Transthyretin, a Biomarker for Nutritional Status and Ovarian Cancer

To the Editor: Zhang et al. elaborately describe three new serum biomarkers for the detection of ovarian cancer. One biomarker especially, the truncated transthyretin, should be given special attention because transthyretin has traditionally been seen as a biomarker for nutritional status. Transthyretin, then called prealbumin, was described as a so-called visceral protein, synthesized in the liver in response to nutritional supply. Transthyretin plasma levels have thus been used as sensitive biochemical variables of subclinical malnutrition, as both adequacy of protein and energy intakes are reflected in its plasma levels. Plasma levels of transthyretin, however, are also affected by acute and chronic diseases associated with an acute-phase response. Under these conditions, liver activity is concentrated on the synthesis of acute-phase response proteins, resulting in a dramatic drop in visceral proteins (1, 2).

Based on these observations, the conclusion drawn by the authors especially concerning transthyretin as a biomarker for ovarian cancer needs careful consideration. Firstly, arguments in favor of the newly described truncated transthyretin variant as a marker are strengthened by parallel changes in total transthyretin as measured by ELISA. This publication, however, along with our data and that of others shows that such a truncated form of transthyretin comprises a very small fraction of total immunoreactive transthyretin (3). Thus, one must be critical in drawing conclusions on this biomarker based on observations of the intact transthyretin molecule or other variants thereof. Secondly, the catalytic state of the individual greatly effects plasma transthyretin levels. Therefore, when comparing groups of cancer patients in different stages of the disease, one would expect plasma transthyretin levels to be more severely effected in those suffering from late-stage ovarian cancer. In the article, no information was given on the severity of the other cancer groups, so one might assume that they were less severe. One study comparing transthyretin in plasma of women with ovarian cancer against healthy controls supports this assumption. In other nongynecologic malignant disease, this reduction in plasma transthyretin was similar (4). Additionally, in ovarian cancer, ascitic fluid has to be considered as a third compartment into which substantial amounts of transthyretin can be transferred (5). In conclusion, to fully validate the specificity of transthyretin or any fragment thereof as a biomarker for ovarian cancer, a careful selection of controls must be done. Nutritional status as well as inflammatory processes and possible influences of different hepatic diseases should be taken into consideration.

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References

In Response: We agree with Drs. Schweigert and Sehouli in their letter to the editor that validation of specificity of any potential biomarkers requires the careful selection of controls. In our report on three biomarkers identified from serum proteomic analysis for the detection of early-stage ovarian cancer (1) in addition to the main data set for mass spectrometry–based biomarker discovery and cross-validation, a relatively small panel of 142 samples was used for immunoassay test for two of the discovered markers. This panel was not intended as a full-scale validation set. It was used mainly as a preliminary check for obvious problems related to tumor site specificity.

We agree also that one needs to be cautious in drawing conclusions based on results from an immunoassay that was not specifically designed for the truncated form of transthyretin that was discovered through the reported proteomic analysis.

The 142 samples use for immunoassay tests were from archived samples. Influenced by the effectiveness of current detection methods, the stage distributions among the other three cancer groups were indeed somewhat different from that of the ovarian cancer group. Among them, the colorectal cancer group had the most severe stages (most of them were at stage III or IV) and for which the transthyretin level by the immunoassay level by the immunoassay was slightly lower than the control group at a significance level of \( P = 0.01 \). This result is consistent with the point made in the letter by Drs. Schweigert and Sehouli that total transthyretin level may be associated with disease severity. However, in comparison, the much more significant difference in total transthyretin levels between the ovarian cancer group and the controls (\( P = 0.00005 \)) does not seem to be explainable solely by the severity of the ovarian cancer patients.

The truncated form of transthyretin was discovered and cross-validated by comparing proteomic expressions of serum samples from patients with stage I/II epithelial ovarian cancer and healthy controls. Ideally, the immunoassay tests should also be done with early-stage samples. The two immunoassays that we used required a specimen volume much greater than what we had available from our early-stage samples. Lacking an effective early detection test, limitations in sample availability will remain true for biomarker research on early-stage ovarian cancer.

To bring a promising biomarker from research to clinical applications requires extensive validation with careful study design and clinically representative populations. We hope that additional postdiscovery work at our center and by colleagues in the field will generate a sufficient body of scientific evidence to justify such necessary yet costly validation studies. The cautions suggested by Drs. Schweigert and Sehouli will be very much appreciated in this process.

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Reference
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