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Association between miR-200c and the survival of patients with stage I epithelial ovarian cancer: A retrospective study of two independent tumour tissue collections

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Abstract

Background
International Federation of Gynecology and Obstetrics stage I epithelial ovarian cancer (EOC) has a significantly better prognosis than stage III/IV EOC, with about 80% of patients surviving at 5 years (compared with about 20% of those with stage III/IV EOC). However, 20% of patients with stage I EOC relapse within 5 years. It is therefore crucial that the biological properties of stage I EOCs are further elucidated. MicroRNAs (miRNAs) have shown diagnostic and prognostic potential in stage III and IV EOCs, but the small number of patients diagnosed with stage I EOC has so far prevented an investigation of its molecular features. We profiled miRNA expression in stage I EOC tumours to assess whether there is a miRNA signature associated with overall and progression-free survival (PFS) in stage I EOC.

Methods
We analysed tumour samples from 144 patients (29 of whom relapsed) with stage I EOC gathered from two independent tumour tissue collections (A and B), both with a median follow-up of 9 years. 89 samples from tumour tissue collection A were stratified into a training set (51 samples, 15 of which were from patients who relapsed) for miRNA signature generation, and into a validation set (38 samples, seven of which were from patients who relapsed) for signature validation. Tumour tissue collection B (55 samples, seven of which were from patients who relapsed) was used as an independent test set. The Cox proportional hazards model and the log-rank test were used to assess the correlation of quantitative reverse transcription PCR (qRT-PCR)-validated miRNAs with overall survival and PFS.

Findings
A signature of 34 miRNAs associated with survival was generated by microarray analysis in the training set. In both the training set and validation set, qRT-PCR analysis confirmed that 11 miRNAs (miR-214, miR-199a-3p, miR-199a-5p, miR-145, miR-200b, miR-30a, miR-30a*, miR-30d, miR-200c, miR-20a, and miR-143) were expressed differently in relapsers compared with non-relapsers. Three of these miRNAs (miR-200c, miR-199a-3p, miR-199a-5p) were associated with PFS, overall survival, or both in multivariate analysis. qRT-PCR analysis in the test set confirmed the downregulation of miR-200c in relapsers compared with non-relapsers, but not the upregulation of miR-199a-3p and miR-199a-5p. Multivariate analysis confirmed that downregulation of miR-200c in the test set was associated with overall survival (HR 0•094, 95% CI 0•012–0•766, p=0•0272) and PFS (0•035, 0•004–0•311; p=0•0026), independent of clinical covariates.

Interpretation
miR-200c has potential as a predictor of survival, and is a biomarker of relapse, in stage I EOC.