

# Whither $\alpha$ -FP in the diagnosis of hepatocellular carcinoma?

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$\alpha$ -FP is an  $\alpha_1$ -globulin present in high concentration in the fetal serum of mammals. It is the dominant plasma protein in the developing embryo, and is synthesized by the embryonal liver, by the endodermal cells of the visceral yolk sac, and, in very small amounts, by the embryonal intestine.<sup>1</sup> Approximately 80% of fetal hepatocytes synthesize and secrete  $\alpha$ -FP. The protein has been closely conserved throughout phylogenesis, suggesting that it has functions essential to the fetus, although precisely what these functions are remains to be learned. There does, however, appear to be an inverse relationship between serum  $\alpha$ -FP and albumin levels, suggesting that  $\alpha$ -FP might function as fetal albumin.<sup>2</sup> Other possible biological properties of the  $\alpha_1$ -globulin include binding to estrogens and bilirubin, immunosuppressive activity, and a growth-promoting potential.<sup>3</sup> The serum level of the protein remains constant until week 32, when it begins to sharply decrease. After birth, production of  $\alpha$ -FP normally remains completely repressed, and serum concentrations are correspondingly very low.

From the time of birth onwards,  $\alpha$ -FP is synthesized almost exclusively by malignant hepatocytes, although not all of these cells produce and secrete the protein.<sup>4</sup> The molecular mechanism responsible for the reintroduction of synthesis of the protein has yet to be uncovered, but it appears to be the result of increased gene transcription.<sup>5</sup> Production of  $\alpha$ -FP by malignant hepatocytes is permanent, irrespective of the serum concentration attained,<sup>6</sup> although the level may decrease precipitously shortly before death. However, not all malignant hepatocytes produce and secrete  $\alpha$ -FP, and the reason for this is not known.

The measurement of the serum concentration of  $\alpha$ -FP as a confirmation of a clinical diagnosis of hepatocellular carcinoma (HCC) was introduced into clinical practice in the 1970s,<sup>4</sup> with a serum level greater than 500 ng/mL being generally regarded as being diagnostic of the presence of the tumor, although some centers used concentrations of 400 ng/mL and others of 200 ng/mL.

During the past approximately 14 years, however, doubt has been cast on the validity of using  $\alpha$ -FP as a diagnostic marker of HCC in the serum of patients in low incidence regions of the tumor.<sup>7-9</sup> It was realized that a high proportion of HCCs identified using the sophisticated imaging techniques now available showed either the  $\alpha$ -FP level to be within the normal range or, if raised above this range, then only raised to a slight or moderate degree in patients in these urban regions.<sup>7</sup>

By contrast, rural sub-Saharan Black Africans with high incidences of HCC and very limited imaging facilities available have not been subjected during recent years

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to the same careful assessment of the value of  $\alpha$ -FP as a diagnostic marker of HCC as their urban counterparts. The result has been that the only published information on the incidence of HCC in these areas has been based on serum  $\alpha$ -FP levels garnered many years ago. In consequence, the question that needs to be answered is: does the doubt that has been raised regarding the usefulness of  $\alpha$ -FP in the diagnosis of HCC occurring in low incidence populations in First World countries during past years<sup>7-9</sup> also apply to the diagnosis of the tumor which occurs commonly in the rural Black African population?

Unfortunately, the sophisticated imaging techniques now used in the diagnosis of HCC in resource-rich countries with low incidences of the tumor are not available in the rural regions of sub-Saharan Africa where the great majority of the patients with HCC live. In these patients, the mean concentration of the raised serum  $\alpha$ -FP has been shown, using the conventional laboratory methods, to be 70,000 to 80,000 ng/mL,<sup>10</sup> values which are greatly in excess of those in low-incidence regions of the tumor. Moreover, the raised serum concentrations are age-related – the younger the patient, the higher the level attained:<sup>11,12</sup> a diagnostically raised serum  $\alpha$ -FP is found in 96.4% of these Black African patients, with a concentration raised to a diagnostic level in 89.3% in those patients under the age of 30 years, compared with 83.1% in those over the age of 50 years.<sup>13</sup> The mean value of the raised concentrations is 87,366 ng/mL in the younger patients and 43,827 ng/mL in the older patients.<sup>13</sup> In another study of Black African patients with HCC, using a less sensitive method for measuring  $\alpha$ -FP levels, 83.3% of those under the age of 20 years had a raised serum level, as did 74.2% of those between the ages of 30 and 39 years, 54.4% of those between the ages of 40 and 49 years, and 50% of those between the ages of 50 and 59 years.<sup>9</sup> The fact that Black African patients with HCC are appreciably younger than the patients in low incidence regions of the tumor might explain, at least in part, the lower levels found in most geographical regions. Males have a higher incidence of HCC than females. Raised serum  $\alpha$ -FP concentrations are present in 89.7% of rural patients compared with 76.9% of urban patients. This difference is almost certainly explained by the generally younger age of the rural patients. Age-related Black African males and females with HCC have similar serum levels of  $\alpha$ -FP.<sup>6</sup> No obvious correlation exists in Black African patients with HCC between serum  $\alpha$ -FP levels and

any of the clinical or biochemical changes occurring in HCC, or the degree of differentiation, size or stage of the tumor, or survival time after diagnosis.<sup>10</sup> Nor is there a correlation between the serum  $\alpha$ -FP concentration and the presence of chronic hepatitis B virus infection, arguing against the postulate that the protein plays a significant role in the persistence of hepatitis B virus infection.

The question is: will the use of the serum levels of  $\alpha$ -FP in patients thought to be suffering from HCC in rural areas of sub-Saharan Africa, and perhaps of the Far East, continue to be a useful tumor marker of HCC in the foreseeable future, and until such time that the present-day very accurate imaging techniques used to recognize HCC become universally available and replace serum  $\alpha$ -FP levels as diagnostic confirmation of the presence of HCC?

## Disclosure

The author reports no conflicts of interest in this work.

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