Immunohistochemical Expression of BRCA1 and Prostate Cancer Progression in a Large Radical Prostatectomy Cohort

Introduction and Objective: *BRCA1* encodes a tumor suppressor protein that plays an important role in DNA repair. Although *BRCA1* mutations are known to promote carcinogenesis, the role of BRCA1 protein in prostate cancer progression and survival is poorly understood. The objective of this study was to determine the association between tumor expression of BRCA1 protein and survival in men with prostate cancer.
Materials and Methods: Immunohistochemical staining for BRCA1 protein was performed in archival tumor tissue from radical prostatectomy specimens of 589 men participating in the Health Professionals Follow-Up Study. BRCA1 expression was graded as either present or absent by dedicated study pathologists. Tumor proliferation was assessed quantitatively using immunostaining for Ki67. Study participants were followed prospectively from the date of diagnosis until the development of distant metastases or death through 2011. Proportional hazards regression was used to evaluate the association between BRCA1 expression and lethal prostate cancer.
Results: Immunohistochemical staining was positive for BRCA1 protein in 60 patients (10.2%).There was a strong correlation between BRCA1 expression status and Gleason grade, with BRCA1-positive tumors being of higher grade than BRCA1-negative tumors ($p_{trend}=0.01$). Likewise, tumors expressing BRCA1 exhibited a higher proliferative index ($p_{trend}=0.005$). During a median follow-up time of 13.8 years, 58 men (11.0%) in the BRCA1-negative group and 14 men (23.3%) in the BRCA1-positive group developed metastases or died of prostate cancer-related causes. On unadjusted analyses, there was a strong positive association between BRCA1 protein expression and risk of lethal prostate cancer (HR 2.26, 95% CI 1.26–4.04, $p=0.006$). After adjusting for age at diagnosis and Gleason score, there remained a higher risk of lethal prostate cancer in BRCA1-positive tumors, although this association was not statistically significant (HR 1.68, 95% CI 0.93–3.02, $p=0.08$). This association was not significantly attenuated by further adjustment for Ki67 proliferative index.
Conclusions: BRCA1 positive prostate tumors are characterized by dedifferentiation and a high proliferative index, and may be an independent predictor of cancer progression. The biological mechanisms by which BRCA1 may promote tumor survival and the role of BRCA1 expression in guiding therapy in patients with castrate-resistant prostate cancer deserve further study.