ELSEVIER

Journal of Clinical Epidemiology 57 (2004) 858–863

Journal of Clinical Epidemiology

A prospective study linked both alcohol and tobacco to Dupuytren's disease

Nina S. Godtfredsen[a], Hasse Lucht[a], Eva Prescott[a], Thorkild I. A. Sørensen[a], Morten Grønbæk[a,b,*]

[a]*Copenhagen Centre for Prospective Population Studies, Danish Epidemiology Science Centre, Institute of Preventive Medicine, Copenhagen University Hospital, Svanemøllevej 25, DK-2100 Copenhagen, Denmark*

[b]*Centre for Alcohol Research, National Institute of Public Health, Copenhagen, Denmark*

Accepted 17 November 2003

Abstract

Objective: To address the role of alcohol intake and tobacco smoking and the combination of the two on subsequent risk of Dupuytren's disease.

Study Design and Setting: Cohort study of 7,254 subjects enrolled in the Copenhagen City Heart Study (1981–1983). Both self-reported information on lifestyle and objective measures at the baseline examination were linked to presence of Dupuytren's disease at a subsequent examination (1991–1994) using multivariate logistic regression analysis.

Results: A total of 772 subjects had signs of Dupuytren's disease at follow-up. After adjustment for age, sex, educational level, diabetes, and either alcohol or tobacco consumption, respectively, odds ratios for having the disease increased in a dose-dependent manner with increasing levels of alcohol or tobacco intake; however, there was no statistical interaction between heavy smoking and heavy drinking.

Conclusion: Alcohol intake and tobacco smoking are independently associated with increased risk of Dupuytren's disease, and the combination of the two conveys a very large risk.

Keywords: Dupuytren's disease; Alcohol consumption; Tobacco use; Smoking

1. Introduction

Dupuytren's disease has been known for centuries. The pathology is well understood, but the disease etiology is not. In particular, evidence on risk factors associated with certain lifestyles has been conflicting. Furthermore, estimates of disease prevalence have been shown to vary extremely in selected populations, ranging from a low of 2% to a high of 42% [1]. Dupuytren's disease is known to mainly affect middle-aged and elderly Northern European males, and it has a strong genetic predisposition, presumably inherited as an autosomal dominant condition. It has also been linked to diseases and conditions such as non–insulin-dependent diabetes mellitus, epilepsy, arcus corneae (also known as arcus senilis), and hypercholesterolemia [1,2]. With respect to lifestyle factors, special attention has been paid to occupation, alcohol consumption, and cigarette smoking. Most studies have found a positive association between manual labor, previous hand injuries, and intake of either alcohol or tobacco and the risk of Dupuytren's contracture [3–9], but some have not [10–12]. The underlying mechanism behind the contribution of alcohol and smoking to the fibrosis seen in Dupuytren's disease is thought to be mediated through localized ischemia and generation of free radicals; the effect of alcohol on the liver has also been suggested as a causal factor [2,13].

Because smoking and alcohol consumption are correlated [14,15], their interrelationship as causal factors for Dupuytren's disease is an important aspect of the disease etiology. To our knowledge, however, this has never been investigated in an unselected population. A recent matched case–control study [5] found a strong effect of smoking and a moderate effect of alcohol on the risk of developing Dupuytren's disease, without any signs of mutual confounding between these two covariates. A newly published report from a longitudinal study, the Reykjavik Study [3], found positive associations between Dupuytren's disease and manual labor, elevated fasting blood glucose, low body mass index, and heavy smoking. Unfortunately, the role of alcohol was not

* Corresponding author. Tel.:+45-3920-7777; fax:+45-3920-8010.
E-mail address: mg@niph.dk (M. Grønbæk).

0895-4356/04/$ – see front matter
doi: 10.1016/j.jclinepi.2003.11.015

addressed in this study. The aim of the present study was to prospectively examine the influence of amount and type of alcohol consumed and the influence of smoking habits in detail on the subsequent risk of Dupuytren's disease. Furthermore, we addressed the possibility of mutual effect modification (interaction) by these two risk factors on the study outcome.

2. Material and methods

2.1. Study population

The Copenhagen City Heart Study, a prospective investigation of major diseases in a random sample of the general population, was initiated in 1976. The study has been described in detail [16]. The survey in 1976–1978 included 14,223 persons aged 20–93 years (74% of those invited), the survey in 1981–1983 included 12,698 persons (70% of those invited), and the survey in 1991–1994 included 10,127 persons (61% of those invited). The nonresponders who were still alive in 1991–1994 were significantly older than the active study participants; however, there was an equal distribution at the examination in 1981–1983 on factors such as sex and smoking and alcohol habits. The present study sample consisted of 7,254 persons (3,050 men, 4,204 women) who participated in the Copenhagen City Heart Study in 1981–1983 and also in the follow-up in 1991–1994. The survey consisted of a detailed health examination performed by medical doctors, registered nurses, and medical students and a self-administered questionnaire concerning symptoms, diseases, and lifestyle variables. This provided adequate information on alcohol consumption, smoking habits, covariates, and signs of Dupuytren's disease (this last was not assessed in 1981–1983).

2.2. Assessment of alcohol intake, smoking habits, and covariates

Consumption of alcohol and tobacco was based on self-reported information from the questionnaire at the examination in 1981–1983. Alcohol intake was answered by the participants in an average weekly number of drinks of beer, wine, and spirits, respectively. One drink was defined as 12 grams of alcohol, corresponding to one bottle of beer, one glass of wine, or 3 cL of liquor. Alcohol intake was categorized as follows: >1, 1–6, 7–21, 22–35, and $\geqslant 36$ drinks per week. The analyses stratified on type of alcohol were restricted to <1, 1–21, and $\geqslant 22$ drinks per week. Smoking habits were assessed by asking subjects about the average daily number of cigarettes (with and without filter), cheroots, and cigars and the weekly number of packets of pipe tobacco. Former smoking, duration of current smoking, and inhalation habits were also determined. For cheroot and cigar smokers, tobacco consumption was calculated by equating one cheroot to 3 g of tobacco and one cigar to 5 g (one cigarette = 1 g). We then categorized smoking habits at baseline (1981–1983) as follows: Never smokers, former smokers, light smokers (1–14 g/d), moderate smokers (15–24 g/d), and heavy smokers ($\geqslant 25$ g/d). For all current smokers, we used pack-years calculated as daily amount of tobacco in grams multiplied by years of smoking divided by 20 as a measure of cumulated tobacco exposure. Other covariates included in the analyses were age in years (20–49, 50–59, 60–69, $\geqslant 70$), educational level (<8, 8–11,$\geqslant 12$ years of school education), cohabitation status (living with a partner, yes or no), body mass index (i.e., weight in kilograms divided by height in meters squared), physical activity at work (none, light, heavy), serum cholesterol (mmol/L, quartiles), serum glucose (mmol/L, quartiles), and presence of arcus corneae (yes/no).

2.3. Assessment of Dupuytren's disease

Presence of Dupuytren's disease was assessed by trained nurses or medical students at the examination in 1991–1994 as a result of a clinical examination of the subject's hands and entered in the objective schedule as either present or absent. The criteria for evaluating that a subject had Dupuytren's disease were based on clinical signs of thickening of the palmar fascia and flexion contracture in phalanx 4, 5, or both. A photograph from a medical textbook accompanied the objective schedule. The involved health personnel were not aware of the participants' smoking behavior or alcohol consumption at any time.

3. Statistical analysis

In crude and multivariate logistic regression analyses, we estimated the odds ratios for presence of Dupuytren's disease as a function of categories of alcohol intake and smoking habits respectively. Each model included the following potential confounders as categorical variables: age, sex, education, cohabitation, body mass index (BMI), level of physical activity during working hours, blood glucose level, serum cholesterol level, and arcus corneae. In the final model, cohabitation status, BMI, physical activity at work, cholesterol, and arcus corneae were omitted. Owing to the collinearity, it was impossible to include both the amount by type of beverage (beer, wine, or spirits) and the total alcohol intake in the same regression model. For that reason, we estimated the influence of alcohol categorized by drinks per week (0, 1–6, 7–21, 22–35, $\geqslant 36$) in two regressions: (a) total alcohol consumption in drinks per week, without considering beverage type, and (b) alcohol consumption in drinks of each beverage per week, without considering the total intake. The interaction between alcohol and smoking was analyzed separately in a subsequent analysis. Due to the large differences between men and women in prevalence of Dupuytren's disease, as well as in pattern of alcohol and tobacco use, we performed analysis of interaction of sex on risk of Dupuytren's disease for both smoking and alcohol.

Table 1
Study population with demographic characteristics

	Number	Mean age, yr	Number with Dupuytren's disease
Men	3,050	51.8 (SD 11.7)	484 (15.9%)
Women	4,204	53.1 (SD 11.5)	288 (6.9%)
Total	7,254		772 (11%)

Abbreviations: SD, standard deviation.

The interaction models were tested with goodness-of-fit and likelihood-ratio procedures, and the analyses revealed no effect modification for sex. Hence, sex was included in the multivariate model as a normal covariate. SAS statistical software (SAS Institute, Cary, NC, USA) was used for all analyses.

4. Results

Among the 7,254 participants, 772 (11%) had signs of Dupuytren's disease at follow-up: 484 of the 3,050 men (15.9%) and 288 of the 4,204 women (6.9%). The mean age of the participants in 1981–1983 was 52.5 years, and the mean age in 1981–1983 of the 772 participants who had Dupuytren's disease in 1991–1994 was 57.9 years. An overview of the study population is displayed in Table 1. The proportion of smokers increased with increasing alcohol consumption (Table 2). The crude as well as the adjusted models revealed a clear dose–response relationship with both increasing alcohol consumption and increasing tobacco consumption and risk of Dupuytren's disease. Heavy drinkers (⩾36 drinks per week) had an adjusted odds ratio of 2.09 (95% confidence interval CI 1.42–3.06) compared with nondrinkers; heavy smokers (⩾25 g/d) had an odds ratio of 1.73 (CI 1.26–2.39) compared with never smokers (Table 3). The adjusted regression analyses also revealed that age above 60 years, male sex, elevated blood glucose, and low educational level were independent predictors of Dupuytren's disease (Table 4). In contrast, physical activity during work, hypercholesterolemia, BMI, cohabitation status, and presence of arcus corneae were not associated with this disease. Analyses of interaction between smoking and drinking habits showed that never smokers who were heavy drinkers had a risk of Dupuytren's disease of 3.17 (CI 0.99–10.18) compared with nondrinking never smokers, and nondrinkers who were heavy smokers had an odds ratio of 2.08 (CI 0.97–4.45) compared with never smoking nondrinkers and a combination of heavy smoking and heavy drinking conveyed a risk of Dupuytren's disease of 4.20 (CI 2.28–7.75) compared with never smoking nondrinkers (Table 5). With the exception of heavy beer-drinking (adjusted OR 2.02; 95% CI 1.44–2.86), neither type of alcohol nor type of tobacco had a separate influence on risk of Dupuytren's disease, when controlled for total alcohol and total tobacco consumption, respectively (data not shown).

5. Discussion

In this longitudinal population-based study, we showed independent dose–response relationships between both alcohol consumption and smoking on risk of Dupuytren's disease. We did not find any signs of interaction between amount of alcohol and tobacco and subsequent presence of this contracture, nor did we see any independent effect of type of beverage or type of tobacco. Furthermore, in accordance with other studies, we found increasing disease prevalence with age and male sex, and we also found signs of diabetes and low educational level to be associated with disease prevalence. These results are in agreement with the findings from the only other population-based studies on this subject [3,4], taking into consideration that manual labor can be regarded as a proxy for educational attainment. Contrary to our study, the Reykjavik study [3] found that low BMI was correlated with presence of disease. This apparent association could be confounded by smoking habits, however, given the well-known relationship between smoking

Table 2
Baseline characteristics of subjects according to alcohol and tobacco use

	Total alcohol intake, drinks per week[a]					Tobacco consumption, per day				
	0	1–6	7–21	22–35	⩾36	Never	Ex	1–14 g	15–24 g	⩽25 g
Number	2,001	2,331	2,181	468	273	1,699	1,571	1,761	1,660	563
Men, %	19	32	59	81	91	24	48	38	48	75
Age, mean, yr	56	52	52	51	49	53	56	59	51	51
BMI, mean, sex weighted	26	25	25	26	27	25	26	24	25	26
Smokers, %	49	50	60	67	75	5	8	7	11	20
Low education, %	55	36	33	35	40	38	36	42	44	43
Living alone, %	35	25	23	22	33	31	24	27	25	29
Arcus corneae, %	22	18	21	19	24	17	23	23	18	19
Diabetes, %	2	1	1	1	1	1	2	1	1	1
Cholesterol >7 mmol/L, %	20	15	14	10	11	16	17	16	15	11
Physical activity at work, % at highest level	1	2	5	11	15	2	3	4	5	8

Data from Copenhagen City Heart Study 1982; see Schnohr et al., 2001 [16].
[a] One drink is defined as 12 g alcohol.

Table 3
Odds ratios (95% CI) for presence of Dupuytren's contracture according to alcohol intake and smoking habits

	No. of cases	Crude	Adjusted[a]	Fully adjusted[b]
Alcohol, drinks/wk				
0[c]	161	1.00 (—)	1.00 (—)	1.00 (—)
1–6	205	1.07 (0.86–1.33)	1.09 (0.87–1.36)	1.14 (0.91–1.43)
7–21	260	1.49 (1.21–1.83)	1.25 (1.00–1.56)	1.29 (1.02–1.62)
22–35	91	2.65 (2.00–3.51)	2.14 (1.57–2.91)	2.13 (1.55–2.92)
⩾36	55	2.80 (1.99–3.92)	2.31 (1.59–3.34)	2.09 (1.42–3.06)
Smoking				
Never[c]	122	1.00 (—)	1.00 (—)	1.00 (—)
Ex	161	1.48 (1.16–1.89)	1.04 (0.80–1.34)	0.99 (0.76–1.28)
1–14 g/d	187	1.52 (1.20–1.94)	1.30 (1.01–1.66)	1.27 (0.99–1.63)
15–24 g/d	205	1.82 (1.43–2.30)	1.66 (1.30–2.13)	1.53 (1.18–1.96)
⩾25 g/d	96	2.63 (1.97–3.51)	2.06 (1.51–2.81)	1.73 (1.26–2.39)

[a] Adjusted for the other covariate in the table as well as for age (quartiles) and sex.
[b] Adjusted for the other covariate in the table as well as for age (quartiles), sex, blood glucose (quartiles) and level of education (<8, 8–11, ⩾12 years of school education).
[c] Reference is nondrinkers or never smokers.

and low body weight. From the Reykjavik study a cross-sectional case–control study was carried out later to investigate the relationship between current alcohol habits and Dupuytren's disease [12]. No difference in alcohol consumption was found between cases and controls, but this was not a prospective study. Likewise, a study from Malmö, Sweden, found no relationship of Dupuytren's disease with occupational or psychosocial factors [17]; furthermore, the disease prevalence was much lower than in our study or the Reykjavik study.

A number of factors have been proposed to be cofactors in the development of Dupuytren's disease. Inclusion of age, sex, diabetes, and socioeconomic status attenuated the estimates for the relation between both alcohol and smoking and Dupuytren's disease, but both factors were shown to be strongly associated with Dupuytren's disease after adjustment for these other factors. The finding that a combination of heavy smoking and heavy drinking implies an approximately double risk of Dupuytren's disease compared with either heavy smoking or heavy drinking indicates that the mechanisms are independent and that no synergy is taking place.

Table 4
Odds ratios (95% CI) for presence of Dupuytren's contracture according to sex, age, education, and blood glucose level

Risk factor	Adjusted OR[a]
Sex	
Women	1.00 (—)
Men	2.27 (1.89–2.72)
Age, yr	
20–49	0.45 (0.36–0.55)
50–59	1.00 (—)
60–69	1.71 (1.41–2.07)
70–100	2.48 (1.80–3.43)
Education	
High, ⩾12 yr school	1.00 (—)
Medium, 8–11 yr	1.52 (1.17–1.99)
Low, <8 yr	1.60 (1.22–2.10)
Blood glucose[b]	
Elevated	1.00 (—)
Normal	0.29 (0.17–0.48)

Note: Body mass index, presence of arcus cornea, degree of physical activity at work and level of blood cholesterol were not independent risk factors for Dupuytren's disease.
[a] Adjusted for the other covariates in the table as well as for alcohol consumption (4 categories) and smoking (5 categories).
[b] Upper quartile of measured nonfasting blood glucose (mmol/L) as reference.

Our study supports previous cross-sectional studies suggesting a causal relationship between smoking and alcohol and Dupuytren's disease. Only one other report has addressed the question of the possible confounding effect of alcohol on smoking and vice versa in Dupuytren's disease [5]. This was a hospital-based matched case–control study of 222 patients who had undergone an operation for Dupuytren's contracture. The authors found a strong effect of current smoking, OR 2.8, and a more modest effect of alcohol (as defined by the WHO AUDIT score), OR 1.9. These effects were independent; that is, no mutual confounding was observed and no interaction was found. The authors could not, however, rule out any possible residual confounding; furthermore, the analyses were based on dichotomous values of the independent variables (smoking/no smoking, AUDIT score $>$ 7/AUDIT score $\leqslant$ 7). The disparities in study designs and categorization of independent variables can perhaps explain the different tendencies in the results: we find a stronger effect of alcohol and a more modest of smoking in relation to disease risk. Furthermore, we were able to include these risk factors prospectively and in more detail than earlier studies. Due to the design and size of the Copenhagen City Heart Study, we were also capable of controlling for several additional confounding factors. In a prospective cohort study such ours, however, an element of unmeasured confounding cannot be precluded. In the actual case, for instance, we had no information on the participants' dietary habits (except for BMI), which could confound the association between alcohol consumption and Dupuytren's disease,

Table 5
Odds ratios (95% CI) for presence of Dupuytren's contracture according to a combination of drinking and smoking habits

	Alcohol, drinks per week			
Smoking	0	1–20	21–35	⩾36
Never	1.00 (—)[a]	1.35 (0.89–2.05)	2.84 (1.15–7.02)	3.17 (0.99–10.18)
Ex	1.04 (0.63–1.71)	1.32 (0.88–1.97)	3.16 (1.70–5.85)	1.16 (0.42–3.20)
Smoker, 1–14 g/d	1.57 (1.00–2.46)	1.65 (1.11–2.44)	2.45 (1.17–5.13)	2.69 (0.83–8.74)
Smoker ,15–24 g/d	1.66 (1.00–2.77)	2.07 (1.39–3.08)	3.11 (1.81–5.35)	3.95 (2.03–7.67)
Smoker, ⩾25 g/d	2.08 (0.97–4.45)	2.31 (1.42–3.76)	3.72 (1.92–7.21)	4.20 (2.28–7.75)

Note: Adjusted for the other covariate in the table as well as for age (quartiles), sex, blood glucose (quartiles) and level of education (three categories).
[a] Reference is nondrinkers who never smoked.

and our assessment of occupational exposure was rather crude. Nevertheless, any possible unmeasured confounder would have to be very influential to have a significant effect on the association.

Three newly published Scandinavian studies [18–20] investigated the relationship between Dupuytren's disease and mortality and cancer incidence, respectively. A matched case–control study with 26 years of follow-up found a significantly increased mortality among men with Dupuytren's disease, and this excess mortality was especially pronounced with disease onset before the age of 60 [18]. In a study of cancer incidence [19], 15,212 patients treated surgically for Dupuytren's contracture were followed for 29 years by record linkage with the Swedish Cancer Registry. The authors found an increased overall relative risk of cancer of 24%, and, not surprisingly, there was an overweight of cancers related to smoking, alcohol consumption, or both. These studies reflect the relation of Dupuytren's disease to a less healthy lifestyle, which in turn is reflected in increased cancer incidence and increased mortality compared with either relevant control groups or the general population.

In our study, Dupuytren's disease was not considered at the examination in 1981–1983, which means that we could not exclude subjects with Dupuytren's disease at baseline. It is not likely, however, that presence of Dupuytren's disease itself at baseline would influence drinking or smoking habits. Presence of Dupuytren's disease in 1991–1994 was assessed by trained nurses and students, not by surgeons, which may imply a lower sensitivity and specificity. The criteria for defining disease did not include the milder forms, however, so Dupuytren's disease in the current population was probably not overestimated. Furthermore, this is also likely to imply more conservative estimates (i.e., an underestimation) of the true relation between alcohol or smoking and Dupuytren's disease. Interpretation of our results requires some caution, however, especially because staging of Dupuytren's disease was not performed in the present study. Hence, our data do not permit speculations as to whether the dose–response relationship in smoking and alcohol is also related to increasing severity of the disease. To our knowledge, no such study has been conducted. This hypothesis should be pursued in future research of risk factors for Dupuytren's disease.

In conclusion, both alcohol and smoking are strong risk factors for development of Dupuytren's disease. Although excessive use of these substances is subject to far more serious health threats in individual and public health perspectives, these results from an unselected population can be used as a further incentive in alcohol and tobacco intervention.

References

[1] Saar JD, Grothaus PC. Dupuytren's disease: an overview. Plast Reconstr Surg 2000;106:125–34.
[2] Murrell GAC. An insight into Dupuytren's contracture. Ann R Coll Surg Engl 1992;74:156–60.
[3] Gudmundsson KG, Arngrimsson R, Sigfusson N, Bjornsson A, Jonsson T. Epidemiology of Dupuytren's disease: clinical, serological, and social assessment. The Reykjavik Study. J Clin Epidemiol 2000;53:291–6.
[4] Mikkelsen OA. Dupuytren's disease: the influence of occupation and previous hand injuries. Hand 1978;10:1–8.
[5] Burge P, Hoy G, Regan P, Milne R. Smoking, alcohol and the risk of Dupuytren's contracture. J Bone Joint Surg Br 1997;79:206–10.
[6] Attali P, Ink O, Pelletier G, Vernier C, Jean F, Moulton L, Etienne JP. Dupuytren's contracture, alcohol consumption, and chronic liver disease. Arch Intern Med 1987;147:1065–7.
[7] Bradlow A, Mowat AG. Dupuytren's contracture and alcohol. Ann Rheum Dis 1986;45:304–7.
[8] Eadington DW, Patrick A, Collier A, Frier BM. Limited joint mobility, Dupuytren's contracture and retinopathy in type 1 diabetes: association with cigarette smoking. Diabet Med 1989;6:152–7.
[9] An HS, Southworth SR, Jackson WT, Russ B. Cigarette smoking and Dupuytren's contracture of the hand. J Hand Surg [Am] 1988;13B:872–4.
[10] Carson J, Clarke C. Dupuytren's contracture in pensioners at the Royal Hospital Chelsea. J R Coll Physicians Lond 1993;27:25–7.
[11] Fraser-Moodie A. Dupuytren's contracture and cigarette smoking. Br J Plast Surg 1976;29:214–5.
[12] Gudmundsson KG, Arngrimsson R, Jonsson T. Dupuytren's disease, alcohol consumption and alcoholism. Scand J Prim Health Care 2001;19:186–90.
[13] Noble J, Arafa M, Royle SG, McGeorge G, Crank S. The association between alcohol, hepatic pathology and Dupuytren's disease. J Hand Surg [Br] 1992;17:71–4.
[14] Bien TH, Burge R. Smoking and drinking: a review of the literature. Int J Addict 1990;25:1429–54.
[15] Miller NS, Gold MS. Comorbid cigarette and alcohol addiction: epidemiology and treatment. J Addict Dis 1998;17:55–66.
[16] Schnohr P, Jensen G, Lange P, et al. The Copenhagen City Heart Study—Østerbroundersøgelsen. Tables with data from the third examination. Eur Heart J Suppl 2001;3:1–83.

[17] Bergenudd H, Lindgarde F, Nilsson BE. Prevalence of Dupuytren's contracture and its correlation with degenerative changes of the hands and feet and with criteria of general health. J Hand Surg [Br] 1993;18:254–7.

[18] Mikkelsen OA, Hoyeraal HM, Sandvik L. Increased mortality in Dupuytren's disease. J Hand Surg [Br] 1999;24:515–8.

[19] Wilbrand S, Ekbom A, Gerdin B. Cancer incidence in patients treated surgically for Dupuytren's contracture. J Hand Surg [Br] 2000;25: 283–7.

[20] Gudmundsson KG, Arngrimsson R, Sigfusson N, Jonsson T. Increased total mortality and cancer mortality in men with Dupuytren's disease: a 15-year follow-up study. J Clin Epidemiol 2002;55:5–10.