CK2α as a prognostic factor in invasive ductal carcinomas of the breast: cancer recurrence prognosis by surgical sampling

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Abstract

Background Breast cancer is the most common cancer in Japanese and Asian women. Although the 5-year survival rate of these patients is relatively high, recurrences and fatalities do occur. The objective of this work was to develop a reliable prognostic indicator to guide therapeutic intervention without waiting for recurrence or metastasis.

Methods We have previously shown that positive immunohistochemical staining of a protein kinase, CK2α (CSNK2A1), in nucleoli of invasive ductal carcinoma cells is strongly associated with tumour recurrence and poor patient outcomes. For this study, we did an immunohistochemistry investigation of the location of CK2α in the nuclei and nucleoli of formalin-fixed, paraffin-embedded tissue block samples from patients with invasive ductal carcinoma who underwent surgery in 2008–14 but no neoadjuvant chemotherapy at Hoshi General Hospital, Fukushima, Japan. Furthermore, a new study with 59 patients with luminal type breast cancer was done. Patients were followed-up (clinicopathological information and outcomes) for more than 5 years. To characterise CK2α-associated proteins systematically, nuclear and nucleolar extracts were prepared from MCF-7 cells and immunoprecipitated with anti-CK2α antibodies followed by nano-flow liquid chromatography mass spectrometry analysis. We did a Kaplan-Meier analysis to evaluate whether nucleolar CK2 staining might be associated with poor recurrence-free survival. This retrospective study was approved by the Institutional Review Boards of Fukushima Medical University and Hoshi General Hospital.

Findings Samples from 112 patients were included. 105 (94%) of 112 patients with invasive ductal carcinoma had high CK2α expression in nuclei, and 41 (37%) of 112 displayed it predominantly in nucleoli. Clinical and pathological malignancy was strongly correlated with high nuclear and nucleolar CK2α expression. Recurrence-free survival was significantly reduced in patients with positive nucleolar CK2α staining (n=41; median 7·89 years [IQR 4·86–8·86]), comparing with patients with negative nucleolar staining (n=71; median 8·89 years [7·87–9·79]; p<0·0001). Kaplan-Meier analysis showed a decrease of approximately 50% in recurrence-free survival in patients with nucleolar CK2α-positive stain in the triple-negative breast cancer (p=0·0069) and post-operative stage 3 (p=0·0073) groups. By contrast, no patients who relapsed or died in the triple-negative breast cancer group had negative staining for nucleolar CK2α. Evaluation of nucleolar CK2α can be considered as an independent prognostic factor because it reached significance in multivariate analysis (hazard ratio [HR] 5·26 [95% CI 1·35–20·55]; p=0·017). In addition, the HR of nucleolar CK2α-positive staining was less affected by adjustments in Cox proportional multivariate analysis. Cluster analysis showed that nucleolar CK2α-positive staining contributed more than any other clinicopathological factor to predicting the variation in the future length of survival. Analysis with luminal type breast cancer (n=59), in which the risk of recurrence is generally low and which is treated postoperatively with hormone therapy alone, showed that cancer recurrence and poor patient outcomes strongly associate with nucleolar CK2α-positive stain (n=7; p=0·037) by Kaplan-Meier analysis. In this case, nucleolar CK2α is considered a sole independent prognostic factor (HR 2·11 [95% CI 0·27–3·69]; p=0·0087). Evaluation of this method in other solid tumours is ongoing.

Interpretation Our results suggest that the evaluation of nucleolar CK2α-positive staining might be a new and independent prognostic factor that can improve treatment efficacy and patient quality of life after surgical resection of the tumour. The application of this analysis could contribute to early treatment strategy decisions and to companion diagnostics. The protein interactome of nuclear CK2 complexes showed CK2α's role in protein synthesis and RNA post-transcriptional modification. Specifically, a more detailed evaluation of CK2α function in nucleolar events in malignant cells might lead to the development of novel, more accurately targeted anti-cancer therapeutics. In conclusion, evaluating nucleolar CK2α staining in combination with other clinicopathological indicators might allow for a more accurate prediction of future recurrence or metastasis, which cannot be accomplished by current methods.

Funding Japan Agency for Medical Research and Development (grant number 20lm0203006j0004).

Declaration of interests
We declare no competing interests.

Published Online
July 13, 2022

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