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Determinants of active and environmental exposure to tobacco smoke and upper reference value of urinary cotinine in not exposed individuals

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ABSTRACT

The aims of this study were (1) to explore the behavioral and sociodemographic factors influencing urinary cotinine (COT-U) levels in active smokers and in environmental tobacco smoke (ETS)-exposed individuals, (2) to assess the specificity and sensitivity of the questionnaire for identifying active smokers and nonsmokers, and (3) to derive the upper reference value of COT-U in non-ETS exposed individuals. The COT-U levels of 495 adults (age range 18–69 years) who classified themselves as active smokers (29%) or as nonsmokers with (17%) or without (83%) ETS exposure were quantified by LC-MS-MS (quantification limit: 0.1 μg/L, range of linearity: 0.1–4000 μg/L). Median COT-U levels in these groups were 883, 1.38, and 0.39 μg/L, respectively. Significant determinants of COT-U levels in active smokers were the number of cigarettes per day, type of smoking product, smoking environment, as well as time between the last cigarette and urine collection. Among ETS-exposed nonsmokers, significant determinants were living with smokers, being exposed to smoke at home, ETS exposure duration, as well as time between the last exposure and urine collection. When a 30-μg/L COT-U cut-off value was used to identify active daily smoking, the sensitivity and specificity of the questionnaire were 94% and 98%, respectively. For ETS exposure, the COT-U value of 1.78 (0.90 confidence interval 1.75–1.78) μg/L, corresponding to the 95th percentiles of the COT-U distribution in non-ETS-exposed participants, is proposed as upper reference value to identify environmental exposure.

1. Introduction

As human carcinogens, tobacco smoke and smoking are major causes of cancers of the lungs and other body organs. Tobacco smoke is estimated to cause more than 4 million deaths each year worldwide (IARC, 2004). In addition to voluntary exposure through actively smoking, an individual may be involuntarily and passively exposed to tobacco smoke by sharing an environment with smokers. Environmental tobacco smoke (ETS), or passive smoke, is the combination of secondhand smoke, that is the mainstream smoke exhaled by the smoker and side-stream smoke released by the burning tobacco product, and of thirdhand smoke, that is residual tobacco smoke pollutants that remain on surfaces and dust after tobacco has been smoked and react with oxidants and other compounds in the environment to form secondary pollutants (Matt et al., 2011). ETS is a complex mixture of more than 4000 chemicals, whose composition varies with time and environmental conditions. Evidence exists that ETS is carcinogenic to humans (IARC, 2004).

Notwithstanding these data, a recent study estimated the number of daily smokers worldwide at 967 million and the global modeled age-standardized prevalence of daily tobacco smokers at 31.2%, with an average annual rate of decline of 0.9%. Large differences among countries were observed, with some countries experiencing a significant decrease and others a significant increase in the prevalence of smoking (Ng et al., 2014).

The World Health Organization Framework Convention on Tobacco Control, which has been ratified by 177 nations to date, recognizes the need to prevent the harm caused by tobacco use. This group has identified six evidence-based tobacco control measures, known as MPOWER: monitor tobacco use and prevention policies, protect people from tobacco smoke, offer help to quit tobacco use, warn about the dangers of tobacco, enforce bans on tobacco advertising, promotion, and sales, and raise taxes on

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tobacco (WHO, 2003, WHO, 2013). Under this framework, several countries have recently implemented tobacco-free legislation, banning smoking in indoor public places and workplaces, with the aim of protecting the health of nonsmokers. For example, the Italian government banned smoking in all public closed locations in 2003 (Italian Legislation, 2003), after passing a series of laws aimed at restricting tobacco use (Giraldi et al., 2013). Tobacco-free legislation has had several positive effects, including a reduction of air pollution in closed places from fine/ultrafine particles and specific toxic chemicals, such as polycyclic aromatic hydrocarbons (Valente et al., 2007; Repace, 2004). Positive health outcomes have included a significant reduction in the number of hospitalizations for acute coronary events (Barone-Adesi et al., 2011; Jones et al., 2014).

A major problem in self-assessment of ETS exposure is the possible unreliable assessment of the inhaled dose. Several variables affect ETS exposure, including the ETS source, duration of exposure, distance from the source, presence and effectiveness of a ventilation system, and personal characteristics. Therefore, it can be difficult for an individual to estimate the intensity, frequency, and duration of ETS exposure. The same problem exists with the self-reporting of active smoke intensity by smokers, who may underestimate how often they smoke (Connor Gorber et al., 2009; Park et al., 2014). For these reasons, the use of biological monitoring, such as through the determination of nicotine metabolites in body fluids, is recommended as a valid tool to estimate tobacco use (SRNT Subcommittee on Biochemical Verification, 2002).

One popular method of biological monitoring of nicotine exposure is the quantification of cotinine levels in the urine, blood, or saliva. As a metabolite of nicotine, cotinine is a specific and sensitive biomarker of nicotine intake. The metabolite has a relatively long half-life in the body (6–22 h) (Benowitz, 1996; Haufroid and Lison, 1988); thus, cotinine levels in daily smokers are relatively stable and reflect the intake of nicotine over the past 2–3 days (SRNT Subcommittee on Biochemical Verification, 2002). Various tentative cut-off points for urinary cotinine (COT-U) levels, ranging 20–100 μg/L, have been proposed to define active smokers (Haufroid and Lison, 1988; SRNT Subcommittee on Biochemical Verification, 2002; Goniewicz et al., 2011; Fustinoni et al., 2013). However, cut-off points and characteristics (e.g., specificity and sensitivity) need to be established, especially for specific population subgroups, such as pregnant women, adolescents, nondaily smokers, and individuals in smoking cessation programs (Connor Gorber et al., 2009; SRNT Subcommittee on Biochemical Verification, 2002). Given the factors influencing ETS exposure, defining a cut-off point is even more complicated. Tentative COT-U cut-off values for ETS exposure in the range of 2–10 μg/L have been proposed (Haufroid and Lison, 1988; Man et al., 2009; Bavazzano et al., 2007; Fustinoni et al., 2013).

In our previous study, we developed and validated a liquid chromatography-triple quadrupole mass spectrometry (LC-MS-MS) method to quantify COT-U levels. We proposed a cut-off COT-U level of 30 μg/L for identifying active smokers, while the small number of subjects with ETS exposure prevented us from identifying a reliable COT-U cut-off value for the classification of ETS exposure. In this study, we applied the developed method to a large group of individuals. Our goals were (1) to explore the behavioral and sociodemographic factors influencing COT-U levels in active smokers and ETS-exposed individuals, (2) to assess the specificity of sensitivity of the questionnaire for identifying active smokers and nonsmokers, and (3) to derive the upper reference value of COT-U in non-ETS-exposed individuals.

2. Methods

2.1. Study population and sample collection

The data presented in this paper derive from an epidemiological assessment, a cross-sectional biomonitoring study on exposure to emissions from a local urban-waste incineration plant (A.I.A. Study, 2012). Recruitment, interviewing and sampling took place between November 2012 and April 2013. The study population consisted of volunteer adult participants (18–70 years) from the general population of Modena, a medium-sized town in northern Italy (Emilia-Romagna region). Records of the population living in the study area, defined as a 4-km radius around the incineration plant, were extracted from the population register. Then, eligible subjects were randomly selected from the population base, which comprises approximately 40% of the town population. Sampling method implied stratification by gender, age group (18–34, 35–49 and 50–69 yrs.), and exposure. The study sample is similar to the town population in terms of sex, age and citizenship based on a comparison with data of the population register and of the health surveillance system.

Invitations to participate in the study were sent out by post. Individuals were supplied with a study pack containing the invitation letter, the questionnaire, a disposable polyethylene bottle, and the instruction to collect a spot urine sample from the first void of the day. Subjects were telephonically contacted about one week after the dispatch of the invitation letter and those answering positively were invited to the Local Health Unit to provide the biological sample and to complete the questionnaire on personal and lifestyle characteristics. Urine samples were immediately refrigerated at 4 °C and delivered to the laboratory, where they were kept at −20 °C in the dark. Not-respondents and refusals were substituted in appropriate way to maintain the stratification homogeneity and reach a number of about 500 subjects.

All participants were informed about the aims of the research and signed an informed consent form. The study was approved by the ethics committee of the Local Health Authority of Modena. The study has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans http://www.wma.net/e/policy/b3.htm.

2.2. Questionnaire for assessment of active or environmental exposure to tobacco smoke

Subjects completed a questionnaire that included questions about current and past smoke exposure. The used items were adapted from available questionnaires used in large population surveys [www.cdc.org] and had been verified in our previous pilot study (Fustinoni et al., 2013). The questionnaire was reviewed by a trained interviewer at the moment of urine sample collection. To classify current active exposure to tobacco smoke, the following questions were asked: current active tobacco smoking (yes/no), smoking product (cigarette/cigar/pipe/e-cigarette/other), product commercial name, weekly and daily smoking intensities, and smoking environment (only open places/only closed places/both open and closed places). To classify current ETS exposure, the following questions were asked: living with smokers (yes/no), cohabitants smoked in the house (yes/no), working with smokers (yes/no), coworkers smoked in the same room (yes/no), and daily ETS exposure within the last week (yes/no). If a participant answered “yes” to the last question, then information on ETS duration (how many days/week; how many hours/week; how many hours/day), smoking type (cigarette/cigar/pipe smoke), and environment (home/work/leisure time/car; open/closed places) was collected.