Aims Increased expression of senescence markers $p14^{ARF}$ and $p16^{INK4a}$ in breast cancer is associated with an increased risk of disease recurrence and poor survival outcome

ABSTRACT

Breast cancer is a hormonally driven disease. Cellular senescence is an age-related irreversible cell cycle arrest at the G_1 phase upon induction. The aim of this study was to characterize the expression patterns of the senescence markers $p14^{ARF}$, $p16^{INK4a}$ and $p21^{WAF1/Cip1}$ during breast cancer progression in a large patient cohort.

Methods and results

We conducted a retrospective study of 1080 patients with invasive ductal carcinoma, no special type, over an 11-year period. We performed immunohistochemical staining on tissue microarrays that included normal, benign hyperplasia, ductal carcinoma *in situ*and invasive ductal carcinoma tissue from each patient. Invasive ductal carcinomas showed higher expression of $p14^{ARF}$ and $p16^{INK4a}$ but lower expression of $p21^{WAF1/Cip1}$than non-malignant tissues. There were significant correlations of normal, benign, preinvasive and malignant tissues with $p14^{ARF}$, $p16^{INK4a}$ and $p21^{WAF1/Cip1}$ expression ($P < 0.05$). Univariate comparison showed a correlation between high $p16^{INK4a}$ expression and poor survival ($P = 0.000$) and an increased risk of relapse ($P = 0.000$), whereas high $p14^{ARF}$ expression correlated only with an increased risk of relapse ($P = 0.038$). Multivariate analysis showed $p16^{INK4a}$ to be an important prognostic factor for overall survival ($P = 0.011$) and disease-free survival ($P = 0.004$), with $p14^{ARF}$ also being a significant prognostic factor for disease-free survival ($P = 0.043$). Moreover, patients showing both high $p16^{INK4a}$ expression and and high $p14^{ARF}$ expression had an adjusted three-fold increased risk of disease recurrence ($P < 0.05$) and a two-fold increased risk of all-cause-related death ($P < 0.05$).

Conclusions

These finding suggest $p16^{INK4a}$ expression and $p14^{ARF}$ expression may play an important role in the progression of proliferative breast tissue to invasive cancer, and may be useful as prognostic factors.