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Journal

The Prostate, 80(9)

Authors

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Publication Date

2020-06-01

DOI

10.1002/pros.23980

Peer reviewed

HHS Public Access

Author manuscript

Prostate. Author manuscript; available in PMC 2023 October 09.

Published in final edited form as:

Prostate. 2020 June ; 80(9): 687–697. doi:10.1002/pros.23980.

Corpora amylacea in benign prostatic acini are associated with concurrent, predominantly low-grade cancer

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Abstract

Background: Corpora amylacea (CAM), in benign prostatic acini, contain acute- phase proteins. Do CAM coincide with carcinoma?

Methods: Within 270 biopsies, 83 prostatectomies, and 33 transurethral resections (TURs), CAM absence was designated CAM 0; corpora in less than 5% of benign acini: CAM 1; in 5% to 25%: CAM 2; in more than 25%: CAM 3. CAM were compared against carcinoma presence, clinicopathologic findings, and grade groups (GG) 1 to 2 vs 3 to 5. The frequency of CAM according to anatomic zone was counted. A pilot study was conducted using paired initial benign and repeat biopsies (33 benign, 24 carcinoma).

Results: A total of 68.9% of biopsies, 96.4% of prostatectomies, and 66.7% of TURs disclosed CAM. CAM ≥1 was common at an older age ($P = .019$). In biopsies, 204 cases (75%) had carcinoma; and CAM of 2 to 3 (compared to 0–1) were recorded in 25.0% of carcinomas but only 7.4% of benign biopsies ($P = .005$; odds ratio [OR] = 5.1). CAM correlated with high percent Gleason pattern 3, low GG ($P = .035$), and chronic inflammation (CI). CI correlated inversely with carcinoma ($P = .003$). CAM disclosed no association with race, body mass index, serum prostate specific antigen (PSA), acute inflammation (in biopsies), atrophy, or carcinoma volume.

With CAM 1, the odds of GG 3 to 5 carcinoma, by comparison to CAM 0, decreased more than 2× (OR = 0.48; $P = .032$), with CAM 2, more than 3× (OR = 0.33; $P = .005$), and with CAM 3, almost 3× (OR = 0.39, $P = .086$). For men aged less than 65, carcinoma predictive model was: Score = (2 × age) + (5 × PSA) − (20 × degree of CAM); using our data, area under the ROC curve was 78.17%. When the transition zone was involved by cancer, it showed more CAM than in cases where it was uninvolved ($P = .012$); otherwise zonal distributions were similar.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

In the pilot study, CAM ≥1 predicted carcinoma on repeat biopsy ($P < .05$; OR = 8), as did CAM 2 to 3 ($P < .0001$; OR = 30). CI was not significant, and CAM retained significance after adjusting for CI.

Conclusion: CAM correlate with carcinoma. Whether abundant CAM in benign biopsies adds value amidst high clinical suspicion, warrants further study.

Keywords

corpora amylacea; inflammation; peripheral zone; prediction of cancer; prostate cancer; transition zone

1 | INTRODUCTION

Corpora amylacea (CAM) are frequent luminal contents of prostatic acini and appear to increase with patient age.[1,2] They vary in size (from very tiny up to a few millimeters in diameter),[3] shape (round, triangular, or irregular), and color (pink-purple to orange-brown), but are typically pink and round with concentric laminations. They also correlate with prostatic calculi.[2,4]

CAM have been recognized since the 1700s,[5] but their composition, biogenesis, and function are still inconclusive, and various studies using differing methods have produced differing results.[6–9] Cross et al[6] suggested based on immunostaining that CAM were formed from a localized amyloidosis of β2-microglobulin resulting from urinary reflux, while Cohen et al[8] showed sulfated glycosaminoglycans to be the main constituent of CAM with a weak association to β2-microglobulin. The ultrastructural study by Drachenberg et al[7] revealed that both CAM and crystalloids were largely composed of material derived from the components of gland secretory cells, while that of Badea et al[9] revealed amyloid-like fibrils as major components of CAM. Multidisciplinary studies revealed their major components are proteins involved in acute inflammation and amyloid formation, most notably lactoferrin, S100A8/ A9, and myeloperoxidase; and infectious agents possibly play a role.[3,4,10]

Microscopically, CAM are frequently observed in association with damaged epithelium, gland atrophy, and gland occlusion, with adjacent areas of chronic or acute inflammation (Figure 1). Inflammation is postulated to contribute to prostate carcinogenesis, including by physical trauma from CAM.[11] Atrophy is also a possible precursor lesion to cancer development.[12,13]

Pathologists use CAM mainly as a marker for benign acini since CAM are rare in cancer. According to previous studies, CAM were found in 0% to 84% of benign acini of cancer patients, 0% to 55% of high-grade prostatic intraepithelial neoplasia (HGPIN), 0% of atypical small acinar proliferation (ASAP) suspicious for cancer, and just 0.4% to 13% of cancer acini.[14–20] CAM tend to be situated in proximity to cancer,[20] especially low-grade cancer. A study from prostatectomies of cancer patients found an association between CAM and chronic inflammation, low Gleason grade, and higher body mass index (BMI).[20]

We assessed the extent to which CAM in benign acini correlated with cancer in the same or subsequent specimens, raising the question of whether CAM, particularly if

frequent, are “soft” predictors of cancer in benign biopsies. We also assessed, for the first time, the distribution frequency of CAM in prostatectomy tissue between peripheral and transition zones (TZs). To our knowledge, this is the first study to include both benign and cancer specimens from various specimen types in determining associations between CAM, clinicopathologic factors, and concomitant or subsequent cancer.

2 | MATERIALS AND METHODS

2.1 | Specimen population for CAM clinicopathologic assessment

All biopsy, prostatectomy, and transurethral resection (TUR) specimens sequentially diagnosed as benign or cancer during routine prostate sign-out from December 2018 to May 2019 were included. Global diagnoses on biopsy sets also included HGPIN and ASAP.

2.2 | Assessment of clinical and pathologic factors

All hematoxylin and eosin (H&E) stained slides from each patient were examined by two pathologists independently, resolving discrepancies by consensus. In biopsies, all levels (range: 1–3) from all specimen sites (range: 1–13; mean 6.4 sites per patient), including one to two cores per specimen site, were examined. Prostatectomies were submitted entirely if the prostate weight was less than 50 g, or by every other transverse slice if the weight was ≥50 g. TURs were submitted entirely for patients aged ≤60 years; otherwise in 10 blocks.

In benign acini, round to irregular, lamellated bodies were judged as CAM; glandular secretions that were granular and pink (Figure 2), rarely with calcification, were disqualified as CAM. Based on CAM percentage frequencies in the entire set, cases were evenly partitioned into absent (CAM 0), mildly present (CAM 1: <5% of overall acini; usually a few in the entire specimen), moderately present (CAM 2: 5%-25%), and markedly present (CAM 3: >25%). CAM in HGPIN or seminal vesicles were excluded.

Chronic inflammation and acute inflammation were both recorded as absent, mild (<5% of the overall specimen), moderate (5%-25%), or marked (>25%). Atrophy was recorded as absent, mild (<10% of the overall epithelial area), moderate (10%-50%), or marked (>50%). Cancer-associated factors were recorded as Gleason pattern 3 to 5 (percentage), International Society of Urological Pathology (ISUP) grade groups 1 to 5,[21] cribriform pattern (absent or present), and pT stage (2, 3a, 3b in prostatectomies). We further bifurcated grade groups 1 to 2 as low-grade cancer and 3 to 5 as high-grade cancer.[22] The amount of tumor was recorded as single-core and total specimen involvement (percentage) in biopsies, total gland involvement by the tumor (percentage) and tumor maximal dimension (mm) in prostatectomies, and the fraction of tumor-positive chips (percentage) in TURs. For prostatectomies, weight (g) was recorded.

Clinical values obtained included age and serum prostate specific antigen (PSA) at diagnosis, race, and BMI.

2.3 | Zonal frequency distribution of CAM

For ease of distinguishing between peripheral zone (PZ) and TZ CAM, a set of digitized slides of entirely-submitted, whole-mount prostate was used from a subset of patients who

consented during 2014 to 2018 to a radiologic correlation study (principal investigator, PSL). The 325 slides comprised 47 cases containing from 3 to 11 slides per case, dependent on prostate size. For all slides from each case, one pre-designated square measuring 2000 × 2000 pixels (10 880 square microns) was randomly superimposed on the benign tissue of the PZ, and one such square was randomly superimposed on benign tissue of the TZ (the central zone was not assessed). All CAM within each square were then counted by placing a digital mark on each corpus amylaceum and doing automated counting of the marks.

2.4 | Paired biopsies

For the prediction of cancer, 57 total biopsies for which there was a prior benign biopsy were used. The paired biopsies, each from the same man, that were either benign—benign, or benign—cancer, were obtained from 4 prior years. All H&E slides in initial biopsies were blinded and reviewed by three pathologists independently with consensus in discrepancies to evaluate the presence and degree of both CAM and chronic inflammation.

2.5 | Statistical analyses

In the clinicopathologic study, CAM were bifurcated as absent (CAM 0) vs present (CAM ≥1), and also bifurcated as absent to mildly present (CAM 0–1) vs moderate to marked (CAM 2–3). CAM associations with clinical and nonneoplastic pathologic factors were assessed for all specimen types combined and each specimen type separately. For pathologic factors associated with cancer, we evaluated each specimen type separately because of different methods of evaluation and reporting of cancer characteristics. Biopsies with global diagnoses of HGPIN or ASAP were excluded. For correlation of CAM to low- or high-grade cancers, we combined all cancer patients from all specimen types.

SAS software version 9.4 was used for all analyses. Wilcoxon-Mann-Whitney test and the Kruskal-Wallis test were used to compare continuous outcomes between CAM groups. The χ^2 test was used to compare distributions of categorical variables. Exact test was applied for continuity correction of data. To evaluate the association of CAM to the presence of cancer and low- or high-grade cancers and the prediction of cancer in paired biopsies, multiple logistic regression was performed. A $P < .05$ was considered significant.

Zonal distributions of CAM were quantified using two linear mixed effect models. The first model tested the main effect of PZ vs TZ location, whereas the second model included a second main effect of tumor location (PZ, PZ+TZ) and tested the interaction between CAM location and tumor location effects. Both models included tumor grade (high vs low) as a covariate, and included nested random effects for subject and slide.

3 | RESULTS

3.1 | Clinicopathologic specimen study

A total of 386 cases included 270 biopsies, 83 prostatectomies, and 33 TURs. Patients' age ranged from 45 to 89 years (median: 65). There were 337 whites, 38 African-Americans, 9 Hispanics, and 2 Asians. BMI ranged from 14.5 to 50.3 kg/m^2 (median: 28.1). Serum PSA ranged from 0.1 to 1062 ng/mL (median: 6.4).

CAM incidence varied across specimen types ($P < .001$): CAM were found in 68.9% of biopsies, 96.4% of prostatectomies, and 66.7% of TURs. Presence of any CAM (CAM ≥1) was associated with older age (mean ± standard deviation = 65.9 ± 7.7 for CAM ≥1; 63.5 ± 7.5 for CAM 0; $P = .014$) and chronic inflammation presence in any degree, most commonly mild, both before ($P < .001$) and after ($P = .007$) adjusting for concomitant acute inflammation (Table S1). CAM 2 to 3 were also associated with chronic inflammation presence both before ($P < .001$) and after ($P = .016$) adjusting for acute inflammation. No association was found with race, BMI, serum PSA, or acute inflammation.

3.1.1 | Biopsies—Of 270 biopsies, 204 had an overall cancer diagnosis (75.5%), 54 (20%) were benign, 4 (1.5%) high-grade PIN and 8 (3.0%) ASAP. CAM presence in ≥5% of benign acinar area (CAM 2–3) was found in 25% (51/ 204 cases) of cancer but only 7.4% (4/54 cases) of benign biopsies, and carried a 3.4-fold higher association with cancer compared to CAM area <5% (CAM 0–1; $P = .05$; Table 1), with a sensitivity of 25.0%, a specificity of 92.6%, positive predictive value (PPV) of 92.7%, negative predictive value (NPV) of 24.6%, and accuracy of 39.2%. Considering CAM ≥1, 75% (153/204) cases were cancer and 50% (27/54) cases were benign, imparting a 1.5-fold odds ratio (OR; $P = .030$) compared to CAM 0 (Table 2), with sensitivity of 75.0%, specificity of 50.0%, PPV of 85.0%, NPV of 34.6%, and accuracy of 69.8%. CAM 2 to 3, compared to CAM ≥1, had higher PPV and specificity; however, both had low to moderate sensitivity and low NPV. This close association of CAM 2 to 3 was more common in low ISUP grade groups (1 and 2; 76.5% or 39/51 cases with CAM 2–3; 65.4% or 100/153 cases with CAM 0–1; $P = .035$) and it was associated with a higher percentage of Gleason pattern 3 ($P = .044$; Table 1), and lesser percentage of Gleason pattern 5 ($P = .020$) when compared to CAM 0 to 1.

CAM ≥1 was associated with older age ($P = .019$) compared to CAM 0 (Table S2). Age, in this study, was a predictor of cancer ($P = .031$). By logistic regression model, with every year, cancer risk increased by 4%. CAM ≥1 was associated with chronic inflammation presence, most commonly mild degree, both before ($P = .030$) and after ($P < .001$) adjusting for concomitant acute inflammation. Similar to all specimen types combined, CAM 2 to 3 were associated with chronic inflammation presence both before ($P = .003$) and after ($P = .002$) adjusting for acute inflammation (Table 1). No association was found for race, BMI, serum PSA, cribriform pattern, amount of tumor per core or in the total specimen, acute inflammation, or atrophy.

3.1.2 | Prostatectomies—All 83 prostatectomy specimens contained cancer. No CAM were found in three cases. CAM ≥1 was not associated with any clinicopathologic parameters (Table S2). By determining CAM 0 to 1 vs CAM 2 to 3 (Table 1), CAM 0 to 1 was associated with pure chronic inflammation (without concomitant acute inflammation; $P = .015$), whereas CAM 2 to 3 was associated with acute inflammation (but with concomitant chronic inflammation; $P = .007$). Variables that did not correlate with CAM included age, race, BMI, serum PSA, % Gleason pattern, grade group, cribriform pattern, amount of tumor as percent total gland involvement by tumor or tumor maximal dimension, pT stage, and prostate weight.

3.1.3 | TURs—In TURs, 6 out of 33 cases were cancer. CAM did not correlate significantly with any clinical or pathologic measurements (Table 1 and Table S2).

3.1.4 | All cancer patients—Among cancer patients from all specimen types (n = 293; Table 2), CAM 2 to 3 was significantly more common in low-grade cancer ($P = .043$). With increasing amounts of CAM analyzed as CAM = 0, 1, 2, or 3, the likelihood of high-grade cancer diminished ($P = .021$). Odds of high-grade cancer decreased more than two times with CAM 1 (OR = 0.48; 95% confidence interval = 24.39–95.18; $P = .032$), more than three times with CAM 2 (OR = 0.33; 95% confidence interval = 14.26–74.66; $P = .005$), and almost three times with CAM 3 (OR = 0.39; 95% confidence interval = 10.94–120.67; $P = .086$; n = 8 in CAM 3) when compared to CAM 0. Using multiple logistic regression, a predictive model was built for high-grade cancer. The effect of CAM was not statistically significant for men 65 years of age or older. Rounding up and rescaling the model's regression coefficients, two equations were devised. For those who were under 65 years of age, the Score = (2 × age) + (5 × PSA) − (20 × degree of CAM); for those more than 65 years, the Score = (2 × age) + PSA. When these scores were applied to our data, the area under the receiver-operating characteristic curve (AUC) was 78.17% (Figure 3). Using a cut-off point of 158 (meaning a score of 140 would associate a patient with high-grade cancer), the sensitivity of the prediction tool is 46.7%, specificity is 92.6%, and accuracy is 78.5%. These four measures (AUC, sensitivity, specificity, and accuracy) would need validation in another dataset, to overcome the limitation of using the same dataset for purposes of model building and for evaluating these measures.

3.1.5 | Inflammation and cancer—Inflammation has a putative role in carcinogenesis, and our study showed CAM associations with both cancer and chronic inflammation. Thus, we further analyzed the association between inflammation and cancer in the biopsy series (Table 3) and found that absence of both chronic inflammation (all cases, with or without concomitant acute inflammation) and acute inflammation (all cases, with or without concomitant chronic inflammation) had strong associations with a cancer diagnosis: 94% (32/34) of cases with chronic inflammation, $P = .003$% and 84.6% (159/188) of cases with acute inflammation, $P < .001$. Pure chronic inflammation (without concomitant acute inflammation) showed no association with cancer ($P = .510$). No association was found between chronic or acute inflammation and high or low grade of the cancer (Table S3). Of note, there were only two cases of pure acute inflammation, both of mild degree and in benign biopsies.

3.2 | Zonal frequency distribution of CAM

There was no location difference of CAM between PZ and TZ ($P = .81$). Among 47 cases, 23 had PZ tumors only, and 24 had both peripheral and TZ tumors (PZ vs PZ+TZ). Zonal distribution of CAM according to tumor zone is shown (Figure 4). When including interactions with PZ vs TZ, the location interaction term disclosed more CAM in the TZ when the TZ had tumor present (means: 20.0 for CAM in PZ and PZ tumor; 22.4 for CAM in PZ and PZ+TZ tumor; 14.2 for CAM in TZ and PZ tumor; 25.2 for CAM in TZ and PZ+TZ tumor; $P = .012$), but no differences in PZ. This model also allowed for controlling

for the grade of tumor directly, such that it was strictly the presence of any tumor that showed this effect.

Among 47 cases, 19 were low-grade (grade groups 1–2) and 28 were high-grade (grade groups 3–5). No significant differences were found between CAM in the PZ in high-grade cancer, in the PZ in low-grade cancer, in the TZ in high-grade cancer, or in the TZ in low-grade cancer (means: 20.1, 21.3, 21.7, and 16.5, respectively; $P = .37$ for PZ vs TZ; $P = .77$ for low-grade vs high-grade).

3.3 | Paired biopsy study

A total of 33 of the benign biopsies were followed by a benign repeat biopsy, and 24 benign biopsies were followed by a cancer repeat biopsy. Follow-up time ranged from 6 months to 9 years, mean follow-up time 2.3 years.

CAM predicted cancer in subsequent biopsies, either using the criterion of CAM presence (CAM ≥1; OR = 8.36; 95% confidence interval = 1.02–393.34; $P < .05$) or that of moderate to marked degree of CAM (CAM 2–3; OR = 29.96; 95% confidence interval = 3.74–1397.41; $P < .0001$; Table 4). CAM 2 to 3, compared to CAM ≥1, had higher PPV (92.3% vs 48.9%) and specificity (97.0% vs 27.3%) with sensitivity of 50.0% and NPV of 72.7%. After adjusting for chronic inflammation, both CAM ≥1 and CAM 2 to 3 were still significant; thus, with either the presence or absence of chronic inflammation, CAM ≥1 and CAM2 to 3 still predicted cancer. Notably, chronic inflammation did not predict cancer in subsequent biopsy ($P = .23$; Table S4).

4 | DISCUSSION

In this study, 74.6% of all specimen types showed CAM in benign prostatic acini. Most prior studies included only cancer patients, were conducted in a specific type of specimens,[20] or did not study mainly CAM. Notably, cancer specimens had a higher incidence of CAM in benign acini compared to benign specimens. Furthermore, among prostatectomies, 96.4% contained CAM.

The presence of CAM and CAM with ≥5% acinar involvement were associated with older age and chronic inflammation in all specimen types combined and biopsies. In biopsies, the presence of CAM, especially in ≥5%, proved to be a previously-unrecognized indicator of a cancer diagnosis. A total of ≥5% CAM also correlated with ISUP grade group 1 to 2, a high percentage of Gleason pattern 3, and a low percentage of Gleason pattern 5.

The paired biopsy (pilot) study showed that ≥5% CAM were associated with cancer, whereas chronic inflammation was not associated with cancer. Previously, there were few studies on CAM and their association with cancer and clinicopathologic factors. Our findings are concordant with previous studies showing an association of CAM with low Gleason grade.[15,20] Since prostatic calculi may arise from calcification of CAM, the studies on the association of prostatic calculi to cancer showed results ranging from no association,[23] to a positive association between large prostatic calcuIi and prostate cancer.[24] Dell'Atti et al[25] suggested a role of prostatic calculi in carcinogenesis, as they found 63.3%

of patients with prostatic calculi in the PZ had cancer on biopsy with no association to Gleason grade.

One explanation of the association between CAM and cancer in biopsies is our finding that CAM increased with age, just as cancer does. Thus, prostatic CAM may be part of the normal aging process, as are CAM in the brain. CAM found in various organs seem to have different and yet unclear biogenesis, composition, and function.[26–28] Some constituents of CAM among organs are shared but in varying proportions. S100A8/A9 proteins, one of the major protein components found in prostatic CAM and suggested to be associated with aging prostate,[3] were in many human disorders, both nonneoplastic and neoplastic,[29] including prostate cancer.[30]

Age alone did not explain the association of CAM and cancer. CAM ≥5% in the current study did not correlate with age. Moreover, this study found that CAM ≥5% was significantly associated with cancer only for men under age 65. Thus, other variables could explain the increased CAM amount in cancer, such as chronic inflammation which was associated with CAM presence and CAM ≥5% in all specimen types combined and biopsies. Similarly, Dupre et al[20] studied CAM in prostatectomies and reported an association of CAM presence in any degree with chronic inflammation. Prostatectomies in the current study did not support a CAM—chronic inflammation association, but the small sample size and skewed distribution (n = 3 in CAM absent, n = 80 in CAM present) may have been responsible. Nevertheless, after bifurcating as CAM 0 to 1 (n = 39) vs 2 to 3 (n = 44), CAM ≥5% was associated with pure chronic inflammation, suggesting a possible association of CAM presence and chronic inflammation in prostatectomy specimens. An association of CAM ≥5% with acute inflammation emerged in prostatectomy specimens, although after adjusting for concomitant chronic inflammation, this finding was not significant. Since in everyday practice, acute inflammation is commonly seen with chronic inflammation, cases with acute inflammation without chronic inflammation are rare. The lack of this association in biopsies might be attributable to the focal nature of acute inflammation or sampling variations. In sum, CAM were associated with chronic and possibly acute inflammation, consistent with the composition of CAM from acute inflammatory proteins and a possible role of prior infection in the biogenesis of CAM.[4,10]

Since we found associations of CAM with concurrent cancer and CAM with chronic inflammation, it was possible that CAM were a mere epiphenomenon of a chronic inflammation—cancer relationship. However, degrees of acute and chronic inflammation were inversely associated with cancer (Table 3), precluding that possibility. Whether inflammation has a positive or negative association with prostate cancer remains uncertain. A previous study suggested that physical trauma by CAM was one of the causes of prostatic inflammation, other causes being infection, chemical irritation from urine influx, dietary factors, hormonal imbalances, and autoimmune response; and that inflammation was related to prostate carcinogenesis.[11] Other studies supported a positive association of inflammation and cancer with inflammation being associated with higher risk or more aggressiveness of prostate cancer.[22,31] Numerous studies have been done, including mouse models, in search of inflammatory-related prostate cancer pathways and for preventive and therapeutic purposes.[32–34] On the other hand, several studies showed a negative

association of inflammation with prostate cancer, whereby inflammation presence was associated with a lower risk or less aggressiveness of cancer, and better prognosis.[35–41] A proposed explanation is inflammation being a host defense mechanism or protecting against prostate cancer. The human immune system is complex, and can both promote or fight against cancer.[42] Inflammation also commonly occurs in the general population with or without clinical prostatitis and in benign prostatic hyperplasia. The mechanism of how benign hyperplasia-related inflammation differs from inflammation in prostate cancer is still unclear, but a difference was found in inflammatory cell types and proportions between the two entities.[43] Again, our study showed an inverse relationship of both chronic and acute inflammation to cancer, suggesting that the CAM-cancer association is not driven by CAM being associated with inflammation. Thus, CAM may relate to carcinogenesis by a different mechanism. The pathways for CAM biogenesis might differ between normal and cancerous prostate, that is, how their production is increased in the cancer population, and among cancer patients themselves because not all cancer patients had CAM. Also, disturbance of the clearance mechanism such as obstruction by the tumor may cause stasis of CAM within the prostate. More studies are needed because it is currently unclear: (a) how CAM are produced and what causes increased or decreased CAM production; (b) whether CAM represent a normal aging process, despite the current study; (c) whether CAM maintain their form, dissolve, or get calcified into calculi; and (d) whether CAM remain in the prostate after production or there is a clearance mechanism removing CAM.

Regarding CAM zonal distribution, Dupre et al[20] found fewer CAM in TUR specimens than in prostatectomy specimens. We found CAM in two-thirds of TURs, all from the TZ, and two-thirds of biopsies, mainly from the PZ. This argues for a random CAM distribution. We also performed counting of CAM in the TZ vs PZ in prostatectomy tissue only, which controls for specimen type (since TURs are predominantly benign). Our digital study further reinforced that CAM in benign acini were associated with cancer presence since increased CAM were found in the TZ if the tumor involved the TZ (regardless of grade, in addition to tumor presence in the PZ). The absence of a correlation between PZ CAM and tumor probably reflects the fact that all cases had a PZ tumor. Overall, according to our findings, we hypothesize that CAM are associated with the normal aging process and inflammation in the prostate. Their increased production in the cancer population is possibly stimulated by a different protective mechanism that occurs only when there is a tumor. Moreover, functional prostatic glands can produce CAM regardless of zonal location. Some CAM may then grow in size, obstruct glands, and cause atrophy or damage to the glands.

There are some limitations to our study. First, in biopsy specimens, we did not exclude cases which might have had a prior biopsy before the study period, causing possible discordance in the presence and degree of CAM between biopsies in the same patient due to sampling variation; however, in the paired biopsy study there was 93% concordance between CAM 0 to 1 vs 2 to 3. Similarly, in the biopsy study of the inflammation and cancer relationship, we did not exclude patients who might have elevated serum PSA or had a prior biopsy before the study period that could have created inflammation in the specimen. However, we did not find a positive association of inflammation with cancer such that patients who had a prior biopsy were more likely to have a clinical suspicion of cancer. Second, in the paired biopsy study, our sample size was limited to 57 simply because the number

of patients with a benign biopsy followed by a second biopsy is a small fraction of total biopsies; attaining higher-powered results would require a multiinstitutional study. Third, in the study of CAM and low- or high-grade cancer, we combined cancer patients from all specimen types and there might be Gleason score discordance between biopsy and subsequent prostatectomy in some individual patients which could affect the results. Fourth, since CAM are frequently observed microscopically in association with atrophy, we graded atrophy as absent or present in the overall specimen area of biopsies, and the results showed no association. Atrophy increases with age. It is commonly in proximity to cancer, and proliferative inflammatory atrophy is proposed as a precursor to HGPIN and cancer. Like inflammation, studies on the association of atrophy and cancer showed both positive[35,44] and negative[45–48] associations. In a prior study,[12] we showed that whenever atrophy abutted cancer, it was disproportionately close to Gleason pattern 3 cancer foci even after adjusting for the lesser frequency of higher-grade cancer foci in the study. The current study did not distinguish whether or not CAM were found within lumens of atrophic glands, which might yield different results. Last, no standard grading system applies to the evaluation of chronic inflammation, acute inflammation, or atrophy in each specimen type. This may have confounded results in previous studies on the relationship between inflammation and cancer. Pathologists do not routinely report the presence and degree of inflammation and atrophy, and those who do, use various grading systems.[43,49] For assessing CAM, the difference between CAM 0 to1 and CAM 2 to3 is simple and reproducible in routine practice, that is, <5% vs ≥5% presence. Such reporting would be an additional task for pathologists, but further study of it is warranted particularly for benign biopsies in the face of a (persistently) elevated serum PSA.

5 | CONCLUSION

CAM may not be merely a marker for benign glands but also a “tipping point” indicator that may increase suspicion of concurrent cancer and help decide on the necessity of repeat biopsies. CAM presence, especially in ≥5% of acini in benign biopsy specimens, maybe an easily assessible, risk factor, although CAM assessment would place a minor additional burden on pathologists, and confirmatory studies would be needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding information

National Cancer Institute, Grant/Award Number: R01CA218144

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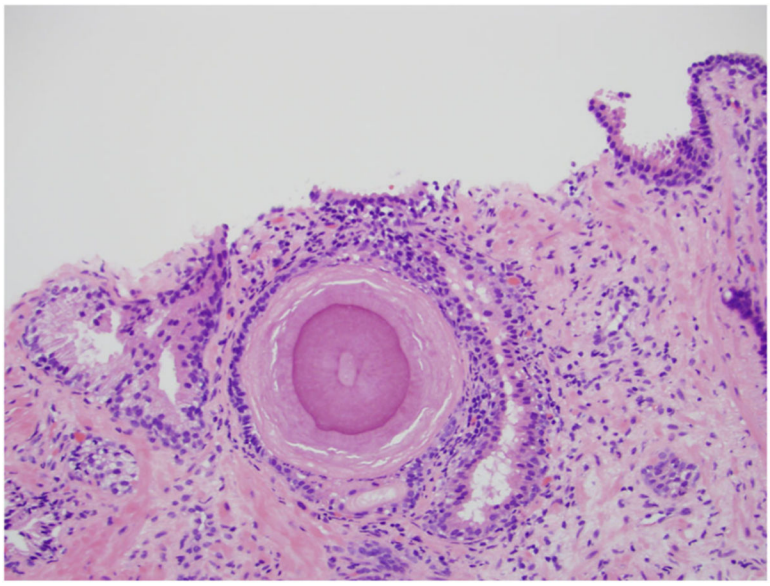

FIGURE 1.
Corpora amylacea are frequently observed in association with damaged epithelium, gland atrophy, and surrounding chronic inflammation

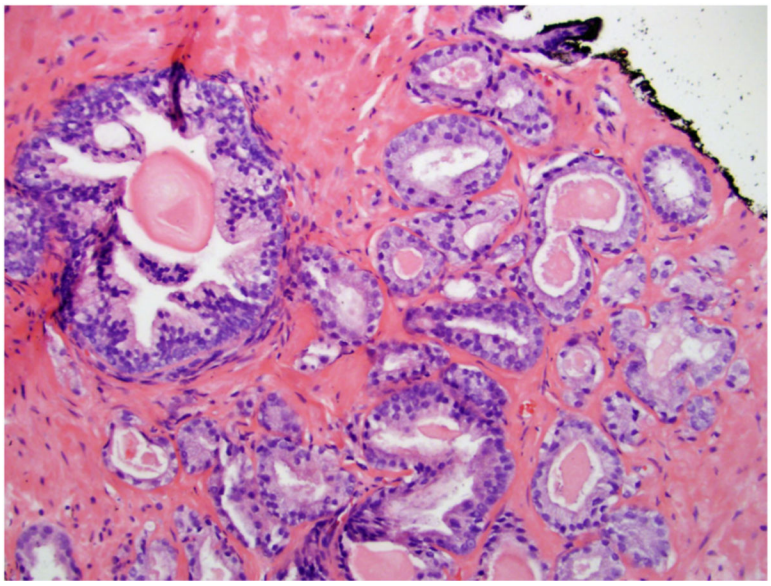

FIGURE 2.
Corpora amylacea are round, homogeneous, and laminated (left) while cancer gland secretions are irregular (right)

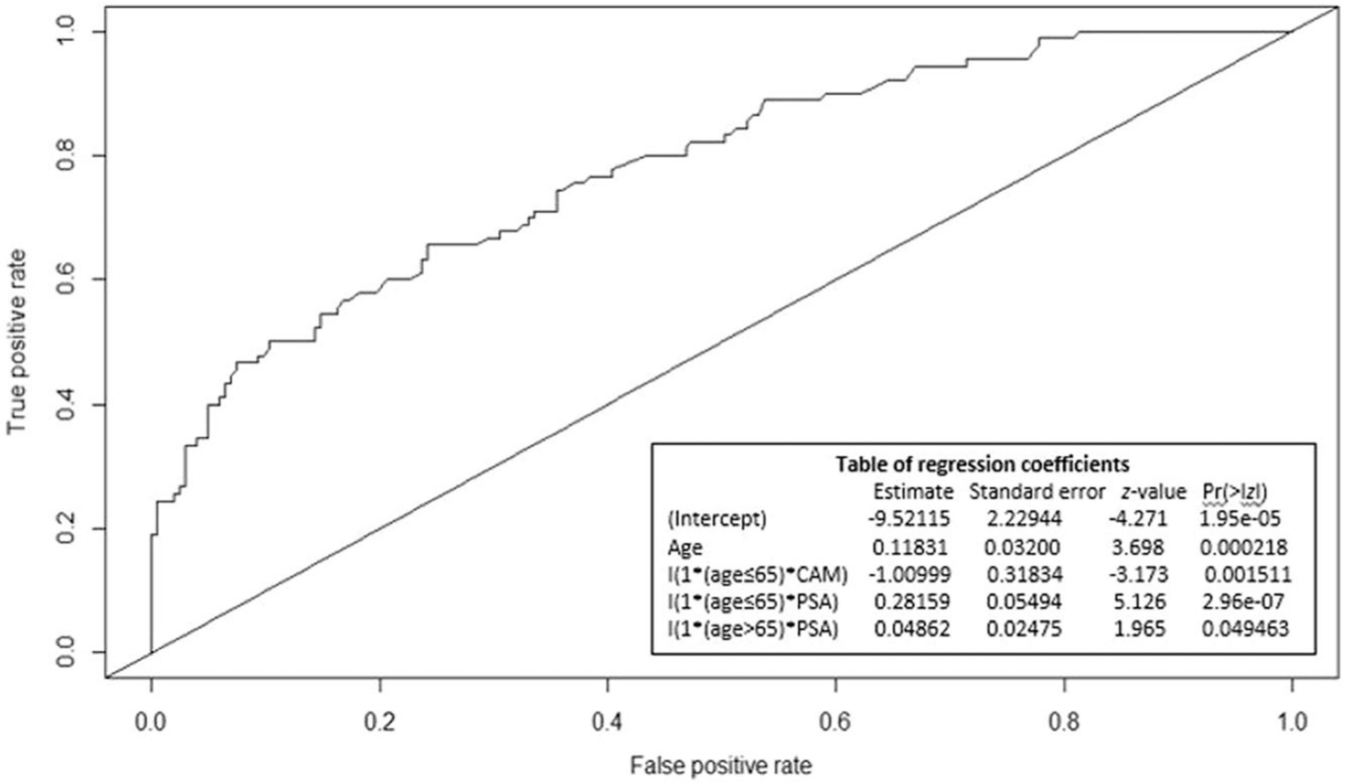

FIGURE 3.

Prediction of high-grade (grade groups 3–5) cancer. For those who were under 65 years of age, the Score = (2 × age) + (5 × PSA) − (20 × degree of CAM); for those more than 65 years, the Score = (2 × age) + PSA. Receiver-operating characteristic (ROC) curve with AUC of 78.17%; after excluding CAM from the model, the AUC decreased from 78.2% to 71.8%. The table of regression coefficients is included. AUC, area under the receiver-operating characteristic curve; CAM, corpora amylacea

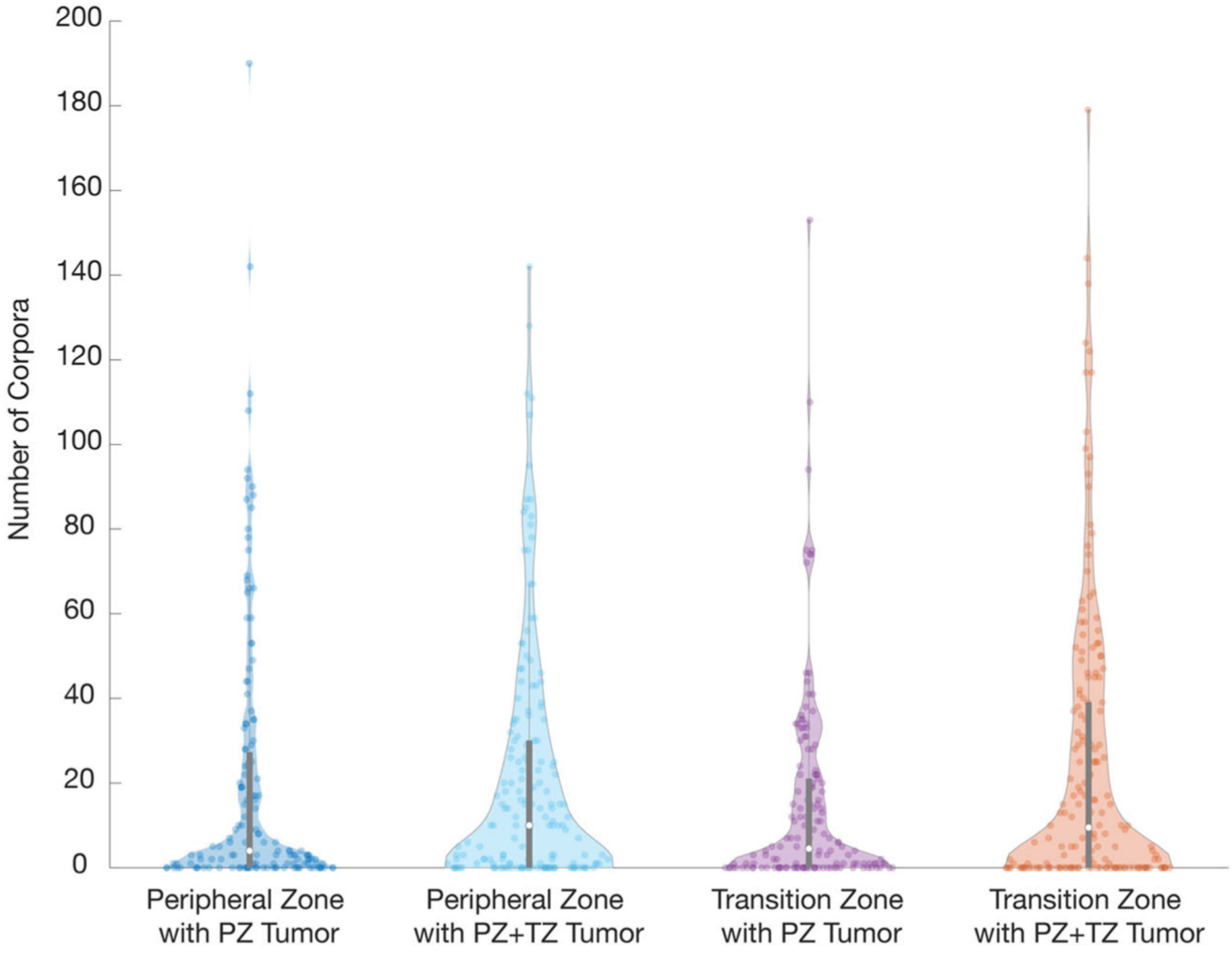

FIGURE 4.

Violin plots from the digital study of the zonal frequency distribution of CAM showing association of increased amount of CAM in the transition zone with the presence of transition zone tumor. Dots on the bars represent the median. Two slides that were outliers were excluded. CAM, corpora amylacea

TABLE 1

Clinicopathologic features in biopsies and prostatectomies and corpora amylacea (CAM) 0–1 vs 2–3

		Biopsy, N = 270				Prostatectomy, N = 83		
Corpora abundance	**N**	**CAM 0–1, N = 215**	**CAM 2–3, N = 55**	***P***	**N**	**CAM 0–1, N = 39**	**CAM 2–3, N = 44**	***P***
Age (y)				.942[a]				.277[a]
Mean ± SD		65.0 ± 7.7	65.1 ± 6.3			63.1 ± 6.3	64.3 ± 6.9	
Median (min, max)		65 (45, 86)	65 (54, 80)			63 (52, 79)	65 (51, 75)	
Race, N (%)				1.000[b,c]				.662[b,c]
Whites	233	185 (79.4)	48 (20.6)		78	36 (46.2)	42 (53.8)	
African-Americans	29	23 (79.3)	6 (20.7)		5	3 (60.0)	2 (40.0)	
Hispanics	7	6 (85.7)	1 (14.3)		0	0 (0.0)	0 (0.0)	
Asians	1	1 (100.0)	0 (0.0)		0	0 (0.0)	0 (0.0)	
BMI, kg/m^2				.813[a]				.425[a]
Mean ± SD		28.9 ± 5.2	28.9 ± 4.4			28.7 ± 4.5	30.0 ± 5.6	
Median (min, max)		28.0 (14.5, 50.3)	28.6 (19.5, 42.6)			28.5 (20.7, 40.4)	29.8 (18.9, 44.1)	
Serum PSA, ng/mL				.453[a]				.077[a]
Mean ± SD		21.2 ± 89.2	27.6 ± 142.2			8.9 ± 13.9	9.7 ± 7.1	
Median (min, max)		6.4 (0.1, 1033)	6.7 (2.3, 1062)			5.8 (1.5, 90.1)	6.9 (3.6, 42.2)	
Histology, N (%)				.005[b]				NA
Benign	54	50 (92.6)	4 (7.4)		0	0 (0.0)	0 (0.0)	
Cancer	204	153 (75.0)	51 (25.0)		83	39 (47.0)	44 (53.0)	
Gleason pattern (%), mean ± SD, median (min, max)								
3		70.7 ± 34.1	82.2 ± 25.8	.044[a]		64.5 ± 34.7	69.6 ± 30.6	.844[a]
		90 (0, 100)	95 (0, 100)			80 (0, 100)	81 (0, 100)	
4		24.7 ± 28.8	17.3 ± 24.8	.096[a]		30.2 ± 29.5	27.4 ± 26.4	.993[a]
		10 (0, 99)	5 (0, 90)			20 (0, 85)	19 (0, 95)	
5		4.6 ± 13.4	0.5 ± 2.0	.020[a]		5.3 ± 9.1	3.0 ± 7.1	.135[a]
		0 (0, 85)	0 (0, 11)			0 (0, 35)	0 (0, 35)	
Cribriform pattern, N (%)				.057[b]				.229[b]

		Biopsy, N = 270			Prostatectomy, N = 83			
Corpora abundance	**N**	**CAM 0–1, N = 215**	**CAM 2–3, N = 55**	***P***	**N**	**CAM 0–1, N = 39**	**CAM 2–3, N = 44**	***P***
Absent	156	112 (71.8)	44 (28.2)		42	17 (40.5)	25 (59.5)	
Present	48	41 (85.4)	7 (14.6)		41	22 (53.7)	19 (46.3)	
ISUP grade group, N (%)				.035[b,c]				.367[b,c]
1	65	45 (69.2)	20 (30.8)		4	3 (75.0)	1 (25.0)	
2	74	55 (74.3)	19 (25.7)		57	23 (40.4)	34 (59.6)	
3	23	18 (78.3)	5 (21.7)		12	7 (58.3)	5 (41.7)	
4	7	3 (42.9)	4 (57.1)		1	1 (100.0)	0 (0.0)	
5	35	32 (91.4)	3 (8.6)		9	5 (55.6)	4 (44.4)	
Amount of tumor, mean ± SD, median (min, max)								
Maximal single core (%)		51.9 ± 32.6	42.3 ± 32.2	.074[a]		…	…	…
		55 (2, 100)	35 (2, 100)					
Total specimen (%)		16.9 ± 20.5	12.5 ± 18.3	.124[a]		25.1 ± 21.7	25.3 ± 16.3	.473[a]
		8 (0.1, 91.5)	6.4 (0.1, 84.8)			16 (2, 95)	25 (1, 80)	
Tumor dimension, mm		…	…	…		19.6 ± 7.6	19.2 ± 7.6	.913[a]
						19 (9, 38)	20.5 (2, 44)	
Prostate weight, g								.203[a]
Mean ± SD		…	…	…		40.7 ± 13.8	45.6 ± 18.1	
Median (min, max)						36.7 (21, 79.2)	40.3 (17.4, 94.5)	
pT stage, N (%)								.428[b,c]
2		…	…	…	54	23 (42.6)	31 (57.4)	
3a		…	…		23	12 (52.2)	11 (47.8)	
3b		…	…		6	4 (66.7)	2 (33.3)	
Chronic inflammation, N (%)				.003[b,c]				.571[b,c]
Absent	36	32 (88.9)	4 (11.1)		4	3 (75.0)	1 (25.0)	
Present, mild	207	168 (81.2)	39 (18.8)		63	30 (47.6)	33 (52.4)	
Present, moderate	26	14 (53.8)	12 (46.2)		12	5 (41.7)	7 (58.3)	
Present, marked	1	1 (100.0)	0 (0.0)		4	1 (25.0)	3 (75.0)	
Acute inflammation, N (%)				.567[b,c]				.007[b,c]

		Biopsy, N = 270				Prostatectomy, N = 83		
Corpora abundance	**N**	**CAM 0–1, N = 215**	**CAM 2–3, N = 55**	***P***	**N**	**CAM 0–1, N = 39**	**CAM 2–3, N = 44**	***P***
Absent	196	154 (78.6)	42 (21.4)		44	27 (61.4)	17 (38.6)	
Present, mild	71	58 (81.7)	13 (18.3)		28	7 (25.0)	21 (75.0)	
Present, moderate	3	3 (100.0)	0 (0.0)		9	5 (55.6)	4 (44.4)	
Present, marked	0	0 (0.0)	0 (0.0)		2	0 (0.0)	2 (100.0)	
Atrophy, N (%) Absent	87	64 (73.6)	23 (26.4)	.327[b,c]		…	…	…
Mild	142	115 (81.0)	27 (19.0)			…	…	
Moderate	40	35 (87.5)	5 (12.5)			…	…	
Marked	1	1 (100.0)	0 (0.0)			…	…	

Note: Transurethral resection specimen data not shown.

Abbreviations: BMI, body mass index; ISUP, International Society of Urological Pathology; SD, standard deviation.

[a] Wilcoxon-Mann-Whitney test.

[b] The χ^2 test.

[c] Exact test.

TABLE 2

Association of corpora amylacea (CAM) with low-grade vs high-grade cancer in CAM 0–1 vs 2–3 and in each degree of CAM with odds ratio (OR) and 95% confidence interval (CI)

		High-grade cancer (ISUP grade group 3–5)		
Total N = 293	**Low-grade cancer (ISUP grade group 1–2) N = 203**	**N = 90**	**OR (95% CI), *P* value[a]**	***P***
CAM 0–1, N = 197 (%)	129 (65.5)	68 (34.5)	⋯	.043[b]
CAM 2–3, N = 96 (%)	74 (77.1)	22 (22.9)	⋯	
CAM 0, N = 58 (%)	31 (53.4)	27 (46.6)	1.00 (Reference)	.021[b]
CAM 1, N = 139 (%)	98 (70.5)	41 (29.5)	0.48 (24.39–95.18), $P = .032$	
CAM 2, N = 72 (%)	56 (77.8)	16 (22.2)	0.33 (14.26–74.66), $P = .005$	
CAM 3, N = 24 (%)	18 (75.0)	6 (25.0)	0.39 (10.94–120.67), $P = .086$[c]	

[a]OR (95% CI), compared to CAM 0, with Fisher's exact test *P* value.

[b]The χ^2 test.

[c]Higher variability (wider confidence interval for comparing CAM 0 vs 3) is likely related to a smaller number of CAM 3 samples, which also affects *P* value.

TABLE 3

Inflammation is inversely associated with cancer in biopsies

Total N = 258	**Benign, N = 54**	**Cancer, N = 204**	***P***
Chronic inflammation (all), N (%)			003[a]
Absent, N = 34	2 (5.9)	32 (94.1)	
Present, mild, N = 197	42 (21.3)	155 (78.8)	
Present, moderate, N = 26	9 (34.6)	17 (65.4)	
Present, marked, N = 1	1 (100.0)	0 (0.0)	
Acute inflammation (all), N (%)			<.001[a]
Absent, N = 188	29 (15.4)	159 (84.6)	
Present, mild, N = 67	23 (34.3)	44 (65.7)	
Present, moderate, N = 3	2 (66.7)	1 (33.3)	

[a]Wilcoxon-Mann-Whitney test.

TABLE 4

Paired biopsy study with statistical data of corpora amylacea (CAM) categorized as CAM 0 vs ≥1 and as CAM 0–1 vs 2–3

	Histology							OR (95% CI)
Total N = 57	**2nd Cancer biopsy**	**2nd Benign biopsy**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**Accuracy (%)**	***P***
CAM ≥1	23	24	95.8	27.3	48.9	90.0	56.1	8.36 (1.02–393.34)
CAM 0	1	9						<.05
CAM 2–3	12	1	50.0	97.0	92.3	72.7	77.2	29.96 (3.74–1397.41)
CAM 0–1	12	32						<.0001

Abbreviations: CI, confidence interval; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value.