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ORIGINAL PAPER

Is increased body mass index associated with the incidence of testicular germ cell cancer?

Klaus-Peter Dieckmann · Jörg Thomas Hartmann · Johannes Classen · Malte Diederichs · Uwe Pichlmeier

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Abstract
Purpose Epidemiological and ecological evidences suggest a positive association of overweight and obesity with the risk of testicular germ cell cancer (GCC). Previous controlled trials reported conflicting results. The present study aimed to analyse the putative association of overweight with GCC risk in a large patient sample and to summarize previous data.
Methods A total of 8,498 GCC patients were enrolled in a nationwide multicentric case control study. Self-reported body dimensions were recorded for calculation of the body mass index (BMI; kg/m^2). For comparison, 2,070 age-matched male probands of the latest German National Health Survey (NHS) were employed. Patients and controls were categorized according to age as follows: 18–29, 30–39, and 40–49 years, respectively, and according to BMI, as follows: <18.5; 18.5 to <25; 25 to <30; >30 kg/m^2, respectively. Frequencies of BMI-categories in the three age groups were tabulated and compared statistically. The literature was searched for previous controlled trials regarding BMI and GCC risk.
Results The median BMI of all GCC patients is 24.69 kg/m^2. Overall comparison of frequencies of BMI categories of cases and controls did not reveal any significant difference. However, in young men (18–29 years) BMI categories 25 to <30 kg/m^2 and >30 kg/m^2 were significantly more frequent in GCC patients than in controls ($p < 0.00001$). Nineteen previous studies were identified in the literature, one of which being clearly in accordance with the present hypothesis, one being antithetical while the remaining studies were inconclusive in various aspects.
Conclusion The results of this population-based study lend support to two hypotheses regarding the pathogenesis of GCC: First, as high-calorie nutrition is the most important reason for increased BMI, it appears conceivable that nutritional factors are involved in the pathogenesis of GCC. Second, as nonseminoma is the most prevalent histological subtype among younger patients, the association of increased BMI with incidence of GCC in this particular subgroup may point to divergent pathogenetic pathways of nonseminoma and seminoma, respectively.

Keywords Body mass index · Germ cell neoplasm · Nonseminoma · Seminoma · Obesity

K.-P. Dieckmann (✉) · M. Diederichs
Klinik für Urologie, Albertinen-Krankenhaus,
Suentelstrasse 11a, 22457 Hamburg, Germany
e-mail: DieckmannKP@t-online.de

J. T. Hartmann
Klinik für Onkologie und Hämatologie,
Universitätsklinik Tübingen, Tübingen, Germany

J. Classen
Institut für Radioonkologie,
St. Vincentius Kliniken, Karlsruhe, Germany

U. Pichlmeier
Institut für Medizinische Biometrie und Epidemiologie,
Universitätsklinikum Eppendorf, Hamburg, Germany

Introduction

Overweight and obesity represent a pandemic problem in many of the Western countries (Mensink et al. 2005; Hedley et al. 2004) and even in some of the developing countries adiposity has notably begun to spread among subpopulations (James and Ralph 1999). Overweight is caused by a long-standing positive energy balance in a given individual largely based on excess consumption of food consisting of animal-derived fats and of sugar-like carbohydrates. The body mass index (BMI) or Quetelet's Index as calculated by the body weight divided by the second dimension of height (kg/m^2) has been shown to provide a valuable measure of the degree of overweight (Willet 2006). According to the World Health Association (WHO), the entire spectrum of BMI values is subdivided into the following five categories: BMI < 18.5 kg/m^2, 18.5 to <25 kg/m^2, 25 to <30 kg/m^2, 30 to <40 kg/m^2, and >40 kg/m^2, representing underweight, normal weight, overweight, obesity, and excessive obesity, respectively. The latter two categories (obesity and excessive obesity) are linked up in many analyses. There is abundant evidence to show that any increase of BMI beyond the overweight threshold of 25 kg/m^2 is associated with an incremental load of chronic illnesses (Ogden et al. 2007). For the most part, cardiovascular, metabolic and degenerative skeletal diseases, respectively, are involved with obesity. But, the overall mortality from cancer is also significantly associated with increased BMI (Samanic et al. 2006; Pischon et al. 2008). Accordingly, Western-type nutrition with high amounts of saturated fat and sugar-like carbohydrates has been found to promote the evolution of many malignancies (Weisburger 1997; Bianchini et al. 2002; Calle et al. 2003).

Testicular germ cell cancer (GCC) is typically a neoplasia of young adult men. Pathogenetically, this disease is thought to originate during embryogenesis based on genetic factors and secondary to endocrinological imbalances during pregnancy (Dieckmann and Pichlmeier 2004). Yet, environmental factors are strongly suspected to be also involved in tumorigenesis (Richiardi et al. 2007) and this assumption is derived from the epidemiological observation of constantly increasing incidence rates of GCC since many decades (Huyghe et al. 2007).

So far, it is unknown which particular environmental factors are actually involved with GCC pathogenesis. However, there are several epidemiological reports that may suggest high-calorie nutrition to play a role in GCC pathogenesis. Accordingly, two ecological studies had clearly demonstrated that GCC incidence is related to per capita fat intake (Armstrong and Doll 1975) and cheese consumption, respectively (Ganmaa et al. 2002). Notably, the worldwide increasing incidence rates of GCC are mirrored by an escalation of the overweight pandemic. Geographically, GCC is prevalent in high-income Western countries where obesity prevails, too. Conversely, GCC is extraordinarily rare in low-income developing countries where obesity is likewise rare (Purdue et al. 2005). Further, obesity in adult life may—to a certain degree—reflect fetal malnutrition or even maternal starvation during pregnancy (Ravelli et al. 1976; Roseboom et al. 2006). As initiation of GCC is thought to come about during embryogenesis, overweight in adulthood could thus conceivably point to events relevant to pathogenesis occurring prenatally.

In addition, incidence rates of GCC used to be quite low among the ethnic groups of Black Americans and Hispanics, respectively (Purdue et al. 2005). The obesity pandemic turned out to be an exceptional problem among these groups (Ogden et al. 2006). Notably, several years after the onset of that pandemic, GCC incidence rates have started to rise markedly in these subpopulations (McGlynn et al. 2005; Holmes et al. 2008).

In all, there is some observational suggestion that the incidence of GCC may be associated with BMI greater than 25 kg/m^2 (Bjørge et al. 2006). However, the data reported so far are rather conflicting mainly due to methodological inconsistencies among the trials (McGlynn et al. 2007). So, the aim of the present investigation was to explore the presumed association of GCC with increased BMI in a sufficiently large patient sample (Dieckmann 2007), to summarize previous data relating to this issue, and thus to find a reasonable conclusion regarding the hypothesized association of GCC with BMI.

Methods

In a population-based multicentric case control study, a total of 10,522 patients were registered by 228 participating institutions (appendix) from all regions across Germany. All of the cases were at least 18 years of age, all being of Caucasian descent, and all having histologically confirmed testicular GCC (Dieckmann 2007). Recruitment started in 2002 and was terminated by the end of 2005. Cases treated during 1995–2005 were eligible. Roughly 60% of the cases were enrolled retrospectively. Years of birth of cases ranged from 1950 to 1984. Self-reported measures of height (m) and weight (kg) were registered. The BMI was calculated.

For comparison, data of the recent German National Health Survey (NHS) were employed (Ellert et al. 2006). That survey was conducted from September 2003 through March 2004 by the Robert Koch Institut, Berlin, on behalf of the German Ministry of Health. A representative sample of 7,000 randomly selected adult probands aged 18–70 years, from all regions across Germany were interviewed by telephone according to their individual health status including individual body dimensions. As results of that survey, tabulations of BMI in various age groups and subpopulations were reported. These data are freely accessible (http://www.rki.de).

As subjects of both genders and of all ages had been included in the NHS a refinement of that sample had to be done to allow for appropriate comparison with the sample of GCC patients. Thus, all of the male probands aged 18–49 years were selected from the Health Survey sample resulting in a total of 2,070 men suitable for controls.

For appropriate comparison of GCC cases with the control set, 2,024 patients had to excluded from the original patient set ($n = 10{,}522$) because of unfitting ages (too old or too young, respectively). Thus, a sample of $n = 8{,}498$ GCC patients resulted for analysis.

Both, cases and controls were categorized according to age into the following groups: 18–29 years, 30–39 years, and 40–49 years, respectively. With respect to BMI, the categories of the WHO were employed (vide supra) with combining the groups of obesity and excessive obesity.

Data were initially stored by means of commercially available databank software (Microsoft Access for Windows). Statistical analysis was accomplished by employing SAS software package (V.9.1.3) on the Windows platform.

Statistical analysis involved, first, descriptive tabulation of BMI according to age categories, and second, the Wilcoxon–Mann–Whitney test for statistical comparison of groups. Significance level was defined as $p < 0.05$. A formal calculation of relative risks (odds ratios) was not feasible because no individual BMI values of control subjects were available.

To look for previous controlled trials regarding the potential association of BMI with testicular GCC, a literature survey was performed by employing electronic search systems (PubMed) and hand-search of pertinent literature.

Results

The median BMI regarding the total patient sample ($n = 8{,}498$) amounts to 24.7 kg/m^2 which represents a value within normal BMI limits. With respect to age categories 18–29, 30–39, and 40–49 years, the corresponding median BMI values of cases were 23.9, 24.9, and 25.6 kg/m^2, respectively. More details relating to descriptive statistical analysis are provided in Table 1. Unfortunately, no corresponding data of the control sample are available for direct comparison regarding these results.

Table 2 documents the frequencies of BMI categories among age groups of cases and controls, respectively. Overall it appears that the prevalence of obesity (i.e. BMI > 30 kg/m^2) is slightly higher in GCC patients than in healthy controls, but this trend does not achieve statistical significance ($p = 0.187$). However, in the subpopulation of men aged 18–29 years, the BMI categories of 25 to <30 kg/m^2 and >30 kg/m^2, respectively, are markedly more frequent among GCC patients than in controls. Also, in this subpopulation subnormal BMI is less frequent among GCC when compared to controls (2.5 vs. 3.6%). Only in this age group, statistical significance is achieved ($p < 0.00001$) regarding the hypothesis of a higher BMI in cases compared to controls.

The literature search revealed 19 previous controlled trials reporting on BMI and GCC risk (Table 3). Three reports were not entered into this list (Akre et al. 2000; Nord et al. 2003; Sagstuen et al. 2005) because data of those studies were most probably included in a comprehensive cohort study published in 2006 on behalf of the Norwegian Cancer registry (Bjørge et al. 2006). If the present study is included, a total of 16,619 patients have been investigated regarding this issue so far. A formal meta-analysis is not feasible because of grossly divergent methodological designs among studies. In a semi-quantitative approach, the reports were categorized with respect to their results as follows: Significant positive association of increased BMI with GCC risk; insignificant trend towards positive association; null finding; insignificant trend towards negative association, and significant inverse association, respectively. The numbers of studies relating to each of these categories and the corresponding numbers of patients are listed in Table 4. In all, the majority of studies had reported null findings, while only one study presented a positive significant association of GCC with BMI.

Discussion

Overall results

The central result of the present study is the lack of formal evidence for an association of BMI and risk of GCC. Taking all patients of all age groups together, the present analysis failed to demonstrate significantly increased frequencies of BMI > 25 kg/m^2 among GCC patients. These data appear to be mature because the present trial is by far the largest reported so far exploring a putative association

Table 1 BMI in various age groups of patients with germ cell cancer: descriptive analysis

Age groups (years)	Min BMI (kg/m^2)	BMI 25th pctl (kg/m^2)	Median BMI (kg/m^2)	BMI 75th pctl (kg/m^2)	Max BMI (kg/m^2)	Mean BMI (kg/m^2)	SD (kg/m^2)
18–29 ($n = 3{,}298$)	16.16	21.86	23.89	26.30	56.80	24.46	3.86
30–39 ($n = 2{,}991$)	15.43	23.09	24.93	27.41	59.87	25.58	4.02
40–49 ($n = 2{,}209$)	17.36	23.53	25.59	28.08	45.27	26.12	3.90
All ages ($n = 8{,}498$)	15.43	22.64	24.69	27.17	59.87	25.24	4.00

Min minimum BMI, *pctl* percentile, *Max* maximum BMI, *SD* standard deviation

Table 2 Frequencies of BMI categories in various age groups of GCC patients and controls

BMI (kg/m^2)	Entire sample, all ages				Age 18–29 years				Age 30–39 years				Age 40–49 years			
	GCC		NHS		GCC		NHS		GCC		NHS		GCC		NHS	
	Percent	Number (n)	Percent	Number (n)	Percent	Number (n)	Percent	Number (n)	Percent	Number (n)	Percent	Number (n)	Percent	Number (n)	Percent	Number (n)
<18.5	1.46	124	1.4	29	2.46	81	3.6	23	0.9	27	0.7	5	0.72	16	0.1	1
18.5 to <25	52.55	4,466	53.62	1,110	61.64	2,033	69.8	438	50.02	1,496	48.1	368	42.42	937	44.9	304
25 to <30	35.07	2,980	35.85	742	27.71	914	21.6	136	37.65	1,126	41.7	319	42.55	940	42.4	287
>30	10.92	928	9.13	189	8.19	270	5.00	31	11.43	342	9.50	73	14.31	316	12.60	85
Total	100	8,498	100	2,070	100	3,298	100	628	100	2,991	100	765	100	2,209	100	677
	$p = 0.1872$				$*p < 0.00001$				$p = 0.6058$				$p = 0.3085$			

NHS National Health Survey (Ellert et al. 2006); p values relate to Wilcoxon–Mann–Whitney test; * significant

of BMI and GCC risk. As shown in the literature survey the majority of previous trials are well in line with our result as 10 of 20 studies reported null findings and one study even found an antithetical result (Petridou et al. 1997).

The subgroup of young men may be different

However, two aspects of the present analysis render that conclusion still somehow indefinite. First, in the present analysis, the youngest age category comprising of the largest group of patients did in fact demonstrate a clearly significant association of BMI > 25 kg/m^2 (i.e. overweight and obesity, according to WHO definition) with GCC. We did not stratify the sample of cases into histological subgroups of seminoma and nonseminoma. But, according to long standing clinical experience nonseminoma grossly predominates among patients younger than 30 years (Horwich 1996; Mikuz and Colecchia 2007; Krege et al. 2008). Thus, it appears safe to assume that nonseminoma cases will predominate in the age group of 18–29 years of the present sample, too, while among the older patients seminomas will prevail. Consequently, it appears conceivable that the subgroup of nonseminoma might be associated with BMI > 25 kg/m^2. Accordingly, a Canadian case control study had reported a clearly significant association of nonseminoma with BMI while pure seminoma was not associated (Garner et al. 2003). Although there is consensus that testicular germ cell tumours (i.e. seminoma and nonseminoma) are uniformly initiated in utero (Oosterhuis and Looijenga 2005; Dieckmann and Skakkebaek 1999) it is not unreasonable to assume separate pathways of pathogenesis of the two histological subgroups during later clinical development. In fact, a number of clinical epidemiological observations are in favour of that assumption (Coupland et al. 1999; Aschim et al. 2006). So, our finding of a significant association of increased BMI with GCC risk selectively in young patients might indeed corroborate the view of separate pathogenetic pathways of seminomas and nonseminomas, respectively.

Further in support of the BMI hypothesis is the literature survey that revealed six studies with distinct albeit insignificant trends towards the association of BMI with GCC (Table 4). Accordingly, only two studies reported antithetical trends and solely one excessively small study revealed a significantly inverse result (Petridou et al. 1997). Although this type of analysis is clearly far from representing a formal meta-analysis it affords at least some suggestion of a possibly existing association of increased BMI with GCC.

General aspects of the association of overweight with cancer risk

Overweight and as a consequence a BMI > 25 kg/m^2 is usually caused by a long standing positive energy balance

Table 3 Synopsis of controlled trials regarding BMI in GCC patients

Author	Country	Type of study	Pts (*n*)	Results
Lin and Kessler (1979)	USA	CC (not specified)	205	p/a (no further data)
Kleinteich and Marx (1983)	GER	CC (not specified)	64	Trend towards inverse association; height divided by weight (cm/kg), no BMI data
Swerdlow et al. (1989)	GB	CC (hospital controls)	254	n/s OR 1.96 (0.82–4.66) (obesity group vs. BMI < 20); trend towards higher BMI in GCC
Davies et al. (1990)	DK	CC (military servicemen)	438	n/s OR 0.8 (0.4–1.8) (highest vs. lowest quintile)
UK Testicular Cancer Study Group (1994)	GB	CC (patients)	794	n/s weight and height reported, no BMI data
Thune and Lund (1994)	N	Cohort (pop.)	46	n/s weak trend towards higher BMI in GCC
Gallagher et al. (1995)	CAN	CC (health insurance)	510	n/s OR 1.1 (0.7–1.7) (BMI > 28 vs. BMI < 21)
Petridou et al. (1997)	GR	CC (hospital visitors)	97	n/a OR 0.7 (0.3–1.6) (obesity group vs. normal BMI); low BMI (<21) OR 2.8 (1.2–6.4)
Srivastava and Kreiger (2000)	CAN	CC (pop.)	212	n/s insignificant trend towards higher BMI in GCC
Dieckmann and Pichlmeier (2002)	GER	CC (hosp.)	353	n/s OR 1.49 (CI 0.26–8.45) (obesity group vs. normal BMI)
Walcott et al. (2002)	USA	CC (friends)	159	n/s 19.5% obesity in GCC vs. 25% in controls
Garner et al. (2003)	CAN	CC (pop.)	601	n/s subgroup NS with BMI > 31 OR 3.66 (1.87–7.15)
Richiardi et al. (2003)	S	Cohort (hospital)	365	n/s OR 0.71 (0.43–1.16) (BMI > 25 vs.<25)
Rasmussen et al. (2003)	S	Cohort (military conscripts)	144	n/s OR 0.93 (lowest vs. highest tertile)
Pan et al. (2004)	CAN	CC (pop.)	608	n/s OR 1.16 (95% CI 0.8–1.6) (obesity group vs. normal BMI)
Hardell et al. (2006)	S	CC (pop.)	889	n/s (no further data)
McGlynn et al. (2007)	USA	CC (military servicemen)	767	n/s OR 1.06 (0.66–1.69) (obesity group vs. normal BMI)
Stang et al. (2006)	GER	CC (pop.)	258	n/s OR 0.96 (0.61–1.51) (upper vs. lowest quartile)
Bjørge et al. (2006)	N	Cohort (pop.)	1,357	n/s OR 0.83 (0.58–1.17) (obesity group vs. normal BMI) trend towards inverse association
This study	GER	CC (pop.)	8,498	n/s age group 18–29 years significant association

p/a positive association, *n/a* negative association, *n/s* nonsignificant, *OR* odds ratio, (in brackets) 95% confidence limits, *pop.* population based controls

Table 4 Descriptive analysis of studies regarding BMI in GCC patients

	Number of studies (*n*)	Patients involved (*n*)
Significant positive association	1	205
Insignificant trend towards positive association	6	9,964
Null finding	10	4,932
Insignificant trend towards negative association	2	1,421
Significant inverse association	1	97
Total	20	16,619

between high-calorie nutrition and physical activity (Thorling 1996). Rarely, muscle growth alone resulting from particular physical exercise may result in BMI > 25 kg/m^2. Notably, two case control studies found protective effects of physical activity with respect to GCC risk (UK Testicular Cancer Study Group 1994; Gallagher et al. 1995). So, this observation might be another weak suggestion of the relevance of increased BMI and related over-nutrition regarding GCC pathogenesis.

The biological mechanisms linking over-nutrition and the putative promotion of testicular neoplasms remain elusive. Several hypotheses have been advanced to account for the association of obesity with cancer in general involving dysregulation of hormone metabolism, production of reactive oxygen types, oxidative DNA damage, and malfunction of carcinogen-metabolizing enzymes (Pan et al. 2004; Pischon et al. 2008) as well as lack of protective factors imparted by imbalanced high-calorie nutrition (Thorling 1996). Moreover, obesity induces a state of hyperinsulinism (Renehan et al. 2008) which increases the activity of the insulin like growth factor I (IGF-I). This factor is known to promote cell growth specifically proliferation of neoplastic cells. It is at least conceivable that obesity-related hormonal imbalances or IGF-I related mechanisms might advance and promote the growing and development of GCC progenitors.

Body mass index at the time of diagnosis (as investigated here) is usually linked to overnutrition within a recent time-frame. Overall, the present analysis does not demonstrate a clear-cut association of recent overnutrition with the incidence of GCC in general. However, our data as well as the results of the literature survey are not unequivocally straightforward. It is at least conceivable that high-calorie nutrition may promote the development of those germ cell tumours arising in the group of young patients. It could be speculated that the transition from GCC precursors to frank malignancy may be advanced by high-energy intake and the associated metabolic disorders.

Association of GCC with other anthropometric measures

GCC has been found to be significantly associated with adult height, (McGlynn et al. 2007) and high-calorie nutrition during infancy has been suggested as a causal link (Dieckmann et al. 2008).

Noteworthy, BMI has been found to increase excessively in GCC patients during follow-up after chemotherapy (Nord et al. 2003; Nuver et al. 2005). This deviation is not universally found (Huddart and Norman 2003) and, obviously, it does not relate to aetiology and pathogenesis of GCC. Probably, the BMI increase after systemic therapy is caused by metabolic changes secondary to treatment toxicity. Thus, these reports are not relevant to the present analysis since our goal had been to elucidate the role of increased BMI on to the incidence of GCC.

Methodological aspects

The present study has some strengths. The number of patients involved herein is exceptionally higher than in previous studies. Moreover, selection bias is improbable because the patient sample had been enrolled from more than 200 institutions across Germany thus representing national standard. The set of controls represents national standard, too. These subjects had been randomly selected to generate a representative sample with the purpose of pointing up the current health status of German individuals. So, selection bias among controls is unlikely, too. In all, chance results are thus left at a minimum. Yet, the study does also have its share of weaknesses. Notably, the only information available regarding controls is the frequency of BMI categories among various age groups (Ellert et al. 2006). We do not have individual anthropometric measures of control subjects. Thus, calculation of odds ratios and multivariate analysis with adjusting for particular parameters is not feasible. In addition, the number of controls is markedly lower than the number of cases leaving some chance of statistical confounding due to this imbalance. Nonetheless, the set of controls had been carefully selected to build up a representative population (Thefeld et al. 1999). Therefore, we believe that confounding because of inappropriate controls is rather improbable. Another drawback is the lack of differentiation of the patient sample into histological subgroups.

Conclusion

Overall, there is no association of increased BMI with risk of GCC. High calorie nutrition during adulthood does probably not advance the pathogenesis of GCC in general. However, GCC is not a homogeneous disease, morphologically and clinically. Among patients younger than 30 years, there is a clear association of increased BMI with incidence of GCC. And thus, the present data indicate that in this particular subgroup high-calorie intake could indeed promote the development of testicular malignancy. Further, as among the patients younger than 30 years nonseminoma is much more prevalent than pure seminoma, the present data could also point to divergent pathogenetic pathways of the two histological subtypes.

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Conflict of interest statement None.

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