CORRESPONDENCE

Inconsistent results or inconsistent methods? A plea for standardisation of biomarker sampling in mesothelioma studies

Reproducibility is a quality that all biomarkers must demonstrate before entering the clinical arena. In October's issue of *Thorax*, Creaney *et al*[1] reported important diagnostic performance data regarding fibulin-3 in malignant pleural mesothelioma (MPM). Their results (plasma area under the curve (AUC) 0.671, sensitivity 21%) are remarkably discordant with those reported by Pass *et al*,[2] using the same assay in a similarly designed study (plasma AUC 0.974–0.997, sensitivity 97%). Although some discordance is expected, this pattern is common in the MPM biomarker literature. Creaney *et al* propose logical reasons for the differences observed, but do not mention the potential confounding impact that inconsistencies in the timing of biomarker measurements may have had, particularly in relation to pleural biopsies, pleurodesis and surgical palliation.

Studies in other cancers demonstrate that tumour biopsies, resection[3] and peritumoural inflammation[4] can have marked effects on biomarker expression, with different mechanisms affecting different markers. Patients with MPM are commonly subjected to repeated, large-volume biopsies, frequently involving surgery and often combined with an intensely inflammatory pleurodesis, or even surgical dubulking. Yet, these factors are rarely acknowledged in MPM studies. An important earlier study which did assess the reproducibility of pleural fluid mesothelin levels found a small but statistically significant fall after pleurodesis and sufficient variation in paired samples from patients not undergoing biopsy or pleurodesis to result in diagnostic reclassification of 2/51 patients.[5]

Creaney *et al* report that biomarker measurements were made 'within 1 month of diagnosis' suggesting that some may have been taken after these potentially confounding events. In the study by Pass, biomarker measurements were made in tertiary surgical centres and almost certainly following extensive pleural intervention. Such methodological inconsistencies introduce systematic error, making it difficult to compare studies or accurately assess biomarkers, whether these are single molecules like fibulin-3 or more complex proteomic classifiers, many of which incorporate inflammatory mediators. Ultimately, this approach may lead to incorrect conclusions regarding the futility or worth of novel markers and therapeutic avenues.

This letter is a simple plea to MPM researchers and global biomarker consortia to consider a standardised approach to the timing of biomarker measurements and encourage testing of these in prospective studies which incorporate predefined, early sampling, rigorous subsequent diagnostics and the collection of data on potential confounders, including renal function, body mass index, concomitant drugs and inflammatory indices. This approach is being adopted in the DIAPHRAGM (Diagnostic and Prognostic Biomarkers in the Rational Assessment of Mesothelioma) study, which is currently recruiting across the UK and Ireland.

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REFERENCES

1 Creaney J, Dick IM, Meniawy TM, *et al*. Comparison of fibulin-3 and mesothelin as markers in malignant mesothelioma. *Thorax* 2014;69:895–902.
2 Pass HI, Levin SM, Harbut MR, *et al*. Fibulin-3 as a blood and effusion biomarker for pleural mesothelioma. *N Engl J Med* 2012;367:1417–27.
3 Wong V, Wang DY, Warren K, *et al*. The effects of timing of fine needle aspiration biopsies on gene expression profiles in breast cancers. *BMC Cancer* 2008;8:277.
4 Bergamini S, Bellei E, Reggiani Bonetti L, *et al*. Inflammation: an important parameter in the search of prostate cancer biomarkers. *Proteome Sci* 2014;12:32.
5 Davies HE, Sadler RS, Bielsa S, *et al*. Clinical impact and reliability of pleural fluid mesothelin in undiagnosed pleural effusions. *Am J Respir Crit Care Med* 2009;180:437–44.