Molecular biomarkers in studies on environmental cancer

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Molecular cancer epidemiology studies search for molecular effects associated with the aetiological factors involved in environmental cancer

Biomarkers used for identification of risk factors of cancer in exposed populations have traditionally been classified into markers of exposure, effect, and susceptibility.^{1,2} Along with the advances in our knowledge about molecular biology, human genome, chemical carcinogenesis, and disease mechanisms, a variety of biomarkers of a more molecular nature have been launched and are currently being used widely in this field of research.³⁻⁵ This concept is often called, with some criticism, molecular epidemiology or molecular cancer epidemiology.⁶⁻⁷ As illustrated by Porta and coauthors in their present paper,⁸ there has indeed been a dramatic increase in number of publications in this interdisciplinary field of research over the past decade or so.

In their article, Porta and his colleagues deal with certain aspects of molecular biomarker studies of cancer, in particular those relevant to studies investigating somatic mutations of genes controlling cell growth and differentiation such as DNA “fingerprints”—that is, indicators of the genotoxic nature of a chemical or exposure suspected of causal involvement. The authors themselves have performed several studies on *K-ras* mutations in pancreatic cancer,⁹⁻¹³ with outcomes suggesting associations between *K-ras* mutations and a number of environmental exposures or lifestyle factors. They have found that *K-ras* mutations in a series of exocrine pancreatic cancer cases show associations with tobacco and alcohol consumption,⁹ regular coffee drinking,^{10,11} serum organochlorine concentrations,¹² and occupational exposure to solvents.¹³ In their paper,⁸ Porta and colleagues discuss another recent study on pancreas cancer and *K-ras* mutations that failed to observe association with serum levels of organochlorines or PCBs.¹⁴ The authors refer to a number of points that they view as limitations in the US study. These points may, however, be of interest in more general terms, too.

The issues raised by Porta and co-workers need to be carefully taken into

account when conducting studies examining the type and frequency of mutations as features related to tumours developed in the exposed. We have conducted a number of studies on lung cancer and some other types of occupational or environmental cancers using *p53* and *K-ras* mutations as molecular biomarkers.¹⁵⁻²⁰ This work has illustrated that matters related to the quality of the biomarker data, such as the quality of the tumour sample (fresh versus paraffin wax embedded tumour tissue)—and consequently that of the resulting DNA—, use of complementary techniques in mutation detection for increasing the sensitivity (for example, mutation screening combined with sequencing), strict criteria in sequence identification (for example, two independent PCR products), as well as issues of study design emerge all as crucial factors.

To highlight the value of molecular biomarker studies, another example, in addition to *K-ras* mutations in pancreatic cancer, can be discussed—that is, lung cancer, exposure to tobacco smoke, and *p53* mutations. Extensive data on the biological effects of tobacco smoking, including its well documented genotoxicity, have strengthened the causal role of tobacco smoke exposure in lung cancer and largely justified use of biomarkers in studies on lung cancer and environmental tobacco smoke (ETS) also.^{21,22}

It is well known that more than 50% of lung cancers carry a *p53* mutation.^{23,24} We and others^{15,20,25-27} have shown that smokers have significantly more *p53* mutations than non-smokers. The most common type of *p53* mutation is a guanine (G) to thymine (T) transversion,^{24,26} and experimental evidence demonstrating the correspondence between mutational hotspots observed in lung tumours and formation of benzo(a)pyrene—and other polycyclic aromatic hydrocarbon (PAH)—DNA adducts exists.^{28,29} Furthermore, G to T transversions, infrequent in human tumours other than HCC,²⁴ are currently

believed to reflect the molecular signature of mutagenic constituents (especially that of benzo(a)pyrene and other PAH compounds) in tobacco smoke detectable in tumour DNA.³⁰

In a European multicentre study on lung cancer among ETS exposed non-smokers, we found that lifelong non-smokers exposed to spousal ETS have an increased risk of *p53* mutations in comparison with non-exposed non-smokers.²⁰ This and other similar findings²⁷ provide support to other data suggesting that the development of lung cancer in ETS exposed non-smokers shares some key features, such as *p53* mutations, with that seen in smokers. Thus, molecular biomarkers found to be informative of biological alterations associated with high level exposure (smoking), may be used to give valuable information about low level exposure (ETS), often the most challenging environmental exposure situation to be investigated.

Recent work has determined that biological markers not only provide us information about exposure, effects, or susceptibility, but may serve as indicators of increased risk of cancer.³¹ A Nordic-Italian prospective cohort study observed that a high rate of chromosomal aberrations were significant predictors of cancer risk.³² More recently, a case-control study nested within the prospective Physicians' Health Study found that increased levels of PAH and other aromatic DNA adducts in white blood cells were able to predict the risk of lung cancer in current smokers.³³

Molecular cancer epidemiology studies aim at elucidating the aetiology and molecular mechanisms of environmental cancers, with the ultimate goal for improved cancer prevention. Also, molecular markers may be of assistance in early detection and diagnosis, especially of diseases currently with long latency periods, late diagnosis, and poor prognosis such as lung cancer.³⁴

In my view, despite the many weaknesses and methodological difficulties we still face today, as discussed here in depth by Porta and others,⁸ molecular biomarker studies are likely to provide us with tools valuable in risk assessment and in the prevention of environmental cancer, as we have already started to see.³⁵⁻³⁷

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