Objective: The aim of the present study was to investigate the immunohistochemical expressions of FoxO1, Annexin 2 and p53 in association with the clinicopathological parameters in order to define their roles in the development of renal cell carcinoma (RCC). Materials and Methods: Immunohistochemical analyse of FoxO1, Annexin 2 and p53 expressions were performed on the sections of 10 non-neoplastic kidney and 70 clear cell RCC (cRCC) tissues. The association between FoxO1, Annexin 2 and p53 expressions and the clinicopathological parameters as well as, the correlation between these markers were analysed. Results: The expressions of Annexin 2 and p53 were significantly higher in cRCC than the non-neoplastic kidney tissues (p<0.0001, p=0.014, respectively). There was not any significant difference between cRCC and non-neoplastic kidney groups regarding the expression of FoxO1 (p>0.05). Annexin 2 and p53 expressions were significantly strong in cases with higher nuclear grade (p=0.001, p<0.0001 respectively) and pT stage (p<0.0001, p<0.0001 respectively). We also found significant association between expressions of these markers and lymphovascular invasion (p<0.05). FoxO1 expression was significantly strong in cases with lower nuclear grade (p<0.0001) and pT stage (p=0.001). There was a significant association between FoxO1 expression and lymphovascular invasion (p<0.05). In addition, a positive correlation was found between Annexin 2 and p53 expressions (r=0.522). Furthermore a negative correlation was found between Annexin 2 and FoxO1 (r=0.587), as well as FoxO1 and p53 expressions (r=0.690) in cRCC cases. Conclusion: According to our results we suggest that FoxO1, Annexin 2 and p53 expressions may involve in differentiation, progression, and the aggressiveness of cRCC. However, further studies are needed to approve our findings and to clarify the role of these markers in the development of cRCC.