

Commented Summary from Current Medical Literature

Polycyclic aromatic hydrocarbon exposure in oesophageal tissue and risk of oesophageal squamous cell carcinoma in north-eastern Iran

Summary: Objective To evaluate the association between polycyclic aromatic hydrocarbon (PAH) exposure in oesophageal epithelial tissue and oesophageal squamous cell carcinoma (ESCC) case status in an ESCC case-control study in a high-risk population in north-eastern Iran.

Methods Tissue microarrays (TMAs) of non-tumoral oesophageal biopsies from patients with biopsy-proven ESCC and gastrointestinal clinic patients with no endoscopic or biopsy evidence of ESCC (control subjects) in a rural region in north-eastern Iran were immunohistochemically stained. Immunohistochemistry was performed using monoclonal antibodies 8E11 and 5D11 raised against benzo[a]pyrene (B[a]P) diol epoxide (BPDE)-I-modified guanosine and BPDE-I-modified DNA, respectively. Staining intensity was quantified by image analysis and the average staining in three replicates was calculated. The main outcome measure was adjusted ORs* with 95% CIs** for the association between antibody staining intensity and ESCC case status. **Results** Cultured ESCC cells exposed to B[a]P *in vitro* showed dose-dependent staining with 8E11 but not with 5D11. With 8E11, sufficient epithelial tissue was available in the TMA cores to analyse 91 cases and 103 controls. Compared with the lowest quintile of 8E11 staining in the controls, adjusted ORs for the 2nd to 5th quintiles were 2.42, 5.77, 11.3, and 26.6 (95% CI 5.21 to 135), respectively (p for trend <0.001). With 5D11, 89 cases and 101 controls were analysed. No association between staining and case status was observed (ORs for the 2nd to 5th quintiles were 1.26, 0.88, 1.06, and 1.63 (95% CI 0.63 to 4.21), p for trend=0.40). **Conclusions** Dramatically higher levels of 8E11 staining were observed in non-tumoral oesophageal epithelium from patients with ESCC than from control subjects. This finding strengthens the evidence for a causal role for PAHs in oesophageal carcinogenesis in north-eastern Iran. [*OR=Odds ratio, **CI=Confidence interval]

Source: Abedi-Ardekani B, Kamangar F, Hewitt SM, Hainaut P, Sotoudeh M, Abnet CC, Taylor PR, Boffetta P, Malekzadeh R, Dawsey SM. *Gut*. 2010 Jun 28. [Epub ahead of print]

Comment: The study by Abedi-Ardekani and colleagues¹ provides clear evidence, in a well defined case-control study, of a strong dose-response relationship between levels of polycyclic hydrocarbon adducts in normal oesophageal epithelium and the presence of oesophageal cancer. The results do not prove a causal relationship, and 'reverse causation', as a result of the cancer leading to a change in eating or smoking habits and thereby increasing exposure, cannot be ruled out. Even so, they add to efforts to identify the causes of the unusually high rates of oesophageal cancer in the Golestan region. In this context, several questions can now be addressed, as the authors indicate: 1) How well does the level of these adducts parallel oesophageal cancer incidence in other high-risk regions such as Central China; 2) Is this read-out of exposure different in other regions of Iran where oesophageal cancer is less prevalent, and gastric cancer is common? 3) Can such associations provide evidence that polycyclic hydrocarbons are a major contributor to risk in the high-risk areas, and can the source of the exposure be identified? 4) Can measurement of adducts provide a prospective indicator of cancer risk in populations undergoing surveillance? 5) In this case, might adduct levels in more accessible tissue such as buccal epithelium or even blood provide a more practicable measure for epidemiological and public health studies? 6) Are adduct levels raised in other tissues, and is there a correlation with cancer incidence in these tissues also?

The high oesophageal cancer incidence in particular geographic regions such as Golestan and Central China has long raised the question of an interplay between exposures and the genetic make-up of the

populations of these regions. It is difficult to know whether and how inherited genetic variation might affect the levels of the adducts reported in this study, which are cytoplasmic-implicating protein adducts, which are less subject to modification by repair, and presumably the result of direct rather than systemic exposure. But taking the adducts as simply a measure of exposure, it remains possible that genetics influences individual response to that exposure and so the risk of genetic or epigenetic changes or tissue injury that can lead to carcinogenesis. It may be of interest (although possibly challenging) to investigate whether adduct levels measured by immunohistochemistry of the epithelium can be correlated to the prevalence of specific mutations or DNA adducts in the same epithelium, or to other measures of biological effect; and whether there are consistent patterns that can be interpreted in terms of an interaction of genetics and exposures.

This study also raises a general point about the study of the normal epithelium in relation both to mechanisms of carcinogenesis and to prediction of individual risk. One can approach the problems of early detection and of prevention in a population based way – in the UK, for example, eat plenty of fruit, take exercise, have breast or colonic cancer screening from age 50. These approaches are generally not targeted at individuals (except by age), nor are they based on understanding of mechanism. But better measures of individual risk might allow the targeting of interventions to groups within the population where the cost/benefit balance would be greatest. Understanding of the mechanism of risk might open the way both to mechanism-based prevention, and to intermediate markers which could provide early read-out of effect. The problem is that exposures are mostly difficult to identify and to measure; and although genome-wide association studies have identified some of the common genetic variation that determines the spread of genetically determined risk in the population,² most of the genes are proving very difficult to find. Moreover, even if we could identify the genes and the relevant exposures, we still do not know how, in mathematical or biological terms, their effects combine.

Perhaps the normal epithelium can do this for us. It seems probable that most of the genetic and exposure determinants of risk are expressed through their effects on the normal epithelium. In the case of lung

cancer, where there is a major, defined exposure which is cigarette smoke, the question might resolve to: ‘how do individuals differ in their response to cigarette smoke injury?’. Individual response might be evident from measures of DNA damage and repair and inflammatory response in the normal airway epithelium or submucosa. There are already data to suggest that differences in gene expression pattern in the normal airway epithelium of smokers are associated with lung cancer risk.³

A signature of polycyclic hydrocarbon adducts in normal oesophageal epithelium will be a valuable epidemiological tool. Maybe exploring deeper to identify a combined read-out of the effects on the epithelium of exposures and the genetic influences that modify them, will one day allow us to understand cancers in terms of complex perturbations of gene networks.⁴ These network signatures will provide an integrated read-out of the exposures and genes that we cannot identify and don’t yet know how to combine. They will indicate targets through which to restore the perturbations that increase risk, and read-outs to monitor success.

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