INTRODUCTION

In 2001, the US Institute of Medicine (IOM) reported that, since smoking-related diseases were dose-related and because epidemiological studies showed a reduction in the risk of smoking-related diseases following cessation, it might be possible to reduce smoking-related disease risk by developing potential reduced exposure products. More recently, the IOM provided an outline of the kinds of studies that would be required to provide sufficient scientific evidence to demonstrate reduced risk. In addition to pre-clinical toxicity testing using in vitro systems and animal models, the IOM proposed the use of biomarkers of exposure to specific tobacco toxicants to establish internal dose to the consumer and suggest their use as disease risk biomarkers, with the caveat that there is currently no evidence that a single or group of constituents is solely responsible for a given disease. They also suggested that for a biomarker of exposure to be accepted as a biomarker of risk or a surrogate endpoint of disease, there should be a strong biological rational as well as compelling data from clinical and epidemiologic studies.

Biomarkers of exposure alone are unlikely to provide sufficient evidence of disease risk, as there is a lack of mechanistic data to link most of them to established clinical endpoints of disease or disease-preventive states. The evidentiary process of determining this link was defined as “Biomarker Qualification” by the IOM. From theoretical and practical standpoints, we propose that the qualification of a biomarker linking an exposure with biological processes is distinct from one that would link exposures or biological processes to clinical endpoints. Thus, we use the term ‘biomarkers of biological effect’ (BOBE) for the former and ‘biomarkers of potential harm’ for the latter.

As part of the qualification process, it follows that two key requirements of BOBE are that they (i) are able to consistently distinguish between smokers and never-smokers, and that (ii) upon smoking cessation, BOBE levels significantly change towards those seen in never-smokers (reversible). Thus, candidate BOBEs identified from literature which reported smoking cessation studies. Longitudinal analysis of each candidate BOBE over time, using each subject as their own control is now required to ensure that responses are consistent. Furthermore, significant correlations with smoking consumption and biomarkers of exposure would add support to the BOBEs in the qualification process.

METHODS

This cohort was formed from the baseline measurements of a larger study which is registered with Current Controlled Trials (number ISRCTN18262356) and the protocol has been published. The study was designed and conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonisation for Good Clinical Practice and German law. The protocol and the informed consent forms were approved by the ethics committee of the Ärztekammer Hamburg. All subjects were sourced from the Hamburg area and provided written informed consent prior to the start of the study.

A total of 246 subjects were included in this study and were divided into three groups, current smokers, ex-smokers and never-smokers. The groups were matched for age, gender, ethnicity and BMI (Table 1). Samples collected from the participants included 24-hour urine, whole blood, serum, plasma and erythrocyte lystate. The analytical methods used for each biomarker can be found in Haswell et al.

To confirm smoking status, the following biomarkers of exposure were measured and shown in Table 1.

RESULTS

Of the 27 candidate biomarkers assessed, the following 14 were found to be significantly different between current and ex-smokers (Table 2): Urinary 8-iso-PGF2α (Type III) and 11-dehydrothromboxane B2 (P<0.001). Plasma MCP-1, neutrophil elastase, leukotriene B4, acetic acid, HDL and oxidised LDL cholesterol.

Cys-thiol cysteine catalytic activity and malondialdehyde (all P<0.001). Serum total antioxidant capacity (P=0.0001)

Whole blood total WBC, neutrophil and monocyte count (all P<0.001).

Of these BOBEs 12; urinary 8-iso-PGF2α (Type III), plasma MCP-1, neutrophil elastase, leukotriene B4, acetic acid, HDL and oxidised LDL cholesterol, cys-thiol cysteine catalytic activity and malondialdehyde did not show any significant difference between smokers and never-smokers (data not shown).

CONCLUSIONS

These data indicate that 12 of the 27 candidate biomarkers assessed in this study are potentially useful tools for the assessment of smoking cessation following a smoking cessation study.

Longitudinal analysis of each candidate BOBE over time, using each subject as their own control is now required to ensure that responses are consistent. Furthermore, significant correlations with smoking consumption and biomarkers of exposure would add support to the BOBEs in the qualification process.

REFERENCES


