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Short Commentary Open Access

Meta-analysis of Aurora Kinase A (AURKA) Expression Data Reveals a Significant Correlation between Increased AURKA Expression and Distant Metastases in Human ER-positive Breast Cancers

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Of all human carcinomas, breast cancer (BrCa) is worldwide the most frequently occurring tumor in women [1]. Most breast cancer patients succumb to their disease as a result of tumor metastasis [2,3]. It is therefore important to elucidate the factors which effect BrCa progression, therapy resistance and metastasis. Accumulated evidence could demonstrate that breast cancer is a very complex and intrinsically heterogeneous disease, which progresses through accumulation of genomic aberrations that enable development of cancer-specific pathophysiological changes such as unlimited growth in even nutrient limited environments and metastasis to distant organs [4,5]. Recent advances in technology, such as DNA and RNA microarrays, have allowed to deconvolute some of the heterogeneity and complexity of somatic BrCa genetics. Using RNA microarray-derived expression data, breast cancer has been classified into five molecular subtypes: normal breast like, luminal A, luminal B, HER2$^+$/ERBB2$^+$, and basal-like. Among these molecular subtypes, basal-type breast cancer is associated with a most aggressive growth and poor prognosis [6]. Based on these molecular findings, some improvements have been made in diagnosis and treatment of breast cancer. However, for most patients, the prognosis and disease-free survival times have not changed dramatically. This is likely due to mechanisms by which gene amplifications affect survival or other aspects of cancer pathophysiology most of which are not well understood. Thus, mechanistic and functional studies of molecular changes in breast cancer-are urgently required.

The long arm of human chromosome 20, termed 20q, is frequently found amplified in a wide variety of human solid tumors among them BrCa [7-12]. Several studies reported that amplification of 20q is associated with poor clinical outcome of cancer and serve as an indicator for cancer progression and metastasis [7,13]. Multiple genes encoded on 20q have been identified as candidate oncogenes in BrCa including Aurora-A kinase (AURKA) [14,15], ZNF217 [16], UBE2C [17] and TPX2 [18]. AURKA is a key regulator of chromosome segregation and cytokinesis [14,15,19]. Over expression of AURKA in tumors is correlated with clinically aggressive disease [20]. A wealth of functional data exists showing that over expression of AURKA leads to centrosome amplification, chromosomal instability and oncogenic transformation [14,15,21-23]. Furthermore, over expression of AURKA in transgenic mouse models resulted in the development of mammary gland tumors [24,25]. These data indicate that AURKA possesses oncogenic activity and may be a valuable therapeutic target in cancer therapy [26,27]. Consequently, several small-molecule inhibitors of Aurora-A kinase have been developed and are currently undergoing clinical trials [28].

We conducted a meta-analysis of AURKA expression in human breast cancer samples using Breast Cancer Gene-Expression Miner v3.0 (bc-GenExMiner v3.0) software [29,30]. Consistent with recent reports [31], patients with high *AURKA* mRNA expression levels (greater than median expression) had significantly decreased survival (any event [AE]) compared to those with low *AURKA* mRNA levels (less than median expression) (hazard ratio (HR) =1.62; 95% CI: 1.44-1.83; p<0.0001) (Figure 1A). Surprisingly, we also found that high *AURKA* mRNA levels significantly decreased metastatic relapse (MR)-free survival (HR=1.75; 95% CI: 1.50-2.05; p<0.0001) (Figure 1B).

Estrogen receptor (ER) and nodal status in breast cancer is an important predictor of recurrence and greatly influences treatment regimens. We, therefore, performed univariate Cox proportional hazards model analysis on each of the 18 possible pools corresponding to every combination of population (nodal and estrogen receptor status) and event criteria (MR or any event [AE]) to assess the prognostic impact of *AURKA* expression on patients with different ER and nodal statuses. As summarized in table 1, we found that high *AURKA* expression shortened both AE- and MR-free survival only in the groups of ER$^+$ or ER^m patients, not in the group of ER$^-$ patients. To further clarify these results, we performed a subset analysis of *AURKA* in ER-positive and ER-negative tumors. High levels of *AURKA* expression were significantly associated with shorter AE- and MR-free survival in patients with ER-positive, but not ER-negative tumors (Figures 1C-F).

The molecular subtype of human BrCa is another important prognostic factor. Therefore, the tumors were assigned into normal-like, luminal A, luminal B, HER2$^+$, and basal-like subtype based on criteria described by Hu et al. [32]. This resulted in samples assigned as normal-like (n=451), luminal A (n=720), luminal B (n=507), HER2$^+$ (n=255), basal-like (n=652), or unclassified (n=329). Overall, expression levels of *AURKA* were highest in basal-like tumors and lowest in normal-like tumors. However, it is interesting to note that, among these groups, in normal-like, luminal A as well as B subtypes, patients with high expression levels of *AURKA* presented with significantly decreased AE-free survival (in normal-like subtype: HR=1.39; 95% CI:1.01-1.91; p=0.040; in luminal A subtype: HR=1.34; 95% CI: 1.06-1.70; p=0.014, and in luminal B subtype: HR=1.18; 95% CI:1.02-1.36; p=0.030). On the other hand, there was no significant effect of *AURKA* expression levels on AE-free survival in HER2$^+$ and basal-like subtype (in HER$^+$

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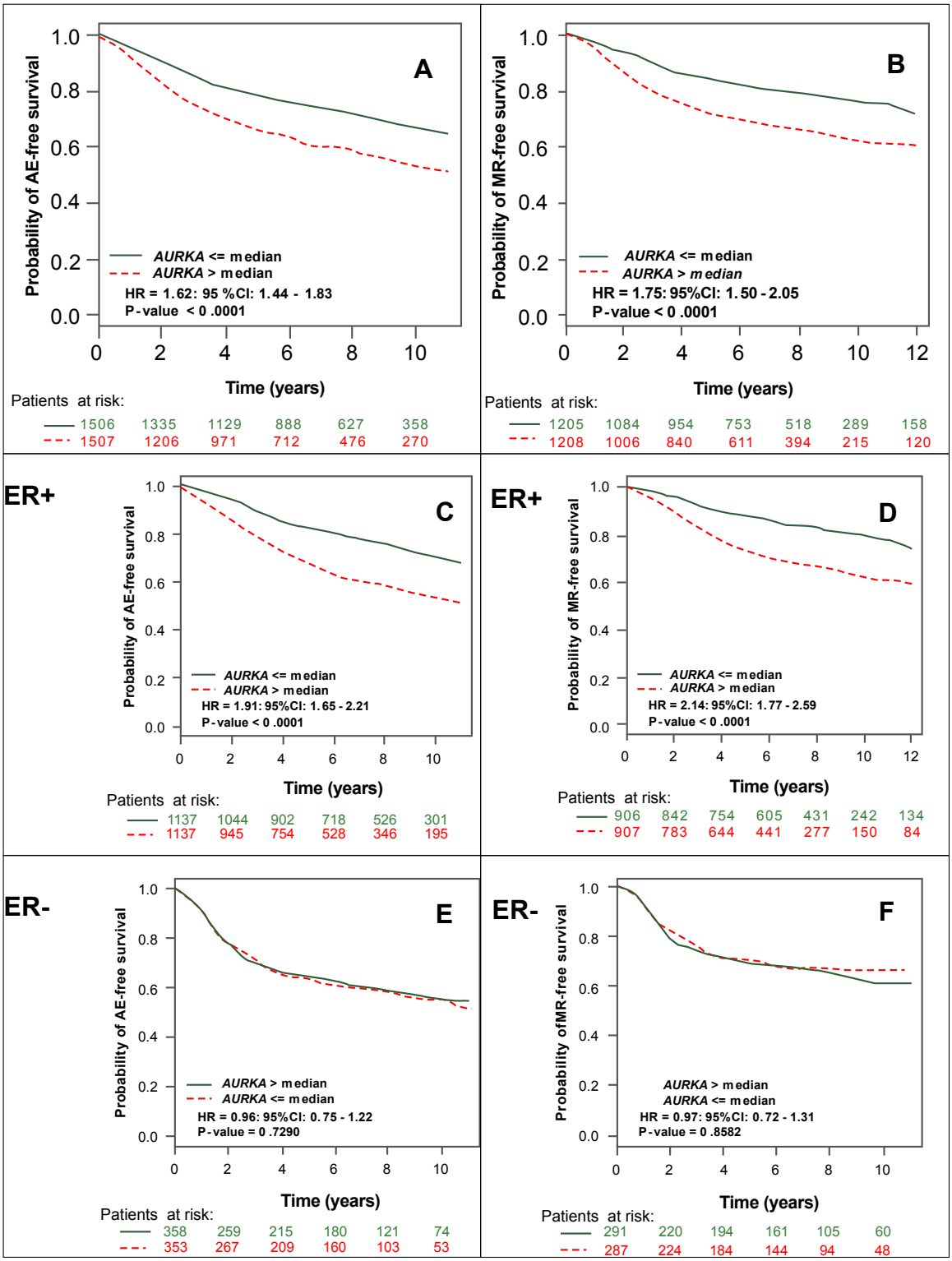

Figure 1: Evaluating the prognostic impact of *AURKA* mRNA expression on any event (AE) and metastatic relapse (MR)-free survival. Kaplan-Meier's survival curves for breast cancer patients according to tumor expression of *AURKA* are presented. The p values shown were obtained from a long-rank test among two groups. (A) Association of *AURKA* expression with AE-free survival. (B) Association of *AURKA* expression with MR-free survival. (C-F) Effect of *AURKA* expression levels on AE- and MR-free survival according to ER status. Kaplan-Meier estimates of AE- and MR-free survival according to the *AURKA* expression levels are shown. The p values were obtained from a long-rank test among two groups.

	Population and event criteria			p-Value	HR (95% CI)	No. Patients	No. Events
	Node status	ER Status	Event				
1	Nm	ER+	AE	<0.0001	1.40 (1.30-1.52)	2274	769
2	Nm	ERm	AE	<0.0001	1.32 (1.23-1.40)	3013	1076
3	Nm	ER+	MR	<0.0001	1.46 (1.33-1.62)	1813	463
4	Nm	ERm	MR	<0.0001	1.37 (1.26-1.48)	2413	658
5	N-	ER+	AE	<0.0001	1.45 (1.30-1.61)	1357	404
6	N-	ERm	AE	<0.0001	1.33 (1.21-1.45)	1760	568
7	N-	ER+	MR	<0.0001	1.48 (1.31-1.69)	1176	272
8	N-	ERm	MR	<0.0001	1.34 (1.20-1.49)	1539	385
9	N+	ERm	MR	0.0001	1.33 (1.15-1.53)	643	217
10	N+	ERm	AE	0.0008	1.21 (1.08-1.36)	816	376
11	N+	ER+	MR	0.0009	1.34 (1.13-1.60)	506	162
12	N+	ER+	AE	0.0051	1.22 (1.06-1.39)	640	278
13	N+	ER-	MR	0.2322	1.21 (0.89-1.65)	133	55
14	N+	ER-	AE	0.2566	1.14 (0.91-1.44)	172	98
15	Nm	ER-	AE	0.3084	1.07 (0.94-1.23)	711	300
16	N-	ER-	MR	0.4299	0.91 (0.73-1.15)	347	111
17	Nm	ER-	MR	0.4505	1.07 (0.90-1.26)	578	191
18	N-	ER-	AE	0.9803	1.00 (0.82-1.22)	383	159

Node or ER status (+: positive, -: negative, m: mixed); AE: any event; MR: metastatic relapse; HR: hazards ratio

Table 1: Prognostic impact of *AURKA* expression level in 18 possible pools corresponding to every combination of populations (nodal and estrogen receptor status).

subtype: HR=1.06; 95% CI: 0.76-1.46; p=0.74, and in basal-like subtype: HR=0.94; 95% CI: 0.78-1.13; p=0.50).

In conclusion, the meta-analysis of transcriptional profiles showed that *AURKA* expression levels may be a useful prognostic factor for patients with ER-positive, normal-like and luminal A- or B-type BrCa tumors.

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Conflict of Interest

The authors declare no conflict of interest.

References

1. Siegel R, Naishadham D, Jemal A (2012) Cancer statistics, 2012. CA Cancer J Clin 62: 10-29.
2. Grayson M (2012) Breast cancer. Nature 485: S49.
3. Rice J (2012) Metastasis: The rude awakening. Nature 485: S55-57.
4. Almendro V, Fuster G (2011) Heterogeneity of breast cancer: etiology and clinical relevance. Clin Transl Oncol 13: 767-773.
5. Di Cosimo S, Baselga J (2010) Management of breast cancer with targeted agents: importance of heterogeneity. Nat Rev Clin Oncol 7: 139-147.
6. Carey L, Winer E, Viale G, Cameron D, Gianni L (2010) Triple-negative breast cancer: disease entity or title of convenience?. Nat Rev Clin Oncol 7: 683-692.
7. Wullich B, Riedinger S, Brinck U, Stoeckle M, Kamradt J, et al. (2004) Evidence for gains at 15q and 20q in brain metastases of prostate cancer. Cancer Genet Cytogenet 154: 119-123.
8. Tsafrir D, Bacolod M, Selvanayagam Z, Tsafrir I, Shia J, et al. (2006) Relationship of gene expression and chromosomal abnormalities in colorectal cancer. Cancer Res 66: 2129-2137.
9. Scotto L, Narayan G, Nandula SV, Arias-Pulido H, Subramaniyam S, et al. (2008) Identification of copy number gain and overexpressed genes on chromosome arm 20q by an integrative genomic approach in cervical cancer: potential role in progression. Genes Chromosomes Cancer 47: 755-765.
10. Ramakrishna M, Williams LH, Boyle SE, Bearfoot JL, Sridhar A, et al. (2010) Identification of candidate growth promoting genes in ovarian cancer through integrated copy number and expression analysis. PLoS One 5: e9983.
11. van Dekken H, Paris PL, Albertson DG, Alers JC, Andaya A, et al. (2004) Evaluation of genetic patterns in different tumor areas of intermediate-grade prostatic adenocarcinomas by high-resolution genomic array analysis. Genes Chromosomes Cancer 39: 249-256.
12. Karhu R, Mahlamaki E, Kallioniemi A (2006) Pancreatic adenocarcinoma -- genetic portrait from chromosomes to microarrays. Genes Chromosomes Cancer 45: 721-730.
13. Postma C, Terwischa S, Hermsen MA, van der Sijp JR, Meijer GA (2007) Gain of chromosome 20q is an indicator of poor prognosis in colorectal cancer. Cell Oncol 29: 73-75.
14. Fu J, Bian M, Jiang Q, Zhang C (2007) Roles of Aurora kinases in mitosis and tumorigenesis. Mol Cancer Res 5: 1-10.
15. Vader G, Lens SM (2008) The Aurora kinase family in cell division and cancer. Biochim Biophys Acta 1786: 60-72.
16. Littlepage LE, Adler AS, Kouros-Mehr H, Huang G, Chou J et al. (2012) The transcription factor ZNF217 is a prognostic biomarker and therapeutic target during breast cancer progression. Cancer Discov 2: 638-651.
17. Hao Z, Zhang H, Cowell J (2012) Ubiquitin-conjugating enzyme UBE2C: molecular biology, role in tumorigenesis, and potential as a biomarker. Tumour Biol 33: 723-730.

18. Aguirre-Portoles C, Bird AW, Hyman A, Canamero M, Perez de Castro I, et al. (2012) Tpx2 controls spindle integrity, genome stability, and tumor development. Cancer Res 72**:** 1518-1528.

19. Jackson JR, Patrick DR, Dar MM, Huang PS (2007) Targeted anti-mitotic therapies: can we improve on tubulin agents? Nat Rev Cancer 7**:** 107-117.

20. Lassmann S, Shen Y, Jutting U, Wiehle P, Walch A, et al. (2007) Predictive value of Aurora-A/STK15 expression for late stage epithelial ovarian cancer patients treated by adjuvant chemotherapy. Clin Cancer Res 13**:** 4083-4091.

21. Zhou H, Kuang J, Zhong L, Kuo WL, Gray JW, et al. (1998) Tumour amplified kinase STK15/BTAK induces centrosome amplification, aneuploidy and transformation. Nat Genet 20**:** 189-193.

22. Godinho SA, Kwon M, Pellman D (2009) Centrosomes and cancer: how cancer cells divide with too many centrosomes. Cancer Metastasis Rev 28**:** 85-98.

23. Schvartzman JM, Sotillo R, Benezra R (2010) Mitotic chromosomal instability and cancer: mouse modelling of the human disease. Nat Rev Cancer 10**:** 102-115.

24. Zhang D, Hirota T, Marumoto T, Shimizu M, Kunitoku N, et al. (2004) Cre-loxP-controlled periodic Aurora-A overexpression induces mitotic abnormalities and hyperplasia in mammary glands of mouse models. Oncogene 23**:** 8720-8730.

25. Zhang D, Shimizu T, Araki N, Hirota T, Yoshie M, et al. (2008) Aurora A overexpression induces cellular senescence in mammary gland hyperplastic tumors developed in p53-deficient mice. Oncogene 27**:** 4305-4314.

26. Harrington EA, Bebbington D, Moore J, Rasmussen RK, Ajose-Adeogun AO, et al. (2004) VX-680, a potent and selective small-molecule inhibitor of the Aurora kinases, suppresses tumor growth *in vivo*. Nat Med 10**:** 262-267.

27. Lok W, Klein RQ, Saif MW (2010) Aurora kinase inhibitors as anti-cancer therapy. Anticancer Drugs 21**:** 339-350.

28. Warner SL, Stephens BJ, Von Hoff DD (2008) Tubulin-associated proteins: Aurora and Polo-like kinases as therapeutic targets in cancer. Curr Oncol Rep 10**:** 122-129.

29. http://bcgenex.centregauducheau.fr/BC-GEM/GEM_Accueil.php?%20js=1

30. Jezequel P, Frenel JS, Campion L, Guerin-Charbonnel C, Gouraud W, et al. (2013) bc-GenExMiner 3.0: new mining module computes breast cancer gene expression correlation analyses. Database (Oxford): bas060.

31. D'Assoro AB, Liu T, Quatraro C, Amato A, Opyrchal M, et al. (2013) The mitotic kinase Aurora-A promotes distant metastases by inducing epithelial-to-mesenchymal transition in ERalpha(+) breast cancer cells. Oncogene.

32. Hu Z, Fan C, Oh DS, Marron JS, He X, et al. (2006) The molecular portraits of breast tumors are conserved across microarray platforms. BMC Genomics 7**:** 96.

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