tumors were Dgs, and 52% of the T were Tgs (Table 2).

Survival from Breast Cancer Death. A significantly better survival was seen for patients with genomically stable compared with genomically unstable breast carcinomas as determined by the SSI ($P = 2.7E-08$; Fig. 1). This finding was consistent over the three different ploidy groups: A ($P = 0.0038$), D ($P = 0.040$), and T ($P = 0.0081$) tumors (Fig. 1). In contrast, no significant survival difference could be seen between the three ploidy categories within the stable ($P = 0.23$) and unstable ($P = 0.12$) subtypes (data not shown). This indicates that genomic stability as measured by SSI rather than ploidy captures the metastatic potential of breast carcinomas. Similar results were found when distant metastasis-free and overall survival was analyzed.

The genomic instability seems to be a continuous, rather than a dichotomous, property. Breast tumors with an SSI value beyond the cutoff of 8.8% in particular showed continuous progression to higher instability. This tendency was apparent when we compared subgroups of patients with low SSI values ($n = 296$, mean = 6.5 ± 1.6), medium SSI

Table 1. Patient age and breast cancer characteristics

Age at diagnosis (y)	60.9 (26-93)
Histologic type	
Ductal	711 (80%)
Lobular	108 (12%)
Medullar	16 (2%)
Not specified	55 (6%)
Tumor stage*	
T _{1a}	8 (1%)
T _{1b}	102 (11%)
T _{1c}	440 (49%)
T ₂	307 (34%)
T ₃	22 (2%)
Not determined	11 (1%)
Nodal status*	
N ₀	345 (39%)
N ₁	284 (32%)
Not determined	261 (29%)
Elston grade [†]	
Grade 1	27 (3%)
Grade 2	134 (15%)
Grade 3	283 (32%)
Not determined	446 (50%)

*Tumor-node-metastasis classification (Union International Contre Cancer 1997).

[†]Elston-Ellis modification of Scarff-Bloom-Richardson grading system (C.W. Elston and J.O. Ellis).

⁴<http://www.r-project.org/>.

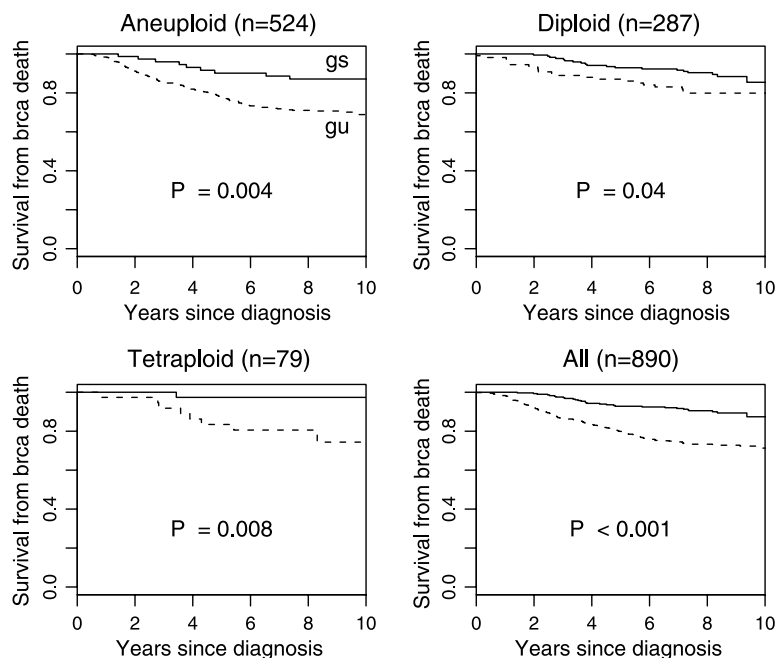


Figure 1. Survival from death due to breast cancer within different ploidy groups and overall. The patients are categorized to genomically stable (*gs*, solid curves) and unstable (*gu*, dashed curves) subtypes of diploid, tetraploid, and aneuploid breast carcinomas. The *P* value in each panel is from the two-sided log-rank test.

values ($n = 296$, mean = 12.6 ± 2.2), and high SSI values ($n = 297$, mean = 29.1 ± 13.0). There was a significant difference in breast cancer-specific survival between these subgroups ($P = 3.7E-11$; Fig. 2).

Other Putative Prognostic Factors. The Agu breast tumors were, on the average, 2.9 mm larger than Ags tumors ($P < 0.03$; Table 3), a difference also seen for D (2.9 mm) and T (4.5 mm) tumors but not reaching statistical significance in the latter two subgroups. Remarkably, genomic instability did not seem to be associated with local lymph node metastases (Table 4), suggesting that they can function as independent prognostic factors.

We found that Elston grades 1 and 2 tumors were more common in the genomically stable subtypes compared with the genomically unstable tumors, whereas grade 3 tumors were more abundant among genomically unstable tumors. Note also the increasing frequency of higher Elston grades among the genomically unstable tumors, but not among the genomically stable tumors. This difference was statistically significant in the A and D tumors (Table 5). Ags carcinomas comprised less grade 1 tumors (5%) than Dgs and Tgs tumors did (17% and 14%, respectively; Table 5).

There was no significant difference in ER and progesterone receptor status between the genomically stable and genomic-

cally unstable subtypes within the D and T tumors ($P = 1$; Tables 6 and 7). Within the A tumors, however, Agu carcinomas showed significantly more often ER and progesterone receptor negativity than Ags carcinomas ($P < 0.001$; Tables 6 and 7). Comparing Ags and Dgs subtypes, we did not detect any significant difference in hormone receptor status. However, comparing Ags and Tgs tumors, the Ags tumors showed significantly more ER positivity than the Tgs tumors did (Table 6).

Finally, we found that within the Elston grade 3, lymph node-positive, and ER-positive subgroups, patients with genomically unstable tumors had significantly worse survival compared with genomically stable tumors ($P = 0.01$, 0.002 , and $7.2E-5$, respectively; Fig. 3). Among all other subgroups, we observed the trend toward worse survival for the genomically unstable tumors, but they were not significant, mainly because there were too few events in these subgroups (Fig. 3).

Discussion

This study confirms that objective measurement of genomic instability by means of SSI allows tumor characterization into genomically stable and unstable subtypes with different clinical implications. Using information from 890 patients with primary breast cancers, we showed that (a) the genomically stable subtype had significantly better prognosis compared with genomically unstable subtype, consistently within A, D,

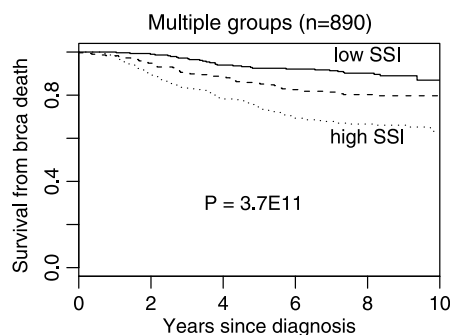


Figure 2. Survival from death due to breast cancer at low (solid curve), medium (dashed curve), and high (dotted curve) levels of genomic instability.

Table 3. Average tumor size in different ploidy groups

	Genomically stable		Genomically unstable		<i>P</i> *
	Tumor size [†]	<i>n</i>	Tumor size [†]	<i>n</i>	
Aneuploid	19.9 ± 10.4	77	22.8 ± 12.0	441	0.03
Diploid	17.9 ± 10.5	176	20.8 ± 13.3	108	0.06
Tetraploid	18.4 ± 10.0	40	22.9 ± 12.7	37	0.09
All	18.5 ± 10.4	293	22.4 ± 12.3	586	<10E-6

**P* value of Student's *t* test.

[†]Average tumor size in mm ± SD.

Table 4. Percentage of node-positive tumors in different ploidy groups

	All	Genomically stable*	Genomically unstable*	<i>P</i> [†]
Aneuploid	49% (191/387)	39% (22/57)	51% (169/330)	0.08
Diploid	35% (63/181)	31% (32/104)	40% (31/77)	0.21
Tetraploid	49% (30/61)	55% (17/31)	43% (13/30)	0.45
All	45% (284/629)	37% (71/192)	49% (213/437)	0.01

*Percentage and counts of node-positive tumors.

†*P* value of Fisher's exact test comparing genomically stable and unstable tumors.

or T tumors; (b) no survival difference could be seen between different ploidy categories within genomically stable and unstable tumors; (c) genomic instability was independent of lymph node metastasis; (d) Ags tumors were significantly smaller and more likely to be ER and progesterone receptor positive compared with Agu tumors; (e) among D and T tumors, genomic instability was independent of receptor status; and (f) Agu and Dgu carcinomas were more likely to be of Elston-Ellis grade 3 compared with their genomically stable counterparts.

These results indicate that human breast adenocarcinomas comprise two profoundly different subpopulations, the genomically stable and the unstable. The nature of this aspect of genomic stability is independent of the cytometric DNA-index value of the respective tumor stemline(s) and correlates with patient prognosis. In fact, it seems that genomic instability in terms of high variance of cellular DNA content is more directly related to prognosis than the average cell DNA content as measured by the standard ploidy categories. Intriguingly, genomic instability seems independent of lymph node metastasis, and among D and T tumors it is independent of hormone receptor status, which means that genomic instability can provide an independent prognostic value to these standard clinical factors. Hence, it seems that genomic instability is a marker of distant, but not local, metastasis. In contrast to lymph node status, Elston grade seems to determine breast tumor characteristics that are more closely related to genomic instability. We showed strong evidence that genomic instability does add extra information to these standard prognostic factors.

The genetically stable subpopulation is more prevalent in the D (62%) and T (52%) than in the A tumors, where only 15% of the tumors possessed a low percentage of cells with nonmodal DNA content. Genomic stability, as we have defined, measures how well the chromosomes are distributed or rearranged in the daughter cells during cell division, so its correlation with prognosis provides a direct evidence of the role of genomic instability in tumor progression. We are currently investigating differentially expressed proteins between the genomically stable and unstable breast tumors within various ploidy groups to further characterize this phenomenon of genomic instability.

Table 6. Percentage of ER-positive tumors in different ploidy groups

	All	Genomically stable*	Genomically unstable*	<i>P</i> [†]
Aneuploid	75% (351/467)	98% (55/56)	72% (296/411)	<2E-6
Diploid	95% (205/216)	95% (107/113)	95% (98/103)	1.00
Tetraploid	88% (44/50)	88% (15/17)	88% (29/33)	1.00
All	82% (600/733)	95% (177/186)	77% (423/547)	<3E-9

*Percentage and counts of ER-positive tumors.

†*P* value of Fisher's exact test comparing genomically stable and unstable tumors.

It is generally accepted that most cancers show genomic instability compared with their corresponding benign cells and that instability may occur at the nucleotide level or the chromosomal level (13). It has also been suggested that the instability caused by base alterations occurs in only a small subset of cancers, whereas the vast majority of cancers exhibit genomic instability at the chromosomal level (1). In leukemia, lymphomas and mesenchymal tumors, chromosomal translocations leading to fusion genes or transfer of genes to the promoter of another gene, are believed to be the important chromosomal aberrations (14, 15). In epithelial tumors, the predominant abnormalities causally involved in oncogenesis are thought to be gene mutations and deletions (16, 17), and four to seven somatic genetic alterations are thought necessary for development of cancer (18). This differential role of chromosomal translocations as initial events in epithelial and hematologic carcinogenesis might be because in leukemias, there exist a few translocations that are very frequent, whereas the rest is as rare as in the epithelial tumors. Furthermore, the cytogenetic analysis in solid tumors is more difficult than in hematologic malignancies (19).

Unstable breast tumors, as measured by high SSI, show a high percentage of DNA content values deviating from the mode of the distribution, which is a sign of clonal heterogeneity of the constituent tumor cells. They show cell cycle irregularities, as their cyclin A and E mRNA is highly overexpressed, and centrosome aberrations can be detected in a four times higher percentage of cells than in those of the stable subtype (11, 20). We received comparable results from investigating the genomically unstable breast cancer-derived cell line MDA-MB-231 (21). Considering the cell cycle irregularities and high percentage of tumor cells with centrosome aberrations, which, in turn, might be in part the cause of clonal heterogeneity through segregation errors of chromosomes at cell division, it seems quite unlikely that the aggressive unstable tumor type is caused solely by a few point mutations and deletions.

In summary, we believe that ploidy status and genomic stability of a specified human breast carcinoma is a promising prognostic factor that may complement established prognostic factors.

Table 5. Distribution of Elston grade in the different ploidy groups

	Genomically stable			Genomically unstable			<i>P</i> *
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3	
Aneuploid	5% (2/40)	60% (24/40)	35% (14/40)	3% (7/246)	20% (50/246)	77% (189/246)	<8E-7
Diploid	17% (14/81)	43% (35/81)	40% (32/81)	4% (2/47)	32% (15/47)	64% (30/47)	0.01
Tetraploid	14% (2/14)	36% (5/14)	50% (7/14)	0% (0/16)	31% (5/16)	69% (11/16)	0.27
All	13% (18/135)	47% (64/135)	39% (53/135)	3% (9/309)	23% (70/309)	74% (230/309)	<3E-12

NOTE: Elston grade is the Elston-Ellis modification of Scarff-Bloom-Richardson grading system.

**P* value of Fisher's exact test.

Table 7. Percentage of progesteron receptor-positive tumors in different ploidy groups

	All	Genomically stable*	Genomically unstable*	<i>P</i> [†]
Aneuploid	56% (255/456)	73% (41/56)	54% (214/400)	0.01
Diploid	75% (159/212)	75% (83/110)	75% (76/102)	0.88
Tetraploid	77% (37/48)	81% (13/16)	75% (24/32)	0.73
All	63% (451/716)	75% (137/182)	59% (314/534)	<7E-5

*Percentage and counts of progesterone receptor-positive tumors.

[†]*P* value of Fisher's exact test comparing genomically stable and unstable tumors.

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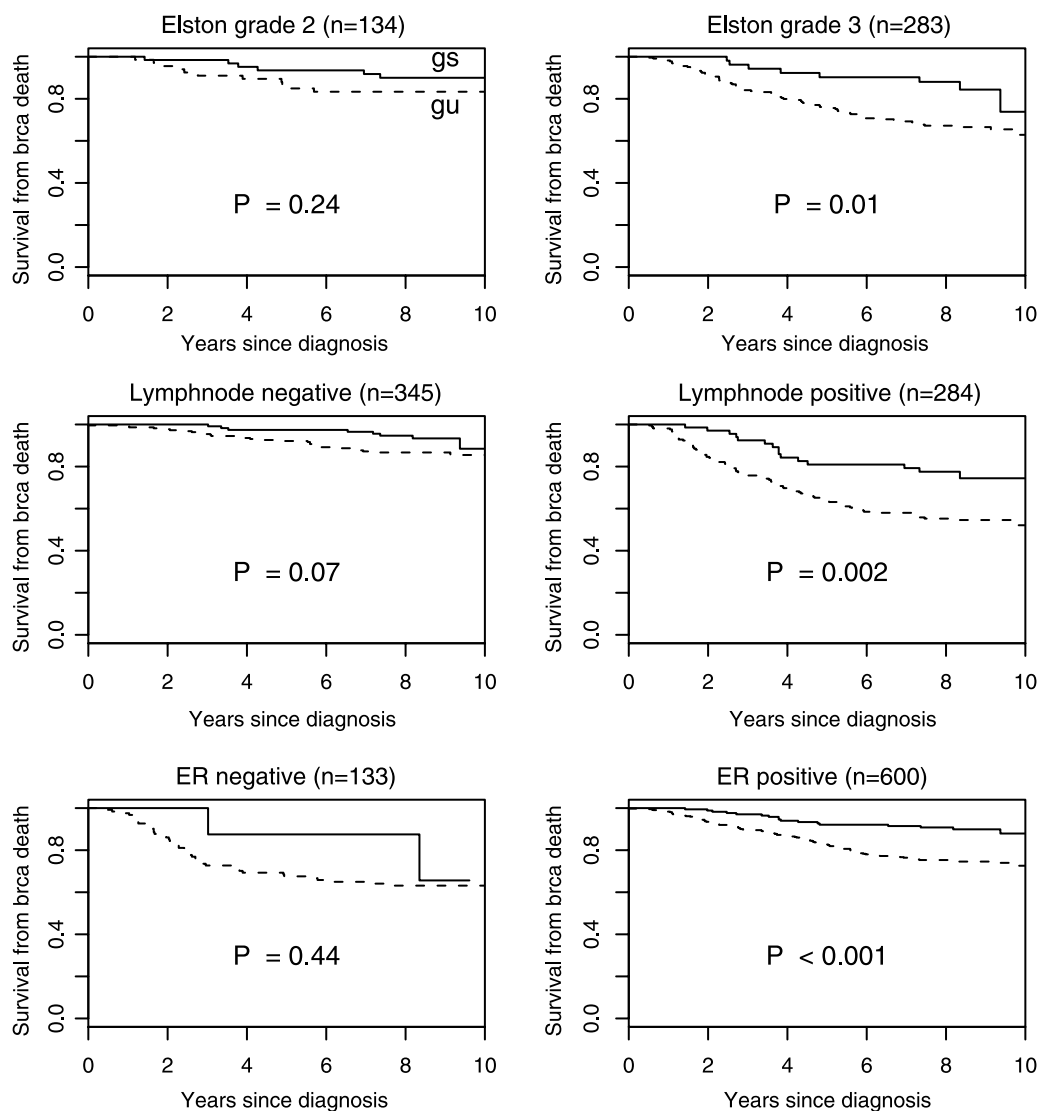


Figure 3. Survival from death due to breast cancer within standard clinical subgroups, including Elston grade, lymph node status, and ER status. The patients are categorized to genomically stable (solid curves) and unstable (dashed curves) subtypes. The *P* value in each panel is from the two-sided log-rank test.

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