SMOKING, ALCOHOL AND THE RISK OF DUPUYTREN'S CONTRACTURE

PETER BURGE, GREG HOY, PADRAIC REGAN, RUAIRIDH MILNE

From the Nuffield Orthopaedic Centre, Oxford, England

We investigated the association of Dupuytren's contracture with smoking and with alcohol by a case-control study in which 222 patients having an operation for this condition were matched for age, operation date and gender with control patients having other orthopaedic operations. Fifty of the cases were also each matched with four community controls. Data were collected by postal questionnaire.

Dupuytren's contracture needing operation was strongly associated with current cigarette smoking (adjusted odds ratio 2.8 (95% confidence interval (CI) 1.5 to 5.2)). The mean lifetime cigarette consumption was 16.7 pack-years for the cases compared with 12.0 pack-years for the controls (p = 0.016). Dupuytren's contracture was also associated with an Alcohol Use Disorders Test score greater than 7 (adjusted odds ratio 1.9 (95% CI 1.02 to 3.57)). Mean weekly alcohol consumption was 7.3 units for cases and 5.4 units for controls (p = 0.016). The excess risk associated with alcohol did not appear to be due to a confounding effect of smoking, or vice versa.

Smoking increases the risk of developing Dupuytren's contracture and may contribute to its prevalence in alcoholics, who tend to smoke heavily.

P. Burge, FRCS, Consultant Hand Surgeon
Nuffield Orthopaedic Centre, Windmill Road, Headington, Oxford OX3 7LD, UK.

G. Hoy, FRACS, Consultant Orthopaedic Surgeon
Alfred Hospital, PO Box 315, Prahran, 3181 Victoria, Australia.

P. Regan, FRCS (Plast), Consultant Plastic Surgeon
Stoke Mandeville Hospital, Mandeville Road, Aylesbury, Buckinghamshire HP21 8AL, UK.

R. Milne, MFPHM, Consultant in Public Health Medicine
Department of Public Health and Primary Care, University of Oxford, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE, UK.

Correspondence should be sent to Mr P. Burge.

Dupuytren's disease of the hand affects about 10% of men over the age of 65 years in Northern Europe and has a strong genetic predisposition,[1] but exogenous factors may initiate or aggravate the condition in susceptible individuals. Several studies have shown a high prevalence of Dupuytren's disease in alcoholic patients,[2-5] but the effect of lower levels of exposure to alcohol is not clear. In an unmatched case-control study, current heavy drinking was strongly associated with Dupuytren's contracture in men,[6] but no association was found in a case-control study of residents of a home for ex-servicemen.[7]

Several lines of evidence link microvascular impairment with Dupuytren's disease, leading to the hypothesis that smoking may affect the risk of Dupuytren's contracture by its influence on local blood flow in the hand. Studies which examined the exposure to cigarette smoke have produced conflicting results.[8-10] Smoking and drinking habits are correlated,[11,12] but previous studies of these in Dupuytren's disease have not considered the possible confounding effect of one on the other.

We performed a matched case-control study to examine exposure to smoking and to alcohol in patients who had had an operation for Dupuytren's contracture.

PATIENTS AND METHODS

We reviewed the cases of 245 consecutive patients operated on for Dupuytren's contracture at the Nuffield Orthopaedic Centre, Oxford, between January 1988 and December 1991. They were matched by gender, age (five-year bands) and operation date (half calendar years) to a hospital control group selected at random from 12 000 patients having elective operations for other orthopaedic disorders; joint replacement for osteoarthritis of the hip or knee, foot surgery, knee arthroscopy and hand surgery accounted for 75% of the operations. Patients suffering from carpal tunnel syndrome were excluded, because smoking and carpal tunnel compression may be associated.[13] We also excluded patients admitted to the rheumatology ward because a low alcohol consumption has been reported in patients with rheumatoid arthritis.[14]

To simplify the collection of our community controls group, cases were ranked by the number of partners in their family doctor's group practice. The first 50 patients with Dupuytren's disease from the largest practices were each

matched by age and gender to four community controls drawn at random from the practice list of their general practitioner. We replaced community controls if they had undergone surgery for Dupuytren's contracture.

Community controls were sent a postal questionnaire regarding their occupation, past medical history, smoking and alcohol consumption. Failure to respond after two questionnaires and a telephone reminder, or loss of a control by death or incapacity led to the random selection of a replacement. A letter with each questionnaire explained that the study concerned past illnesses and aspects of lifestyle, but to reduce recall bias, the hypotheses under test and the direction of any expected effect were not stated. Questions on socio-economic status (occupation and years of full-time education after the age of 14 years) and other illnesses preceded questions on smoking and drinking. Subjects were assigned to a socio-economic group according to the Standard Occupational Classification.[15]

The questions on smoking included current and former smoking habits, the age at which smoking started and the year in which it ceased. Both cases and controls were classified as current smokers if they were smoking during the year of the operation. The number of cigarettes smoked per day, the number of cigars per day and the amount of pipe tobacco per week were recorded for current and ex-smokers. Lifetime cigarette consumption was expressed as pack-years of smoking.

Data on alcohol consumption were collected using questions from the WHO Alcohol Use Disorders Identification Test (AUDIT),[16] which was developed as a screening instrument for hazardous alcohol consumption in the primary-care setting. The questionnaire concentrates on the consumption and frequency of intoxication rather than the lack of control and the adverse consequences of addiction. Responses to each question were scored from 0 to 4, giving a maximum possible score of 40. We chose an AUDIT score greater than 7 to indicate heavy drinking, corresponding to a consumption of at least 21 units of alcohol per week *and* a positive response to one or more questions on drinking behaviour, adverse psychological reactions or alcohol-related problems.

The size of the study was chosen to give 90% power to detect a relative risk of 2.0 at the 5% level of significance, given a prevalence of smoking of 21% (the national prevalence for 'current smoking') for men over 60 years of age in 1992/93.[17] The study was approved by our research ethical committee.

Statistical analysis. The paired *t*-test was used for comparison of means and matching was maintained in all analyses. We performed a case-control matched analysis of smoking and alcohol as risk factors for Dupuytren's contracture by computing odds ratios as estimates of the relative risk, using conditional logistic regression with Egret version 0.26.1 software (SERC Corporation, Seattle, Washington).

Conditional logistic regression is a form of logistic regression analysis which is applicable to matched case-control studies. It allows adjustment for the confounding effects of a variable on which cases and controls have not been matched. An alternative approach is a stratified 2×2 table method, restricting the analysis to case-control sets which are homogeneous for the variable in question, but the loss of data may weaken the power of the analysis. Conditional logistic regression models the effect of confounding variables such as socio-economic group in a multivariate analysis which also includes the exposures of interest.

The odds ratio is the ratio of the odds that a case is a current smoker to the odds that a control is a current smoker. It is also equivalent to the ratio of the odds of being a case for current smokers to the odds of being a case for non-smokers in the study.

It gives an estimate of the relative risk, which is the ratio of the incidence of Dupuytren's contracture in smokers to its incidence in non-smokers, and it will be numerically equal to the relative risk in the case of a rare disease. For a common disease, the odds ratio will tend to overestimate the relative risk. Although the population prevalence of Dupuytren's disease in the UK is approximately 10% for men aged 55 to 64 years,[18] only a few of these have a contracture which needs surgery. About 80 operations were performed annually over the period of the study in our hospital, which serves a population of approximately 500 000. Since all our cases were patients undergoing surgery, Dupuytren's contracture as defined in our study is relatively rare and therefore the odds ratio is a good approximation of the relative risk.

RESULTS

Hospital control study. Valid questionnaires were received from 222 of 245 cases (91%); ten patients had died. In all, questionnaires were sent to 270 hospital controls and 251 community controls (response rates 82% and 80%, respectively); 22 of the hospital controls had died. An excess of socio-economic groups I and II in cases over hospital controls is consistent with the cases' longer full-time education after the age of 14 years (Table I). Since smoking is less prevalent in socio-economic groups I and II, these differences tend to underestimate any association of Dupuytren's contracture with smoking. No socio-economic group difference was seen in the community study.

After adjustment for socio-economic group, the hospital control study showed a strong positive association of Dupuytren's contracture with current cigarette smoking (odds ratio 2.8 (95% confidence interval (CI) 1.5 to 5.2; p = 0.002; Table II).

The lower proportion of smokers among controls was not due to an effect of illness on smoking habits; only eight cases and nine controls had given up smoking within five years of operation. The mean number of cigarette pack-years was 16.7 SD 22.3 for cases and 12.0 SD 19.7 for

Table I. Details of the populations studied in the hospital and the community case-control studies

	Hospital study				Community study			
	Cases	(%)	Controls	(%)	Cases	(%)	Controls	(%)
Number	222	100	222	100	50	100	200	100
Socio-economic group								
I	17	8	12	5	4	8	16	8
II	56	25	43	19	14	28	60	30
IIIn	19	9	26	12	5	10	27	14
IIIm	53	24	67	30	15	30	58	29
IV	41	18	43	19	7	14	20	10
V	3	1	3	1	0	0	5	3
Unclassified	33	15	28	13	5	10	14	7
Mean number of years of education after age 14 (SD)	2.1 (2.9)		1.7 (2.8)		2.0 (2.3)		2.4 (3.0)	
Mean age at operation (SD)	63.2 (12.0)		63.0 (12.0)		60.0 (11.3)		60.4 (11.5)	
Current smokers	51		31		11		22	
AUDIT score >7 for alcohol	39		23		10		23	

Table II. The results of fitting several conditional logistic regression models to the matched pairs in the hospital-control and community-control studies, reported as odds ratios with 95% confidence limits in parentheses. The hospital control data are adjusted for socio-economic group

	Hospital controls		Community controls	
Model	Smoking*	Alcohol*	Smoking	Alcohol
Smoking	2.8 (1.5 to 5.2)		2.2 (1.0 to 5.0)	
Alcohol		1.9 (1.0 to 3.6)		2.0 (0.9 to 4.7)
Smoking + alcohol	2.6 (1.4 to 5.0)	1.8 (0.9 to 3.3)	2.0 (0.9 to 4.6)	1.7 (0.7 to 4.1)

* smoking, current cigarette smoking; alcohol, AUDIT score >7

controls (t = 2.42, p = 0.016).

Dupuytren's contracture was associated with an AUDIT score of greater than 7 (odds ratio 1.9 (95% CI 1.02 to 3.6); p = 0.048), after adjustment for socio-economic group (Table II). The mean weekly alcohol consumption was 7.3 SD 8.8 units for cases and 5.4 SD 7.8 units for controls (t = 2.24, p = 0.016). Dupuytren's contracture was also associated with drinking on more than one day each week (odds ratio 2.2 (95% CI 1.4 to 3.6)).

We found no interaction between current smoking and an AUDIT score of >7 when the regression model containing these variables was compared with a model also containing their cross-product term (i.e., the effects of tobacco do not vary with the level of exposure to alcohol, and vice versa). Confounding between smoking and alcohol was minimal (Table II) since the odds ratios were scarcely changed when both exposures were included in the regression model.

Community control study. Similar results were obtained in the community control study (Table II). Since the community study gives an estimate of the community prevalence (p) of smoking and alcohol consumption (AUDIT score >7), the fraction of the burden of Dupuytren's contracture in the community due to smoking can be expressed as the population attributable risk p(OR-1)/(p(OR)+(1-p), where OR is the odds ratio.[19] The population attributable risk for smoking was 10% and for alcohol 8%. The attributable risk (OR-1)/OR, which estimates the excess risk of Dupuytren's contracture in an individual as a result of exposure, was 50% for smoking and 41% for alcohol consumption with an AUDIT score of >7.

DISCUSSION

The results of our matched case-control study show a strong effect of smoking and a moderate effect of alcohol on the risk of developing Dupuytren's contracture. The absence of confounding between smoking and alcohol is interesting, given that drinkers tend to be smokers,[12] but is consistent with the effect of these exposures in other diseases such as cancer of the upper respiratory and digestive systems.[20] The high frequency of Dupuytren's contracture in alcoholic patients may be explained by the combined effects of alcohol and smoking, since heavy smoking is common in alcoholics. The study lacked the power to show dose-related risks of exposure but the validity of the findings is supported by the close agreement between our hospital-control and community-control studies.

Case-control studies are susceptible to systematic errors of bias, especially in the selection of controls. We minimised selection bias by including all patients having an operation during the study period and by using explicit protocols for the selection of controls. Our use of only those patients who had surgery for Dupuytren's contracture eliminated diagnostic uncertainty and restricted the study to severely-affected patients in whom the effects of exposure may be more obvious.

The use of hospital controls from the same hospital, matched for age, gender and date of operation was intended to minimise any systematic differences between cases and controls. Some of the non-responding patients and controls had died or were incapacitated. Since death or incapacity is more likely among smokers and drinkers at any given age, the responders may be less likely to be smokers or heavy drinkers. There were more non-responders (and deaths) among controls than cases, and it is possible therefore that there was a minor degree of bias, but this is likely to be small.

The patients' smoking behaviour may have influenced referral to hospital and the decision to operate. Bias is introduced, however, only if the influence differs between cases and controls. The decision to operate is determined not only by fitness for anaesthesia but also by severity of pain or disability. Illnesses associated with smoking may exclude patients from major surgery such as joint replacement but not from surgery for Dupuytren's contracture. By contrast, painful osteoarthritis of the hip or knee is a stronger indication for surgery than contracture of a finger; smokers may be referred for the treatment of severe hip pain but not for Dupuytren's contracture. These possible biases will tend to operate in different directions. In practice, the use of epidural anaesthesia at our hospital allows joint replacement in all but the most unfit individuals. Furthermore, only about one-third of the controls were undergoing joint replacement; the other two-thirds had operations similar in magnitude to fasciectomy (other hand surgery, foot surgery and knee arthroscopy), for which similar criteria for fitness would be used. The similarity in odds ratios between hospital and community controls supports our view that these factors have led to no serious systematic bias. With the exception of carpal tunnel syndrome, which was excluded from our study, there is no evidence that the orthopaedic disorders suffered by controls are more, or less, common in smokers or drinkers.

Self-reported data on smoking and alcohol may understate consumption by 10% or more,[17] but are less likely to underestimate prevalence. Bias is introduced only if underreporting differs between cases and controls.

The prevalence of smoking in our hospital controls (14%) was lower than the national figure of 21% for men aged over 60 years.[17] The prevalence at all ages, however, was 2% lower in the Oxford Health region than in England as a whole, and a 1991 survey of elderly people in ten family practices in the Oxford region showed a current smoking prevalence of 16% in those aged 65 years and over;[21] the two practices near Oxford showed prevalences of 11% and 13%. The prevalence of smoking in our hospital controls therefore is within the range expected from local population data.

The low prevalence of smoking in community controls cannot be compared with national data, because the 50 cases were selected by the size of the doctor's practice.

Matching by age, gender and family practice was intended to ensure that controls were drawn from the same population as cases and would have the same potential for exposure.

We chose current smoking status as the main measure of exposure to tobacco for three reasons. First, self-reporting of smoking is probably less likely to understate prevalence than consumption. Secondly, past smoking habits may be reported less accurately than current smoking and thirdly, other diseases associated with tobacco, such as heart disease and cancer, show a decline in risk after cessation of smoking. Since current smoking status, however, may underestimate the effect of past smoking habits on Dupuytren's disease in ex-smokers, we also estimated lifetime consumption as cigarette pack-years.

The observation that Dupuytren's contracture is common in alcoholic patients has been supported by several uncontrolled studies, but evidence from controlled studies is conflicting. Su and Patek[5] compared heavy drinkers with a control group consisting of non-drinkers and moderate drinkers in Boston. The prevalence of Dupuytren's disease was higher among heavy drinkers in the 51- to 60-year age band but not in the 41-to-50 or over-60 bands. A comparison of alcoholic patients with unmatched non-alcoholic controls admitted to a gastroenterology unit showed a high prevalence of Dupuytren's contracture in alcoholics, but no association with chronic liver disease.[2] An unmatched case-control study[6] found a strong association between Dupuytren's contracture and heavy alcohol consumption in patients admitted for surgery, using hospital control subjects. No association was found, however, between the prevalence of Dupuytren's contracture and alcohol consumption in a home for retired servicemen.[7]

Studies of smoking in relation to Dupuytren's contracture have also given conflicting results. Cigarette smoking was associated with Dupuytren's contracture in both type-2 diabetic and non-diabetic subjects.[10] A comparison with national age-matched control data, however, found no association.[8] A hospital-control study[9] showed a twofold greater prevalence of smoking in patients with Dupuytren's contracture, but it is not clear that the controls were comparable with the cases with regard to variables which may influence the prevalence of smoking, such as age, gender and socio-economic status.[17]

It is difficult to interpret previous reports of smoking and alcohol consumption in Dupuytren's contracture, as potential confounding effects between them had not been considered. Given the close association between smoking and drinking habits,[12] it is possible that the observed association of Dupuytren's contracture with alcoholism is explained by smoking. Our study clarifies the risks associated with smoking and with alcohol, but does not exclude the possibility of a degree of residual confounding between these exposures.

It is conventional to assess confounding variables by estimating whether the effect of the study variable is weak-

ened by control for confounding variables in the regression analysis. On this basis, confounding between alcohol and smoking was minimal in our study, and we could conclude that these exposures have largely independent effects on the risk of Dupuytren's contracture.

Controlling for the effect of a confounding variable, however, may be inadequate or incomplete if the measurement of that variable is inaccurate (residual confounding).[22] Errors in the measurement of a variable may be inherent in the collection of data (imperfect recall, under-reporting) or introduced in the analysis, for example by categorising continuous data. For a dichotomous variable such as current smoking, the error in measurement is probably small. The measurement of alcohol consumption may be subject to considerable error, however, because of poor recall or under-reporting which may cause disproportionate errors at high levels of consumption. Furthermore, the use of a scoring system to categorise a continuous variable such as consumption may result in mis-classification of some cases. For this reason, we cannot exclude the possibility that some of the effects of alcohol on the risk of Dupuytren's contracture are due to smoking, and vice versa.

The association between Dupuytren's contracture and smoking may be related to changes in the blood flow of the hand, which is reduced by 29% by inhaling two cigarettes.[23] There are several lines of evidence which link microvascular impairment and Dupuytren's disease. A study of type-2 diabetic patients showed that limited joint mobility and Dupuytren's contracture were independently associated with the microvascular complications of diabetes.[24] Microvascular occlusion is a characteristic histological feature of Dupuytren's contracture,[25] and Murrell[26] suggested that narrowing of microvessels may be initiated by ageing, genetic factors or environmental exposures, leading to localised ischaemia and the generation of oxygen free radicals. A positive feedback mechanism has been proposed: free radicals derived from endothelial cells damage the surrounding tissue and stimulate the proliferation of fibroblasts which synthesise collagen, leading to further microvascular narrowing and local ischaemia.[27] More work is needed to unravel the relationships between smoking, diabetes and Dupuytren's contracture.

We consider that patients who present with Dupuytren's disease should be informed of the association with alcohol and smoking. Advice to stop smoking and reduce excessive alcohol consumption is based on other, more serious, risks to health,[28] but the presence of Dupuytren's disease may act as a further incentive to reduce exposure to these substances.

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