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Expired-air carbon monoxide as a predictor of 16-year risk of all-cause, cardiovascular and cancer mortality

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ABSTRACT

Background. Measurement of expired-air carbon monoxide (EACO) is commonly used to ascertain non-smoking status, although it can also reflect exposures not related to smoking. Our aim was to assess 16-year mortality according to EACO measured at baseline, in a general population.

Methods. Our analysis was based on the Third French MONICA population survey (1994–1997). Causes of death were obtained 16 years after inclusion, and assessment of determinants of mortality was based on Cox modeling.

Results. EACO was measured in 2232 apparently healthy participants aged 35-64. During follow-up, 195 deaths occurred (19% were due to cardio-vascular (CV) causes and 49% to cancer). At baseline, the mean EACO was 11.8 (±7.4) ppm, 4.6 (±2.5) ppm, 4.3 (±2.2) ppm for current, former and never smokers, respectively ($P < 0.001$). After adjustment for main mortality risk factors and smoking, the hazard ratio (HR) for total mortality was 1.03[95% confidence interval: 1.01–1.06] per 1-unit increase in EACO, and it was 1.04[1.01–1.07] for cancer mortality. Adjusted HR for CV mortality was 1.05[1.01–1.10] but did not remain significant after additional adjustment for smoking (0.98[0.91–1.04]). Interactions between EACO and smoking were not significant.

Conclusions. In a general population, baseline EACO is an independent predictor of 16-year all-cause and cancer mortality, after adjustment for confounders including smoking. Given that the effect of EACO is similar among smokers and non-smokers, EACO is probably not solely related to smoking but could also be a marker of inhaled ambient carbon monoxide and/or endogenous production. Besides, smoking better predicts CV mortality than EACO.

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Introduction

Expired-air carbon monoxide (EACO) measurement is a simple and cheap method commonly used to ascertain non-smoking status in ex-smokers. However EACO is not only a marker of smoking, it also reflects inhaled ambient carbon monoxide (CO) and endogenous production of CO related to vasoactive, oxidative and inflammatory processes (Durante, 2002; Owens, 2010). Although the health effects of smoking and acute carbon monoxide intoxication are well known, EACO has not been studied so far as a potential predictor of long-term mortality.

The aim of this study was to assess the 16-year risk of all-cause, cardiovascular and cancer mortality according to EACO levels measured at baseline, in a sample selected from the general population.

Methods

Study population and design

The study design comprised one single baseline (1994–1997) interview of the participants and one single baseline measurement of EACO and biomarkers. An administrative follow-up was then organized to record vital status of all participants until December 31, 2011. A sample of 3402 subjects was randomly recruited from the general population to participate in the Third French MONICA Cross-Sectional Survey on the prevalence of cardiovascular risk factors (Kuulasmaa et al., 2000; Marques-Vidal et al., 2004). Middle-aged men and women (35-64 years old), living in northern (Lille area), north-eastern

Abbreviations: CO, Carbon monoxide; CV, Cardio-vascular; CI, Confidence interval; EACO, Expired-air carbon monoxide; GGT, Gamma-glutamyl transpeptidase; HR, Hazard ratio; HDL cholesterol, High density lipoprotein cholesterol; IDI, Integrated discrimination improvement; IQR, Inter-quartile range; LDL cholesterol, Low density lipoprotein cholesterol; MCV, Mean corpuscular volume; SD, Standard deviation.

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(Strasbourg area) or south-western France (Toulouse area), were recruited between December 1994 and July 1997. Polling lists available in each town hall of the survey areas were used to obtain the stratified random sample. Stratification was applied according to center, town size (rural versus urban), age and gender, in order to obtain 200 subjects in each 10-year age group (35–44, 45–54 and 55–64 years), gender and center. No incentive to participate (in particular no financial incentive) was offered. Written informed consent to participate in the study was obtained from each subject after full explanation of the nature of the research. The participation rate was 66% (Marques-Vidal et al., 2004).

Since we aimed to study apparently healthy people, subjects with the following medical histories were excluded from the analyses: clinical or subclinical ischemic heart disease (International Classification of Disease, 9th revision, codes 410.0 to 414.9, $n = 86$), clinical or subclinical atherosclerotic cerebrovascular disease (433.0 to 438.9, except codes 437.3 to 437.7, $n = 25$), documented atherosclerosis in other arteries such as aorta, renal or lower limb arteries (440.0 to 440.9, $n = 10$), chronic renal failure (585.0 to 585.9, $n = 1$), chronic respiratory insufficiency (496.0 to 496.9, $n = 3$), chronic heart failure (428.0 to 428.9, $n = 9$), chronic liver disease or cirrhosis (571.0 to 571.9, $n = 4$) and cancer, excluding benign neoplasms and in-situ carcinoma (140.0 to 209.9 and 235.0 to 239.9, $n = 50$). Overall, 179 participants (5.3%) were excluded from the following analyses because of these criteria. Besides, 991 other participants were excluded from the analyses since they had no measurement of EACO (EACO was measured only in a sub-sample of the 3 French centers), leading to a sample of 2232 persons.

Vital status on December 31, 2011 was obtained for each participant through the national database that records each year all deaths occurring in French citizens living inside or outside the French Territory (National Identification Register of Private Individuals, Répertoire National d'Identification des Personnes Physiques (RNIPP)) (CESP (Centre de recherche en Epidémiologie et Santé des Populations) – INSERM – Université Paris Sud). This database is currently used to assess vital status in France. In previous similar works, the information brought by the RNIPP database was compared to the data recorded in the civil registration. Less than 1.5% of discrepancies were noted between the two sources of data. All dates and causes of death were obtained for participants who died during the follow-up. Main and associated causes of death were provided by the French National Institute of Health Research (CépiDc–INSERM) which systematically collects and codes (using the International Classification of Diseases coding system) data recorded on death certificates. Death from a cardio-vascular (CV) cause (hypertensive disease, ischemic heart disease, conduction disorders, cardiac dysrhythmias, heart failure, atherosclerotic cerebrovascular disease, atherosclerosis and sudden death) during the follow-up was assessed by a committee of four medical doctors every time CV disease was reported as the main cause of death, or when it was mentioned as an associated cause, if the main cause was a plausible complication of CV disease. The same methodology was applied for the assessment of death from a cancer cause. Authorizations to use these data were obtained in accordance with the French law (Commission nationale de l'informatique et des libertés (CNIL): authorization 355152v1, September 3, 2008).

The study protocol was approved by an institutional ethics committee (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale (CCPPRB), Lille, France), on January 19, 1995 (CP 95/04) in accordance with the French law on human biomedical research and the Declaration of Helsinki.

Questionnaires and measurement of clinical parameters

At baseline, extensive questionnaires were filled in by a specifically trained medical staff during a face-to-face interview with the participant. Information on exposures was collected. Data concerning socio-economic level, medical history, cardiovascular risk factors, lifestyle habits and drug intake were recorded. Lipid-lowering, antihypertensive and hypoglycaemic drug use was assessed as the current consumption of a drug prescribed by a physician for treating cholesterol, blood pressure or glucose disturbances. Educational level was assessed by a report of graduation or level of school drop-out. Smoking was categorized as current, former and never smoking. Consumption of cigarettes, cigars, cigarillos and pipe were taken into account. For current and former smokers, smoking was also assessed in pack-years. Alcohol consumption was quantified in grams of alcohol per day with a 7-day recall method applied to a typical week. Height, weight and arterial blood pressure (mean of two measurements performed with a standard sphygmomanometer in a sitting position after a 5-minute rest, at least) were measured according to standardized protocols by the medical staff. Hypertension was assessed for people with blood pressure ≥160/95 mmHg, thus using, to avoid false positives, the threshold recommended for single measurements at the time of recruitment (1994–1997) (The fifth report of the Joint National Committee on Detection, 1993). Body mass index was calculated as weight divided by the square of height in meters (kg/m^2). Obesity was assessed for people with body mass index ≥30 kg/m^2 (Centre for Public Health Excellence at NICE (UK) and National Collaborating Centre for Primary Care (UK), 2006).

Laboratory methods

At baseline, blood samples were taken after at least 10 h of overnight fasting. Serum total cholesterol and triglycerides were measured by enzymatic assays (Boehringer, Mannheim, Germany). High density lipoprotein cholesterol (HDL cholesterol) measurement was performed after sodium phosphotungstate–magnesium chloride precipitation of apo B-containing lipoproteins. Low density lipoprotein cholesterol (LDL cholesterol) was determined by the Friedewald formula when triglycerides were below 4.6 mmol/L (400 mg/dL) (Friedewald et al., 1978). Glucose levels were measured using a conventional enzymatic method based on hexokinase-glucose-6-phosphate dehydrogenase. Diabetes was assessed for subjects receiving hypoglycaemic drugs or exhibiting fasting blood glucose ≥7 mmol/L (126 mg/dL). Gamma-glutamyl transpeptidase (GGT) were measured using enzymatic methods on an automated analyzer (Dade-Behring, Paris, France). Mean corpuscular volume (MCV) was calculated (in μm^3) by dividing hematocrit by red blood cell count (number of red blood cells per μm^3). GGT and MCV were used to identify excessive alcohol consumption potentially leading to health consequence such as altered liver function.

Expired-air carbon monoxide measurement

EACO measurement was performed only once, at the end of the baseline physical examination (which lasted 2 h in average), with a validated (Irving et al., 1988) portable carbon monoxide monitor (Micro Smokerlyzer, Bedfont Scientific Ltd, Kent, England). Calibration of the monitor was carried out with Bedfont's 50 ppm carbon monoxide in air calibration gas every month during the recruitment. In a sub-sample of 26 subjects (including 14 current smokers) two measures of EACO were done at a few minutes interval in order to assess the reproducibility of the measures. The intraclass correlation coefficient was 0.995[0.989–0.998].

Statistical analysis

Statistical analysis was performed on STATA statistical software, release 11.2 (STATA Corporation, College Station, TX, USA). All reported *P*-values were two-sided and the significance threshold was <0.05.

We first described and compared characteristics of participants according to tertiles of EACO. Categorical variables were compared between groups using the χ^2-test (or Fisher's exact test when necessary). ANOVA or Student's *t*-test were used to compare the distribution of continuous data (Kruskal–Wallis's or Mann–Whitney's tests were used when the distribution of the continuous variable departed from normality or when homoscedasticity was rejected). *P*-values were corrected using the Bonferroni correction for multiple comparisons.

Survival analysis was then conducted. Events were cases of death (all-cause, CV and cancer death) and exposure were defined by EACO levels at baseline. Kaplan–Meier survival curves were drawn and differences in survival functions were tested between tertiles of EACO using the log-rank test. Hazard ratios (HRs) for all-cause mortality and 95% confidence intervals (CI) were assessed using a Cox model. For CV and cancer mortality, we used a proportional subdistribution hazard model which is an extension of the Cox model to the situation of competing risks (Fine and Gray, 1999). Survival models were adjusted for the following standard risk factors in addition to smoking (never/former/current and in pack-years): center, age, gender, educational level, GGT and MCV (for all-cause, CV and cancer mortality). Models addressing all-cause and CV mortality were additionally adjusted for blood pressure, LDL-cholesterol and diabetes. Physical activity was initially included in survival models as a potential confounder but was finally removed, first because it was not independently associated to 16-year all-cause, CV or cancer mortality, and secondly because adjusting for physical activity had no significant impact on the hazard ratios related to EACO effect. As we showed that EACO exhibited a linear relationship with increased all-cause, CV and cancer mortality, HRs for mortality were expressed per 1-unit change in EACO. Since the log-linearity hypothesis was not fully respected, the following continuous variables were transformed into ordered categorical data: age (35–44, 45–54 and 55–64 years), GGT (<60 UI/L and ≥60 UI/L), MCV (<95 μm3 and ≥95 μm3), blood pressure (<160/95 mmHg and ≥160/95 mmHg), and LDL cholesterol (<5.2 mmol/L (200 mg/dL) and ≥5.2

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