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Role of hypermethylation of RASSF1A promoter and serum glypican-3 among Egyptian patients with hepatocellular carcinoma

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Background: Hepatocellular carcinoma (HCC) is one of the most aggressive malignancies worldwide and one of the main causes of cancer-related mortality globally. Its incidence is increasing at alarming rates. The presence of cirrhosis is the major risk factor and this is largely due to chronic HCV and HBV infection. Serum alpha-fetoprotein (AFP) has insufficient sensitivity and specificity for detection of hepatocellular carcinoma (HCC). Aberrant hypermethylation of tumor suppressor genes e.g., RASSF1A is one of the most frequent and early mechanisms involved in HCC development, so that it could help to select high-risk populations and thus to modulate the indications of screening procedures. Moreover, estimation of serum level of certain up regulated proteins as glypican-3 (GPC-3) in HCC could be a promising biomarker for screening and early HCC detection. Recently, *RASSF1A* gene and glypican-3 (GPC-3) were suggested as the novel biomarkers for the detection HCC.

Objectives: To determine the role of serum GPC-3 in the early diagnosis of HCC and to evaluate the frequency of tumor suppressor gene *RASSF1A* hypermethylation in whole blood from HCC patients.

Methods: The study included 80 subjects: 30 patients with HCC and elevated AFP; 30 with liver cirrhosis. In addition, 20 healthy subjects were included as a control group. Clinical and radiological features (abdominal ultrasonography and/or abdominal triphasic computed tomography) were recorded. Liver function tests, complete blood cell count and serum AFP were measured. Serum GPC-3 values were determined by ELISA technique and detection of promoter methylation status of *RASSF1A* using methylation specific PCR.

Results: This study revealed that serum levels of GPC-3 were significantly elevated in patients with HCC compared with liver cirrhosis and control groups ($p < 0.001$). Also, serum GPC-3 levels with cut-off value of 2.72 ug/L had a sensitivity (93.0%) and specificity (94%). The obtained results showed a significant *RASSF1A* promoter hypermethylation in HCC subjects that was 83.3% in comparison to healthy control subjects as well as in comparison to subjects with non HCC chronic liver disease.

Conclusion: Glypican-3 should be included in the screening programs for early HCC detection among cirrhotic patients as a rapid, sensitive, non-invasive and cost-effective diagnostic biomarker. Detection of methylated *RASSF1A* promoter is useful marker for HCC screening in high risk vulnerable patients and early HCC diagnosis.

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