Professor Kenneth C. Anderson

Editor-in Chief

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On behalf of my co-authors, I am submitting the enclosed material “*Diagnostic Role of APC Promoter Methylation in Non-Small Cell Lung Cancer (NSCLC): A Integrate-Analysis of Published Articles and Microarray Data*” for possible publication in *Clinical Cancer Research*. It has not been submitted for publication nor has it been published in whole or in part elsewhere. I attest to the fact that all authors listed on the title page have read the manuscript, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to *Clinical Cancer Research*.

APC has been considered one of most important biomarker for early diagnosis of cancer while there was still not yet any quantitative assessment for the sensitivity and specificity in NSCLC. We systematically integrate 3298 NSCLC and its counterparts from published articles and DNA methylation microarray data to discover the association between DNA methylation and NSCLC. A significant association was observed between APC promoter methylation and Lung cancer, with an aggregated odds ratio (OR) of 3.79 (95%CI 2.22, 6.45) in random effect model. Pooled sensitivity and specificity were 0.548(95%CI: 0.42-0.67, P<0.0001) and 0.776(95%CI: 0.62-0.88, P<0.0001), respectively. The AUC of the APC methylation test in NSCLC was 0.64, meanwhile larger AUC were found in serum group (0.67) than in tissues (0.64). And we found the specific of CpG site, ratio of adenocarcinoma to squamous cell carcinoma and control type(heterogeneous or autogenous) were most important heterogeneity sources. Gender, TNM stage, methylation detection methods, tissue or serum showed no significant associations with APC methylation in NSCLC diagnosis. Therefore, APC promoter hypermethylation would be a promising dignosis biomarker, and better diagnosis efficiency were found for APC methylation test in serum group than that in tissue group, suggesting APC promoter hypermethylation would be an excellent dignosis biomaker in remote non-invasive media.

Meta-analysis for the diagnosis role of methylation biomarker is booming gradually (EJHG, BJC, IJC etc), along with substantial relevant articles increasing. However, all these meta-analysis were conducted imitately to the traditional meta-analysis to SNP-risk associated related meta-analsis. The present study made a comprehensive and professional analysis for methylation diagnostic ability with SROC and independently validation with methylation microarray data, which we believe, will become to a novel methodology and template for the future methylation meta analysis.

We certify that we have participated sufficiently in the work to take public responsibility for the appropriateness of the experimental design and method, and the collection, analysis, and interpretation of the data.

Best Regards.

Yours Sincerely,

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May 12, 2013