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Mutation Research 592 (2005) 102–118
Fundamental and Molecular Mechanisms of Mutagenesis
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Perspectives on the molecular epidemiology of aerodigestive tract cancers

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Available online 14 July 2005

Abstract

Improving laboratory techniques and the greater availability of genetic data have led to a flurry of publications from molecular epidemiologic studies on aerodigestive tract cancers. Inconsistent results have been observed in studies of sequence variants, due to limitations such as small sample size, possible detection of false positives, moderate prior probabilities that each SNP confers a substantial increase in cancer risk, and publication bias. Meta- and pooled-analyses were shown to be effective in elucidating modest increases in aerodigestive tract cancer risk attributable to sequence variants. Phenotypic assays developed to quantify an individual's DNA repair capacity have been applied to epidemiological studies on aerodigestive tract cancers. Epigenetic events have also been studied in tumor progression and as susceptibility factors for aerodigestive tract cancers, in smaller scale studies. It is imperative that limitations of previous studies are addressed for future research in the molecular epidemiology of aerodigestive tract cancers. Some recommendations for future research are to: (i) incorporate multiple markers of different types (ex. genotype and phenotype data), (ii) enhance statistical power by conducting studies with larger sample size, and developing consortia to coordinate research efforts, (iii) improve marker selection via a hybrid strategy of incorporating data on evolutionary biology and physico-chemical properties of amino acids, with haplotype/tag SNP data, (iv) employ novel statistical

Abbreviations: ADH, alcohol dehydrogenase; APC, adenomatous polyposis coli; 5-AZA-CdR, 5-azacytidine2′deoxycytidine; BPDE, benzo(a)pyrene diol epoxide; BRCA1, breast cancer1; CCND1, cyclin D1; CDH1, cadherin 1; CDH13, cadherin 13; CDK4, cyclin-dependent kinase 4; CDKN1A, cyclin-dependent kinase inhibitor 1A; CDKN2A, cyclin-dependent kinase inhibitor 2A; CDKN1B, cyclin-dependent kinase inhibitor 1B; CHEK2, checkpoint homolog 2; CSB, Cockayne's syndrome complementary group; CYP1A1, cytochrome P-450; DAP, death associated protein; DAPK, death-associated protein kinase 1; ERCC1, excision repair cross-complementing rodent repair deficiency complementation group 1; FHIT, fragile histidine triad; GST, Glutathione-*S*-transferase; GTBP, G/T mismatch-binding protein; MGMT, O-6-methylguanine-DNA methyltransferase; MLH1, mutL homolog 1; MS, methionine synthase; MSH2, mutS homolog 2; MTHFR, methylene tetrahydrofolate reductase; NSCLC, non small cell lung cancer; OGG1, 8-oxoguanine DNA glycosylase; PARP, poly(ADP-ribose) polymerase; PMS2, postmeiotic segregation increased 2; RAR-β2, retinoic acid receptor, β2; RASSF1A, Ras association (RalGDS/AF-6) domain family 1; RMPI, relative mean pixel intensity; SAM, *S*-adenosylmethionine; SCLC, small cell lung cancer; XPB, xeroderma pigmentosum complementing group B; XPC, xeroderma pigmentosum complementation group C; XPD, xeroderma pigmentosum D; XPG, xeroderma pigmentosum; complementation group G; XRCC, X-ray repair complementing defective repair in Chinese hamster cells

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0027-5107/$ – see front matter
doi:10.1016/j.mrfmmm.2005.06.007

methods such as hierarchical modeling with Bayesian adjustments, false positive reporting probability and modeling of complex pathways. Consortia have been initiated for head and neck cancer (International Head and Neck Cancer Epidemiology Consortium (INHANCE)) and lung cancer (International Lung Cancer Consortium (ILCCO)) with the aim to share comparable data, to focus on rare subgroups such as nonsmokers and to coordinate laboratory analyses. Such collaborative efforts and integration across disciplines will be essential in contributing to the elucidation of genetic susceptibility to aerodigestive tract cancers.

Keywords: Cancer; Epidemiology; Genotype; Phenotype; Methylation; Head and neck cancer; Lung cancer

1. Introduction

The field of epidemiology has contributed significantly to identifying tobacco as the major risk factor for lung cancer, and tobacco and alcohol as the major risk factors for head and neck cancers. Head and neck cancers are a related group of cancers that involve the oral cavity, pharynx and larynx. In the United States, cigarette smoking is estimated to account for 90% of lung cancer cases among men and 79% of lung cancer cases among women [1]. Approximately 80% of head and neck cancer cases among men and 61% of cases among women are attributed to smoking and alcohol drinking [2]. Over the last several decades, reductions in tobacco use have contributed to a substantial decrease in the incidence of these tobacco- and alcohol-related cancers.

In complement to classical epidemiology, the field of molecular epidemiology has the potential to contribute to the elucidation of genetic susceptibility and events occurring during the pre-clinical phases of cancer development, between carcinogen exposure and clinical cancer diagnosis. In addition to data from interview of study subjects, molecular epidemiology uses laboratory-based measures on biological samples. More specifically, biomarkers of exposure, of early stages of disease and of genetic susceptibility are used as research tools in molecular epidemiology.

Currently, improving laboratory techniques for measurement of carcinogens and hormones, mutation analyses, and high-throughput genotyping, are contributing to rapid development in the field of cancer molecular epidemiology. The surge in available data on sequence variants has led to a flurry of molecular epidemiology studies investigating associations with cancer risk in the literature. Phenotypic assays developed in efforts to quantify an individual's DNA repair capacity have also been applied to epidemiological studies on aerodigestive tract cancers. Epigenetic events, which refer to factors that affect gene expression and can be transmitted to daughter cells but are not encoded in the DNA sequence, have also been investigated in tumor progression and as susceptibility factors.

Tobacco-related cancers are of special interest in molecular epidemiology because tobacco smoking is a strong risk factor involving numerous carcinogens that are thought to interact with a variety of genetic factors. Important research questions bearing on the etiology of these tobacco-related cancers remain. Which gene sequence variants confer cancer risk? Do differences in DNA repair capacity affect an individual's cancer susceptibility? If so, which DNA repair pathways are more important, and under what circumstances? Are there factors external to the DNA sequence that contribute to cancer susceptibility, such as variability in epigenetic events? Molecular epidemiology has the potential to lead to a better understanding of these aspects in cancer etiology, which may in turn contribute to prevention efforts. Ideally, establishing combinations of sequence variants that confer a high cancer risk may allow for identification of high-risk individuals to target prevention efforts. Elucidation of epigenetic phenomena may help to establish an early detection marker or target for chemoprevention. In this review, we will critically evaluate the progress made and the challenges faced in these research areas for aerodigestive tract cancers.

2. Sequence variants and susceptibility

Linkage analyses followed by positional cloning led to the discovery of high-risk susceptibility genes for other cancers, such as APC, MLH1, MSH2, BRCA1, and BRCA2. However, high-penetrance susceptibility