Multivariate analysis of risk factors for testicular cancer: a hospital-based case-control study in the Czech Republic

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Growing incidence of testicular cancer around the world stimulates research attempting to explain the trends. This study quantified the contribution of different types of potential risk factors for testicular germ-cell cancer (TGCC) with differentiation between seminoma and non-seminoma.

A standardized questionnaire containing demographic data, pre- and perinatal factors, social, lifestyle and occupational parameters was prepared. The data file consists of n = 356 TGCCs (seminoma: n = 195; non-seminoma: n = 161) and n = 317 controls, frequency matched on age to cases. The following factors were significantly associated with the risk of TGCCs in univariate analyses (ORs): atrophic testis (5.3), smoking over 12 pack-yr (4.9), cryptorchidism (2.9), testicular trauma (2.0), birth weight under 3,000 g (1.6), low degree of education (3.0) in correlation with manual occupation (2.3) and finally, overall familial cancer history (1.5) and familial history of breast (1.8) and prostate cancer (3.9). On the other hand, maternal age over 20 yr (OR < 0.4) and moderate recreational sport activity (OR = 0.5) significantly reduced the risk of TGCCs. A significant risk was associated with cryptorchidism (OR = 2.9; 95% CI = 1.5 – 5.9) where orchidopexy was delayed after 5 yr of age (OR = 5.2; 95% CI = 1.5-18.1). Delayed orchidopexy was associated namely with the risk of seminomas (OR = 7.5; 95% CI = 2.1-26.7). Only some of the variables were retained in multivariate model for TGCCs as well as for histological subtypes (multivariate adjusted OR for all TGCCs): atrophic testis (5.9), family history of prostate cancer (4.8), cryptorchidism (3.8) and interaction term 'low degree of education & manual occupation' (3.0). Familial history of breast cancer elevated risk of TGCCs and of seminomas (OR: 2.01 – 2.18). Birth weight under 3,000 g was retained in a multivariate model for TGCCs with a borderline significance (OR = 1.67). We could not rule out any type of risk factors, as each one was significantly represented in the final multivariate models. Familial cancer history remained to be an influential risk factor, altogether with some lifestyle and occupational parameters. This suggests that both environmental exposures and genetic inheritance can play role in the moderation of the risk of TGCC.

Keywords: testicular cancer, risk factors, case-control study

Testicular cancer (TC) is the most frequent malignancy in young men, mostly diagnosed from 20 to 45 years of age. These neoplasms represent a diverse group with dominant occurrence of testicular germ cell cancers (TGCC; 95% of all TC). TC incidence has increased significantly around the world in the past few decades [1–3]. Recent trends in the Czech Republic also suggest an increase in TC age-standardized incidence rate (by 22.4% in the period 1995 – 2004; [4]).

The growing incidence stimulates epidemiological research that attempts to explain the trends. Although many studies focused on risk factors for TC, the aetiology of this cancer remains largely unknown and future research is suggested [5, 6]. Only a few risk factors for TC are consistently established, including cryptorchidism, carcinoma *in situ* and exposure to estrogen *in utero* [7]. Although the exact mechanisms are still not known, many studies proved critical importance of pregnancy and prenatal characteristics for the development of TC [8–11]. Of course, many other factors affecting the individual's later life may also play a role in the aetiology of TC; however, the evidence is still unclear or even conflicting in different studies.

Our study attempts to contribute to the current discussion on aetiology of TC [5, 6, 12]. We seek to quantify the contribution and mutual interactions of very different types of

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potential risk factors for TGCCs with further differentiation between seminoma and non-seminoma. The risk power of hereditary, pre- and perinatal factors – in combination with a wide range of social and lifestyle factors – is assessed, using data from epidemiologically well-defined Czech population.

Patients and methods

Parameters, subjects and data. For the purpose of this study, we prepared a standardized questionnaire containing demographic data and a complex set of risk factors including maternal health, pre- and perinatal factors, social parameters, personal lifestyle and occupational history. The key parameters identifying the TGCC patient are as follows: diagnosis (coded according to the International Classification of Diseases, ICD-10), date of diagnosis, age at diagnosis, cancer location and histology, TNM classification and staging [13]. The type of TGCCs was binary classified as pure seminoma and as other histological type, coded as non-seminoma. The latter group thus includes also tumors with mixed histology. The questionnaires were always filled in with the assistance of an experienced physician. The histological types were additionally extracted from pathology reports and hospital information systems. If needed, the characteristics of the patient's health history were verified using his health care documentation. All participants were asked to give permission for the anonymous processing of collected data.

The questionnaires were digitized using an on-line database where data can be used for further clinical and epidemiological research. The validity of the registry can be regarded as high due to double digitization and subsequent control of key variables. Criteria for the exclusion of a record from the analysis were as follows: incorrect or insufficient identification of cancer (12 cases), missing information on important covariates (18 cases, 6 controls) or another inconsistency in parameters (24 cases, 13 controls). Additionally, 2 cases with TC of non-germ cell type were excluded. The study was also strictly limited to men whose parents were known and described in terms of age, health status and cancer burden in order to eliminate bias in the familial risk analysis. After applying all inclusion/exclusion criteria, the resulting file consists of n = 356 TGCCs and n = 317 matched controls.

Participants were recruited in two important Czech cancer centers – Thomayer University Hospital in Prague (181 cases, 191 controls) and Masaryk Memorial Cancer Institute in Brno (175 cases, 126 controls). Testing for effects of participating centers revealed no significant difference in recruitment frequency, histological types of TC and in age distribution of cases and controls (data not shown). All participants were Caucasians. Cases were diagnosed with primary TGCC in the period 2000 – 2006 (aged 18 – 64 yr at the time of diagnosis). The age of parents was not limited. Controls were men with verified health status, frequency matched on age to cases. Controls were recruited among blood donors, among healthy persons accompanying the patients (not relatives) and partially among hospital personnel. The recruitment of controls was facilitated by quoting the age groups. The quoting was partially skewed to include adequate number of men younger than 24 years in order to reach comparable age distribution with cancer cases. The control recruitment was fully random within each age stratum. The recruitment took place in the period of 01/2005 – 01/2007.

Statistical data analysis. All analyses were carried out separately for TGCCs and for seminomas and non-seminomas. For each histological group, we carried out exactly the same set of analyses as for all cancer cases. The risk factors were coded as binary variables and if necessary, the quantitative factors were categorized according to quartiles in their sample distribution. Frequency analysis or robust summary statistics (median, percentiles) were used to summarize values of examined variables. Standard univariate statistical techniques were used to test the differences between groups of patients and controls, ML chi-square test for ordinal variables and Mann-Whitney U test for continuous variables. One-way ANOVA model was applied to compare means of quantitative variables among histological subtypes of TGCCs and controls.

Unconditional logistic regression was used for all analyses. All univariate models were adjusted only for age of men as the matching variable (age taken as continuous variable). Only model for smoking intensity quantified as pack-years was further adjusted for years since quitting. Estimated odds ratio (OR) was supported with 95% confidence intervals (CI). The significance tests were always two-sided, based on the likelihood ratio test [14]. In the case of categorized quantitative variables, the test for linear trends was performed taking median of each category and performing logistic regression evaluated by Wald's χ^2 statistics. The same statistics was applied in the heterogeneity test based on multinominal logistic regression comparing histological subtypes with controls for groups defined by risk factors [15]. In addition to age as adjusting variable, multivariate ORs were adjusted for all the variables entering the model. It ensured that the outcome from multivariate regression measured the effect of a particular parameter, after adjusting for all important attributes. The significance of interaction terms in the multivariate models was successively tested comparing log-likelihood difference between models with and without the terms. Significant and contributing interactions were incorporated as independent variables.

All p values were derived from two-tailed testing with universal limit 0.05 for the statistical significance. In agreement with many previous studies, we decided to present the original outcomes without additional corrections for multiple comparisons. Instead of it, achieved ORs were correctly sorted according to level of significance and borderline significance was carefully interpreted. The study was also supported by prospectively optimized power analysis. It ensures 85% power to detect and odds ratio of 2.0 or more for factors with a prevalance of 5% and 90% power to detect OR of 2.0 or more for factors with a prevalence of 10%.

Table 1. Distribution of the matching variables and social covariates among TGCCs and controls

	All TGCC cases (N = 356)		**Controls** (N = 317)		**Seminoma cases** (N = 195)		**Non-seminoma cases** (N = 161)	
Age group (years)								
18-24	39	(11.0 %)	36	(11.4 %)	11	(5.6 %)	28	(17.4 %)
25-29	77	(21.6 %)	88	(27.8 %)	33	(16.9 %)	44	(27.3 %)
30-34	74	(20.8 %)	81	(25.6 %)	39	(20.1 %)	35	(21.8 %)
35-39	59	(16.6 %)	40	(12.5 %)	37	(19.0 %)	22	(13.7 %)
40-44	48	(13.5 %)	31	(9.8 %)	33	(17.0 %)	15	(9.3 %)
45-49	24	(6.7 %)	18	(5.7 %)	19	(9.7 %)	5	(3.1 %)
50-54	25	(7.0 %)	14	(4.3 %)	19	(9.7 %)	6	(3.7 %)
55-59	6	(1.7 %)	6	(1.9 %)	2	(1.0 %)	4	(2.5 %)
60-64	4	(1.1 %)	3	(1.0 %)	2	(1.0 %)	2	(1.2 %)
p level[2]		*p = 0.384*				*p = 0.001*		
Living place								
Village	131	(36.8 %)	61	(19.2 %)	77	(39.5 %)	54	(33.5 %)
Small town	126	(35.4 %)	104	(32.8 %)	69	(35.4 %)	57	(35.4 %)
Big town (city)	99	(27.8 %)	152	(48.0 %)	49	(25.1 %)	50	(31.1 %)
p level[2]		*p < 0.001*				*p = 0.375*		
Education								
Primary/skilled	130	(36.5 %)	50	(15.8 %)	70	(35.9 %)	60	(37.3 %)
Secondary	152	(42.7 %)	190	(59.9 %)	77	(39.5 %)	75	(46.5 %)
University	74	(20.8 %)	77	(24.3 %)	48	(24.6 %)	26	(16.2 %)
p level [2]		*p < 0.001*				*p = 0.296*		

Legend to Table 1.
[1]Main lifetime living place [2]Significance of ML-χ^2 test for differences between TGCCs and controls or between seminoma and non-seminoma cases

Table 2. Distribution of age, histological types and clinical stages in the Czech National Cancer Registry (NCR) and in the examined sample of TGCCs

Variables and categories	**NCR** (Diagnostic period 2000 – 2004)			**Examined TGCCs** (Diagnostic period 2000 – 2006)		
	All TGCCs	**Seminoma**	**Non-seminoma**	**All TGCCs**	**Seminoma**	**Non-seminoma**
No. of cases	1924	1077	847	356	195	161
Prevalence of clinical stages						
I	60.3 %	65.6 %	53.7 %	60.9 %	67.2 %	53.4 %
II	18.0 %	17.5 %	18.8 %	24.7 %	22.0 %	27.9 %
III	15.1 %	9.8 %	21.7 %	14.3 %	10.8 %	18.6 %
Unknown	6.5 %	7.1 %	5.8 %	–	–	–
Prevalence of T categories						
T0	0.3 %	0.2 %	0.4 %	0.3 %	0.5 %	0 %
T1	63.1 %	65.5 %	60.2 %	67.7 %	69.7 %	65.2 %
T2	22.3 %	20.0 %	25.3 %	23.8 %	20.5 %	27.9 %
T3	11.2 %	11.0 %	11.5 %	8.1 %	9.2 %	6.8 %
Tx	3.1 %	3.3 %	2.7 %	–	–	–
Age at diagnosis (years)						
Mean	35	39	31	34	37	31
Median	34	38	29	33	37	29
25/75[th] percentile	27/41	31/45	24/35	27/40	29/42	25/36
10/90[th] percentile	21/55	25/57	19/48	23/48	25/49	22/43

Results

The Table 1 documents the age distribution as matching variable between cases and controls. The case (control) series had a mean age of 35 yr (34 yr) and a median of 33 yr (32 yr). The age statistics of the histological subtypes is calculated in Table 2. On average, non-seminoma cases were younger than seminoma cases (mean age 32 yr and 37 yr).

Among TGCC patients, there appeared to be a significantly increased prevalence of men with low degree of education (pri-

mary or skilled) than controls. There was also a significant asymmetry in the type of living place between TGCCs and controls, the latter living more frequently in big towns. Neither education nor type of living place appeared to affect the distribution between seminomas and non-seminomas (Table 1).

All relevant risk factors from the questionnaire were listed in Table 3. All factors were retained in the analyses provided that they occurred in at least one TGCC case. Nevertheless, some variables were strongly limited in their discrimination potential due to very low prevalence (diseases in personal health history, hereditary defects, etc.) or, on the other hand, due to ubiquitous occurrence (declared vegetable and fruit consumption, dietary fat preferences).

The Tables 4–6 document a complex set of univariate logistic regression-derived odds ratios (ORs) with 95% confidence intervals. Only associations that reached minimum level of significance ($p < 0.05$) were listed according to the type of variable (maternal and reproductive health history in Table 4, social and lifestyle factors in Table 5 and family cancer history in Table 6).

As for the reproductive history and health-related factors (Table 4), we found elevated ORs among men with positive history of cryptorchidism, atrophic testis and declared testicular trauma. Newborns with low birth weight (< 3,000 g) revealed only borderline significance of risk for TGCCs and for seminomas. Maternal age in all categories above 20 yr of age significantly reduced risk of the development of TGCCs. The protective effect of maternal age > 20 yr was slightly more pronounced in non-seminomas than in seminomas but without significant difference (p of trend test > 0.173, p of heterogeneity test = 0.202). The significant risk association of cryptorchidism (OR = 2.94; 95% CI = 1.46 – 5.91) further increased when the time of orchidopexy was taken into account. The cut-off time was identified at 5 years, orchidopexy after 5 yr of age achieved highly significant OR = 5.24 (95% CI = 1.52-18.12). Odds ratio for seminomas was significantly elevated among the cryptorchidic men with orchidopexy after 5 yr of age (OR = 7.47, 95% CI = 2.09 – 26.66) while this risk factor was not significant for non-seminomas (OR = 2.66, 95% CI = 0.58 – 12.10) (Table 4). No significant risk was detected in hypospadia, phimosis, epidydimitis, orchitis and other diseases in the men's health history.

Among examined dietary factors, only smoking reached significantly elevated ORs for the whole group of TGCCs, as well as for seminomas and non-seminomas (Table 5). Neither categorized smoking history nor adjusted pack-years contributed to the discrimination between histological subtypes (p of the heterogeneity test ranged from 0.199 to 0.594). Smoking history reached weak significance, separating only pure non-smokers from both former and active smokers. Quantified pack-years appeared to be a more sensitive risk indicator, namely in the category of heavy smokers with more than 12 pack-yr (OR = 4.93; $p < 0.001$). The increasing ORs with increasing pack-yr revealed consistently significant trend both for seminomas and non-seminomas.

There were no significant differences between seminomas and non-seminomas in the risk profiles of occupational, social and lifestyle factors (Table 5). In addition to already described significantly increased risk association of low degree of education, we identified elevated ORs among men working manually (OR = 2.87, 95% CI = 1.88-4.41), with occupational physical activity (OR = 2.26, 95% CI = 1.65 – 3.10) and among those who declared regular night work for at least 3 years prior to the diagnosis (OR = 1.48, 95% CI = 1.07 – 2.06). The analysis of contingency tables (data not shown) proved a significant inter-correlation among all these social and occupational attributes. These characteristics at least partially reflect the same situation, i.e. occupation associated with manual work and relatively low degree of education (manual workers, drivers). The type of main living place stands in a rather different position: a significant reduction of ORs among inhabitants of big towns was confounded with an increased prevalence of men with office-like work and students. The elevated OR among men living in rural places (OR = 1.63, 95% CI = 1.04-2.45) achieved very borderline significance only for TGCCs (Table 5).

As for factors related to passive or active life style, the only significant association was proved in the case of the protective effect of a moderate recreational sport activity (defined as non-professional activity carried out max. 1-2 times per week). Here, age adjusted OR for all TGCCs as well as for histological subtypes was significantly reduced in comparison with people without any sport activity as referent category (ORs < 0.4; Table 5). Neither the type of professional activity nor any specific sport activity (biking, motor biking, horse riding) changed significantly OR values. Similarly, no significant effect was observed adjusting any type of sport activity for life periods, including professional sport at puberty.

Summed counts of neoplasms in family history appeared to be associated with a significantly increased risk of TGCC (Table 6). It refers to the occurrence of any neoplasms among relatives, positive history in close relatives being slightly more significant (OR = 1.72; 95% CI = 1.32-2.49) than in distant relatives (OR = 1.42; 95% CI = 1.04-1.95). Familial cancer history did not contribute significantly to the differentiation of histological types, although there were numerically increased ORs in seminomas as compared with non-seminomas (Table 6).

Among all specifically questioned cancer diagnoses (breast, prostate, GIT, ovary, testes), only positive familial history of breast and prostate cancer elevated significantly risk of TGCC. History of prostate cancer significantly increased ORs in all examined groups and although OR was higher for non-seminomas (OR = 4.68; 95% CI = 1.19-18.44) than for seminomas (OR =3.25; 95% CI = 1.09 – 11.21), we could not distinguish the groups (heterogeneity test: p = 0.526). Familial history of breast cancer achieved only borderline significance of a global OR (OR = 1.83; 96% CI = 1.02-3.42) and of OR for seminomas (OR = 1.93; 96% CI = 1.02-3.85).

Table 3. Potential risk factors in the study that occurred in at least one TGCC case

MATERNAL HEALTH, REPRODUCTIVE HISTORY, CHILDBIRTH AND NEWBORN CHILD	Control	TGCC
Any abnormality during the pregnancy (in binary code)[1]	10.7 %	21.1 %
Nausea	0.6 %	1.7 %
Hypertension	0.3 %	0.8 %
Bleeding	0.0 %	0.6 %
Proteinuria	0.4 %	0.6 %
Diabetes	0.3 %	0.0 %
Maternal age (yrs)[2]	26 (23-32)	24 (20-29)
Birth weight (kg)[2]	3.6 (3.2-4.2)	3.2 (2.8-3.9)
Birth length (cm)[2]	51 (42-55)	50 (38-52)
Birth order		
1st	55.5 %	57.3 %
2nd	32.5 %	30.6 %
≥ 3rd	22.0 %	12.1 %
Cryptorchidism	3.4 %	9.6 %
Orchidopexy after 5 yr of age	0.9 %	4.8 %
DISEASES AND COMPLICATIONS		
Infectious diseases		
Rubella	29.9 %	26.9 %
Morbilli	36.9 %	37.6 %
Mumps	42.9 %	46.6 %
Any defect of urogenital system	4.7 %	2.0 %
Varicocele	3.8 %	1.4 %
Phimosis	4.1 %	1.2 %
Orchitis	1.6 %	0.6 %
Epididymitis	1.6 %	2.5 %
Atrophic testis	1.3 %	6.8 %
Inguinal hernia	13.3 %	10.9 %
Testicular trauma	15.8 %	26.4 %

DIETARY FACTORS	Control	TGCC
Prevailing type of fat in diet		
Vegetable	73.8 %	74.5 %
Animal	26.2 %	25.5 %
Vegetable and fruit consumption	98.4 %	93.5 %
Intensive alcohol consumption	22.7 %	19.1 %
Smoking history (any)	41.6 %	53.5 %
Pack-years of smoking[3]	3.0 (0.5-22.0)	7.6 (2.3-22.6)
LIFESTYLE FACTORS		
Occupational physical activity	31.9 %	51.4 %
Occupational night work	29.3 %	39.0 %
Recreational physical activity	84.6 %	71.9 %
Professional sport		
Overall	24.2 %	24.3 %
At puberty	18.5 %	19.6 %
Special types of sport		
Biking	78.2 %	71.9 %
Motor biking	21.1 %	24.2 %
Horse riding	6,3 %	6.4 %
SOCIO-ECONOMIC STATUS AND RESIDENT HISTORY[4]		
Main lifetime occupation		
Office-like work	49.1 %	38.8 %
Student	24.8 %	4.4 %
Manual worker	22.1 %	48.3 %
Driver	3.9 %	8.5 %
FAMILY CANCER HISTORY		
History of any neoplasms		
Close relatives (parents, siblings)	14.8 %	22.2 %
Other relatives[5]	30.3 %	38.2 %
History of specified cancer diagnoses (in all relatives)		
Testicular cancer	1.3 %	2.8 %
Breast cancer	5.0 %	9.3 %
Prostate cancer	0.8 %	3.7 %
Ovarial cancer	5.4 %	3.9 %
GIT cancer	13.6 %	17.1 %

Legend to Table 3.

[1]Binary code that aggregates both specified problems during the pregnancy (bleeding, nausea, proteinuria, diabetes, hypertension) and not-specified reporting on risk events

[2]Quantitative variables expressed as median and 10%-90% percentiles

[3]Median and 10%-90% percentiles of pack-yrs adjusted for time since quitting

[4]Categories of education and living place are described in table 1

[5]Includes grandparents, uncles and aunts, nieces, nephews

Table 4. Prenatal, perinatal and reproductive health history of men with TGCC and of controls in univariate logistic regression analysis [1]

Variables and categories	All TGCCs (n = 356)		Seminoma (n = 195)		Non-seminoma (n = 161)		Heterogeneity test (χ^2, p level)
	- Adjusted OR (95% confidence interval) [2]						
Any abnormity during the pregnancy[3]	2.22	(1.43; 3.44) *	2.49	(1.53; 4.07) *	1.91	(1.12; 3.26) +	1.05 (p = 0.305)
Maternal age (yrs)							
15-19 (referent)	1.00	(referent)	1.00	(referent)	1.00	(referent)	
20-24	0.39	(0.13; 0.76)*	0.40	(0.14; 1.06)	0.26	(0.09; 0.69)*	
25-29	0.29	(0.22; 0.89) +	0.44	(0.15; 1.17)	0.23	(0.09; 0.63)*	1.62 (p = 0.202)
30-34	0.25	(0.11; 0.74) +	0.51	(0.39; 0.91) +	0.21	(0.07; 0.66)*	
≥ 35	0.24	(0.07; 0.81) +	0.31	(0.29; 0.75) +	0.32	(0.08; 1.31)	
Test for trend		*p = 0.196*		*p = 0.279*		*p = 0.173*	
Birth weight (g)							
< 3,000	1.66	(1.03; 2.68) +	1.74	(1.04; 3.16) +	1.58	(0.88; 2.84)	
3,000 – 3,999 (referent)	1.00	(referent)	1.00	(referent)	1.00	(referent)	0.03 (p = 0.867)
≥ 4,000	0.90	(0.49; 1.62)	0.95	(0.46; 1.99)	0.81	(0.38; 1.73)	
Cryptorchidism	2.94	(1.46; 5.91)*	3.78	(1.98; 6.80)*	2.65	(1.17; 5.99)*	0.25 (p = 0.617)
Orchidopexy after 5yr of age	5.24	(1.52; 18.12)*	7.47	(2.09; 26.66)*	2.66	(0.58; 12.10)	3.90 (p = 0.048)
Atrophic testis	5.27	(1.80; 15.47)*	4.69	(1.47; 14.85)*	6.23	(1.93; 20.20)*	0.03 (p = 0.951)
Testicular trauma	2.02	(1.37; 2.98)*	2.07	(1.31; 3.26)*	1.96	(1.23; 3.12)*	0.13 (p = 0.719)

Legend to Table 4.

[1]Only associations with p < 0.05 for at least one subgroup are included. (+) mark for OR significant at the level p< 0.05; (*) mark for OR significant at the level p< 0.01. [2]OR: odds ratio (adjusted for men's age) with 95% confidence interval

[3]Binary code that aggregates both specified problems during the pregnancy (bleeding, nausea, proteinuria, diabetes, hypertension) and not-specified reporting on risk events

Following are the variables that were retained in the multivariate model (Table 7) as significant for TGCCs as well as for both histological subtypes (listed with OR for all TGCCs): atrophic testis (OR = 5.88), family history of prostate cancer (OR = 4.81), cryptorchidism (OR = 3.83) and interaction variable "low degree of education & manual occupation" (OR = 3.01). Family history of breast cancer remained in multivariate model for TGCCs and seminomas with OR values 2.01 – 2.18. Finally, low birth weight category (< 3,000 g) was retained only in a model for all TGCCs with a borderline significance of OR = 1.67.

TheTable 8 summarizes the survey of testicular self-examination (TSE) that was administered simultaneously with the main study questionnaire. Majority of control men (65%) were uninformed about the TSE and only minor part of them practiced TSE at least irregularly (22.1%). In comparison with controls, the TGCC patients declared significantly higher awareness of TSE (69.7%) as well as more regular practicing (irregularly 17.9%; regularly as recommended 46.9%). Awareness and practicing of TSE were not associated with age, education or cryptorchidism. Significantly increased awareness and practicing of TSE were found among men with history of testicular trauma or atrophic testis.

Discussion

The epidemiology of testicular cancer in the Czech Republic is defined in the Czech National Cancer Registry (NCR) that ensures an obligatory notification of all newly diagnosed cases of cancer since 1976 including regular follow-up [4, 16, 17]. Age standardized incidence rate (ASR) in the Czech population increased from 3.9/100,000 in 1980 to 8.2/100,000 in 2004. Mean annual increase of ASR reached 0.15/100,000 in the period 1995 – 2004. Very similar growing trend has been reported from many European countries [1, 3, 18–21]. Similarly increasing ASR of testicular cancer for the Czech and neighboring Slovak population is also documented in national epidemiological portals of both countries [4, 22]. The prevalence of main histological types of TC in the Czech NCR is similar to commonly published profiles [13, 23]. As for the period 1995 – 2004, the Czech NCR contains 3,800 records on primary testicular cancer. TGCCs form 96.2 % (n = 3,655) of all the histologically verified testicular tumors with the following structure: seminomas (53.8 %) and other TGCCs (42 4 %). Non-seminomas of one histological type (embryonal carcinoma, choriocarcinoma, teratoma, yolk sac tumor, polyembryoma) form 24 % of all TGCCs. Primary non-germ cell testicular tumors form 2.2 % of all TC records (n = 84).

Of course, our hospital-based data cannot be fully representative to all patients with testicular cancer in the Czech population. Therefore, all detected risk associations are discussed here with respect to potential sources of selection bias. We however documented satisfying comparability with the Czech National Cancer Registry (NCR) both in the age distribution and in the prevalence of histological subtypes of TGCCs. As documented in Table 2 and in Figure 1, there was

Table 5. Lifestyle and social factors of men with TGCC and of controls in univariate logistic regression analysis.[1]

Variables and categories	All TGCCs (n = 356)		Seminoma (n = 195)		Non-seminoma (n = 161)		Heterogeneity test (χ^2, p level)
	- Adjusted OR (95% confidence interval) [2]						
Smoking history							
Non smoker (referent)	1.00	(referent)	1.00	(referent)	1.00	(referent)	
Former smoker	1.50	(1.02; 2.03) +	1.08	(0.65; 1.77)	1.42	(1.01; 2.62) +	0.28 (p = 0.594)
Active smoker	1.60	(1.10; 2.33) +	1.57	(1.02; 2.41) +	1.75	(1.04; 3.23) +	
Smoking (pack – years)[3]							
Non smoker (referent)	1.00	(referent)	1.00	(referent)	1.00	(referent)	
0.1-2.5	1.36	(0.65; 2.82)	1.21	(0.48; 2.99)	1.51	(0.63; 3.65)	1.68 (p = 0.199)
2.6 – 12.0	3.30	(1.69; 6.42)*	2.59	(1.21; 5.56) +	3.21	(1.96; 9.02)*	
≥ 12.1	4.93	(1.63; 12.58)*	3.68	(1.75; 8.78) +	5.06	(2.56; 18.21)*	
Test for trend	*p = 0.037*		*p = 0.044*		*p = 0.031*		
Occupational physical activity	2.26	(1.65; 3.10)*	2.25	(1.55; 3.25)*	2.27	(1.54; 3.36)*	0.02 (p = 0.976)
Occupational night work	1.48	(1.07; 2.06) +	1.38	(1.03; 2.23) +	1.65	(1.09; 2.47) +	0.01 (p = 0.951)
Occupation							
Office-like work (referent)	1.00	(referent)	1.00	(referent)	1.00	(referent)	
Students	0.15	(0.07; 0.32)*	0.08	(0.03; 0.29)*	0.18	(0.07; 0.45)*	
Manual workers	2.87	(1.88; 4.41)*	2.36	(1.46; 3.84)*	3.62	(2.13; 6.17)*	1.94 (p = 0.164)
Drivers, servicemen	2.70	(1.19; 6.14) +	2.31	(0.91; 5.82)	3.31	(1.17; 8.63) +	
Education							
Primary and skilled	3.04	(2.05; 4.52)*	2.89	(1.81; 4.60)*	3.07	(1.92; 4.88)*	
Secondary (referent)	1.00	(referent)	1.00	(referent)	1.00	(referent)	0.28 (p = 0.593)
University	1.11	(0.75; 1.67)	1.29	(0.81; 2.07)	0.89	(0.51; 1.53)	
Living place							
Village	1.63	(1.04; 2.45)+	1.54	(0.96; 2.49)	1.55	(0.93; 2.71)	
Small town (referent)	1.00	(referent)	1.00	(referent)	1.00	(referent)	0.42 (p = 0.515)
Big town, city	0.54	(0.37; 0.77)*	0.49	(0.31; 0.76)*	0.60	(0.38; 0.94)+	
Sport activities							
No sport activity (referent)	1.00	(referent)	1.00	(referent)	1.00	(referent)	
Recreational sport activity	0.49	(0.32; 0.72)*	0.57	(0.36; 0.89)*	0.43	(0.27; 0.69)*	0.01 (p = 0.932)

Legend to Table 5.

[1]Only associations with $p < 0.05$ for at least one subgroup are included. (+) mark for OR significant at the level $p< 0.05$; (*) mark for OR significant at the level $p< 0.01$. [2]OR: odds ratio (adjusted for men's age) with 95% confidence interval

[3]Adjusted for years since quitting; categorized according to quartiles of the control sample distribution.

no significant discrepancy or tendency of bias. The case series included 54.8% of seminomas (n = 195) and 45.2% of non-seminomas (n = 161). This corresponded to the NCR that comprise 56.0% seminomas and 44.0% non-seminomas (Table 2). Age and clinical stage distribution of seminomas and non-seminomas in the study corresponded to the NCR data (Figure 1, Table 2). Our histology-specific analyses of risk factors should therefore give reliable outcomes.

Comparing controls and cases in demographic and social factors, we recognized decreased proportion of TGCCs with high education degree and decreased proportion of TGCCs living in big towns (Table 1). Because education and living place were not matching variables, we checked their sample distribution against official Czech population statistics [24, 25]. Aggregated data of controls and TGCCs corresponded to the official statistics (residents living in big towns: study sample = 36.8 %, Czech population data = 32.4 %; people with primary education or skilled: study sample = 26.4 %, Czech population data = 29.1 %). Therefore, there should be no systematic bias and both education and living place were included in the risk analyses as potentially influencing factors.

There is a remarkable inconsistency in the literature comparing histological types of TGCCs from the viewpoint of risk factors. For example, increased risk of seminomas was found in newborns with birth weight < 2.5 kg [11, 26], while in other studies, it was rather attributed to non-seminomas [9, 27]. The general conclusion is that there is only a little variation in risk factors between seminomas and non-seminomas [28]. Our study suggests also only a few variables that significantly differentiated OR values between histological subtypes. It was the case of orchidopexy after 5 yr of age that was significantly associated only with seminomas (OR = 7.47; 95% CI = 2.09-26.66). Low birth weight (< 3,000 g) achieved a slightly higher OR values for seminomas (OR = 1.74) than for non-seminomas (OR = 1.58),

however without any significant differentiation of histological subtypes. Similar profile was observed for positive familial history of breast cancer that was associated with seminomas (OR = 1.93; $p < 0.05$) and not associated with non-seminomas (OR = 1.55, $p = 0.296$). In our multivariate outcomes, seminomas differed from non-seminomas in significant risk association with breast cancer and increased OR values of cryptorchidism (Table 7).

All documented regression analyses indicated relatively increased variability of risk associations within non-seminomas than within seminomas. Although it is rather inconsistently reported in literature, seminomas appear to be increasingly more associated with risk factors than non-seminomas [12, 27]. Possible explanation could be found in the origin and structure of histological types. Seminomas developed from germ cells and are relatively more homogeneous than non-seminomas with higher compositional diversity [29]. Furthermore, non-seminomas can be developed from carcinoma *in situ* independently or sequentially via seminomas. This can be hypothetically regarded as another source of heterogeneity in the non-seminoma group and it might also indicate the processes requiring some additional risk factors [12, 30]. Our study suggests that different histological groups have different degree of association with some risk factors, whose differentiation may be obscured by combining the groups in one analysis.

Numerous studies were focused on pre- and perinatal factors. As it is excellently summarized in reviews given by Garner et al. [5] and Richiardi et al. [6], several already published results generate rather inconsistent knowledge in this field. Namely low birth weight, birth order, nausea and bleeding during the pregnancy have been associated with increased risk [31-33]. We found significant risk association only for the nonspecific binary score aggregating any problem during the pregnancy (Table 4). However, none of the complications achieved significantly elevated OR if analyzed separately. At this point, we should mention the potential influence of recall bias in such retrospective searching for events that happened 20-30yrs ago. Finally, our score aggregating complications during the pregnancy was not retained in multivariate adjusted analysis and was excluded as confounding variable of low birth weight (< 3,000 g).

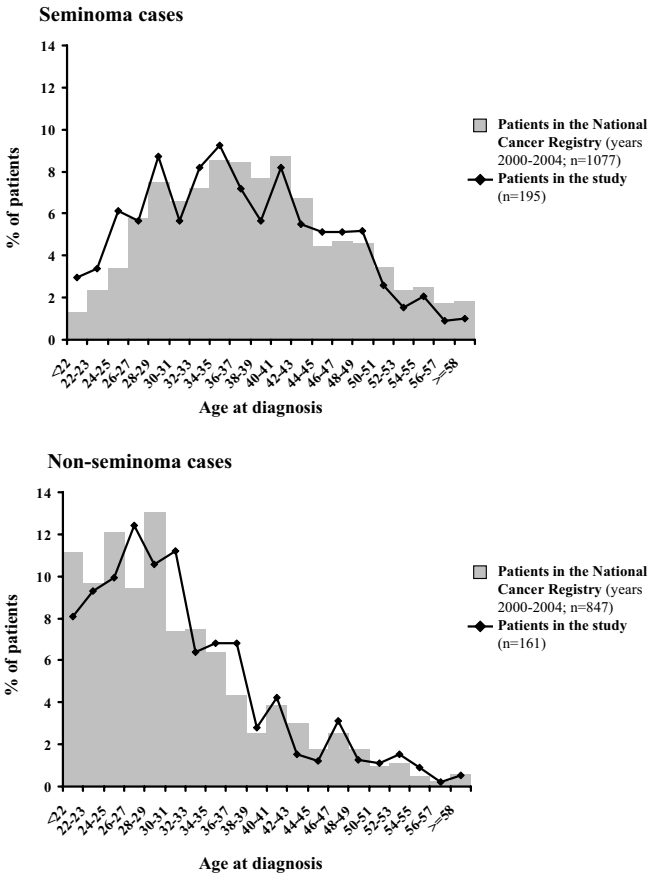

Figure 1. Distribution of age at diagnosis in the study sample of TGCCs in comparison with the Czech National Cancer Registry as population background

Table 6. Family cancer history of men with TGCC and controls in univariate logistic regression analysis.[1]

Variables and categories	All TGCCs (n = 356)		Seminoma (n = 195)		Non-seminoma (n = 161)		Heterogeneity test (χ^2, 1d.f.; p level)
	- Adjusted OR (95% confidence interval)[2]						
History of any neoplasm							
All relatives	1.48	(1.09; 2.02) *	1.67	(1.13; 2.45) *	1.37	(1.01; 1.99) *	0.42 (p = 0.526)
Close relatives	1.72	(1.02; 2.49) *	1.94	(1.19; 3.19) *	1.34	(1.02; 1.91) *	0.34 (p = 0.561)
Distant relatives	1.42	(1.04; 1.95) *	1.44	(0.97; 2.15)	1.34	(0.83; 2.15)	0.01 (p = 0.914)
History of specified diagnoses: in all relatives							
Breast cancer	1.83	(1.02; 3.42) *	1.93	(1.02; 3.85) *	1.55	(0.72; 3.39)	1.17 (p = 0.279)
Prostate cancer	3.96	(1.11; 14.09) *	3.25	(1.09; 11.21) *	4.68	(1.19; 18.44) *	0.40 (p = 0.526)

Legend to Table 6.

[1]Only associations with $p < 0.05$ for at least one subgroup are included. (+) mark for OR significant at the level $p < 0.05$; (*) mark for OR significant at the level $p < 0.01$; [2]OR: odds ratio (adjusted for men's age) with 95% confidence interval

Table 7. Results of multivariate logistic regression models for all TGCCs and the subtypes of seminoma and non-seminoma with all risk factors[1]

All TGCCs (n = 356)			**Seminoma** (n = 195)			**Non-seminoma** (n = 161)		
Risk factors	*OR (95% CI)*[2]		**Risk factors**	*OR (95% CI)*[2]		**Risk factors**	*OR (95% CI)*[2]	
Atrophic testis	5.88	(2.04; 16.78)	Atrophic testis	6.25	(2.41; 17.52)	Atrophic testis	6.31	(1.96; 19.81)
Family history of prostate cancer	4.81	(2.33; 16.83)	History of cryptorchidism	4.11	(2.42; 7.10)	Family history of prostate cancer	4.91	(2.18; 18.18)
History of cryptorchidism	3.83	(2.46; 5.70)	Family history of prostate cancer	4.01	(1.61; 17.11)	Low education degree & manual occupation	3.44	(2.17; 5.47)
Low education degree & manual occupation	3.01	(2.15; 5.41)	Low education degree & manual occupation	2.81	(1.92; 4.40)	History of cryptorchidism	2.29	(1.56; 5.59)
Family history in breast cancer	2.01	(1.05; 3.66)	Family history of breast cancer	2.18	(1.06; 4.48)			
Birth weight < 3,000 g	1.67	(1.03; 2.60)						

Legend to Table 7.

[1]Only associations with $p < 0.05$ for at least one subgroup are displayed.

[2]OR: odds ratio with 95% confidence interval (adjusted for men's age and all the other characteristics in the table in a multivariate analysis)

Low birth weight was kept in multivariate model only for all TGCCs. It is in agreement with prevailing findings of the other authors [5, 11, 34].

Cryptorchidism is widely accepted as risk factor associated with a two- to eight-fold elevated risk of TC [35]. Our study also found a significant risk associated with cryptorchidism for all TGCCs (OR = 2.94) as well as for seminomas (OR = 3.78) and non-seminomas (OR = 2.65). We further found even more increased ORs if orchidopexy is performed at the age of 5 years or later (all TGCCs: OR = 5.24; seminoma: OR = 7.47; non-seminoma: OR = 2.66). These results correspond to several studies that indicated increasing risk of TC and more likely of seminoma in undescended testes with orchidopey after 10-14 yr of age or not performed (OR ranging typically from 3 to 10; [36-38]). There is however sparse data on the effect of orchidopexy before age of 10 years. A few studies that analyzed orchidopexy in such young boys did not report significant effect [37, 39, 40]. Our data suggests that there can be a significant risk effect of orchidopexy before the age of 10 years with a significant cut-off point for arising risk in the age of 5 years. Late orchidopexy appears to modulate the risk, although the concrete value of OR is probably partially influenced by the clinical selection bias (disputable comparability of patients treated in very young age with the others).

Our study presents an increased prevalence of low degree of education among TGCC patients, regardless of the histological subtype (OR = 2.8 – 3.0). Some previous studies showed risk association of high level of education for TC, others found no effect [5, 38]. Expectedly, we found low degree of education to be associated with manual occupation in plants and in rural areas. Therefore, the factor of education cannot be discussed separately. There is no relevant explanation why either education or type of occupation should be an independent risk factor for TGCC. Instead of it, we argue for the combined effect of these factors as it is reflected by highly significant interaction term of them ($p < 0.001$).

The combined effect of low degree of education and of manual work was retained in all multivariate risk models, even if adjusted for the other variables including inherited defects and familial cancer history (Table 7). Correlation of low education and manual occupation indicates even more complex underlying lifestyle association because the same group of men claimed no sport activity, more sedentary lifestyle and increased intensity of long-term smoking. All these factors tend to separate individuals with specific lifestyle that corresponds to relatively hard manual occupation. Such exposures can start relatively early in life, even immediately after the puberty in age of 16–18 years. Typical schedule of education of skilled men in the Czech Republic covers 8-9 years in any type of primary school (starting in the age of 6 yr) plus 3-4 years in some training college where they are already exposed to the occupational conditions. The age distribution of testicular cancer allows for effective exposures in early adulthood and the age around puberty has been suggested as a period with probably increased risk of TC promotion [6,41].

Lifestyle factors are closely related to the risk effect of smoking [38, 42]. Although we recognized smoking as a risk factor in univariate analyses, there is lack of supportive multivariate result and we can speculate that smoking can operate as confounder of some type of lifestyle or occupation. At this point, we employed data of the Czech National Cancer Registry, where the smoking history is coded in all records except

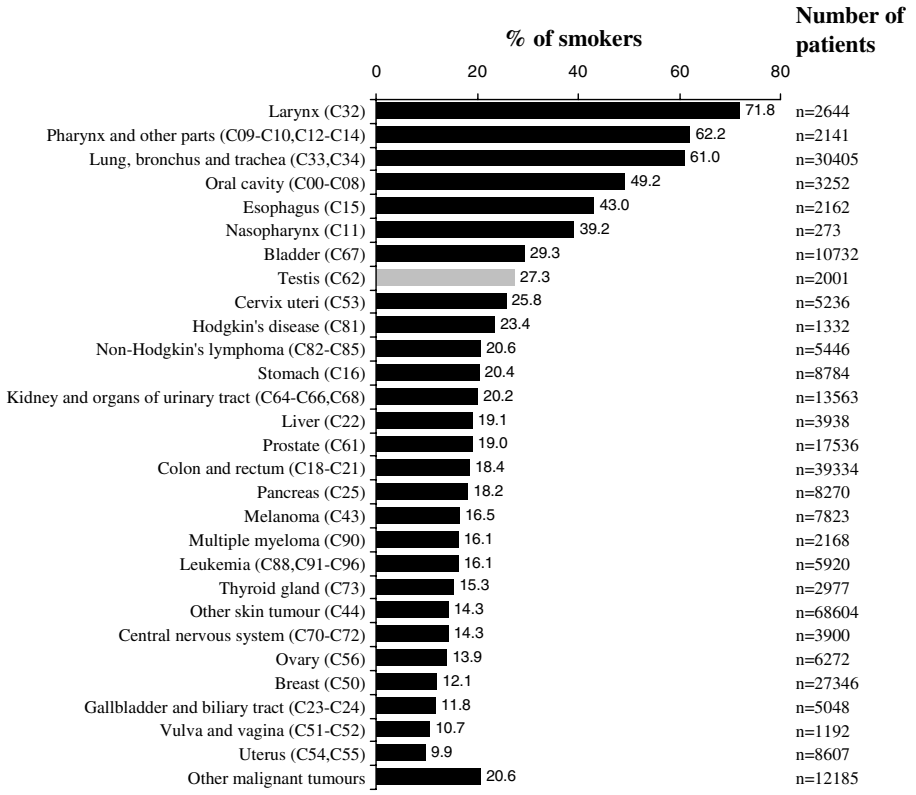

Figure 2. Prevalence of smokers in records of the Czech National Cancer Registry (period 2000–2004).

for DCO cases (Figure 2). NCR data documents the position of testicular cancer in the middle of all cancer diagnoses, with only 27.3% prevalence of smokers. This supports the conclusion that smoking can only weakly modulate the risk level for TC, highly probably in association with the other risk factors. Independent risk effect of smoking is very disputable.

We have no exact explanation for the borderline significance of risk of TGCCs among men living in rural areas. The effect was observed only for the whole TGCC group and lost its significance both for seminomas and non-seminomas. Furthermore, no such effect was retained in the multivariate analysis. Therefore, it might be related to the composition of the study sample. A clear evidence for independent risk influence of rural/urban areas and living places does not exist [5, 43].

Although we detected remarkably elevated ORs among men that claimed testicular trauma in past, we finally dropped out this parameter from the multivariate models due to the following reasons, also discussed in literature [5, 44]. Firstly, the history of trauma can be influenced by recall bias and indeed we found increasing frequency of traumatic events reported for the periods very close to the time of cancer diagnosis (data not shown). This suggests that the trauma could make the injured patients more careful and facilitate the diagnosis of already growing tumor. Secondly, patients with reported testicular trauma declared significantly increased awareness, as well as practicing intensity of testicular self-examination (TSE, Table 8). This again indirectly indicates their higher interest in health surveillance. Our survey however showed that proportion of Czech men practicing TSE is very small. Approximately 50 % of TGCCs do not perform TSE monthly and more than 35 % do not practice TSE at all. Similar results were reported by other authors [45, 46]. Based on a retrospective study of 1,832 patients with TC diagnosed in the period 1993 – 2002, Ondrusova and Ondrus [21] also concluded that Slovak men are poorly informed about the possibility of TC occurrence.

Many familial studies proved evidence of the risk role of inherited factors. It holds namely for testicular cancer, brothers of TC patients have 8-fold increased risk of TC and sons of fathers with TC have 4-fold elevated risk [47]. Familial TC history can be also associated with increased occurrence of cryptorchidism suggesting that there is a relationship between urogenital maldevelopment and predisposition to testicular neoplasia [48]. However, the prevalence of testicular cancer among relatives of our sample was too low to allow statistically significant discrimination of cases and controls. Nevertheless, we found a significant risk association with overall familial cancer history and with prostate and breast carcinoma (Table 6). Several studies already described the

Table 8. Awareness and practice of testicular self-examination (TSE) declared by TGCCs and controls in relation to selected other factors

Groups	Awareness of TSE	Practicing of TSE	
		Irregularly	Regularly
TGCCs vs. controls			
Controls (n = 317)	35.0 % *	13.3 %	8.8 % *
TGCCs (n = 356)	69.7 % *	17.9 %	46.9 % *
Atrophic testis			
No (n = 645)	52.7 % *	15.7 %	28.1 % *
Yes (n = 28)	67.9 % *	14.3 %	50.0 % *
Testicular trauma			
No (n = 529)	49.7 % *	15.5 %	25.1 % *
Yes (n = 144)	66.7 % *	16.7 %	43.1 % *
Cryptorchidism			
No (n = 628)	53.2 %	15.8 %	28.5 %
Yes (n = 45)	55.6 %	15.6 %	35.6 %
Education			
Primary or skilled (n = 180)	49.4 %	16.1 %	31.7 %
Secondary (n = 342)	56.1 %	16.4 %	28.7 %
University (n = 151)	51.7 %	13.9 %	26.5 %

* Mark of statistically significant difference between controls and TGCCs or between yes/no categories of the other categorizing factors (M-L χ^2 test; $p < 0.05$)

risk of familial cancer history for testicular cancer, including specific position of breast cancer and prostate cancer [49, 50]. Similarly to our study, Walschaerts et al. [50] have actually published increased ORs for breast cancer in family (OR = 1.77, 95% CI = 1.20 – 2.60). The authors also confirmed this effect in a multivariate model constructed in the same way as we present here. Corresponding findings were presented also by other authors [51, 52]. Walschaerts et al [50] also found increased OR for familial history of prostate cancer (OR = 1.80; 95% CI = 1.08-3.02), but without subsequent confirmation in multivariate system. In our study, we met significant risk elevation due to familial history of prostate cancer without any confounding influence of other variables. Such result seems to be in contrast with negative findings published by Hemminki and Chen [49] or by Westergaard et al. [53].

Conclusion

Based on the employed multivariate strategy, we could not rule out effects of any category of risk factors for TGCC. Each type of factors had its statistically significant representative in the multivariate risk model. Our study documented that a wide set of risk factors generates numerous confounding effects that cannot be detected in univariate systems. Multivariate modeling with a special focus on interactions among variables is therefore highly recommended. Familial cancer history remains an influential risk factor in multivariate models altogether with lifestyle and occupational parameters. It documents that both environmental exposures and genetic inheritance can play some role in moderation of the risk of TGCC. Our study suggests that seminomas and non-seminomas may have different degree of association with some risk factors, whose differentiation may be obscured by combining the groups in one analysis.

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