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New and Emerging Diagnostic and Prognostic Immunohistochemical Biomarkers in Prostate Pathology

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Abstract

The diagnosis of minimal prostatic adenocarcinoma can be challenging on prostate needle biopsy, and immunohistochemistry may be used to support the diagnosis of cancer. The International Society of Urologic Pathology currently recommends the use of the basal cell markers high–molecular-weight cytokeraratin and p63, and α-methylacyl-coenzyme-A racemase. However, there are caveats associated with the interpretation of these markers, particularly with benign mimickers. Another issue is that of early detection of presence and progression of disease and prediction of recurrence after Clinical intervention. There remains a lack of reliable biomarkers to accurately predict low-risk cancer and avoid over treatment. As such, aggressive forms of prostate cancer may be missed and indolent disease may be subjected to unnecessary radical therapy. New biomarker discovery promises to improve early detection and prognosis and to provide targets for therapeutic interventions. In this review, we present the emerging immunohistochemical biomarkers of prostate cancer PTEN, ERG, FASN, MAGI-2, and SPINK1, and address their diagnostic and prognostic advantages and limitations.

Keywords

prostate cancer; biomarkers; diagnosis; prognosis; PTEN; ERG; MAGI-2; SPINK1; FASN

The diagnosis of prostatic adenocarcinoma is based on the evaluation of a combination of cytologic and architectural features. However, evaluation based solely on morphology is often insufficient, particularly in cases with minimal carcinoma. Immunohistochemistry is commonly used to support the morphologic impression of prostate cancer. The most commonly used markers include those specific for basal cells, high–molecular-weight cytokeratin (HMWCK) and p63, and α-methylacyl-CoA racemase (AMACR). Although typically adenocarcinoma lacks expression of basal cell markers, benign lesions such as adenosis, atrophy, or benign glands may also demonstrate similar basal cell loss.[1–4] Conversely, HMWCK staining in a nonbasal distribution and aberrant diffuse expression of p63 may occasionally be observed in prostate cancer.[5–7] In addition, AMACR also stains 5% to 21% of benign prostatic glands,[1,3,8,9] and up to 18% of cases of adenosis,[10]

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which limits its specificity for the diagnosis of adenocarcinoma. The current International Society of Urologic Pathology recommendations suggest using "HMWCK, or p63 or a combination of the two with AMACR either in a double or triple cocktail" for the workup of "small foci of atypical glands suspicious for prostatic adenocarcinoma."[11] However, successful treatment of prostatic adenocarcinoma relies not only on sensitive and specific methods used for diagnosis, but also on prognostication of progressive versus indolent disease and detection of recurrence. Current advances in molecular techniques have provided new methods for biomarker discovery. This review will focus on discussing new concepts and existing challenges of emerging prognostic markers of prostatic adenocarcinoma, and address their utility in the immunohistochemical diagnosis of prostate cancer.

ETS-RELATED GENE (ERG)

Biology and Role in Tumorigenesis

ERG, located on chromosome 21q22.2 encodes a member of the erythroblast transformation-specific (*ETS*) family of transcriptions factors, which includes 30 *ETS* family genes.[12] The proteins encoded by this gene are mainly expressed in the nucleus and act as activators or repressors of transcription, affecting development and differentiation of multiple cell types. Initially reported by Tomlins et al,[13] *ERG* gene fusion with the androgen-driven promoter of the *TMPRSS2* gene is the most common recurrent genetic alteration in prostate cancer, accounting for 50% of Clinically localized prostate cancers in prostatespecific antigen-screened patient cohorts,[14] and with a reported frequency of 15% in a population-based cohort.[15] Gene fusions involving other *ETS* family members, primarily *ETV1* but also *ETV4* and *ETV5*, together constitute <10% of prostate cancer genetic abnormalities.[16,17] *ERG* translocation has been detected in 10% to 20% of highgrade prostatic intraepithelial neoplasia (HGPIN) adjacent to prostate cancer harboring the ERG fusion, but it is otherwise infrequent in isolated HGPIN. This suggests a possible early role for ERG in the progression from HGPIN to cancer.[18] In prostate cancer, the result of the *TMPRSS2*:ERG translocation induces the promoter region containing androgen-sensitive elements of *TMPRSS2* to fuse with the coding region of *ERG*, leading to androgen-induced *ERG* overexpression.[13]

Prognostic Value of ETS-related Gene

The prognostic value of ERG is a matter of debate. Several studies have described an association between *ERG* fusion and poor prognostic indicators, including higher Gleason grade, pathologic stage, biochemical recurrence, metastases, and cancer-specific mortality.[15,19–24] However, other studies have shown no correlation with outcome and biochemical recurrence.[25–27]

Clinical Applications

The diagnostic utility of ERG has been evaluated in several studies. ERG expression by immunohistochemistry was detected in 9% of prostatic "atypical glands suspicious for carcinoma."[28] When using a combined ERG/AMACR/HMWCK/p63 immunohistochemistry, ERG and AMACR were positive in 45% and 94% of prostate cancers, while ERG modified an initial diagnosis of atypical glands to prostate cancer

in 28% cases.[29] In a study of limited prostatic adenocarcinoma, combined p63 and ERG staining detected 42% of carcinoma, and ERG expression was identified in 5% of HGPIN cases and in rare cases of benign glands adjacent to cancer.[30] In another study, 36% of prostatic adenocarcinomas, 27% of HGPIN, 13% of HGPIN with adjacent atypical glands, and none of benign mimickers were positive for ERG. Furthermore, ERG demonstrated higher specificity for cancer than AMACR (0.87 vs. 0.23), but lower sensitivity (0.36 vs. 0.95).[31] ERG expression was also detected in 58% of intraductal carcinomas and 27% of borderline intraductal proliferations,[32] and ERG rearrangements were identified in 45% of prostatic small cell carcinomas, but not in lung small cell carcinomas.[33] Intertumoral and intratumoral heterogenous ERG expression by immunohistochemistry has been described.[30,34,35] Figure 1 illustrates examples of the utility and role of ERG in routine Clinical applications.

A strong correlation between ERG gene rearrangements by fluorescence in situ hybridization (FISH) and immunohistochemistry has been reported with sensitivity and specificity ranging from 95.7% to 100% and 96.5% to 100%, respectively. However, despite high specificity, the potential utility of ERG in biopsy specimens is limited in view of the relatively frequent expression in foci of HGPIN adjacent to adenocarcinoma, low sensitivity, and intratumoral heterogeneity.[11]

PHOSPHATASE AND TENSIN HOMOLOG (PTEN)

Biology and Role in Tumorigenesis

PTEN, localized on chromosome 10 encodes a phosphatase that dephosphorylates phosphatidylinositol-3,4,5-trisphosphate, a second messenger in the phosphatidylinositide 3-kinase (PI3K)-protein kinase B (PKB) signaling pathway. By negatively regulating the (PI3K)/PKB signaling pathway it functions as a tumor suppressor. As a result, mutation of PTEN is a key step in disinhibition of the PI3K-PKB pathway, which in turn becomes over-active in prostate cancer. *PTEN* alterations consist of genomic deletions with heterozygous and, less likely homozygous mutations,[37–42] epigenetic silencing,[43,44] posttranscriptional regulation,[45] and proto-oncogenic miRNA-dependent regulation.[46] Haploinsufficiency may also contribute to genomic instability.[47–49]

Prognostic Value of Phosphatase and Tensin Homolog

Frequent *PTEN* alterations are associated with Clinically significant prostate cancer, high Gleason score, and biochemical recurrence. *PTEN* loss is infrequent in Gleason score 6 biopsies,[49] and has not been detected in HGPIN, suggesting a later event in carcinogenesis.[50,51] Genomic deletion of *PTEN* and loss of PTEN expression in Gleason score 6 biopsies have been associated with increased risk of upgrading at radical prostatectomy,[52] and unfavorable Clinical outcome.[38,53–55] PTEN inactivation may also be implicated in the mechanisms of progression to androgen independence.[56,57] *PTEN* deletion or mutation has been reported in 20% to 40% of localized cancers,[53,57,58] and up to 60% of metastases.[38]

Methods of Measurement

Although FISH is the gold standard for detection of genomic alterations of *PTEN*, recently immunohistochemistry has been validated as an alternative assay in prostate cancer[59] (Figs. 2A, B). This may provide additional benefits to PTEN detection as a screening methodology, in view of the relatively inexpensive and less cumbersome immunohistochemistry-based methods, as well as the potential to detect PTEN loss by alternative mechanisms that would not be otherwise detected by FISH, such as posttranscriptional, epigenetic, and proto-oncogenic miRNA-dependent regulation. In a manual and Clinical-grade automated platform, sensitivity of PTEN immunohistochemistry for hemizygous and homozygous deletion was 87% and 86% versus 65% and 97%, respectively.[59,60]

Intratumoral and intertumoral PTEN heterogeneity has been demonstrated by immunohistochemistry and FISH, likely reflecting the presence of an “index tumor” or different tumor clones, and reflecting different biology underlying different morphologic forms of prostate cancer[49,61,62] (Fig. 2C). Although heterogenous expression has also been observed for ERG, the pattern of PTEN loss is even more diverse, with 68% of cases demonstrating partial loss and 32% demonstrating complete loss in tumor cells by immunohistochemistry, versus 42% and 5% of cases with intertumoral and intratumoral staining heterogeneity for ERG.[63]

Clinical Applications

Although PTEN has been predominantly identified as a prognostic rather than diagnostic marker for prostate cancer, recent studies have shown cytoplasmic PTEN loss in the majority of intraductal carcinoma and atypical intraductal cribriform proliferation cases, and intact PTEN expression in HGPIN, suggesting a potential role for this marker in distinguishing intraductal carcinoma from PIN and in the differential diagnosis of atypical intraductal cribriform proliferations of the prostate.[32,50]

FATTY ACID SYNTHASE (FASN)

Biology and Role in Tumorigenesis

FASN is a 250 to 270kD multifunctional, homodimeric enzyme that synthesizes long-chain fatty acids. The main product of FASN is a 16-carbon fatty acid, palmitate. In normal conditions FASN converts excess carbohydrate into fatty acids, which are esterified to storage triacylglycerols and represent a source of energy obtained through β-oxidation. In a well-nourishment state with sufficient levels of dietary fat, FASN has a limited role, as fatty acids are normally obtained through the diet.[64] The enzyme is expressed minimally in normal cells, but highly in liver and adipose tissue.

A significant role of FASN in cancer biology has been documented in several studies. FASN upregulation could be induced by an increased use of the glycolytic pathway for energy production, leading, in turn to an increase in the substrates for de novo fatty acid synthesis (Warburg effect).[65,66] Alternatively, actively proliferating tumor cells could activate mechanisms to supply the increased demand of structural components of the cell membrane.[66] In the redox balance despite surrounding conditions of extreme highly hypoxic

and acidotic environment of tumors, FASN hypoxia, contributing to develop alternative survival overexpression could result in a significant improvement in mechanism.[65,67,68] Finally, FASN can act as a prostate cancer oncogene by inhibiting the intrinsic pathway of apoptosis in mouse models.[69]

Prognostic Value of Fatty Acid Synthase

FASN expression has been detected in multiple cancer types, including kidney, pancreas, lung, colorectal, ovarian, breast, stomach, prostate, retinoblastoma, and soft tissue sarcomas,[70–77] among others. Higher levels of FASN correlate with increasing tumor burden, later stages of disease, and poor prognosis.[78–83]

FASN overexpression has been described in prostate cancer in several studies.[67,69,80,84–86] FASN germline polymorphisms have been significantly associated with risk of lethal cancer,[87] while correlation with higher Gleason grade has been identified with nuclear FASN expression by immunoblot analysis of cell lysates, immunohistochemistry, and confocal microscopy.[79] Further, immunohistochemical expression of FASN was a significant predictor of cancer progression,[80] as well as pathologic stage.[88]

Clinical Applications

FASN expression has been detected by immunohistochemistry in the cytoplasm of normal prostatic epithelium and HGPIN with significantly higher intensity in neoplastic tissue (Fig. 3) and with a pattern of staining that was sufficiently distinct in prostatic adenocarcinoma compared to benign glands.[89] In a comparison study with AMACR, 91% of AMACR-negative neoplastic glands demonstrated cytoplasmic FASN expression,[90] and both markers showed comparable areas under the curve in receiver operating characteristic analysis, and comparable sensitivity, specificity, and accuracy rates at optimal cutoff intensities.[89] Thus, FASN could represent a potential marker to complement but not substitute AMACR in the diagnosis of prostatic adenocarcinoma.

MAGI-2

Biology and Role in Tumorigenesis

Membrane-associated guanylate kinase, WW and PDZ domain containing 2 (MAGI-2), also known as S-SCAM, GKAP[91,92] or atrophin interacting protein-1[93] is a member of the membrane-associated guanylate kinase with an inverted arrangement of protein-protein interaction domains family, which also includes MAGI-1 and MAGI-3. There are 3 isoforms of MAGI-2-α, MAGI-2-β, and MAGI-2-γ, which are generated by differential translational initiations from multiple sites.[94] Membrane-associated guanylate kinases are highly expressed in mouse brain at synaptic junctions,[92,93] and *MAGI-2* gene mutations have been implicated in neurological diseases such as schizophrenia,[95] and infantile spasms.[96] MAGI-2 is also expressed in kidney podocytes, where it interacts with the slit diaphragm protein nephrin. Studies in MAGI-2 knock-out mice have demonstrated that loss of MAGI-2 expression leads to slit diaphragm disruption, podocyte foot process effacement, and severe podocyte loss. MAGI-2-null mice develop rapidly progressive glomerular disease and renal failure.[97] In the intestine, MAGI-2 binds to G-protein-coupled receptor involved

in fluid and electrolyte secretion[98] and has been implicated in the pathogenesis of celiac disease[99] and inflammatory bowel disease.[100]

In cancer biology, MAGI-2 acts as a scaffolding protein that interacts with signaling proteins in multiple pathways, including PTEN.[101,102] MAGI-2 binds to the C-terminus of PTEN through its PDZ domain in a yeast 2-hybrid assay, resulting in increased PTEN stability and phosphatase activity.[101] MAGI-2 rearrangements with frame shift mutation have been demonstrated in a melanoma Cancer Cell line.[103] In hepatocellular carcinoma, MAGI-2 upregulates PTEN expression by decreasing protein degradation and inhibits cell migration and proliferation,[104] whereas epigenetic silencing has been shown in cervical cancer.[105] In lung cancer, miR-134, miR-487b, and miR-655 target MAGI-2 and promote epithelial-mesenchymal transition, a mechanism involved in the process of metastasis.[106]

Role of MAGI-2 in Prostate Cancer

Previous studies have proposed that rearrangements of the *MAGI-2* gene could alter the interaction of MAGI-2 with PTEN or other scaffolding proteins, including SMAD3, β-catenin, or the activin type 2 receptor.[107] In cell culture, MAGI-2 inhibited epithelial-mesenchymal transition, a key event in the mechanism of invasion and metastasis, while miRNA-induced downregulation of MAGI-2 was permissive for transforming growth factor β−1–induced resistance to the tyrosine kinase inhibitor gefinitib.[106] *MAGI-2* gene rearrangement, including two independent but closely aligned inversions and two long-range intrachromosomal inversions have been recently demonstrated.[108] Mutation of MAGI-2 is theorized to contribute to prostate carcinogenesis by driving PKB phosphorylation.[109] A recent study has shown decreased expression of MAGI-2 mRNA in prostate cancer and prostate Cancer Cell lines, with no difference in expression between benign prostatic hyperplasia and normal tissue. Genetic alterations of PTEN result in loss of MAGI-2 mRNA, but not always PTEN mRNA.[110]

Clinical Applications

We have previously demonstrated that MAGI-2 staining by immunohistochemistry is expressed in 96% of adenocarcinomas with different Gleason grades and 21% of adjacent benign tissue with a trend in decreased staining intensity in higher Gleason grades (Fig. 4). MAGI-2 was positive in secretory cells and focally in basal cells with predominantly cytoplasmic and focally nuclear expression. Intensity of cytoplasmic staining of MAGI-2 was significantly higher in HGPIN and cancer compared with benign glands and benign prostatic hyperplasia by both visual and image analysis.[111] There was no significant difference in MAGI-2 expression in HGPIN and adenocarcinoma, suggesting that this marker may not be useful in differentiating these lesions. In another study, MAGI-2 and AMACR were similarly significantly overexpressed in cancer in all ranges of Gleason grades compared with benign glands. At all H-score cutoffs, MAGI-2 was more sensitive but less specific in distinguishing benign from malignant glands by receiver operating characteristic analysis. Using digital analysis, the area under the curve for AMACR was higher than that for MAGI-2. However, visual evaluation showed that MAGI-2 had slightly higher accuracy than AMACR in distinguishing between benign glands and adenocarcinoma with a greater discriminatory power, especially evident in foci of adenocarcinoma that

lacked AMACR expression. Thus, MAGI-2 could be of Clinical utility in the evaluation of prostate needle biopsy material, especially when other markers are not discriminatory.[112]

SERINE PEPTIDASE INHIBITOR, KAZAL TYPE 1 (SPINK1)

Biology and Role in Tumorigenesis

SPINK1 is a trypsin inhibitor secreted from acinar cells of the exocrine pancreas, and prevents trypsin-catalyzed intra-acinar premature activation of zymogens. Overexpression of SPINK1 protein has been associated with oncogenic properties in several studies. SPINK1 has been found to be the most overexpressed gene in hepatitis C virus–induced hepatocellular carcinoma by gene expression profiling.[113] Overexpression of SPINK1 protein has also been detected in carcinoma of the colon,[114,115] lung,[116] and pancreas.[117]

In prostate cancer, *SPINK1* has been identified as the second-ranked candidate oncogene from transcriptomic data in a “cancer profile outlier analysis” detecting “oncogene outliers,” genes with a systematic increase in expression in a small number of cancer samples.[118] SPINK1 is overexpressed in about 5% to 10% of prostate cancers (Fig. 5).[118] Although the majority of SPINK1-positive cancers have been observed in *ETS* rearrangement–negative prostate cancers, recent studies have detected SPINK1 overexpression in 4% of ERG-positive cases.[119] SPINK1 overexpression has been associated with an increased risk of disease progression and biochemical recurrence in hormonally and surgically treated prostate cancer cohorts,[118,120,121] higher Gleason scores and African American population.[27] However, other studies have shown no significant association between SPINK1 and Gleason grade, tumor stage and biochemical recurrence, as well as prostate cancer mortality.[119]

Clinical Applications

The role of SPINK1 in dual immunohistochemistry with ERG has been explored to assess tumor clonality in prostate biopsies with discontinuous involvement by prostate cancer. In this setting, 25% of biopsies with discontinuous tumor involvement had discordant ERG/SPINK1 cancer foci, consistent with molecularly distinct cancer in the same core. This finding may have significant impact in the evaluation of percent of core involved by prostate cancer and eligibility for active surveillance protocols.

CONCLUSIONS

Immunohistochemistry plays a very important role in diagnostic surgical pathology of the prostate, especially in the setting of minimal prostatic adenocarcinoma. However, caveats in the interpretation of currently recommended immunohistochemical markers, particularly with benign mimickers may limit the usefulness of these studies. With recent advances in understanding of molecular pathways associated with prostate cancer, new biomarkers with prognostic and diagnostic potential have been developed. However, the Clinical value of the proposed biomarkers awaits definitive confirmation as Clinically reliable indicators with high specificity for the diagnosis and prognosis of prostate cancer.

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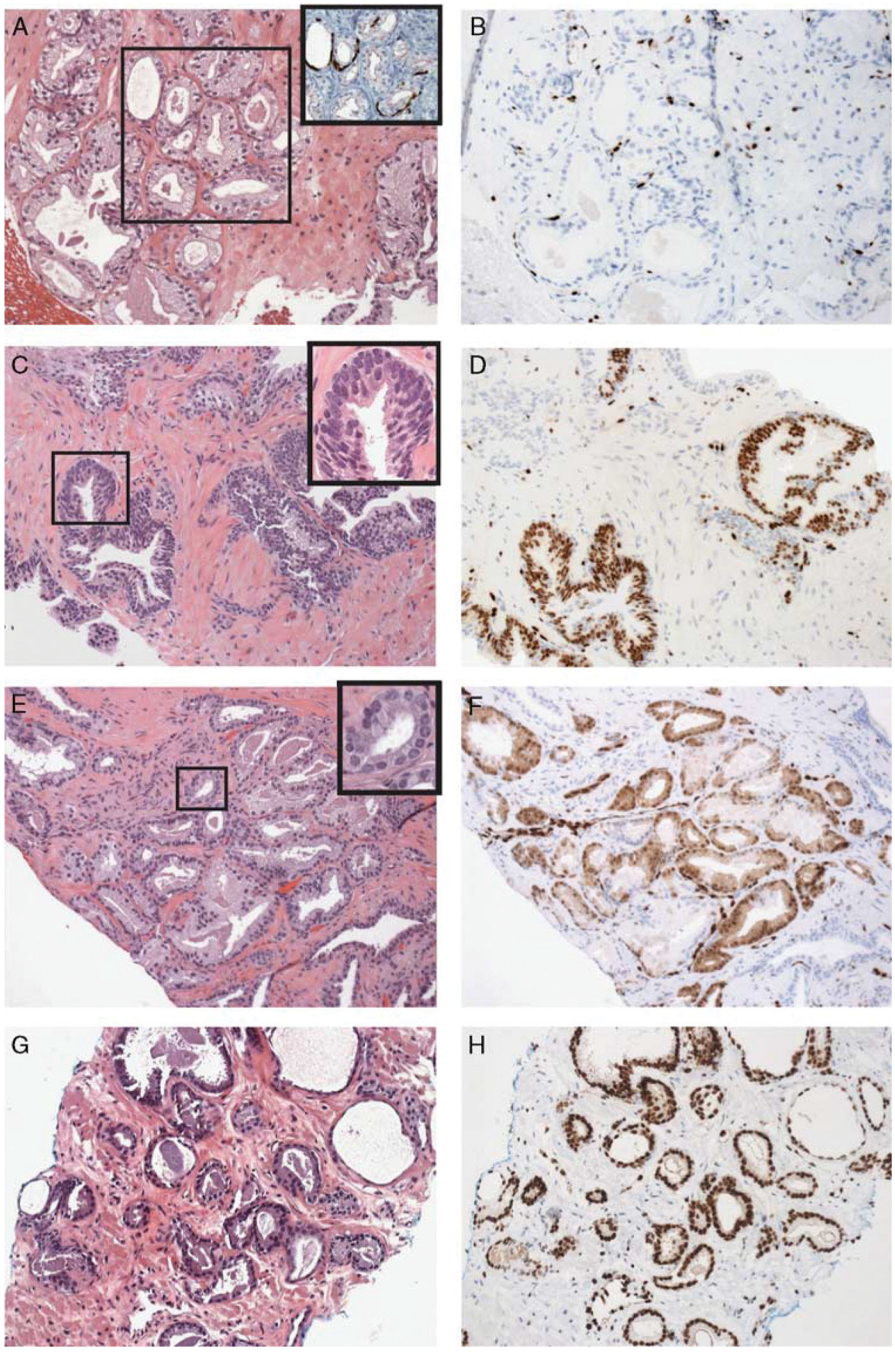

FIGURE 1.

A and B, Adenosis (inset of A: prostate cocktail immuno staining) with negative staining for ETS-related gene (ERG). C and D, High-grade prostatic intraepithelial neoplasia with positive ERG staining. Insect of C shows nuclear atypia and prominent nucleoli. E and F, Small focus of atypical glands with positive ERG staining. Insect of E shows focal nuclear atypia. G and H, Gleason 6 adenocarcinoma with positive ERG staining (original magnification, _20). Reprinted from Tomlins et al[36] with permission from Archives of

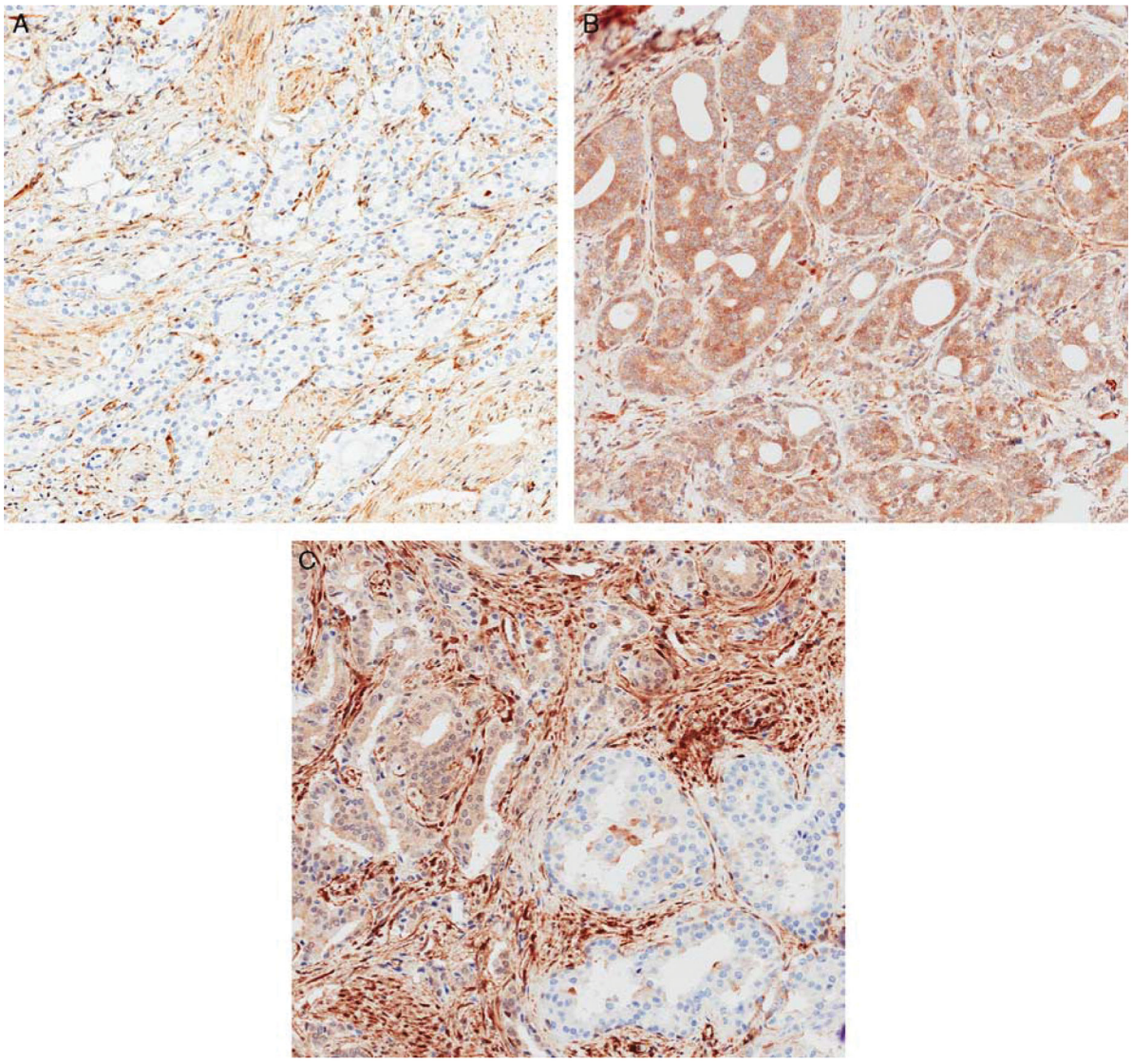

FIGURE 2.

Phosphatase and tensin homolog (PTEN) expression by immunohistochemistry in prostate tissue: A, cancer with PTEN loss. The intervening stroma shows retained PTEN expression. B, Cribriform adenocarcinoma with retained PTEN expression. C, Heterogenous PTEN expression in malignant glands (original magnification, × 200).

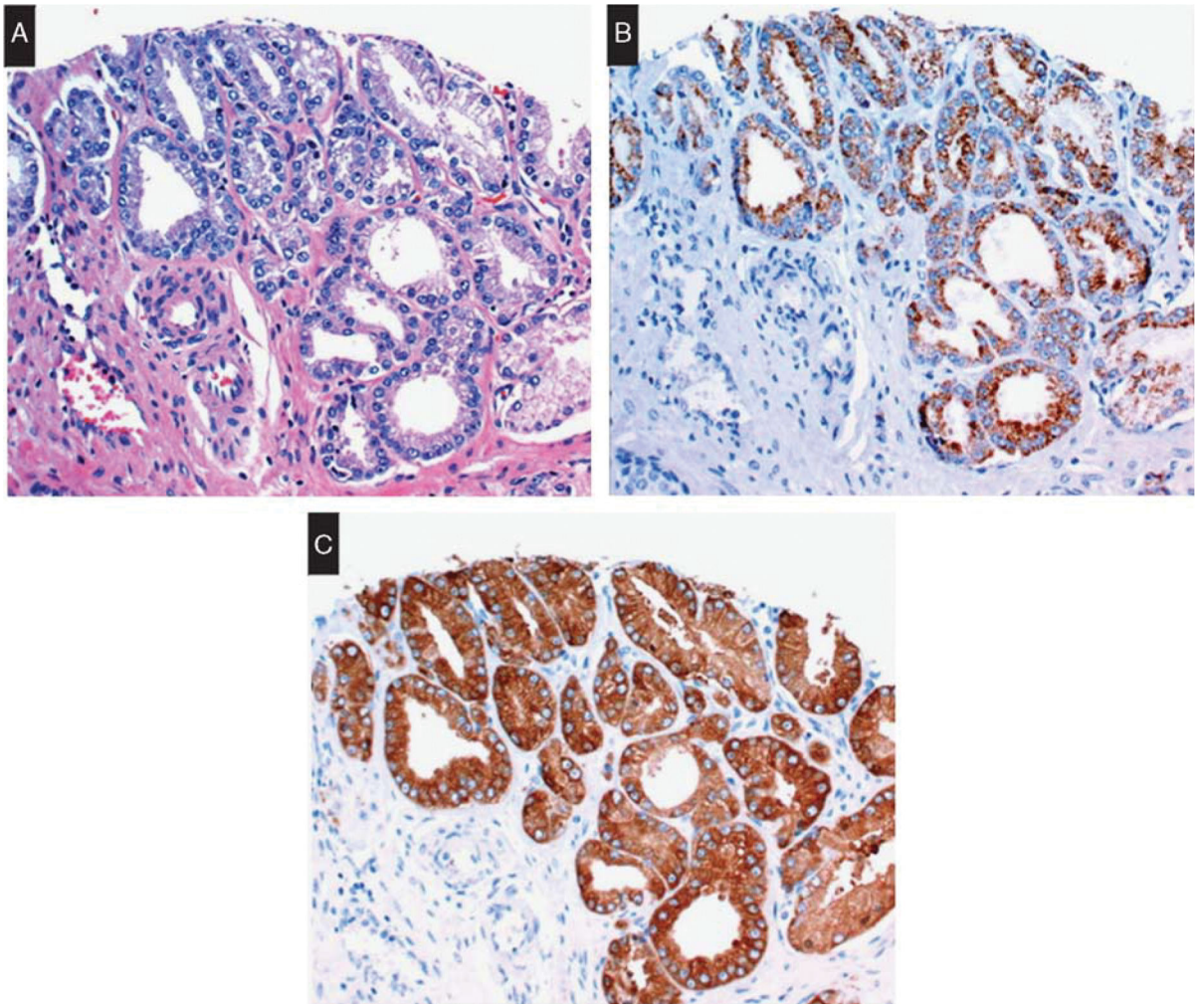

FIGURE 3.

Fatty acid synthase in prostatic adenocarcinoma. A, Focus of Gleason 6 adenocarcinoma. B, Cytoplasmic AMACR expression. C, Cytoplasmic FASN expression. Reprinted from Wu et al[89] with permission from Oxford University Press. Copyright 2016 Copyright Clearance Center Inc. All permission requests for this image should be made to the copyright holder.

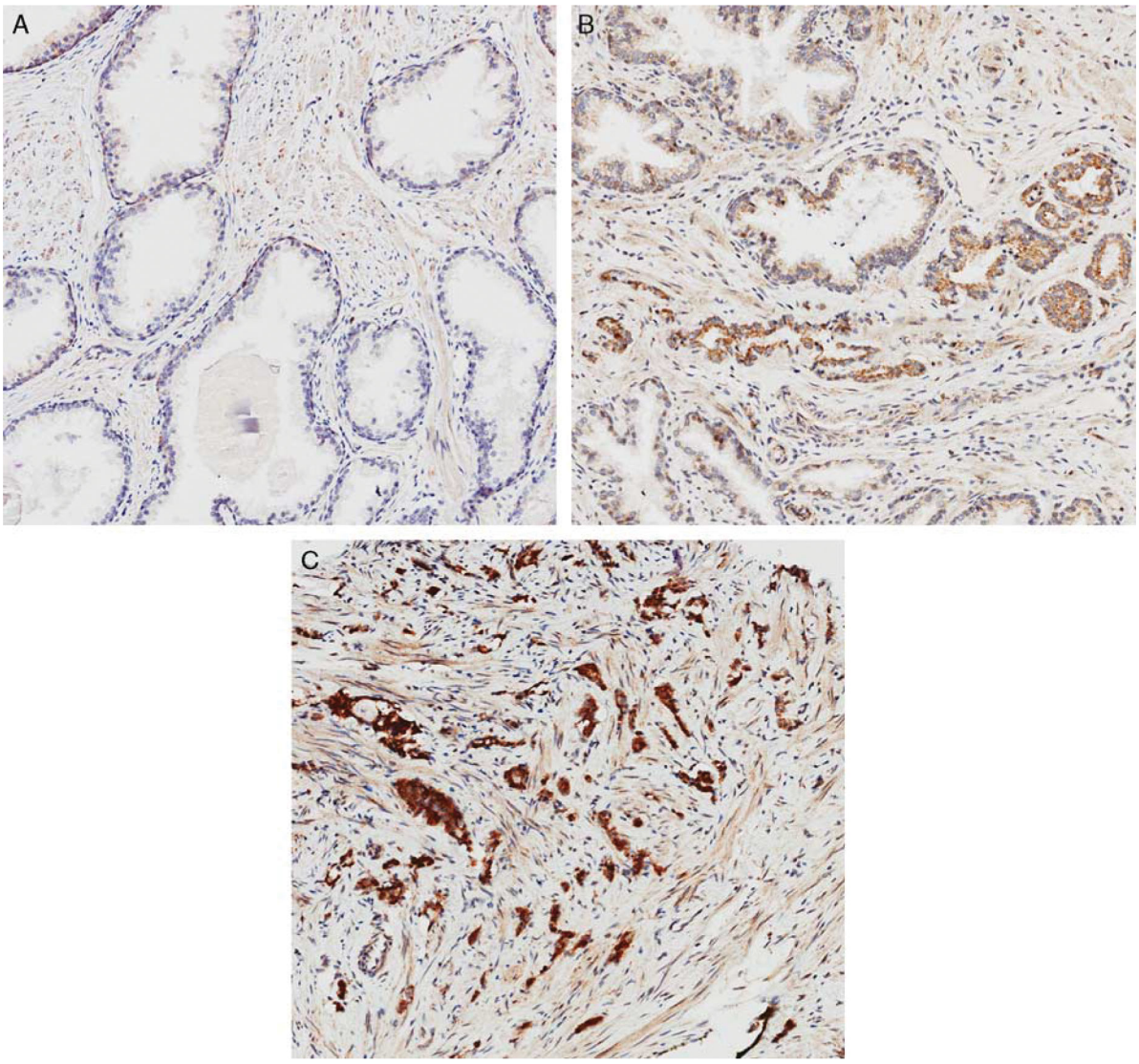

FIGURE 4.

MAGI-2 expression by immunohistochemistry in prostate tissue: A, benign glands with focal basal cell staining for MAGI-2 and lack of expression in secretory cells. B, A small focus of Glason pattern 3 adenocarcinoma infiltrating between benign glands. Focally benign glands show weak cytoplasmic MAGI-2 expression. C, Gleason pattern 5 adenocarcinoma with strong MAGI-2 expression (original magnification, × 200).

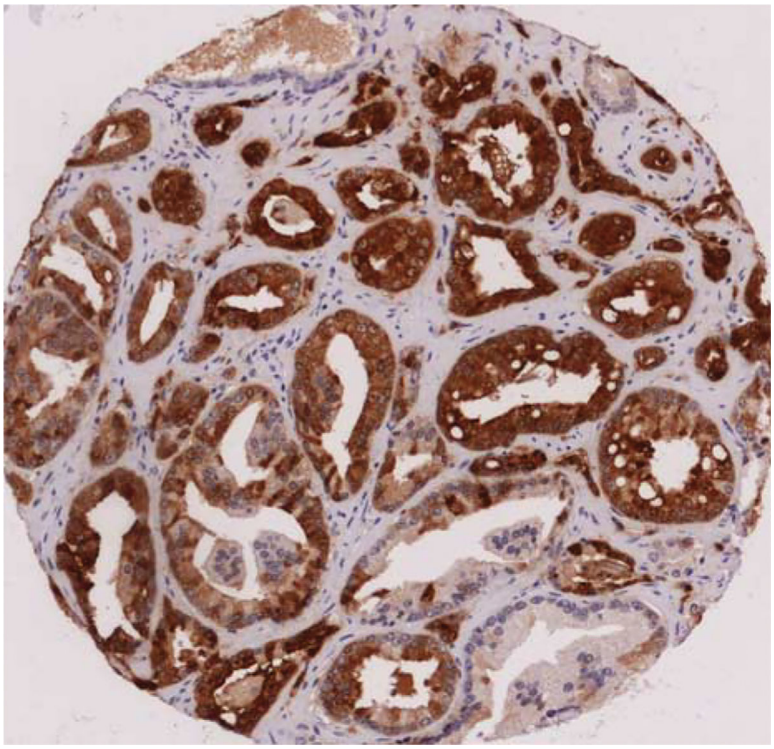

FIGURE 5.
SPINK1 expression in Gleason 6 prostatic adenocarcinoma (original magnification, × 100). Image courtesy of Dr Richard Flavin, Center for Molecular Oncologic Pathology; Department of Histopathology, St. James's Hospital and Trinity College Dublin Medical School, Dublin, Ireland (rflavin@stjames.ie).