Prostate cancer is the most common cancer type in men and is the second cause of death, due to cancer, in patients over 50, after lung cancer. Prostate specific antigen (PSA) is a widely-used tumor marker for prostate cancer. Recently, PSA is discovered in non-prostatic cancer tissues in men and women raising doubts about its specificity for prostatic tissues. PSA exists in low serum level in healthy men and in higher levels in many prostate disorders, including prostatitis and prostate cancer. Thus, a supplementary tumor marker is needed to accurately diagnose the cancer and to observe the patient after treatment. Recently, soluble human leukocyte antigen-G (sHLA-G) has been introduced as a new tumor marker for different cancer types, including colorectal, breast, lung and ovary. The present descriptive-experimental study was carried out including patients with malignant prostate tumor, patients with benign prostate tumor and a group of health men as the control group, as judged by an oncologist as well as a pathologist. After sterile blood sampling, sHLA-G was measured by enzyme-linked immunosorbent assay in each group. The data was then analyzed using one-way ANOVA. P≤0.05 was considered as statistically significant. The results showed that the mean of sHLA-G level was high in patients. Also, it was found that there was a significant difference in sHLA serum level between the three groups. The data revealed that sHLA-G can be a novel supplementary tumor marker in addition to PSA to diagnose prostate cancer.