The aim of the present study was to investigate the immunohistochemical expression of NGF, GDNF and MMP-9 in benign prostatic hyperplasia (BPH), high grade prostatic intraepithelial neoplasia (HGPIN) and prostate cancer (PC), and to analyse their association with the clinicopathological parameters in PC cases. Immunohistochemistry was performed on the tissue microarray (TMA) sections of 30 BPH, 40 HGPIN and 121 primary PC tissues. There was a significant difference regarding the expression of NGF and GDNF between PC and HGPIN (p<0.0001; p<0.0001), and PC and BPH (p=0.001; p<0.0001), but not between HGPIN and BPH (p>0.05). Furthermore, MMP-9 expression was significantly different among all groups (PC vs. HGPIN, p<0.0001; PC vs. BPH, p<0.0001; HGPIN vs. BPH, p=0.001). NGF, GDNF and MMP-9 expression was significantly stronger in cases with high Gleason score (p<0.0001, p=0.004, p<0.0001 respectively) and pT stage (p=0.046, p=0.004, p=0.001, respectively) in PC cases. All these markers were also associated with perineural, lymphovascular and extraprostatic invasion (p <0.05). In addition, a positive correlation was found between NGF and MMP-9 (p<0.0001, r=0.435), NGF and GDNF (p<0.0001, r=0.634), and GDNF and MMP-9 (p<0.0001, r=0.670) in PC cases. According to our results we suggest an interaction between NGF, GDNF and MMP-9 during the transition to malignancy in PC. Also this interaction may involve in regulating PC cell differentiation, tumor invasion, progression, and the aggressiveness of PC.