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Are alcohol intake and smoking associated with mycosis fungoides? A European multicentre case–control study.

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Abstract

The incidence of mycosis fungoides (MF) is low, and the aetiology of the disease is unknown. The aim of this study was to investigate whether wine consumption protects against the disease and whether smoking constitutes a risk factor. This paper is part of the *European Rare Cancers Study* that tries to determine the risk factors for seven selective rare cancers, including mycosis fungoides, involved in the development of cancer. A multicentre case–control study was conducted in six European countries. Only incident cases with confirmed histology were included in the analysis which include a total of 76 cases of MF and 2899 controls. Wine intake had no protective effect; on the contrary the consumption of more than 24 g of alcohol per day was associated with a high risk of MF (odds ratio (OR) = 3.02, 95% confidence interval (CI), 1.34–6.79), after adjusting for centre, country, age, sex and education. There was a dose-dependent increase in the risk of MF with increased smoking habits, albeit the observed trend was not statistically significant. A combined exposure to high tobacco and alcohol use yielded a significantly increased risk factor for MF ($P = 0.0073$). Alcohol intake was associated with MF.

Keywords: (MEDLINE): Mycosis fungoides; Alcohol; Tobacco; Case–control study

1. Introduction

The term cutaneous T-cell lymphoma (CTCL) was introduced by Lutzner and colleagues in 1975 to describe a group of malignant lymphomas with primary manifestations in the skin [1]. Mycosis fungoides (MF) is a rare cancer that affects less than 1 per 1000 in the European population. The reported standardised incidence rates for CTCL, of which MF is a subgroup, differs between countries from 0.13 to 0.90 per 100 000 persons-years [2,3]. Although the reported incidence of CTCL has increased in most countries, this may be due to improvements in diagnosis and early detection [3].

Since the disease develops with alterations in the cellular immune response mediated by Langerhans' cells [4], viral infections [5], occupational exposures [6] or a family history of allergic or atopic diseases [7] have been suggested as possible risk factors. The existing studies are, however, small and often of poor quality. Since the disease is rare, common habits like dietary factors and wine consumption may, for example have protective

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effects, perhaps via anti-oxidative mechanisms. A recent study showed wine consumption to be associated with a low incidence of cancers of the upper digestive tract [8]. No study has addressed the relationship between MF and alcohol intake. Fischmann and colleagues [9] described an association with tobacco smoking, but without reference to any comparison group; 86% of their series of patients with MF were smokers.

The aim is of this study is to investigate whether wine consumption protects against MF and if MF is associated with smoking.

2. Patients and methods

A multicentre case–control study was conducted in Denmark, France, Germany, Italy, Spain and Sweden. From 1995 to 1997, we recruited incident cases between 35 and 70 years of age at the time of diagnosis within well-defined regions. Case ascertainment was based upon records from hospitals, pathology departments and regional or national registers. For all the centres, the study base was defined prior to case ascertainment by geographical boundaries, except in Spain where hospital cases defined the study base.

Patients with a clinical diagnosis of MF were referred to pathologists of each country in order to confirm the clinical diagnosis. We enrolled cases of MF according to International Classification of Diseases (ICD) codes or according to codes from the International Classification of Diseases for Oncology (ICD-O). After that, all diagnoses were checked by the study reference pathologists, and the following criteria were recoded: (1) multiple pautrier microaggregates; (2) diffuse infiltration of atypical lymphocytes within the epidermis among many individuals; (3) small intra-epidermal clusters of few atypical lymphocytes; (4) individual intra-epidermal atypical lymphocytes; (5) a dense upper dermal bandlike interface infiltrate, including atypical lymphocytes; (6) a mild to moderate polymorphous upper dermal infiltrate including atypical lymphocytes with a focal interface pattern; and (7) extension of the infiltrate into the deep dermis. The following combinations of these criteria were taken to be diagnostic for MF: 1, 2, or the combinations 3+4+5 or 3+4+6+7 (ICD-O 1976: Morphology and Topocode). The reference pathologist accepted 78% of all enrolled cases. Table 1 shows the ascertainment of cases and controls in the study. Only confirmed cases (classified by pathologists as definitive) were included in this study.

Population controls were selected from population rosters in Denmark, France, Germany, Italy and Sweden. In Spain, hospital controls were selected among hospitalised patients with colon cancer, and a similar second control group was also included in Denmark. Controls were frequency matched by age (in 5-year age groups), sex and region (each country has several centres and each centre could be comprised of several regions). Table 1 provides data for recruitment, pathology review and response rates. Controls were selected to serve seven case groups in this study. We used all controls to simulate the exposure distribution in the study base for the MF cases.

Cases and controls were interviewed by trained interviewers face to face (32% of cases and 60.30% of controls, with variability between countries) or by telephone; in either case we used a standardised questionnaire on lifestyle factors, social factors (age, educational qualifications, marital status), smoking, alcohol and drug use, medical history and environmental exposure (mainly occupational exposure). If the selected person was too ill to respond, a next of kin was

Table 1
Ascertainment and data collection in the study of mycosis fungoides (MF)[a]

Country	Cases[b]						Controls[b]				
	Reference pathologist (RP)				Total cases interviewed						
	Enrolled	Confirmed (definite)	Unconfirmed (only classified as possible)	I.S.[c]	*n*	(%)	Enrolled	I.P.[d]	I.S.	Total interviewed	(%)
Denmark	13	9	4	1	6	46	1011	559	15	574	57
Sweden	3	3	–	–	3	100	407	229	1	230	57
France	33	19	9	–	26	79	630	476	9	485	77
Germany	10	4	4	–	6	60	1542	721	8	729	47
Italy	29	13	10	3	20	69	391	296	6	302	77
Spain	45	37	8	–	43	96	580	523	56	579	100
Total	133	83[e]	35	4	104	78	4561	2804	95	2899	64

[a] The period of interview was from 1995 to 1997.
[b] Totals may differ due to missing data.
[c] I.S., interview with surrogate.
[d] I.P., interview with the enrolled person
[e] All definite cases sum up to 83, but they include non-responders. Total number of cases confirmed (classified as definite) and interviewed were 76.

selected (surrogate responder). Four cases and 95 controls were replaced by surrogates. The median length of time between diagnosis and interview was a little less than 7 months (range 1–9 months). The controls were interviewed around 1 month later than the cases.

The questions on smoking and drinking habits were addressed for the time period of 5 years prior to the interview. The questions for current and ex-smokers were: "Do you smoke on average more than 1 cigarette per day? and Have you formerly been smoking more than 1 cigarette per day for more than 1 year?"; "If you have stopped smoking, how old were you when you stopped?", "How old were you when you started smoking regularly?" (cigarettes with filter, cigarettes without filter, cigars, hand-rolled cigarettes or pipes, and how many units of each did you smoke); "How much did you smoke daily 5 years ago?" (cigarettes with filter, cigarettes without filter, cigars, hand-rolled cigarettes or pipes and the amount of units of each). Participants were classified as "current smokers" if they smoked at the time of the interview or during the previous 2 years prior, and as "ex-smoker" if they had stopped smoking before that time. We furthermore calculated the cumulative amount of smoking as the accumulated packs of cigarettes (number of cigarettes per day/20×365.25×years of smoking). In the case of hand-rolled cigarettes, 1 g of tobacco was considered equivalent to one cigarette. We divided the smoking variable into three categories according to packs per year: 0, from 0.01 to 25, and more than 25 packs.

Case and controls were asked about how much alcohol they drank per day on average 5 years prior to the interview (by type of alcoholic beverage). There were five possible answers (never, less than 1 glass/can/drink, 1–2 glasses/cans/drinks, 3–5 glasses/cans/drinks or more than 6). Each category was translated into a volume (centilitres) and the total alcohol consumption was quantified into grams using the following transformations per litre: wine 94 g, aperitif 145 g and spirit (liquor and aperitif) 317 g. A country-specific value for beer was used (from 3.8 to 6.3% of alcohol — the volume was converted into a gram value using the density of ethanol = 0.8 g/ml). We then calculated the total alcohol intake (the sum of alcohol in grams on average per day), total wine intake, beer intake and spirit intake for all the subjects in the study (Table 2).

The educational level was dichotomised into school education up to and including 15 years of age or >15 years.

2.1. Analyses

A priori classifications were made of the exposures of interest. We checked the exposure distribution among cases and controls in each country and looked for associations with exposure in different age, sex and educational levels at each centre level. Odds ratios (ORs) were estimated by means of unconditional logistic regression methods including a categorical variable for each centre [16]. Ninety-five per cent confidence intervals (CI) were calculated by using the standard error for the log (ln) of the ORs.

All adjusted analyses included the variables centre, age (in the following categories: 35–45, 46–55, 56–65 and over 66 years old), country, sex and education. We also included the year of the interview, since this was the

Table 2
Odds ratios (ORs) for mycosis fungoides (MF) according to smoking habits and alcohol intake 5 years prior to interview[a]

Smoking, alcohol		Cases (76) *n* (%)	Controls (2899) *n* (%)[b]	Unadjusted OR	95%CI	Adjusted OR[c]	95%CI
Smoking	Never	38 (50)	1236 (43)	1.0		1.0	
(packs per year)	1–20	14 (18)	738 (25)	0.62	0.33–1.14	0.94	0.49–1.82
	21–40	13 (17)	547 (19)	0.77	0.40–1.46	1.20	0.60–2.41
	>41	11 (14)	378 (13)	0.95	0.47–1.87	1.30	0.60–2.81
Alcohol, total	Never	9 (12)	423 (15)	1.0		1.0	
(g alcohol/day)	0.01–24	27 (36)	1168 (40)	1.08	0.50–2.32	2.70	1.20–6.11
	>24	40 (53)	1308 (45)	1.43	0.69–2.98	3.02	1.34–6.79
Beer	Never	33 (43)	1049 (36)	1.0		1.0	
(g alcohol/day)	0.01–14	38 (50)	1437 (50)	0.84	0.52–1.34	1.41	0.85–2.35
	>14	5 (7)	413 (14)	0.38	0.14–0.99	0.78	0.28–2.12
Wine	Never	13 (17)	733 (25)	1.0		1.0	
(g alcohol/day)	0.01–14	39 (51)	1374 (47)	1.60	0.84–3.01	2.47	1.27–4.81
	>14	24 (32)	792 (27)	1.70	0.86–3.38	1.81	0.84–3.88
Spirit[d]	Never	25 (33)	1098 (38)	1.0		1.0	
(g alcohol/day)	0.01–14	44 (58)	1601 (55)	1.20	0.73–1.98	1.92	1.12–3.30
	>14	7 (9)	200 (7)	1.53	0.65–3.59	2.29	0.92–5.68

[a] The period of interview was from 1995 to 1997.
[b] The total differs due to missing data.
[c] Adjusted analyses included the variables centres, age, country, sex and education.
[d] Spirit is the sum of liquor and aperitifs

Table 3
Odds ratio[a] for mycosis fungoides (MF) according to the combined use of alcohol and tobacco[b]

Total alcohol intake (g alcohol/day)	Tobacco use (pack years)									Total alcohol intake adjusted for tobacco use
	0			1–24			>24			
	Cases *n* (%)	Controls *n* (%)	OR (95% CI)	Cases *n* (%)	Controls *n* (%)	OR (95% CI)	Cases *n* (%)	Controls *n* (%)	OR (95% CI)	OR (95% CI)
0	9 (12)	259 (9)	1.0	–	84 (3)	–	–	79 (3)	–	1.0
1–24	17 (22)	540 (19)	2.24 (0.93–5.35)	6 (8)	376 (13)	1.76 (0.56–5.44)	4 (5)	249 (9)	1.89 (0.52–6.83)	2.71 (1.20–6.13)
>25	12 (16)	436 (15)	1.80 (0.70–4.62)	12 (16)	428 (15)	2.37 (0.87–6.44)	16 (21)	444 (15)	2.86 (1.00–7.59)	3.02 (1.34–6.82)
Tobacco use adjusted for total alcohol intake			1.0			0.91 (0.49–1.68)			1.10 (0.59–2.07)	

[a] Adjusted for centres, age, sex and education. Logistic regression. Results based upon 76 cases and 2899 controls.
[b] The period of interview was from 1995 to 1997.

reference time concerning exposure recordings for the cases and controls. Furthermore, we included potential risk factors that were associated with wine consumption and tobacco smoking among the controls. We used the 'change in estimate principle' to decide whether a variable confounded or not. If a variable changed the effect estimate (OR) more than 10% when excluded from the full model, it was retained in the model.

Effect modification was evaluated by estimating the OR based upon the joint distribution of alcohol and tobacco consumption (Tables 3 and 4).

3. Results

Most study subjects were from Spain (Table 1), where 96% of the cases participated in the study and 100% of the selected hospital controls. The lowest participation rate for the controls was seen in Germany (47%). The mean patient age was 4.32 years (standard deviation (S.D.) = 11.26 years; range 33–71 years). Among cases the male-to-female ratio was 40/36.

Table 2 shows that smoking was not significantly associated with MF. After adjustment for potential confounders, responders with a moderate to high intake of alcohol had an OR above 1. Wine consumption showed no preventive effect and all types of beverages were associated with an increased risk for MF. The analyses presented in Table 2 were similar in males and females and did not differ significantly by centre (Table 3).

Table 3 shows no modifications of effect from smoking according to a multiplicative model. A dose–response association was seen for alcohol intake after adjustment for smoking. The OR also increased slightly for tobacco use adjusted for alcohol intake. A high consumption of tobacco as well as alcohol yielded a significantly increased risk for MF (OR = 2.86; 1.00–7.59; $P = 0.0503$). Similar findings were found for wine intake (Table 4).

4. Discussion

The study showed a positive association between MF and alcohol intake. No protective effect of wine consumption was seen. Apparently, smoking did not increase the risk of MF nor did it modify the effect of alcohol intake.

Table 4
Odds ratio[a] for mycosis fungoides (MF) according to the combined use of wine and tobacco[b]

Wine intake (g alcohol/day)	Tobacco use (pack years)			Wine intake adjusted for tobacco use
	0	1–24	>24	
	OR (95% CI)	OR (95% CI)	OR	
0	1.0	1.93 (0.90–4.10)	0.42 (0.05–3.47)	1.0
1–25	0.41 (0.05–3.33)	1.71 (0.70–4.14)	1.75 (0.43–7.08)	2.41 (1.26–4.63)
>25	0.45 (0.06–3.69)	2.47 (1.0–6.10)	1.25 (0.35–4.45)	1.29 (0.49–3.40)
Tobacco use adjusted for wine intake	1.0	0.92 (0.50–1.70)	1.19 (0.69–2.23)	76 cases/2899 controls

[a] Adjusted for region, age, sex and education. Logistic regression. Results based upon 76 cases and 2899 controls.
[b] The period of interview was from 1995 to 1997.

The alcohol effect did not differ according to the different type of beverage. Since alcohol intake varies across the countries, we evaluated the consumption of each type of beverage in the different countries and found no significant differences in the association ($P = 0.1767$).

Alcohol intake '*per capita*' is high in most of the participating European countries; among the controls, 45% had an alcohol intake above 24 g alcohol/day.

Cigarette smoking and alcohol consumption were self-reported events and may thus be under-reported, especially among cases — which will bias ORs towards unity. In contrast, the lower response rates in the controls compared with the cases may bias the results found for high values if controls with a high intake were less likely to respond. However, this cannot be confirmed. The fact that we did not find that the ORs varied between different regions (which had different response rates) suggests there was little study selection bias relative to the non-responders.

MF is a disease with a long clinical phase and an uncertain onset [9,10]. Lifestyle factors may easily change during this period as a result of the symptoms rather than as a cause of them. For this reason, we only included information 5 years prior to the date of interview.

Most of the cases came from Spain, and only colon cancer controls were available in this centre. If smoking and alcohol intake are risk factors for colon cancer [11], then we would underestimate the associations in the centres. We did find a higher OR for alcohol intake in countries outside Spain (2.13 (95% CI 1.05–5.42) in all other centres, and 1.28 (95% CI 0.84–2.28) in Spain) which indicates that colon cancer may be associated with a high alcohol intake [12–15].

It should be taken into consideration that alcoholic beverages contain other compounds, in addition to alcohol, and for this reason we looked at the estimated effect for the specific beverages. Nothing indicated that the risk for one type of alcoholic beverage differed from the other beverages containing alcohol. The study is, however, small and did not have sufficient power to detect minor to moderate differences. However, the results indicate that the effect may be, at least partly, related to alcohol.

Alcohol is expected to be a risk factor for cancer in organs where intake may produce direct tissue damage, and no possible mechanism underlying an effect on MF is known or suspected. However, high alcohol concentrations may cause liver damage which could impair the metabolism of carcinogens and may be correlated with poor dietary habits.

In any case, alcohol cannot be a risk factor that operates alone, and further research should be conducted in an attempt to identify the small subgroup of people who may be susceptible to this exposure.

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Appendix

The European study group on occupational causes of rare cancers

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