1003 Natural History of Human Papillomavirus Infection in Non-Vaccinated Males: Low Clearance Probability in High-Risk Genotypes

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Background: Human papillomavirus (HPV) infection is one of the most common sexually transmitted infection in both genders. HPV is the main cause of cervical carcinomas in women, and is responsible for anal, penile and oropharyngeal cancer in men. It is therefore imperative to lower the prevalence of HPV infection in the male population. In this study, we aimed to investigate the clearance of type-specific genital HPV infection in a series of heterosexual, non-HPV vaccinated males whose female partners were positive to DNA-HPV tests.

Design: Men attending the same Sexually Transmitted Diseases Center between January 2005 and December 2006 were considered for this long-term longitudinal cohort study. All subjects (n=1009) underwent a urologic visit and microbiological tests on first void, midstream urine and total ejaculate samples. One hundred and five patients were positive to HPV-DNA (n=105; 10.4%; mean age: 34.8±5.8) and consented to clinical examination and molecular diagnostic assays for HPV detection scheduled every six months (median surveillance period of 53.2 months; range: 48-71 months). According to Munoz et al., HPV genotypes were classified into high-risk, probable high-risk and low-risk. HPV positive samples which did not hybridize with any of the type-specific probes were referred to as positive non genotype-able.

Results: At enrollment, the distribution of HPV genotypes was as follows: high-risk HPV (n=37), probable high-risk HPV (n=6), low-risk HPV (n=23), non genotype-able HPV (n=39). A high HPV genotype concordance between stable sexual partnersemerged (kappa=0.92; p<0.001). At the end of the follow-up period, 71/105 (67.6%) subjects were negative for HPV (mean viral clearance time: 24.3 months). With regard to HPV genotype, viral clearance was documented in 14/37 (37.8%) high-risk HPV cases, 6/6 (100%) probable high-risk HPV cases, 20/23 (86.9%) low-risk HPV cases, 31/39 (79.5%) non genotype-able cases. The high-risk HPV genotypes showed the lowest rate and probability of viral clearance (p<0.001).

Conclusions: In our series, high-risk HPV infections were more likely to persist over time when compared with other HPV genotypes. The good HPV genotype concordance between female partners and enrolled males may be the key to extending vaccination programs to all men with high-risk HPV positive partners.

1004 TERT Promoter Mutations in Aggressive Variants of Urothelial Carcinoma

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Background: Somatic activating mutations in the promoter of the *telomerase reverse transcriptase (TERT)* gene are the most common genetic mutations in urothelial carcinoma (UC) of the bladder and upper urinary tract. Little is known, however, about *TERT*-mutation status in the relatively uncommon but clinically aggressive plasmacytoid (PUC) and micropapillary (MPC) variants. Our group is persuing a *TERT* promoter mutations (*TERT-mut*) urine based screening assay for bladder cancer. We evaluated the presence of *TERT-mut* in PUC and MPC of bladder.

Design: We retrospectively identified 48 MPC and 16 PUC cases from our archives (2005-2014). All slides were reviewed to confirm the diagnosis. 33 MPC cases and 10 PUC cases had FFPE blocks available for DNA analysis. Intratumoral areas of non-micropapillary and non-plasmacytoid histology were also evaluated when present. Samples were analyzed with Safe-SeqS, a sequencing error-reduction technology, and sequenced using Illumina MiSeq as previously described (Kinde, I et al. Cancer Res 2013: 367).

Results: Overall, *TERT-mut* was detected in 91% (39 of 43) of all cases. All 33 cases of pure MPC as well as UC with focal micropapillary features demonstrated *TERT-mut*. 56% of pure PUC cases were also positive. Similar to conventional UC, the predominant mutations identified occurred at positions -124 (C228T) (90%) and -146 (C250T) (10%) bp upstream of the *TERT* ATG start site.

In heterogeneous tumors with focal variant histology,intratumoral concordant mutations were found in variant (MPC or PUC) and corresponsing conventional UC.

Tumor Histology	TERT-mut Positive n(%)	C228T n(%)	C250T n(%)	C243T n(%)
PUC (pure plasmacytoid)	5/9 (56)	5(100)	--	--
MPC (Pure micropapillary)	18/18 (100)	15(83)	3(17)	--
Heterogeneous UC with focal micropapillary features	15/15(100)	13(88)	1(6)	1(6)
Heterogeneous UC with focal plasmacytoid features	1/1(100)	1(100)	--	--
Total (n=43)	91	34(79)	4(9)	1(2)

Conclusions: We found *TERT* promoter mutations, commonly found in conventional UC, to be frequently present in MPC and PUC. Our finding of concordant intratumoral mutational alterations in cases with focal variant histology suggests a common cellular origin for both histologic components of this tumor type.

1005 A Reappraisal of Morphologic Differences between Renal Medullary Carcinoma (RMC) and Collecting Duct Carcinoma (CDC) after Exclusion of Newer Subtypes of Renal Cell Carcinoma (RCC): Report from the High-Grade Distal Nephron Adenocarcinoma (HDNA) International Consortium

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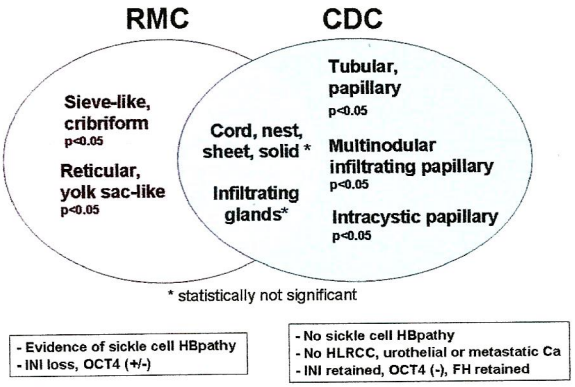
Background: A rare group of lethal high-grade, high-stage infiltrative glandular tumors of the kidney with desmoplasia, herein HDNA, includes previously known categories of RMC, CDC, & RCC unclassified, and an emerging group of Fumarate Hydratase (FH)-deficient tumors of hereditary leiomyomatosis & renal cell carcinoma syndrome (HLRCC). HDNA histomorphology has not been studied comprehensively across these groups to ascertain whether differential growth patterns can assist in classification.

Design: 115 cases of HDNA were collected from 25 international institutions & 10 countries (HDNA International Consortium), and were rigorously classified using contemporary histologic criteria and ancillary tests. The spectrum of morphologic patterns (7 in particular) was critically evaluated and compared between groups.

Results: 115 HDNAs were classified as 33 RMC (INI1-, OCT4+/-, hemoglobinopathy), 40 CDC (INI1+, OCT4-), 33 FH-deficient RCC (FH- and/or 2SC induced), and 9 unclassified RCCs (INI1-, hemoglobinopathy excluded). 10 (20%) cases submitted as CDC were re-classified as FH-deficient RCC based on IHC and/or molecular studies. Comparing morphology between CDC and RMC, infiltrative glandular, cord-like, nested, sheet-like, and solid patterns were shared between both. Sieve-like, cribriform growth and reticular yolk sac-like growth favor RMC (p<0.05), whereas tubular/ papillary growth, multinodular infiltrating papillary growth, and intracystic papillary growth all favor CDC.



Conclusions: In addition to urothelial and metastatic carcinoma, FH-deficient RCC should be excluded before a diagnosis of CDC is rendered. Despite shared morphology of high grade infiltrative adenocarcinoma with desmoplasia, after rigorous characterization and exclusion of emerging RCC subtypes, intriguing, reproducible differences in morphology emerge between RMC and CDC. These features may be of prospective use for triage and classification of cases, empowering future studies of diagnostic & predictive biomarkers.

1006 GSTM1, GSTT1, GSTP1 Polymorphisms, Quality of Life, Habits, Environmental Exposure and Predisposition to Bladder Cancer

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Background: The incidence of bladder tumor has increasing, possibly as a consequence of ongoing environmental pollution and poor personal habits. Previous studies have provided evidences that habits and trace elements are related to development of cancer. The glutathione S-transferases (GSTs) comprise a class of enzymes involved in the detoxification of DNA molecule result of insults exerted by environmental carcinogens. Our aim is to identify the relationship between habits, trace elements and genotype of GSTs with the development of bladder cancer.

Design: This is a case-control study were patients with bladder cancer were compared to healthy individuals. A questionnaire inquiring the habits was applied by a face to face interview. Deletion of GSTM1 and GSTT1 was identified by polymerase chain reaction (PCR) method and the genotype of two single-nucleotide polymorphisms of GSTP1 (rs1695 and rs1138272) was determined using real-time PCR (TaqMan). Serum trace elements (Br, Ca, Cl, Fe, Na, Rb, Se and Zn) were determined directly by using instrumental neutron activation analysis (INAA).

Results: Tobacco increased the risk of bladder cancer with an OR of 2.51 (95% CI, 1.13 to 5.59). People with bladder cancer reported eating more frying food (p <0.05) and less fish and fruit (p <0.05). Practice of physical activity seems to have a protective effect with an OR of 0.34 (95% CI, 0.16 to 0.74). There was a significant decrease of iron (Fe) and chlorine (Cl) (p<0.05), and increased zinc (Zn) in bladder cancer group (p<0.05). GSTM1 null, GSTT1 null and polymorphisms of GSTP1 were not associated with bladder cancer risk.

Conclusions: We have shown that healthy alimentary habits and practice of physical activity can have a protective effect over the development of bladder cancer. The decrease of Fe and Cl and the increase of Zn are also related to an increase in bladder cancer development.