Cancer
Research

Paradoxical Relationship between Chromosomal Instability and Survival Outcome in Cancer

Nicolai J. Birkbak[1,2], Aron C. Eklund[1], Qiyuan Li[1,2], Sarah E. McClelland[5], David Endesfelder[5], Patrick Tan[7,8], Iain B. Tan[9,10], Andrea L. Richardson[2,4], Zoltan Szallasi[1,3], and Charles Swanton[5,6]

Abstract

Chromosomal instability (CIN) is associated with poor prognosis in human cancer. However, in certain animal tumor models elevated CIN negatively impacts upon organism fitness, and is poorly tolerated by cancer cells. To better understand this seemingly contradictory relationship between CIN and cancer cell biological fitness and its relationship with clinical outcome, we applied the CIN70 expression signature, which correlates with DNA-based measures of structural chromosomal complexity and numerical CIN *in vivo*, to gene expression profiles of 2,125 breast tumors from 13 published cohorts. Tumors with extreme CIN, defined as the highest quartile CIN70 score, were predominantly of the estrogen receptor negative (ER⁻), basal-like phenotype and displayed the highest chromosomal structural complexity and chromosomal numerical instability. We found that the extreme CIN/ER⁻ tumors were associated with improved prognosis relative to tumors with intermediate CIN70 scores in the third quartile. We also observed this paradoxical relationship between CIN and prognosis in ovarian, gastric, and non–small cell lung cancer, with poorest outcome in tumors with intermediate, rather than extreme, CIN70 scores. These results suggest a nonmonotonic relationship between gene signature expression and HR for survival outcome, which may explain the difficulties encountered in the identification of prognostic expression signatures in ER⁻ breast cancer. Furthermore, the data are consistent with the intolerance of excessive CIN in carcinomas and provide a plausible strategy to define distinct prognostic patient cohorts with ER⁻ breast cancer. Inclusion of a surrogate measurement of CIN may improve cancer risk stratification and future therapeutic approaches. *Cancer Res; 71(10); 3447–52.* ©*2011 AACR.*

Introduction

Chromosomal instability (CIN) results in numerical and structural chromosomal complexity and is associated with poor prognosis in solid tumors (1, 2), and the acquisition of phenotypic variation promoting drug resistance in yeast models (3). In contrast, in mammalian cells and yeast models, aneuploidy may have a negative impact upon organism fitness and proliferation (4, 5). Indeed, CIN may confer both a tumor promoting and tumor suppressive function in animal model systems (6, 7). Excessive CIN can be introduced in model systems by inactivation of mitotic spindle checkpoint components; this results in gross aneuploidy and cell death (8). Accordingly, elevation of the frequency of chromosome missegregation has been proposed as a strategy to kill tumor cells (8, 9).

Such an opposing relationship suggests that there may be an optimal level of CIN for tumor progression, beyond which further instability provides no growth advantage that may even be deleterious for cancer cell survival (10) through an evolutionary scenario analogous to "mutational meltdown" in bacteria (11) or "error catastrophe" in viruses (12). However, it is not known whether CIN, over a certain threshold, may impact negatively on human tumor growth, or whether very high levels of CIN in human tumors might be associated with improved patient prognosis relative to intermediate levels. If such a relationship exists, it may have important implications for risk stratification and for future therapeutic approaches directed against CIN tumors.

The CIN70 expression signature was derived from a surrogate measure of CIN and is defined as the average expression of 70 genes that correlate with "total functional aneuploidy" in

Authors' Affiliations: [1]Center for Biological Sequence Analysis, Technical University of Denmark, Lyngby, Denmark; [2]Department of Cancer Biology, Dana-Farber Cancer Institute, and [3]Children's Hospital Informatics Program, Harvard Medical School; [4]Brigham and Women's Hospital, Boston, Massachusetts; [5]Translational Cancer Therapeutics Laboratory, CR-UK London Research Institute, London; [6]Royal Marsden Hospital, Downs Road, Sutton, United Kingdom; [7]Duke-NUS Graduate Medical School; [8]Cancer Sciences Institute of Singapore, and [9]Graduate School for Integrative Sciences and Engineering, National University of Singapore; and [10]Department of Medical Oncology, National Cancer Centre Singapore, Singapore

Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

N.J. Birkbak and A.C. Eklund contributed jointly to the work.

Corresponding Author: Charles Swanton, Translational Cancer Therapeutics Laboratory, CR-UK London Research Institute, 44 Lincoln's Inn Fields, London, UK. Phone: 44-207-269-3463; Fax: 44-20-7269-3094; E-mail: charles.swanton@cancer.org.uk or Zoltan Szallasi. E-mail: zszallasi@chip.org

AACR American Association for *Cancer Research*

solid tumors (1). Here we demonstrate that the CIN70 expression signature correlates with both structural chromosomal complexity and numerical CIN, and we use this signature to address the relationship between CIN and outcome in cancer.

Materials and Methods

Gene expression data sets

We obtained raw microarray expression data for 13 publicly available breast cancer cohorts (13–23) and GSE2109 and GSE16446, representing 2,125 individual patients. Additionally, we obtained gene expression data from 3 ovarian cancer cohorts (24–26), 2 squamous non–small cell lung cancer (NSCLC) cohorts (25, 27) and 1 gastric cancer cohort (28).

Data analysis

Duplicate patients were present in some cohorts, but were removed from the analysis. Censored recurrence-free or metastasis-free survival data were available for 1,168 breast cancer patients from 7 cohorts. Estrogen receptor (ER) and erythroblastic leukemia viral oncogene homolog 2 (ERBB2) status was inferred by k-medoids clustering of the expression levels of the *ESR1* and *ERBB2* genes, an approach that correlates well with histological assessment (29). CIN70 scores were calculated as the mean expression of the 70 probe sets matching the 70 genes of the CIN70 signature as described (1). For analysis of combined cohorts, CIN70 scores were first normalized within each cohort by centering the values, and then dividing by the standard deviation. All breast cancer samples in the combined cohorts were stratified into CIN70 quartiles according to the normalized CIN70 scores. These groups were fixed, and were not re-defined for analysis of specific subtypes. Thus, in analysis of specific subtypes, each quartile does not necessarily contain a quarter of the samples. Similarly, for nonbreast cancer cohorts, CIN70 quartiles were defined on the basis of all tumors of the given cancer type.

SNP-based measurements of CIN

Publicly available SNP data based on the Affymetrix 100 k platform (30), representing 281 breast tumor specimens with paired expression data (23), were acquired from GEO. We determined the genome integrity index (GII) as described (31). To determine the total number of DNA breakpoints, we counted the number of DNA segments with an inferred $\log_2$ ratio of greater than 0.3 or less than -0.3. The total number of LOH regions was inferred from regions of allelic imbalance (AI) as described (32). To determine a combined GII/copy number/LOH score, we linearly transformed each set of scores such that its values ranged between 0 and 1, with no aberrations/GII being assigned to 0, and the highest number of aberrations/highest GII score in our cohort assigned a value of 1. We defined the combined aberration score as the mean of the 3 transformed scores.

Statistical analysis

For the breast cancer cohorts and the gastric cancer cohort, survival analysis was performed with time to relapse or, if not available, time to distant metastasis as outcome variable. For the ovarian and squamous lung cohorts, the outcome variable was overall survival. Survival curves were calculated using the Kaplan–Meier method. For univariate Cox regression, significance was estimated with a log rank test. For multivariate regression, significance was estimated using a chi-squared test. In the meta-analyses, the summary estimate was calculated as a weighted average of the individual estimates, where summary weights were calculated as the reciprocal of the variance defined as the squared standard errors. All data analysis and statistics was performed in the R statistical environment version 2.11. All P values are 2 sided. Full methods are available in the Supplementary Methods section.

Results

CIN70 signature is a surrogate measure of structural chromosomal complexity and numerical CIN *in vivo*

To assess structural chromosomal complexity, we used a published cohort of 281 primary breast cancer tumors, 271 of which were profiled with paired SNP and mRNA expression arrays (23, 30). From the mRNA data, we calculated the CIN70 score. From the SNP data, we calculated 3 summary measures of structural chromosomal complexity: (i) the GII, a measure of the proportion of the cancer genome subject to copy number aberrations (31); (ii) the total number of DNA copy number changes; and (iii) the total number of genomic regions with AI (32), a measure correlated with loss of heterozygosity (LOH). Each of the 3 measures was positively and significantly correlated with the CIN70 score (Supplementary Fig. S1, a–c). We combined these 3 DNA-based measures into a single "structural chromosomal complexity" measurement (see the Supplementary Methods section), which was more strongly correlated with the CIN70 score than any of the individual measures (Supplementary Fig. S1d). We then stratified patients into CIN70 score quartiles and found that the tumors with the highest CIN70 score quartile displayed the highest mean structural chromosomal complexity (Fig. 1A), both in all tumors ($P = 1.8 \times 10^{-6}$, t test) and in ER$^-$/ERBB2$^-$ tumors only ($P = 0.0002$).

To address the relationship between the CIN70 score and numerical CIN, we analyzed a cohort of 44 breast cancers with paired DNA image cytometry and gene expression measurements (33) and stratified patients into CIN70 score quartiles. DNA image cytometry provides 2 relevant readouts: DNA index as a proxy for DNA ploidy; and stemline scatter index, discriminating genomically stable from genomically unstable tumors, providing a measure of numerical CIN (33). We found only a borderline significant enrichment of high DNA index in the highest CIN70 quartile ($P = 0.08$, t test; Fig. 1B). In contrast, we found a strong enrichment for genomically unstable tumors in the highest CIN70 quartile (OR $= 15.4$, $P = 0.0006$, Fisher's exact test; Fig. 1C), indicating that the CIN70 score more closely reflects numerical CIN than ploidy status. Together, these results demonstrate that the CIN70 score reflects both structural chromosomal complexity and numerical CIN. Furthermore, the greatest CIN was observed in the highest CIN70 score quartile, which we defined as CIN^{extreme}.
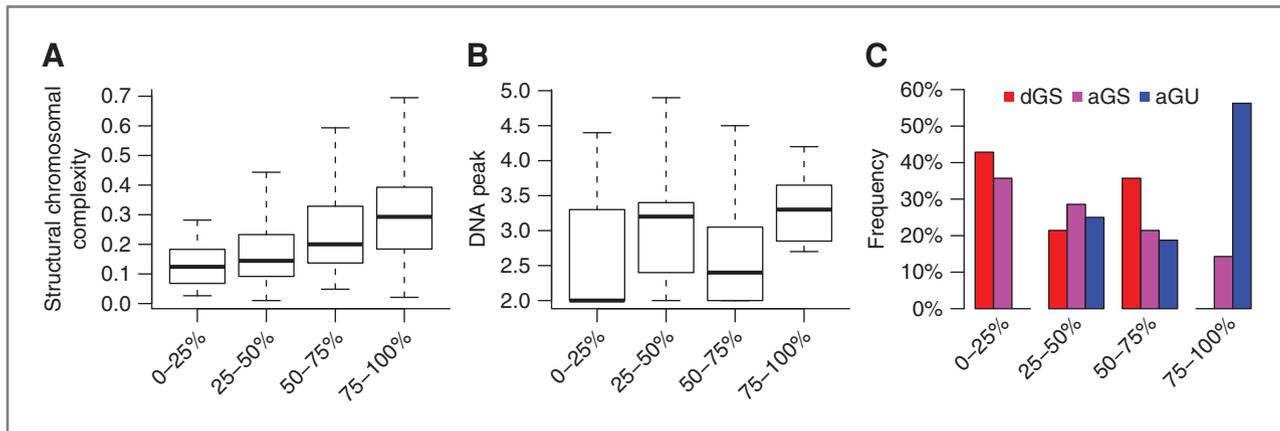
Figure 1. CIN70 score and structural chromosomal complexity. A, the structural chromosomal complexity score based on SNP array data is shown for each CIN70 quartile in 271 breast cancer samples. B, nuclear DNA content versus CIN70 quartile in 44 breast cancer samples. C, frequency of diploid, genomically stable (dGS); aneuploid, genomically stable (aGS); and aneuploid, genomically unstable (aGU) in each CIN70 quartile.

CIN70 distribution in breast tumor subtypes

To assess whether higher-risk breast cancer subtypes exhibit increased levels of tumor CIN, we investigated the distribution of the CIN70 score in ER^+, $ER^-/ERBB2^-$, and $ERBB2^+$ breast cancer subtypes in a pooled analysis of 2,125 patients from 13 publicly available microarray expression data sets. As ER and ERBB2 status were not available for all samples, we inferred ER and ERBB2 subtype from gene expression data using published methods (29). In general, ER^+ tumors displayed the lowest average CIN70 score, whereas $ER^-/ERBB2^-$ tumors displayed the highest average and the broadest distribution of CIN70 scores (Fig. 2A). The majority of $ER^-/ERBB2^-$ tumors occur in the $CIN^{extreme}$, highest CIN70 score quartile, whereas ER^+ breast cancers encompass the lower CIN70 score quartiles (Fig. 2B). We also analyzed CIN70 scores in tumors stratified by intrinsic subtype and noted higher scores in basal-like tumors ($P < 10^{-16}$, Supplementary Fig. S2a and b; ref 34).

Nonmonotonic relationship between CIN70 score and prognosis in $ER^-/ERBB2^-$ breast cancer

As we previously reported (1), a CIN70 score higher than the median was associated with significantly poorer outcome

when considering all patients (Supplementary Fig. S3). However, we hypothesized that if animal and eukaryotic cell models describing intolerance of high levels of CIN were relevant to human breast cancer (4, 5, 8), then excessive CIN, determined by the CIN70 expression signature in the $CIN^{extreme}$ quartile, might be associated with improved clinical outcome in breast cancer patient cohorts. Such an effect would manifest as a nonmonotonic relationship, showing first increasing then decreasing risk of relapse as a function of increasing CIN70 score. $ER^-/ERBB2^-$ breast cancer is considered a high-risk subtype and displays both the greatest range of CIN70 scores and the highest frequency of $CIN^{extreme}$ tumors, providing a relevant patient cohort to address whether $CIN^{extreme}$ might be associated with improved prognosis relative to tumors with intermediate CIN.

In the combined $ER^-/ERBB2^-$ cohort of 265 patients, we observed better clinical outcome for patients with $CIN^{extreme}$ tumors (highest CIN70 score quartile) compared with patients with tumors in the third CIN70 score quartile (Fig. 3A, HR = 0.55, $P = 0.021$, log-rank test). To confirm that this finding was not an artifact of the combined cohort, we also performed a meta-analysis of the individual data

Figure 2. Distribution of CIN70 scores across breast cancer subtypes. A, overall distribution of CIN70 scores across 2,125 breast cancer patients stratified by ER and ERBB2 receptor subtype. Percentages on y-axis denote quartile thresholds. B, distribution of each breast cancer subtype within each of the 4 CIN70 score quartiles.
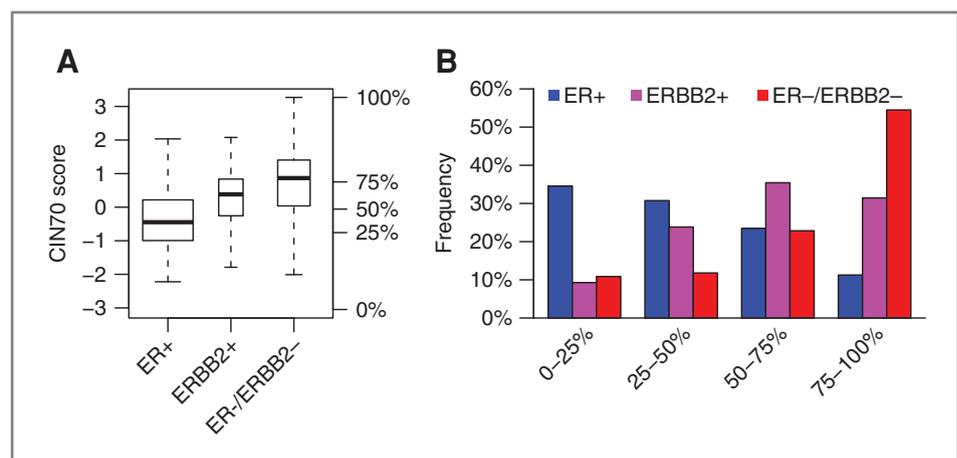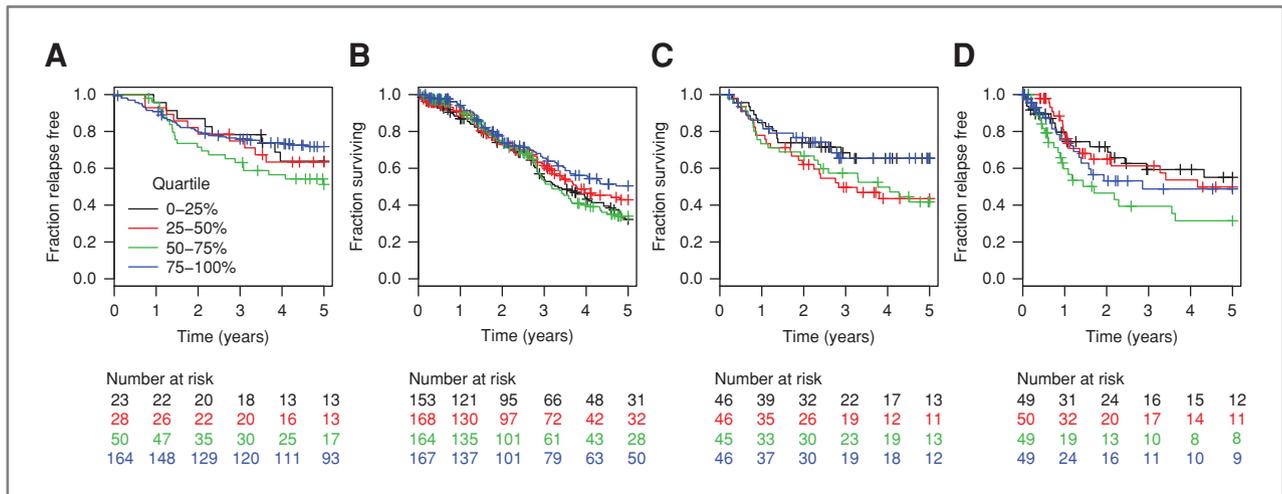
Figure 3. Survival of cancer patients stratified by CIN70 score quartile. Kaplan–Meier survival curves are presented for (A) 265 ER$^-$/ERBB2$^-$ breast cancer patients with recurrence-free or distant metastasis-free survival, (B) 652 patients with ovarian cancer, (C) 183 patients with squamous NSCLC, (D) 197 patients with gastric cancer.

sets, with a similar result (Supplementary Fig. S4, HR = 0.51, P = 0.017). When the cohorts were separated into those patients treated with and without adjuvant therapy, the same relationship was observed, indicating that improved outcome in CIN^{extreme} tumors appears to be independent of treatment (data not shown). In a multivariate analysis of ER$^-$/ERBB2$^-$ patients including age, grade, nodal status, size, and CIN^{extreme} versus third CIN70 score quartiles, CIN^{extreme} was a significant predictor of improved recurrence-free survival (HR = 0.40, P = 0.03, Supplementary Table S1). This difference in predicted relapse-free survival between tumors in the CIN^{extreme} cohort compared with tumors in the third CIN70 score quartile was not detected with Adjuvant!Online (Supplementary Fig. S5, P = 0.60, t test), indicating that standard histopathological approaches do not distinguish these 2 groups.

CIN^{extreme} is associated with improved prognosis in ovarian cancer, squamous NSCLC, and gastric adenocarcinoma

To investigate whether the improved survival observed for patients with CIN^{extreme} tumors was specific for ER$^-$/ERBB2$^-$ breast cancers or was a more general phenomenon in epithelial carcinomas, we acquired data from 3 ovarian carcinoma cohorts, 2 squamous NSCLC cohorts, and a gastric cancer cohort (see Supplementary Methods section). In the ovarian carcinoma meta-data set, CIN^{extreme} tumors were associated with improved recurrence-free survival relative to tumors in the third CIN70 score quartile (Fig. 3B), as observed in the breast carcinoma cohorts. A similar relationship was observed in squamous NSCLC, although CIN^{extreme} was associated with improved prognosis relative to the 2 middle CIN70 score quartiles (Fig. 3C). In the gastric cancer cohort, CIN^{extreme} was associated with similar prognosis to the 2 lowest CIN quartiles, and the third CIN quartile was associated with the poorest prognosis (Fig. 3D).

When we specifically assessed the HR for relapse for each of the 4 CIN quartiles relative to patients in the remaining 3 quartiles in a meta-analysis of the 1,297 patients across the 4 epithelial carcinoma subtypes (ER$^-$/ERBB2$^-$ breast, ovarian, squamous NSCLC, and gastric cancer), the CIN^{extreme} quartile was associated with a significantly improved HR (HR = 0.70, P = 0.0001), in contrast to the third CIN70 score quartile carcinomas which were associated with a significantly worse HR for relapse (HR = 1.32, P = 0.001; Fig. 4; Supplementary Fig. S6a–d). This result is consistent with a nonmonotonic relationship between CIN and outcome, with carcinomas in
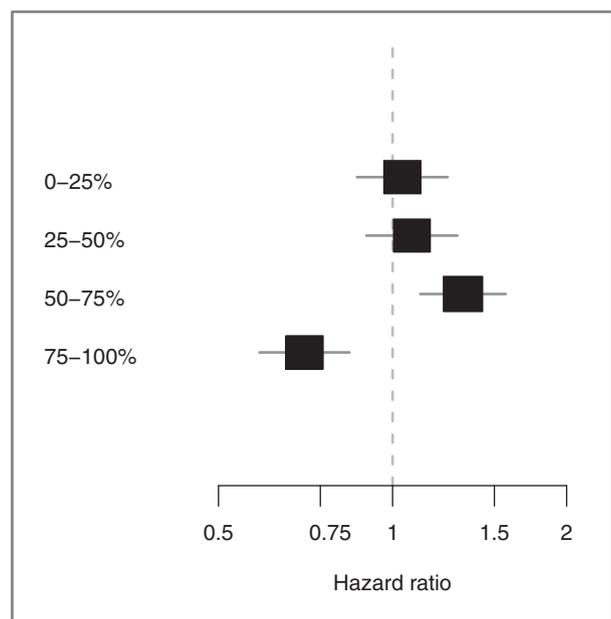

Figure 4. Quartile HR. Forest plots showing the HR of the quartiles. The HR of each quartile is based on a summary estimate of ER$^-$/ERBB2$^-$ breast tumors, ovarian tumors, squamous NSCLC, and gastric tumors.

the CIN^{extreme} score quartile having the best prognosis, whereas carcinomas in the intermediate third CIN70 score quartile are associated with the poorest clinical outcome.

Discussion

Our results based on the CIN70 signature support the hypothesis that although genomic instability improves cancer cell biological fitness and may impact adversely on prognosis, excessive genomic instability may surpass a threshold compatible with cell viability (10). This suggestion is supported by evidence that aneuploidy in eukaryotic cell systems negatively impacts upon cell biological fitness (4, 5) and excessive CIN may induce cell autonomous lethality (8, 9). Given the nonmonotonic nature of the relationship between CIN expression and prognosis, therapeutic strategies to modulate genomic instability may provide a rational approach for future drug development (8, 9). We have presented evidence that the CIN70 signature correlates with both structural chromosome complexity, an expected finding due to the derivation of this signature from a surrogate measure of CIN known as "total functional aneuploidy" (1), and numerical CIN measured by DNA image cytometry, and thus may serve as a stratification tool for genome instability within clinical cohorts.

Development of robust methods to predict patient outcome in ER$^-$ breast cancer is of paramount importance to enhance personalized treatment stratification approaches in this disease. Prognostic expression signatures in ER$^+$ breast cancer such as those underlying the Mammaprint and Oncotype DX tests have been shown to predict tumor genome instability status (33) but have limited prognostic value in ER$^-$ breast cancer (35). Our results derived from a plausible biological hypothesis, demonstrating a nonmonotonic relationship between CIN70 expression and clinical outcome, begin to define an ER$^-$ patient cohort with extreme CIN associated with good prognosis and a cohort with intermediate CIN associated with the worst prognosis, independent of standard histopathological criteria. This nonmonotonic relationship between expression and survival provides a basis for the difficulties encountered in applying "prognostic" gene expression signature sets, which also predict genome instability status, to ER$^-$ breast cancer outcome (35).

In summary, the classification of tumor CIN status might be considered for incorporation into new prognostic models in cancer to validate this approach and form the basis for novel treatment strategies to improve patient prognosis and clinical outcome directed against this pattern of genome instability.

Disclosure of Potential Conflicts of Interest

Grant Support

References

1. Carter SL, Eklund AC, Kohane IS, Harris LN, Szallasi Z. A signature of chromosomal instability inferred from gene expression profiles predicts clinical outcome in multiple human cancers. Nat Genet 2006;38:1043–8.
2. Walther A, Houlston R, Tomlinson I. Association between chromosomal instability and prognosis in colorectal cancer: a meta-analysis. Gut 2008;57:941–50.
3. Pavelka N, Rancati G, Zhu J, Bradford WD, Saraf A, Florens L, et al. Aneuploidy confers quantitative proteome changes and phenotypic variation in budding yeast. Nature 2010;468:321–5.
4. Torres EM, Sokolsky T, Tucker CM, Chan LY, Boselli M, Dunham MJ, et al. Effects of aneuploidy on cellular physiology and cell division in haploid yeast. Science 2007;317:916–24.
5. Williams BR, Prabhu VR, Hunter KE, Glazier CM, Whittaker CA, Housman DE, et al. Aneuploidy affects proliferation and spontaneous immortalization in mammalian cells. Science 2008;322: 703–9.
6. Schvartzman JM, Sotillo R, Benezra R. Mitotic chromosomal instability and cancer: mouse modelling of the human disease. Nat Rev Cancer 2010;10:102–15.
7. Baker DJ, Jin F, Jeganathan KB, van Deursen JM. Whole chromosome instability caused by Bub1 insufficiency drives tumorigenesis through tumor suppressor gene loss of heterozygosity. Cancer Cell 2009;16:475–86.
8. Kops GJ, Foltz DR, Cleveland DW. Lethality to human cancer cells through massive chromosome loss by inhibition of the mitotic checkpoint. Proc Natl Acad Sci U S A 2004;101:8699–704.
9. Janssen A, Kops GJ, Medema RH. Elevating the frequency of chromosome mis-segregation as a strategy to kill tumor cells. Proc Natl Acad Sci U S A 2009;106:19108–13.
10. Cahill DP, Kinzler KW, Vogelstein B, Lengauer C. Genetic instability and darwinian selection in tumours. Trends in cell biology 1999;9:M57–M60.
11. Lynch M, Burger R, Butcher D, Gabriel W. The mutational meltdown in asexual populations. J Heredity 1993;84:339–44.
12. Eigen M. Error catastrophe and antiviral strategy. Proc Natl Acad Sci U S A 2002;99:13374–6.
13. Andre F, Job B, Dessen P, Tordai A, Michiels S, Liedtke C, et al. Molecular characterization of breast cancer with high-resolution oligonucleotide comparative genomic hybridization array. Clin Cancer Res 2009;15:441–51.
14. Chin K, DeVries S, Fridlyand J, Spellman PT, Roydasgupta R, Kuo WL, et al. Genomic and transcriptional aberrations linked to breast cancer pathophysiologies. Cancer Cell 2006;10:529–41.
15. Desmedt C, Haibe-Kains B, Wirapati P, Buyse M, Larsimont D, Bontempi G, et al. Biological processes associated with breast cancer clinical outcome depend on the molecular subtypes. Clin Cancer Res 2008;14:5158–65.
16. Hess KR, Anderson K, Symmans WF, Valero V, Ibrahim N, Mejia JA, et al. Pharmacogenomic predictor of sensitivity to preoperative chemotherapy with paclitaxel and fluorouracil, doxorubicin, and cyclophosphamide in breast cancer. J Clin Oncol 2006;24:4236–44.
17. Lu X, Wang ZC, Iglehart JD, Zhang X, Richardson AL. Predicting features of breast cancer with gene expression patterns. Breast Cancer Res Treat 2008;108:191–201.

18. Miller LD, Smeds J, George J, Vega VB, Vergara L, Ploner A, et al. An expression signature for p53 status in human breast cancer predicts mutation status, transcriptional effects, and patient survival. Proc Natl Acad Sci U S A 2005;102:13550–5.

19. Minn AJ, Gupta GP, Siegel PM, Bos PD, Shu W, Giri DD, et al. Genes that mediate breast cancer metastasis to lung. Nature 2005;436:518–24.

20. Pawitan Y, Bjohle J, Amler L, Borg AL, Egyhazi S, Hall P, et al. Gene expression profiling spares early breast cancer patients from adjuvant therapy: derived and validated in two population-based cohorts. Breast Cancer Res 2005;7:R953–64.

21. Silver DP, Richardson AL, Eklund AC, Wang ZC, Szallasi Z, Li Q, et al. Efficacy of neoadjuvant Cisplatin in triple-negative breast cancer. J Clin Oncol 2010;28:1145–53.

22. Sotiriou C, Wirapati P, Loi S, Harris A, Fox S, Smeds J, et al. Gene expression profiling in breast cancer: understanding the molecular basis of histologic grade to improve prognosis. J Natl Cancer Inst 2006;98:262–72.

23. Wang Y, Klijn JG, Zhang Y, Sieuwerts AM, Look MP, Yang F, et al. Gene-expression profiles to predict distant metastasis of lymph-node-negative primary breast cancer. Lancet 2005;365:671–9.

24. NCI. The Cancer Genome Atlas (TGCA). Available at: http://cancer-genome.nih.gov/

25. Bild AH, Yao G, Chang JT, Wang Q, Potti A, Chasse D, et al. Oncogenic pathway signatures in human cancers as a guide to targeted therapies. Nature 2006;439:353–7.

26. Dressman HK, Berchuck A, Chan G, Zhai J, Bild A, Sayer R, et al. An integrated genomic-based approach to individualized treatment of patients with advanced-stage ovarian cancer. J Clin Oncol 2007;25:517–25.

27. Raponi M, Zhang Y, Yu J, Chen G, Lee G, Taylor JM, et al. Gene expression signatures for predicting prognosis of squamous cell and adenocarcinomas of the lung. Cancer Res 2006;66:7466–72.

28. Ooi CH, Ivanova T, Wu J, Lee M, Tan IB, Tao J, et al. Oncogenic pathway combinations predict clinical prognosis in gastric cancer. PLoS Genet 2009;5:e1000676.

29. Gong Y, Yan K, Lin F, Anderson K, Sotiriou C, Andre F, et al. Determination of oestrogen-receptor status and ERBB2 status of breast carcinoma: a gene-expression profiling study. The lancet oncology 2007;8:203–11.

30. Zhang Y, Martens JW, Yu JX, Jiang J, Sieuwerts AM, Smid M, et al. Copy number alterations that predict metastatic capability of human breast cancer. Cancer Res 2009;69:3795–801.

31. Chin SF, Teschendorff AE, Marioni JC, Wang Y, Barbosa-Morais NL, Thorne NP, et al. High-resolution aCGH and expression profiling identifies a novel genomic subtype of ER negative breast cancer. Genome Biol 2007;8:R215.

32. Li C, Beroukhim R, Weir BA, Winckler W, Garraway LA, Sellers WR, et al. Major copy proportion analysis of tumor samples using SNP arrays. BMC bioinformatics 2008;9:204.

33. Habermann JK, Doering J, Hautaniemi S, Roblick UJ, Bundgen NK, Nicorici D, et al. The gene expression signature of genomic instability in breast cancer is an independent predictor of clinical outcome. Int J Cancer 2009;124:1552–64.

34. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. Nature 2000;406:747–52.

35. Teschendorff AE, Miremadi A, Pinder SE, Ellis IO, Caldas C. An immune response gene expression module identifies a good prognosis subtype in estrogen receptor negative breast cancer. Genome Biol 2007;8:R157.

Cancer Research

AACR American Association for Cancer Research

Paradoxical Relationship between Chromosomal Instability and Survival Outcome in Cancer

Nicolai J. Birkbak, Aron C. Eklund, Qiyuan Li, et al.

Updated version	Access the most recent version of this article at: doi:10.1158/0008-5472.CAN-10-3667
Supplementary Material	Access the most recent supplemental material at: http://cancerres.aacrjournals.org/content/suppl/2011/01/26/0008-5472.CAN-10-3667.DC1

Cited articles	This article cites 34 articles, 14 of which you can access for free at: http://cancerres.aacrjournals.org/content/71/10/3447.full#ref-list-1
Citing articles	This article has been cited by 41 HighWire-hosted articles. Access the articles at: http://cancerres.aacrjournals.org/content/71/10/3447.full#related-urls

E-mail alerts	Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions	To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
Permissions	To request permission to re-use all or part of this article, use this link http://cancerres.aacrjournals.org/content/71/10/3447. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.