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Cured meat consumption increases risk of readmission in COPD patients

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ABSTRACT: Recent studies have shown that a high dietary intake of cured meat increases the risk of chronic obstructive pulmonary disease (COPD) development. However, its potential effects on COPD evolution have not been tested. We aimed to assess the association between dietary intake of cured meat and risk of COPD readmission in COPD patients.

274 COPD patients were recruited during their first COPD admission between 2004 and 2006, provided information on dietary intake of cured meat during the previous 2 yrs, and were followed until December 31, 2007 (median follow-up 2.6 yrs). Associations between cured meat intake and COPD admissions were assessed using parametric regression survival–time models.

Mean±SD age was 68±8 yrs, 93% of patients were male, 42% were current smokers, mean post-bronchodilator forced expiratory volume in 1 s (FEV_1) was 53±16% predicted, and median cured meat intake was 23 g·day^{-1}. After adjusting for age, FEV_1, and total caloric intake, high cured meat intake (more than median value) increased the risk of COPD readmission (adjusted HR 2.02, 95% CI 1.31–3.12; p=0.001).

High cured meat consumption increases the risk of COPD readmission in COPD patients. The assessment of the effectiveness of healthy diet advice should be considered in the future.

KEYWORDS: Chronic obstructive pulmonary disease, follow-up studies, hospitalisation, meat products, public health

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide, and is expected to become the fourth leading cause of mortality by 2030 [1]. Although cigarette smoking is the main risk factor for COPD, interest has recently increased in the hypothesis that specific components of diet could play a role in the development of disease [2, 3]. Fruits and vegetables have captured most of the interest, given their antioxidant properties, and more recently several studies have pointed out that cured meat could have deleterious effects [4–6]. Two US prospective cohorts have shown an increased risk of COPD incidence among subjects reporting higher cured meat intake [5, 6]. This effect has been attributed to the fact that nitrites, which are added as preservatives and colour fixatives during cured meat production [7], could increase the nitrosative stress burden of the lung *via* the formation of reactive nitrogen species [8], causing damage and remodelling of the lung parenchyma [9]. A logical argument is that the lung injury should not only lead to an increased risk of chronic lung disease but also to a worse evolution of disease. However, whether cured meat consumption modifies COPD prognosis has never been tested. The present study aims to assess the association between frequency of cured meat consumption and risk of COPD readmission to hospital in a cohort of COPD patients, in the framework of the Phenotype and Course of COPD (PAC-COPD) study [10]. We hypothesised that subjects with greater intake of cured meat would be at a higher risk of COPD readmission to hospital.

SUBJECTS AND METHODS

Study population

The PAC-COPD cohort, which aims to improve our understanding about the phenotypic heterogeneity of COPD and the extent to which this heterogeneity is related to its clinical course, includes subjects recruited during their first COPD hospital admission at nine university hospitals in Spain between January 2004 and March 2006, and followed up to December 31, 2007. All measures, and the confirmation of COPD diagnosis (post-bronchodilator forced

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expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) ⩽0.70) [11], were obtained during clinical stability at least 3 months after recruitment. Details on recruitment and methods are available elsewhere [10, 12]. The protocol was approved by the ethics committees of all participating hospitals, and written informed consent was obtained from all patients.

Measurements

At baseline, a previously validated 122-item food frequency questionnaire (FFQ) asking for dietary habits in the last 2 yrs was administered by trained interviewers [13, 14]. Cured meat consumption was defined as the total daily consumption (grams per day) of cooked ham, Spanish cured ham, cured and other sausages, and hot dogs, based on five FFQ items.

Baseline sociodemographic characteristics, respiratory symptoms, drug treatment and lifestyle data were obtained using standardised questionnaires. Nutritional status was assessed through body mass index (BMI) and bioimpedance-measured fat-free mass index (FFMI). Post-bronchodilator spirometry (FEV1, FVC and FEV1/FVC), arterial oxygen and carbon dioxide tension (P_{a,O_2} and P_{a,CO_2}, respectively), diffusing capacity of the lung for carbon monoxide, and serum C-reactive protein (CRP) were measured. The Charlson index of comorbidity was obtained by an expert pulmonologist from medical records and personal anamnesis and exploration [15].

All subjects were actively followed until death or until December 31, 2007. Information on COPD readmissions until December 31, 2007 was obtained from the Minimum Basic Dataset Collection (CMBD), a national administrative database. According to the ninth revision of the International Classification of Diseases, COPD exacerbations were defined as any admission with codes 466, 480–6, 490–6 or 518.81 as the main diagnosis. Survival status was obtained for all patients from direct interviews with the patients or their relatives.

Statistical analysis

Sociodemographic, clinical and dietary characteristics were described by mean±SD, median (quartile 1–quartile 3) or n (%),

TABLE 1 Main sociodemographic and clinical characteristics and cured meat intake in 274 chronic obstructive pulmonary disease patients according to cured meat intake level

	All subjects	Low cured meat intake ⩽22.68 g·day^{-1}	High cured meat intake >22.68 g·day^{-1}	p-value#
Subjects n	274	138	136	
Male	255 (93)	133 (96)	122 (90)	0.030
Age yrs	68±8	69±7	67±10	0.012
Primary or higher education	163 (59)	77 (56)	86 (63)	0.210
Active worker	46 (17)	15 (11)	31 (23)	0.008
Low socioeconomic status¶	208 (82)	105 (82)	103 (82)	0.953
BMI kg·m^{-2}				0.055
<20	6 (2)	2 (1)	4 (3)	
⩾20 and <25	53 (19)	21 (15)	32 (24)	
⩾25 and <30	114 (42)	54 (39)	60 (44)	
⩾30	101 (37)	61 (44)	40 (29)	
FFMI kg·m^{-2}	19.8±3.1	20.2±3.1	19.4±3.1	0.025
⩾2 comorbidities+	152 (55)	75 (54)	77 (57)	0.705
Dyspnoea score§	2 (2–3)	2 (2–3)	2 (2–3)	0.402
Post-bronchodilator FEV1 % pred	53±16	52±15	54±16	0.430
P_{a,O_2} mmHg	75±11	75±11	75±11	0.998
$D_{L,CO}$ % pred	66±21	68±20	64±21	0.110
Current smokers	114 (42)	48 (35)	66 (49)	0.021
Regular physical activity kcal·week^{-1}	6709±5160	6328±4581	7094±5678	0.220
Daily energy intake kcal·day^{-1}	2026±611	1819±535	2237±612	<0.001
Total cured meat intake g·day^{-1}	23 (11–34)	11 (5–17)	34 (27–44)	<0.001
Ham	8.6 (0–8.6)	0 (0–8.6)	8.6 (8.6–20)	<0.001
Spanish cured ham	8.6 (2.7–8.6)	2.7 (0–8.6)	8.6 (8.6–8.6)	<0.001
Cured sausages	2.4 (0–7.8)	0 (0–2.4)	7.8 (2.4–7.8)	<0.001
Other sausages	0 (0–3.2)	0 (0–0)	3.2 (0–10)	<0.001
Hot dogs	0 (0–0)	0 (0–0)	0 (0–0)	<0.001
Fruit intake g·day^{-1}	242 (159–355)	221 (148–363)	261 (185–355)	0.142
Vegetable intake g·day^{-1}	282 (208–372)	251 (176–355)	312 (236–388)	0.001
Fish intake g·day^{-1}	55 (36–91)	55 (36–91)	55 (36–91)	0.724

Data are presented as n (%), mean±SD or median (interquartile range), unless otherwise stated. BMI: body mass index; FFMI: fat-free mass index; FEV1: forced expiratory volume in 1 s; % pred: % predicted; P_{a,O_2}: arterial oxygen tension; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide. #: Chi-squared test, t-test or Mann–Whitney U-test as appropriate; ¶: skilled or unskilled manual workers classified as low socioeconomic status; +: Charlson index; §: Modified Medical Research Council score 0–5.

as appropriate. Cured meat intake was treated either as a continuous variable or dichotomised at its median value (22.68 g·day^{-1}), since its biased distribution prevented other categorisations such as quartiles or quintiles. Kaplan–Meier curves of time to first COPD readmission were plotted according to cured meats consumption level, and compared using the log-rank test [16]. Crude and adjusted associations between cured meat intake and time to first COPD readmission were assessed using parametric regression survival–time models, censoring subjects who died before a COPD readmission (n=2) [17]. Age, sex, BMI, FFMI, FEV1, P_{a,O_2}, P_{a,CO_2}, smoking status, physical activity, inhaled corticosteroid treatment, statin treatment, Charlson index of comorbidity, and intakes of energy, fruit, vegetables and fish were tested as potential confounders and included in the final model if they were related to both the exposure and the outcome, or if they modified (>10% change in hazard ratio) the estimates for the remaining variables. Effect modification by smoking status, inhaled corticosteroid treatment, COPD severity and CRP levels was assessed by both stratification of all models and inclusion of interaction terms. Data analysis was conducted using Stata 8.2 (StataCorp, College Station, TX, USA).

RESULTS

From the total PAC-COPD cohort (n=342), 274 patients had available information on diet. No differences regarding sociodemographic characteristics, comorbidities, dyspnoea or lung function parameters were found between patients with and without dietary information, as previously published [13]. Table 1 shows the main characteristics of the 274 COPD patients included in this study, according to daily cured meat intake level. 93% of participants were male with a mean age of 68 yrs. Most subjects had moderate-to-severe COPD (distribution in COPD severity stages: 5% mild, 52% moderate, 37% severe, and 6% very severe). Higher daily cured meat intake was positively related to younger age, current working, current smoking, higher levels of regular physical activity, and lower BMI. Moreover, higher cured meat intake was associated with higher total energy and vegetable intakes, but no relationship was observed with fruits or fish intakes. Median cured meat intake was similar across COPD severity stages (mild: 27 g·day^{-1}, moderate: 24 g·day^{-1}, severe: 21 g·day^{-1}, and very severe: 28 g·day^{-1}; p=0.210).

TABLE 2 Description of the follow-up of 274 chronic obstructive pulmonary disease (COPD) patients

Total days of follow-up	934 (655–1067)
COPD hospital readmissions during follow-up	
Min	0
1st quartile	0
Median	0
3rd quartile	1
Max	13
COPD hospital readmissions during follow-up	
0	177 (65)
1	34 (12)
2	28 (10)
⩾3	35 (13)
Days to first COPD hospital readmission only if readmission[#]	304 (141–622)
Total number of deaths	15 (5)
Deaths before any COPD hospital readmission[¶]	2 (1)

Data are presented as median (quartile 1–quartile 3) or n (%), unless otherwise stated. [#]: n=97; [¶]: subjects censored in time-to-readmission analysis.

As shown in table 2, the median follow-up time was 2.6 yrs with a minimum of 250 days and a maximum of 1,337 days. 97 (35%) subjects had at least one COPD hospital readmission. Although 5% of patients died during follow-up, only two (1%) died before any COPD admission, thus contributing to the analysis until death.

Kaplan–Meier curves show that the time to the first COPD readmission was longer in the low cured meat intake group (p=0.028) (fig. 1). Table 3 shows that both in the crude and adjusted parametric regression survival–time models, higher cured meat intake was related to higher risk of COPD readmission (adjusted HR 2.02, 95% CI 1.31–3.12; p=0.001). The analysis with cured meats consumption as a continuous exposure yielded a positive increasing association between cured meat intake and risk of COPD readmission (fig. 2).

After stratification, the estimate of the association between high cured meat consumption and COPD readmission was lower in subjects treated with inhaled corticosteroids than in subjects not using this treatment (HR 1.88, 95% CI 1.16–3.05 *versus* HR 2.56, 95% CI 0.94–7.02), and lower in subjects with mild and moderate COPD than in severe and very severe COPD patients (HR 1.63, 95% CI 0.85–3.15 *versus* HR 2.29, 95% CI 1.26–4.16), although interaction terms were not statistically significant (p=0.875 and p=0.577, respectively). Stratification according to smoking status or CRP levels showed no differences in the estimates of the association between cured meats and COPD readmission.

DISCUSSION

We found that higher current cured meat consumption increases the risk of COPD readmission to hospital. These results are coherent with previous studies about cured meats and COPD incidence. JIANG *et al.* [4] reported in a cross-sectional study of 7,432 subjects that frequent consumption of cured meat was associated with low lung function (FEV1) and with an increased risk of COPD. Later on, studies of two large US cohorts, one of 42,915 males and the other of 71,531 females, showed that cured meat consumption was associated with the risk of newly diagnosed COPD both in males and females [5, 6]. The hypothesis that cured meats consumption may modify the course of COPD had not been tested before, so our findings will benefit from replication in other COPD cohorts.

Experimental evidence about cured meat components supports the biological plausibility of our findings. There is evidence suggesting that nitrites could cause lung damage. In an experimental study, rats that drank water containing sodium nitrite over a 2-yr period developed pulmonary emphysema [18], although the nitrite concentrations in the study were very high and probably not comparable to those achieved in standard human diets. Biochemical evidence shows that nitrites are pro-oxidants and can generate strong oxidising reactive nitrogen species such as peroxynitrite ($ONOO^-$) and others [19, 20]. These reactive nitrogen species are capable of producing lung damage

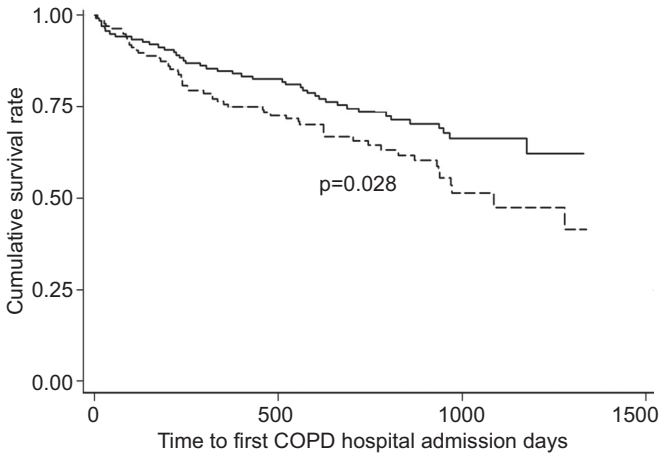

FIGURE 1. Kaplan–Meier survival curves of time to the first chronic obstructive pulmonary disease (COPD) hospitalisation according to cured meat intake. ——: low cured meat intake; ----: high cured meat intake.

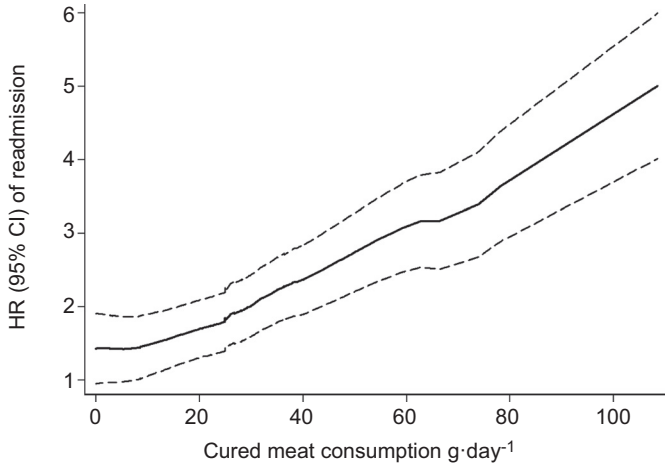

FIGURE 2. Hazard ratio (HR) and 95% confidence intervals (CI) of chronic obstructive pulmonary disease readmission according to cured meat intake. HR (——) and 95% CI (----) were obtained from a parametric regression survival–time model with cured meat intake as a continuous variable, and adjusted for centered age, total caloric intake, and forced expiratory volume in 1 s (FEV_1). The baseline HR (risk of readmission when cured meats consumption equals 0 g·day^{-1}) corresponds to the risk of a patient with mean age, mean total caloric intake and mean FEV_1.

[8], and have been suggested to play a role in the pathogenesis of COPD [9]. Our finding of a weaker effect of high cured meat consumption in subjects treated with inhaled corticosteroids supports the role of nitrites as mediators of the association between cured meats and worse prognosis, since the anti-inflammatory properties of corticosteroids could attenuate the oxidising and pro-inflammatory effects of nitrites. Finally, it has been argued that the largest portion of the nitrite dietary intake could come from vegetables [21], *via* nitrate to nitrite conversion in the mouth and the stomach [22]. However, it has been shown that high nitrate intake does not cause the expected elevated gastric nitrite concentrations [23, 24], or appreciable changes in serum nitrite concentrations [25], thus enhancing the importance of cured meats as direct sources of nitrites. Another potential mechanism that could explain the deleterious effects of cured meats in COPD course involves salt, which is added during the curing process and could enhance the negative impact of cured meats through an increase of the total body water. It could be especially harmful in COPD patients with concomitant pulmonary hypertension or poor haemodynamic status, where a salt excess could worsen these conditions and ultimately increase the risk of exacerbation.

The median intake of cured meats in the cohort (23 g·day^{-1}) was equivalent to eating one slice of ham every day. It was very similar to the 20 g·day^{-1} that was found in the 65–75-yr-old strata of a nutritional survey performed during 2002–2003 in the general population of the same geographic area of the PAC-COPD cohort [26], but higher than the consumption reported in the previously mentioned two large US cohorts [5, 6].

There is evidence that a healthy diet could be a beneficial factor in improving and/or preventing multiple chronic diseases, including chronic lung diseases [2, 3]. However, most influential COPD guidelines, such as those produced by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) or the consensus between the American Thoracic Society and the European Respiratory Society, do not include any specific dietary recommendation to COPD patients, beyond the increase of caloric intake for the prevention of weight loss [11, 27]. This study adds new evidence suggesting that in addition to a

TABLE 3 Crude and adjusted association between high cured meat intake and chronic obstructive pulmonary disease (COPD) hospital readmission in 274 COPD patients with a median follow-up of 2.6 yrs

	Crude HR[#] (95% CI)	p-value	Adjusted[¶] HR (95% CI)	p-value
High cured meat intake >22.68 g·day^{-1}	1.59 (1.06–2.38)	0.024	2.02 (1.31–3.12)	0.001
Age per 5 yrs	1.09 (0.97–1.23)	0.154	1.13 (1.00–1.28)	0.052
Total caloric intake per 100 kcal·day^{-1}	1.00 (0.96–1.03)	0.892	0.98 (0.95–1.01)	0.244
FEV_1 % pred	0.97 (0.96–0.99)	<0.001	0.97 (0.96–0.98)	<0.001

FEV_1: forced expiratory volume in 1 s; % pred: % predicted. Sex, body mass index, fat free mass index, carbon dioxide tension, oxygen tension, smoking status, physical activity, inhaled corticosteroid treatment, statin treatment, the Charlson index of comorbidity, and intakes of fruit, vegetables and fish were tested as potential confounders and finally not included because they were not independently related to both the exposure and the outcome, or if they modified (>10% change in HR) the estimates for the remaining variables. [#]: each line is a single model; [¶]: the entire column is a single model.

possible increase in risk of COPD associated with cured meats [4–6] these foods may also increase risk of exacerbations, thus supporting the need to consider giving specific dietary advice to COPD patients.

A limitation of the present study is the potential measurement error in the estimation of cured meat intake due to the use of a food frequency questionnaire. However, any such misclassification is probably nondifferential and therefore would lead to an underestimation of the effects of cured meats. Following this, the presence of subjects who died prior to any COPD readmission could have produced survival bias. However, the small number of deaths before the first hospital readmission (n=2 (1%)) suggests that this bias, if present, is negligible. Finally, information on dietary changes after baseline was unavailable, although, given the current COPD management, it is unlikely that a first COPD admission could promote a reduction in cured meats consumption.

The main strengths of this study are its longitudinal design along with a very accurate characterisation of the study subjects which allowed appropriate control for confounders. Importantly, the latter also included other potentially relevant food groups such as fruits, vegetables and fish. During the follow-up, all hospitalisations were registered thoroughly, and only those with COPD as a main diagnosis were considered in the analysis. Finally, it is noteworthy that all subjects were recruited during their first COPD hospital admission, as we aimed to identify subjects at a similar state of disease evolution, following the evidence-based medicine recommendations for studies on prognosis [28].

In conclusion, high cured meats consumption was associated with an increase in the risk of COPD readmission in COPD patients. Given the economic and health burden of COPD hospitalisations, the assessment of the effectiveness of healthy diet advice should be considered in the future.

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STATEMENT OF INTEREST

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