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Tobacco smoking and alcohol consumption as risk factors for thymoma – A European case-control study

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Abstract

Purpose

Hardly anything is known about the aetiology of thymoma. This paper presents data regarding tobacco smoking and alcohol consumption in relation to thymoma from the first case-control study performed on this rare tumour.

Methods

A European multi-centre case-control study including incident cases aged 35–69 years with thymoma between 1995 and 1997, was conducted in seven countries. A set of controls, used in seven parallel case-control studies by the same research group was used, including population-based controls from five countries and hospital controls with colon cancer from two countries. Altogether 103 cases, accepted by a reference pathologist, 712 colon cancer controls, and 2071 population controls were interviewed.

Results

Tobacco smoking was moderately related with thymoma (OR 1.4, 95% CI 0.9–2.2), and a tendency to dose-response was shown ($p = 0.04$), with an increased risk for heavy smokers defined as ≥41 pack-years (OR 2.1, 95% CI 1.1–3.9). A high consumption of spirits defined as ≥25 g of alcohol per day was associated with an increased risk of thymoma (OR 2.4, 95% CI 1.1–5.4), whereas no association was found with beer or wine.

Conclusions

Tobacco smoking and a high intake of spirits were indicated as risk factors for thymoma.

1. Introduction

Thymomas are rare tumours originating from thymic epithelial cells, i.e. from the thymus. Thymomas are most often encapsulated benign tumours, but must always be regarded as potentially malignant with possibility of invasiveness, metastatic spread and recurrences. The most common site for metastases is pleura. Some of them are obviously well differentiated carcinomas. The WHO classification separates five categories: medullary, lymphocyte-rich, cortical, mixed, and well differentiated thymic carcinomas [1,2]. The incidence of thymoma in Europe and in the USA is approximately 0.1-0.3 per 100 000 in males and females. Most cases occur between 40 and 60 years of age [3,4]. Thymus is an important part of the immune system, and there is a well-known

association between thymoma and autoimmune disease, especially myasthenia gravis, recently iterated in a study of 85 cases of thymoma [5]. However, thymoma is considered as the causal factor of these disorders, with disappearing of symptoms if the tumour is operated.

Very little is known about the aetiology of thymoma. EBV infection has been reported as a suspect risk factor for thymic carcinomas in some studies as reviewed by Sweeney et al. [3], also including reports that the EBV genome is present in thymomas occurring in Chinese patients. A Japanese report describes a case of suspected causal relationship between HTLV-1 carrier state and thymoma [6]. Furthermore, a case of thymoma among 49 different tumours in a group of patients with HIV infection is reported from Italy [7]. In a register study from England and Wales, not separating thymomas from thymic carcinomas, a birth cohort analysis showed the lowest risk for persons born during the Second World War [8]. Irradiation may be of etiologic interest shown by some reports of synchronous thyroid and thymic malignancy following childhood irradiation [9]. Very few papers report anything about chemical exposures and thymoma. Animal studies have shown that vinyl carbamate may induce thymomas if administered in the first weeks after birth [10]. One case report describes a case of thymoma in a worker exposed to fluorocarbons in an automobile plant [11]. A case series from France with 37 patients with thymic carcinoma showed that half of them (19/37) were smokers, indicating tobacco as a possible risk factor [12].

Since very little is known about risk factors, we performed the first case-control study on this disease, focusing upon life-style factors and occupational exposures. In this paper we present data regarding tobacco and alcohol consumption in relation to thymoma.

2. Material and methods

This study was a part of a large multi-centre case-control project conducted in ten European countries and including seven different rare tumours, among them thymoma, using a large common control group for all the different tumour sites. The project, which has been described in detail in earlier reports [[13], [14], [15], [16]], aimed at including enough cases of the rare tumours investigated by a multi-national effort.

In the thymoma study, cases and controls from the following regions in seven countries were included: Denmark (the whole country); Sweden (Umeå, Örebro/Uppsala, Linköping, Lund); France (Calvados, Côte d´Or, Doubs, Hérault, Isère, Manche, Bas-Rhin, Haut-Rhin, Somme, Tarn); Germany (Hamburg, Bremen, Essen, Saarland), Italy (Torino, Firenze, Padova); Spain (Valencia/Navarra, Pais Vasco); Portugal (Lisboa, Porto). The population of the participating regions of these countries are approximately five million, five million, six million, four million, three million, six million and four million, respectively. Cases of thymoma were also recruited in Latvia and Lithuania, but it was not possible to obtain a sufficient recruitment of cases in these countries, and thus these cases and their corresponding controls were excluded from the analyses.

Incident cases of thymoma in patients aged 35–69 years in these regions were included in a two-year period during 1995–1997, with the exact time somewhat differing between the countries participating [15]. Thus, only newly diagnosed cases were included, no prevalent cases. Case inclusion was ascertained through repeated requests to hospital and pathology departments and/or by frequent screening of cancer and pathology registers. We only included areas where we considered it possible to get a very good coverage of new cases, but of course single cases may have been missed.

All epithelial tumours of thymic origin were included in this study. All histologically verified cases with topography code C37.9 according to ICD-O 1990, and with morphology code 8580/0-8580/3,

were accepted for a centralised pathological review [17]. One reference pathologist (PJ), blinded with respect to exposure status, reviewed a representative HE-stained histological slide together with the report from the local pathology department for all cases. The purpose of review was to secure a uniform morphologic assessment. The reviewed material, often only one HE-stained section, did not allow discrimination between a benign versus a malignant tumour. All cases accepted as "definite" were epithelial thymic tumours. Cases accepted as "possible" were either cases where the slide showed carcinoma, but origin from the thymus could not be proved, or cases with a pathology report classified as "definite" or "possible" with respect to the likeliness of thymoma, where sections were not available. Cases not fulfilling these criteria were excluded.

Population controls were randomly selected from population registers or electoral rolls except for Spain and Portugal, where hospital controls with a diagnosis of adenocarcinoma of the colon were used. The controls were frequency matched with all cancer cases selected in the seven parallel case-control studies, within five years age strata by sex and region. The goal was to select at least four times as many controls as the number of the most common tumour type in each stratum, and this was performed by random selection every three to six months during the study period through the case inclusion period. Since the control groups for all seven cancer types were pooled for the analyses of each cancer type to obtain the best possible precision, a control-case ratio much higher than four was obtained in the thymoma study. This was particularly true for men since two of the other rare cancers studied (gall bladder and breast cancer) were restricted to men. For the same reasons the control group included a larger proportion of younger subjects reflecting the pooling of controls selected for seven different rare cancers of which some were more frequent among the younger population than was the case for thymoma. In Spain and Portugal, hospital controls with a diagnosis of adenocarcinoma of the colon were selected from the same hospitals as the cases, and matched for age and sex. If the index person was dead or too ill to participate, next-of-kin was interviewed if possible [18].

2.1. Exposure assessment

All reported incident cases and all selected controls were approached by mail or telephone, and all who agreed were contacted further. To collect exposure data, interviews were done by specially trained interviewers, face-to-face or by telephone, by means of a highly structured questionnaire. This was developed in co-operation between the different centres, originally written in English and then translated to the different national languages (Danish, Swedish, French, German, Italian, Spanish, Portuguese). The questionnaires included information on socioeconomic and demographic status, life style factors, reproductive and medical history and a detailed occupational history. Questions on lifestyle addressed tobacco smoking and alcohol consumption. Regarding smoking, all subjects were questioned regarding status as current smoker, ex-smoker or never-smoker. A person who quitted smoking within the same age or minus one year of age compared to the age at time of interview was regarded as a current smoker, since disease related factors could have influenced the quitting for that person. Thus, if interviewed at the age of 50 the subject must have quitted smoking by the age of 48 or earlier to be regarded as an ex-smoker. Smoking history was expressed as the cumulative amount of smoking ('pack-years' = number of years as a smoker x number of cigarettes per day/20). The quantity for current smokers was based on the consumption five years ago, whereas for ex-smokers the consumption at the time they were smoking was typically asked for. One cigar was counted as equivalent to five g of tobacco. For hand-rolled cigarettes, cigars, and pipe tobacco, 1 g of tobacco was counted as equivalent to one cigarette. Questions on alcohol consumption asked for the average daily intake of specific types of alcohol five years before the interview. The total daily alcohol intake was computed from the average alcohol content per litre of each beverage: beer, 40 g; wine, 94 g; aperitif, 145 g; liquor, 317 g. Since alcohol habits differ

substantially between countries, e.g., vine versus beer predominance, we also analysed alcohol per country.

2.2. Statistical methods

Adjusted odds ratios (ORs) were obtained by unconditional logistic regression analysis. All models included country (seven categories), year of birth, sex and in the alcohol analyses also tobacco smoking status (two categories). Year of birth was used as a continuous variable [19]. Further adjustment for level of education (two categories) as a proxy of social status, alcohol consumption and body mass index (BMI) (both variables as three categories), as well as a more detailed adjustment for region, did not change the ORs and these adjustments were not included in any of the final models [20].

We used 0–24 g alcohol (corresponding to two drinks) per day as the reference level for total alcohol intake, because non-drinkers were few and differ from the population at large in Europe with respect to other factors (e.g. lifestyle and social factors). For analyses of trend we introduced continuous exposure variables into the models. Due to the small numbers in Table 4 we repeated the analyses using an exact test for stratified analyses (StatXact). This method only allowed for stratification by country (seven levels), year of birth (three levels), and sex. These additional analyses did not change the results significantly, and thus, we have only presented the results from the unconditional logistic regression models. Re-running all the analyses with the exclusion of the colon cancer controls, together with the Spanish and Portuguese cases, did not change these estimates by 10% or more (data not shown).

The study was approved by the Ethic Committees in each of the participating countries or regions.

3. Results

In total, 120 thymoma cases were recruited from seven countries (Sweden, Denmark, France, Germany, Italy, Spain, and Portugal), Table 1. Five of these cases (4%), however, were judged as not eligible by the reviewing pathologist and were excluded from analyses. Of the 115 remaining cases, 93 were classified as "definite" and 22 as "possible". In the latter category the main part, 12, were cases with a definite histopathologic report but without any available slide to review because of refusal from the local pathologist. In seven cases both the report and slide were regarded as possibly thymoma, and in three cases the report indicated that it was possibly a thymoma but the slide was not available.

Table 1. Recruitment of cases with thymoma and controls by country.

	Cases					Controls		
	Identified	Pathology review		Interviewed		Eligible	Interviewed	
	N	Definite[1]	Possible[2]	Yes	No	N	Yes	No
Country								
Denmark[3]	13	9	2	10 (91%)	1 (9 %)	583	320 (55 %)	263 (45 %)
Sweden[3]	14	14	0	10 (71 %)	4 (29 %)	407	230 (57 %)	177 (43 %)
France[3]	26	19	6	25 (100 %)	0 (0 %)	630	485 (77 %)	145 (23 %)
Germany[3]	11	11	0	11 (100	0 (0 %)	1325	733 (55 %)	592 (45 %)

	Cases					Controls		
	Identified	Pathology review		Interviewed		Eligible	Interviewed	
	N	Definite [1]	Possible [2]	Yes	No	N	Yes	No
Country								
Italy [3]	26	21	3	21 (88 %)	3 (12 %)	405	303 (75 %)	102 (25 %)
Spain[4]	20	11	9	19 (95 %)	1 (5 %)	580	579 (99 %)	1 (1 %)
Portugal[4]	10	8	2	7 (70 %)	3 (30 %)	138	133 (96 %)	5 (4 %)
Total	120	93 (78 %)	22 (18 %)	103 (90 %)	12 (10 %)	4068	2783 (68 %)	1285 (32 %)

1 Definitely a case according to strict morphological criteria.

2 Possibly a case according to strict morphological criteria.

3 Population controls.

4 Colon cancer controls.

There was no interview performed in twelve of the 115 included cases. Ten of these refused to participate, one could not be found at the given address and one was dead and no next-of-kin to interview was found. Of the 103 performed interviews, 99 were done with the patient and four were surrogate interviews (spouse 2, child 1, friend 1). The participation rate among cases was 90%, with a range between 70% in Portugal to 100% in France and Germany.

Data on smoking was missing for 10 controls. One person from Spain stopped smoking age 77 but was only 64 years old – we assumed he has just stopped. For each of the four types of alcohol grams alcohol per day were missing for beer (1 case, 15 controls), wine (1 case, 15 controls), liquor (1 case, 16 controls) and aperitifs (1 case, 15 controls).

A total of 4068 controls were selected and among them the interview with the index person was completed for 2688, and with a surrogate person for 95, constituting a total participation of 2783 (68%) among controls, with a variation from 55% in Denmark and Germany to 99% in Spain, Table 1.

The interviews were conducted face-to-face (68%), by telephone (31%) or a combination

(1%). The mean time from diagnosis to interview for cases was 7.8 months.

Sociodemographic and physical characteristics of the cases and controls are shown in Table 2. Age at the time of interview and maximum body mass index (BMI) did not differ between cases and

controls. Cases were with a slightly higher frequency married (85% versus 80%), and more cases than controls were classified as having low educational status (44% versus 38%).

Table 2. Sociodemographic and physical characteristics of 103 cases with thymoma and 2783 controls.

Characteristics	Cases		Controls	
	No.	Percentage	No.	Percentage
Responders:				
Gender, male	55	53	1885	68
Age at 1.1.1995				
35-49 years	33	32	1010	36
50-59 years	34	33	810	29
60-69 years	36	35	963	35
Mean age at 1.1.1995, years	54.5	–	53.4	–
Age at interview				
35-49 years	29	28	883	32
50-59 years	34	33	729	26
60-69 years	40	39	1171	42
Mean age at interview, years	56.3	–	55.5	–
Surrogate interviews	4	4	95	3
Marital status				
Married or living with a partner	87	85	2230	80
Educational status				
Low [1]	45	44	1054	38
Maximum BMI [2], ever had	27.0	–	27.3	–
Non-responders:				
Gender, male	6	50	900	70
Age at 1.1.1995				
35-49 years	2	17	485	38
50-59 years	6	50	354	27
60-69 years	4	33	446	35
Mean age at 1.1.1995, years	57.0	–	53.0	–

1 Left school at the age of 15 years or earlier, no further education.

2 Maximum body mass index ever had (but except the last 12 months before the thymoma).

There was a tendency to an increased risk for thymoma both among subjects who had ever smoked (OR 1.4, 95% CI 0.9–2.2), and among current smokers as defined above (OR 1.5, 95% CI 0.9–2.6), Table 3. Subjects who had quitted smoking showed only a slight risk increase. A dose-response relationship was suggested regarding total smoking quantity, with an increased risk in the highest

exposure category (≥41 pack-years) yielding OR 2.1 (95% CI 1.1–3.9), and a significant trend (p = 0.04). Total years of smoking >20 without regard to quantity gave an OR 1.6 (95% CI 1.0–2.6). We also found that smoking > 10 cigarettes per day five years ago without regard to number of years gave an OR 1.6 (95% 1.0–2.7). Sub-analyses of tobacco use before and after adjustment for alcohol consumption did not change the size of the OR for smoking as a risk factor for thymoma.

Table 3. Odds ratio (OR) and 95% confidence interval (95% CI) for thymomas according to smoking habits, results from a multivariate logistic regressions analysis.

Smoking [1]		**Cases**	**Controls**	**Adjusted**[2] **OR**	**95% CI**
		No.	**No.**		
Never smoked tobacco		40	1064	1.0	–
Ever smoked tobacco		63	1709	1.4	0.9-2.2
Current smoker		34	874	1.5	(0.9-2.6)
Ex-smoker		29	835	1.3	(0.7-2.2)
Years of smoking					
	1-20	15	473	1.3	(0.7-2.4)
	21+	48	1197	1.6	(1.0-2.6)
Smoking quantity 5 years ago[3]					
(cigarettes per day)	1-10	21	568	1.3	(0.8-2.3)
	11+	42	1106	1.6	(1.0-2.7)
Smoking quantity					
(pack-years)[4]	0	40	1113	1.0	–
	1 - 20	28	764	1.4	0.8-2.4
	21 - 40	18	533	1.4	0.8-2.5
	≥41	17	373	2.1	1.1-3.9

1

Never smokers are used as reference for all odds ratios, except for age at starting smoking included in “years of smoking”. Data on smoking was missing for 10 controls. One person from Spain stopped smoking age 77 but was only 64 years old – we assumed he has just stopped.

2

Adjusted for country, age and sex.

3

OR for thymoma according to smoking quantity five years before the interview, or when smoking for ex-smokers, compared with never smokers.

4

Test for trend, p = 0.06.

Alcohol consumption, when considering beer, spirit and wine combined, did not yield any increased risk for thymoma, Table 4. When separated, however, a high intake of spirits (≥ 25 g of alcohol per day) was associated with a statistically significant risk, OR 2.4 (95% CI 1.1–5.4), although based on few exposed cases in this category. Analysed per country, five out of seven countries show an increased risk for this exposure group. No increased risks were seen for beer or wine.

Table 4. Odds ratio (OR) with 95% confidence (95% CI) intervals for thymoma according to drinking habits by country[1].

		All subjects		OR (95% CI)							
Alcohol		**Cases, N**	**Controls, N**	**Denmark**	**Sweden**	**France**	**Germany**	**Italy**	**Spain**	**Portugal**	**All**
Alcohol total [2]	0 – 24	55	1384	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
(grams / day)	25 – 36	28	774	1.3 (0.3-5.5)	0.6 (0.1-4.7)	0.9 (0.3-2.4)	0.8 (0.2-3.3)	1.1 (0.3-3.7)	1.1 (0.4-3.1)	5.2 (0.7-37)	1.0 (0.6-1.7)
	> 37	20	625	1.8 (0.3-11.9)	–	0.7 (0.2-2.4)	0.4 (0.1-3.4)	2.0 (0.6-6.6)	0.7 (0.2-3.0)	1.1 (0.1-12.7)	0.9 (0.5-1.6)
Beer [2]	0	46	1046	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
(grams alcohol /day)	1 – 24	47	1358	0.4 (0.1-2.0)	0.8 (0.2-3.3)	1.5 (0.6-3.9)	0.4 (0.1-1.6)	1.2 (0.5-3.2)	1.0 (0.4-2.7)	1.6 (0.2-11.6)	1.0 (0.6-1.5)
	> 25	10	379	1.0 (0.1-8.1)	–	3.1 (0.8-11.6)	0.3 (0.1-2.4)	–	0.3 (0.1-2.9)	2.1 (0.2-23)	0.9 (0.4-1.9)
Spirit [2]	0	43	1080	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
(grams alcohol /day)	1 – 24	52	1604	0.4 (0.1-1.6)	1.1 (0.3-4.6)	0.8 (0.3-1.9)	0.5 (0.2-2.0)	1.0 (0.4-2.8)	1.7 (0.6-4.7)	0.9 (0.1-6.0)	0.9 (0.6-1.4)
	> 25	8	99	–	–	2.0 (0.2-18.6)	3.4 (0.4-33)	4.0 (0.9-18.7)	2.1 (0.2-19.3)	5.8 (0.5-64)	2.4 (1.1-5.4)
Wine [2]	0	29	713	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
(grams alcohol /day)	1 – 24	61	1752	0.5 (0.1-2.4)	1.2 (0.2-6.2)	0.7 (0.2-1.7)	0.4 (0.1-1.3)	1.2 (0.3-4.9)	1.0 (0.3-2.9)	0.8 (0.1-8.3)	0.8 (0.5-1.2)
	> 25	13	318	–	–	0.2 (0.1-1.4)	–	3.7 (0.7-18)	0.7 (0.1-4.2)	0.7 (0.1-18)	0.8 (0.4-1.7)

1

Adjusted for country, age, sex, and smoking status.

2

Missing information on grams alcohol /day for each of the 4 types of alcohol: beer missing information for 1 case, 15 controls, wine for 1 case, 15 controls, liquor for 1 case, 16 controls, aperitifs for 1 case, 15 controls.

4. Discussion

To our knowledge, no previous epidemiological studies have been made focusing on potential risk factors for thymoma. As a consequence, there are hardly any hypotheses regarding aetiologic factors of importance for this tumour. The obvious reasons for this lack of research concern the rarity of the disease and the heterogeneous pathology with a range from clearly benign tumours through potential malignant thymomas to thymic carcinomas.

The advantage of this study is the large number of histologically verified incident thymoma cases, which has been facilitated by the multi-national co-operation of this project. The participation of seven geographically separated European countries, with different climate, traditions and life style, made it possible to judge the consistence of our findings regarding risk factors.

Since the participation rate for the cases (90%) is better than the corresponding rate of 68% for the controls, selection bias cannot be ruled out. However, almost no differences were seen regarding gender or age between responding and non-responding cases or controls, Table 2. Furthermore, the associations found were rather similar in different countries regardless of participation rate.

Recall bias as a consequence of the use of population controls compared to cases with a tumour disease seems not particularly probable since the associations regarding tobacco smoking and spirits are not seen for beer or wine. Furthermore, no striking differences are seen between the results in Spain and Portugal, using colon cancer controls, compared with the countries using population controls.

Furthermore, in a methodology paper we have described the outcome for colon cancer versus population controls in our series of studies on rare cancers, including thymoma [21]. With controls frequency matched by gender and 5-year age groups, the colon cancer patients had a higher alcohol intake but similar tobacco smoking. This may slightly underestimate the risk for thymoma related to alcohol intake, which thus may be somewhat greater than we have found.

Since no documented risk factors exist for this tumour it is difficult to control for potential confounding.

Tobacco smoking was suggested as a risk factor for thymoma in this study. The association is strengthened by the finding of the highest risks in the highest exposure categories regarding years of smoking, smoking quantity five years before interview and total smoking quantity ("pack-years"). For the latter variable a dose-response tendency was shown.

Since the thymomas are very rare, there is not a special preventive impact of the findings, but they are of scientific interest. A wide variety of epithelial tumours are known to be associated with tobacco smoking, e.g., cancer in the lungs, larynx, oesophagus, urinary bladder, kidneys and pancreas. Thymomas as well represent tumours with epithelial origin and it is not far-fetched that also this kind of tumour may be influenced by the many different carcinogenic substances that are identified in tobacco, even if it is difficult to speculate further regarding the closer mechanisms.

Alcohol consumption overall was not a risk factor for thymoma in this study. However, when only considering spirits we found a more than doubled risk for heavy consumers, defined as ≥ 25 g of

alcohol per day. With the exception of Denmark and Sweden, where no cases were exposed in the highest category, all countries showed an increased risk in this respect, which strengthens the possibility of a true etiologic association.

The mechanisms that may explain the finding of a relation between spirits and thymoma are also quite unknown. Since no effect was demonstrated by wine or beer, however, some other factor in spirits than alcohol may play a role. An unknown confounding factor could also be responsible for the finding. Other lifestyle exposures, medical conditions, occupational exposures or a genetic susceptibility may as well, in combination with tobacco or spirits, play a role for development of thymoma, which may be the focus for further studies [22].

Since no other studies so far have been performed on aetiologic factors in thymoma the findings in this investigation must be regarded as not more than hypothesis generating.

In conclusion, this is the first analytical epidemiology study ever published on thymoma, and the associations with tobacco smoking and spirit consumption must therefore be interpreted with some caution.

Contribution

Study concepts: M.E., L.K., N.A., W.A., P.G., F.M., M.M.S.-V., S.S.

Study design: M.E., L.K., N.A., W.A., P.G., F.M., M.M.S.-V., S.S.

Data acquisition: All

Quality control of data and algorithms: M.E., L.K.

Data analysis and interpretation: M.E., L.K., N.A., W.A., P.G., F.M., M.M.S.-V., S.S.

Statistical analysis: M.E., L.K.

Manuscript preparation: M.E., L.K.

Manuscript editing: All.

Manuscript review: All.

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Appendix A

The European Study Group on Occupational Causes of Rare Cancers

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