

RESEARCH ARTICLE

Obesity and Risk of Bladder Cancer: A Meta-analysis of Cohort Studies

Qi Qin¹, Xin Xu², Xiao Wang², Xiang-Yi Zheng^{2*}

Abstract

Objective: Previous epidemiologic studies demonstrated that obesity might associated with the risk of bladder cancer. However, many of the actual association findings remained conflicting. To better clarify and provide a comprehensive summary of the correlation between obesity and bladder cancer risk, we conducted a meta-analysis to summarize results of studies on the issue. Stratified analyses were also performed on potential variables and characteristics. **Methods:** Studies were identified by searching in PubMed and Wanfang databases, covering all the papers published from their inception to March 10, 2013. Summary relative risks (SRRs) with their corresponding 95% confidence intervals (CIs) were calculated by either random-effect or fixed-effect models. **Results:** A total of 11 cohort studies were included in our meta-analysis, which showed that obesity was associated with an increased risk for bladder cancer in all subjects (RR=1.10, 95% CI=1.06–1.16; $p=0.215$ for heterogeneity; $I^2=24.0\%$). Among the 9 studies that controlled for cigarette smoking, the pooled RR was 1.09 (95% CI 1.01-1.17; $p=0.131$ for heterogeneity; $I^2=35.9\%$). No significant publication bias was detected ($p = 0.244$ for Egger's regression asymmetry test). **Conclusions:** Our results support the conclusion that obesity is associated with the increased risk of bladder cancer. Further research is needed to generate a better understanding of the correlation and to provide more convincing evidence for clinical intervention in the prevention of bladder cancer.

Keywords: Obesity - bladder cancer - risk - meta-analysis - smoking - confounding factor

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Introduction

Bladder cancer is the eleventh most commonly diagnosed type of cancer worldwide (Jemal et al., 2011). In the United States, statistics demonstrated that an estimated 72570 cases were newly diagnosed with bladder cancer, among which 15210 were expected to die in 2013 (Siegel et al., 2013). Compared to other places in the world, Bladder cancer is considered to be a relatively common disease in Europe, North America, and Northern part of Africa (Jemal et al., 2011). Bladder cancer is a sophisticated disease. Both genetic and environmental factors are considered to play important roles in the carcinogenesis of bladder cancer (Murta-Nascimento et al., 2007; Burger et al., 2013; Wang et al., 2013). Although some well-established risk factors such as smoking and exposure to arylamines and schistosomal infection are thought to be directly associated with increased risk of bladder cancer, the mechanism of bladder cancer still remains contradictory (Murta-Nascimento et al., 2007). These factors can not thoroughly explain the difference in bladder cancer rate between ethnicities and genders. Further researches are needed to explore potential risk factors and clarify the interaction between them.

Obesity has already been a universal health problem. Statistics illustrates that almost two thirds of adults in the

United States are currently suffering from overweight (BMI between 25.0 and 29.9kg/m²) or obesity (BMI>30.0 kg/m²), among which 50% are lack of physical exercises (Flegal et al., 2005). Previous epidemiologic studies demonstrated that obesity was associated with the risk of bladder cancer (Lew and Garfinkel, 1979; Whittemore et al., 1984; Harris et al., 1990; Vena et al., 1992; Moller et al., 1994; Wolk et al., 2001; Pelucchi et al., 2002; Tripathi et al., 2002; Calle et al., 2003; Samanic et al., 2004; Cantwell et al., 2006; Samanic et al., 2006; Holick et al., 2007; Reeves et al., 2007; Jee et al., 2008; Koebnick et al., 2008; Larsson et al., 2008; Haggstrom et al., 2011). Some studies showed a positive relationship between obesity and increased risk of bladder cancer (Samanic et al., 2004; Holick et al., 2007; Koebnick et al., 2008). However, most studies illustrated no statistically significant correlation was detected between adiposity and bladder cancer risk (Lew and Garfinkel, 1979; Whittemore et al., 1984; Harris et al., 1990; Vena et al., 1992; Moller et al., 1994; Wolk et al., 2001; Pelucchi et al., 2002; Tripathi et al., 2002; Calle et al., 2003; Cantwell et al., 2006). Koebnick et al took a closer look at the above studies, and he observed that the majority of the studies were limited by small numbers of included cases and controls (Koebnick et al., 2008). Therefore, the actual association between obesity and bladder cancer risk still remained conflicting.

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To better clarify and provide a comprehensive summary of the correlation between obesity and bladder cancer risk, we conducted a meta-analysis to summarize the studies on the issue. Stratified analyses were also performed on potential variables and characteristics.

Materials and Methods

Publication search

Two authors independently performed a systematic literature search in PubMed and Wanfang databases, covering all the papers published from their inception to March 10, 2013, using the following key words: (obesity OR overweight OR “body mass” OR BMI OR “bodyweight” OR anthropometric) and (bladder Cancer or bladder neoplasm or bladder tumor or urothelial cancer or urinary tract cancer). There was no language restriction. Potentially relevant papers were evaluated by checking their titles and abstracts and all the studies matching the eligible criteria were retrieved. Additional studies were identified by a manual search of the references from retrieved articles and reviews.

Inclusion criteria

Studies included in present meta-analysis had to meet all the following criteria: (a) evaluation of the obesity and the risk of bladder cancer, (b) had a cohort design, (c) had sufficient data for calculating relative risk (RR) with 95% confidence interval (CI). Studies on mortality rates from bladder cancer were not included, as it could be confounded by survival related factors. If multiple publications from the same population were available, the most recent or largest study was eligible for inclusion in this meta-analysis.

Data extraction

Data were extracted independently by two authors using a predefined data collection form, with disagreements being resolved by consensus. For each study, the following information were collected: first author’s name, year of publication, the country in which the study was carried out, participant characteristics (age and gender), range for follow-up, sample size (cases and cohort size), methods of ascertainment of obesity and bladder cancer, estimate effects with their 95% CIs, and covariates adjusted for in the analysis. From each study, we extracted the RR estimate that was adjusted for the greatest number of potential confounders. If studies reported results separately for men and women, we combined the sex-specific estimates to generate an estimate for both genders combined.

Statistical methods

If there was a statistical heterogeneity among studies, the combined RRs and 95% CI were estimated by the DerSimonian and Laird method in a random-effect model (DerSimonian and Laird, 1986). Otherwise, the RRs were obtained by Mantel–Haenszel method in a fixed effect model (Mantel and Haenszel, 1959). Subgroup analyses were carried out by (a) gender, (b) geographic region, and (c) smoking status.

Homogeneity of ORs across studies was tested by a Chi-square-based Q statistic and the I^2 score. Heterogeneity was considered significant if the P-value is < 0.10 . The value of I^2 is used to assess the degree of heterogeneity ($I^2 < 25\%$ no heterogeneity; $I^2 = 25\text{--}50\%$ moderate heterogeneity; $I^2 > 50\%$ large or extreme heterogeneity).

Sensitivity analysis was performed, in which the meta-analysis estimates were computed after omission of every study in turn. Cumulative meta-analysis was also conducted through assortment of studies with publication time.

Evaluation of publication bias

Publication bias was assessed using Begg’s test (rank correlation method) and Egger’s test (linear regression method) (Begg and Mazumdar, 1994; Egger et al., 1997). $P < 0.05$ was considered to be representative of a significant statistical publication bias. All of the statistical analyses were performed with STATA 11.0 (Stata Corp, College Station, TX), using two-sided P-values.

Results

Literature search

Figure 1 outlines our study selection process. Briefly, the search strategy generated 1814 articles. Of these, the majority were excluded after the first screening based on abstracts or titles, mainly because they were reviews, case reports, or not relevant to our analysis.

After full-text review of 25 papers, 14 studies were excluded for the reasons as follows: case-control studies ($n = 6$) (Harris et al., 1990; Moller et al., 1994; Pelucchi et al., 2002; Pan et al., 2004; Machova et al., 2007; Attner et al., 2012); overlapping publications from the same study population ($n = 3$); the outcome was cancer mortality ($n = 4$); lack sufficient data ($n = 1$). Thus, a total of 11 cohort studies, which met the inclusion criteria, were included in this meta-analysis (Wolk et al., 2001; Tripathi et al., 2002; Samanic et al., 2004; Cantwell et al., 2006; Samanic et al., 2006; Holick et al., 2007; Reeves et al., 2007; Jee et al., 2008; Koebnick et al., 2008; Larsson et al., 2008; Haggstrom et al., 2011).

Study characteristics

The characteristics of the 11 cohort studies are presented in Table 1. These studies were conducted in the following regions: Europe ($n = 4$) (Wolk et al., 2001;

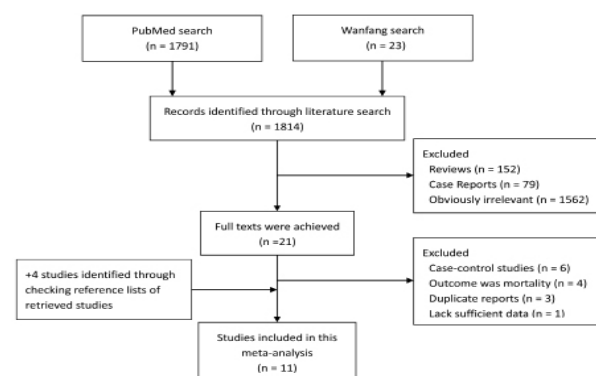
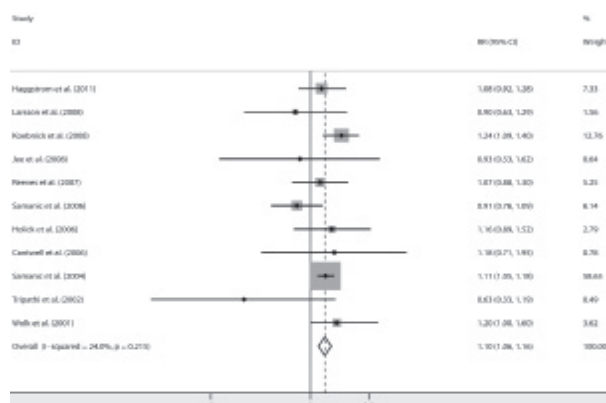


Figure 1. Flowchart of Study Search

Table 1. Main Characteristics of Cohort Studies Evaluating the Association Between Obesity and Risk of Bladder Cancer

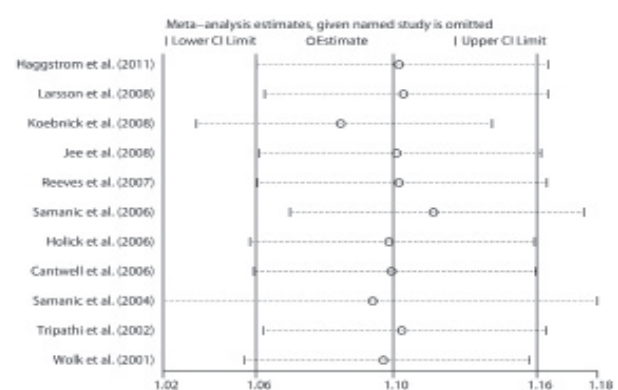
First author, year of publication	Region	Sex and age	Cases/cohort	Follow-up	Obesity assessment	Bladder cancer	Adjusted variables
Haggström et al., 2011	Norway, Austria, Sweden	Men and women aged 30–75 years	1,914/578,700	11.7 years	Not specified	Cancer registry	Smoking, five categories of birth year, age at measurement
Koebnick et al., 2008	USA	Men and women aged 30–75 years	1,719/471,760	3,404,642 person-years	Self-reported	Cancer registry	Gender, age at baseline, race/ethnicity, education, smoking status, intakes of fruits and vegetables, red meat, beverages, and alcohol, and NSAID use
Larsson et al., 2008	Sweden	Men aged 45–79 years	414/45,906	9.3 years	Self-reported	Cancer registry	Age, education, smoking status and pack-years of smoking
Jee et al., 2008	Korea	Men and women aged 30–75 years	2,439/1,213,829	14 years	Measured	Cancer registry	Age, and smoking status
Reeves et al., 2007	UK	Women aged 50–64 years	615/1,222,630	5.4 years	Measured	Cancer registry	Age, region, socioeconomic status, reproductive history, smoking, alcohol, activity
Samanic et al., 2006	Sweden	Men aged 34.3 years (mean)	1,066/362,552	19 years	Measured	Cancer registry	Age, calendar year, smoking status
Holick et al., 2006	USA	Men and women aged 30–75 years	1,572/173,229	5,432,488 person-years	Self-reported	Medical records	Age, pack-years of cigarette smoking and current smoking
Cantwell et al., 2006	USA	Women aged 55.4 years (mean)	167/54,308	15.3 years	Measured	Medical records	Age, calendar year and smoking status
Samanic et al., 2004	USA	Men aged 45–79 years	19,215/4,500,700	12 years	Discharge diagnosis	Hospital visit	Age, race, calendar year
Tripathi et al., 2002	USA	Women aged 55–69 years	112/37,459	13 years	Self-reported	Cancer registry	Age, smoking, regular physical activity, BMI, alcohol, married, occupation lifetime
Wolk et al., 2001	Sweden	Men and women aged 30–75 years	67/28,129	10 years	Physical appearance	Cancer registry	Not specified

**Figure 2. Relative Risks for the Association Between Obesity and Risk of Bladder Cancer in Cohort Studies****Table 2. Subgroup Analysis of Relative Risks for the Association Between Obesity and Bladder Cancer**

Subgroup	References number	RR (95% CI)	Heterogeneity test		
			Q	P	I ² (%)
Gender					
Male	8	1.10 (1.05, 1.16)	7.98	0.334	12.3
Female	8	1.15 (1.02, 1.29)	9.97	0.19	29.8
Geographical region					
Europe	4	1.02 (0.89, 1.16)	4.07	0.254	26.3
USA	5	1.14 (1.04, 1.25)	5.73	0.22	30.2
Adjustment for smoking					
Yes	9	1.09 (1.01, 1.17)	12.49	0.131	35.9
No	2	1.12 (1.05, 1.18)	0.4	0.528	0

RR, relative risk; CI, confidence interval

Samanic et al., 2006; Reeves et al., 2007; Larsson et al., 2008), and USA (n=5) (Tripathi et al., 2002; Samanic et al., 2004; Cantwell et al., 2006; Holick et al., 2007; Koebnick et al., 2008), Asia (n=1) (Jee et al., 2008), and mixed countries (n=1) (Haggstrom et al., 2011). The study population in 5 studies consisted of both sexes (Wolk et al., 2001; Holick et al., 2007; Jee et al., 2008; Koebnick et al., 2008; Haggstrom et al., 2011), 3 studies included men only (Samanic et al., 2004; Samanic et al., 2006; Larsson et al., 2008) and the other 3 studies included women only (Tripathi et al., 2002; Cantwell et al., 2006; Reeves et al., 2007). The cohort ranged in size from 28,129 to 4,500,700. Obesity was ascertained mainly by self-reported or measured height and weight. Diagnosis

**Figure 3. Influence Analysis in the Overall Meta-Analysis.** The figure shows the influence of individual studies on the summary odds ratio (OR). CI, confidence interval

of bladder cancer was mainly based on medical record or cancer registry data. Adjustments were made for potential confounders of one or more factors in all studies. Of these, 9 studies adjusted for smoking (Tripathi et al., 2002; Cantwell et al., 2006; Samanic et al., 2006; Holick et al., 2007; Reeves et al., 2007; Jee et al., 2008; Koebnick et al., 2008; Larsson et al., 2008; Haggstrom et al., 2011).

Quantitative synthesis

As showed in Figure 2, obesity was associated with an increased risk for bladder cancer in all subjects (RR=1.10, 95% CI=1.06–1.16; $p=0.215$ for heterogeneity; $I^2=24.0\%$). Next, we conducted subgroup meta-analysis by various study characteristics (Table 2). When stratifying by gender, the summary RRs with 95% CIs were 1.10 (95% CI 1.05–1.16; $p=0.334$ for heterogeneity; $I^2=12.3\%$) for male, and 1.15 (95% CI 1.02–1.29; $p=0.190$ for heterogeneity; $I^2=29.8\%$) for female. Moreover, in the subgroup analysis by geographical area, the association between obesity and bladder cancer was more significant for studies conducted in USA (RR 1.14, 95% CI 1.04–1.25; $p=0.220$ for heterogeneity; $I^2=30.2\%$) than in Europe (RR 1.02, 95% CI 0.89–1.16; $p=0.254$ for heterogeneity; $I^2=26.3\%$). Cigarette smoking is an established risk factor for bladder cancer, and thus a potential confounder of the relationship between obesity and risk of bladder cancer. Among the 9 studies that controlled for cigarette smoking, the pooled RR was 1.09 (95% CI 1.01–1.17; $p=0.131$ for heterogeneity; $I^2=35.9\%$).

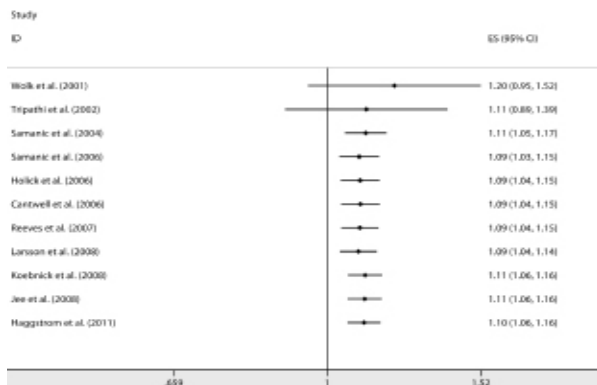


Figure 4. Cumulative Meta-analysis of the Association Between Obesity and Bladder Cancer

Evaluation of heterogeneity

Most I^2 values of heterogeneity were less than 50% and all P values were more than 0.10, indicating no statistically significant heterogeneity between studies (Table 2).

Sensitive analysis

In the sensitivity analysis (Figure3), the influence of each study on the pooled RR was examined by repeating the meta-analysis while omitting each study, one at a time. This procedure proved that our results were reliable and robust.

Cumulative meta-analysis

Cumulative meta-analysis of the association between obesity and bladder cancer was also conducted via the assortment of studies by publication time. The 95% confidence intervals became increasingly narrower with increasing sample size, indicating that the precision of the estimates was progressively boosted by the continual addition of more cases (Figure4).

Publication bias

There was no evidence of significant publication bias either with the Begg’s test (Figure5, $P = 0.213$) or with Egger’s test ($P = 0.244$).

Discussion

The results of our meta-analysis of 11 cohort studies indicated that obesity was associated with a 10% increased risk of bladder cancer (Wolk et al., 2001; Tripathi et al., 2002; Samanic et al., 2004; Cantwell et al., 2006; Samanic et al., 2006; Holick et al., 2007; Reeves et al., 2007; Jee et al., 2008; Koebnick et al., 2008; Larsson et al., 2008; Haggstrom et al., 2011).

As was well-known, the correlation between obesity and bladder cancer risk was more reliable in studies with a rate ratio or hazard ratio to evaluate relative risk than those with a standardized incidence ratio. The actual relative risk might be underrated via using standardized incidence ratio or standardized mortality ratio to evaluate relative risk (Jones and Swerdlow, 1998; Chaturvedi et al., 2008). It was because that if the general population was used to represent the unexposed population, the result would be inevitably biased since it included all types of population except for exposed ones (Jones and Swerdlow,

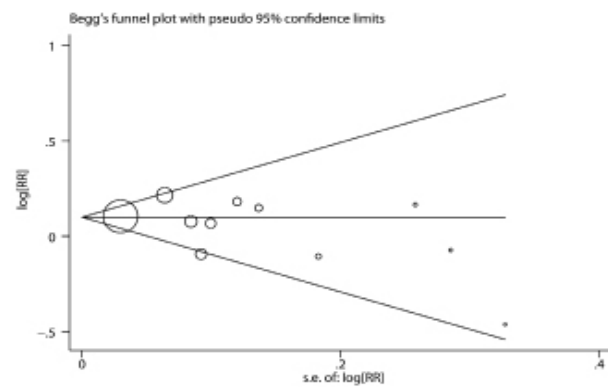


Figure 5. Publication bias in the Studies Included in this Meta Analysis

1998). Therefore, the strength of the summary RRs risk could be attenuated by the results from studies via using standardized incidence ratio to evaluate the relative risk. On the contrary, the results of our analysis were actually statistically significant.

In our meta-analysis, we detected that a statistically significant association between obesity and increased risk for bladder cancer in all subjects (RR=1.10, 95% CI=1.06-1.16). To further demonstrate the correlation between obesity and bladder cancer risk, stratified analyses were conducted. The pooled RR estimates indicated that obesity was associated with an increased risk of bladder cancer while independently analyzed by gender, geographical area and smoking status. When stratifying by gender, the summary RRs with 95% CIs were 1.10 (95% CI 1.05-1.16) for male, and 1.15 (95% CI 1.02-1.29) for female. Furthermore, smoking was an established risk factor for most types of cancer, which could be a potential confounder when assessing the relationship between obesity and bladder cancer risk. In the 9 studies that controlled for smoking, similar result was observed (RR=1.09, 95% CI 1.01-1.17). However, in the stratified analysis by geographical area, the association between obesity and bladder cancer was more significant for studies conducted in USA (RR 1.14, 95% CI 1.04-1.25) than in Europe (RR 1.02, 95% CI 0.89-1.16). We took a closer look at one study from Sweden which illustrated inconsistent results from most of other included studies, in which no significant correlation between obesity and increased bladder cancer risk was observed. The strength of this study included a population-based and prospective design and a large sample size (Larsson et al., 2008). Therefore, the result on whether obesity was associated with increased risk of bladder cancer should be treated cautiously.

The correlation between obesity and increased bladder cancer risk need further research to better clarify the potential mechanism. Best to our knowledge, the relationship between obesity and diabetes, especially type 2 diabetes, is definite. Obese people tend to suffer from diabetes. The role of obesity in the process of carcinogenesis is probably similar to that of diabetes. It is well-known that type 2 diabetes is related to insulin resistance, and up-regulated serum level of IGF-1. IGF-1 could stimulate proliferation and inhibit apoptosis, which could ultimately result in cancer. Previous epidemiological

studies implicated that IGF-I played an important role in the development of breast and colorectal cancers (Key et al., 2010; Rinaldi et al., 2010). Another case-control study detected higher levels of IGF-I in bladder cancer cases than that in controls which was statistically significant (Zhao et al., 2003). The role of IGF-I in the development of bladder cancer was also evaluated via in vivo studies which demonstrated similar results (Dunn et al., 1997). Additionally, diabetes was also found to be related to an increased risk of urinary tract infection (Funfstuck et al., 2012) and urinary tract calculi (Chen et al., 2012), which was associated with various histologic types of bladder cancer, such as transitional cell carcinoma (Chow et al., 1997; Jankovic and Radosavljevic, 2007).

One major advantage of our analysis was that with larger sample size and summarized statistics, we elevated the reliability and accuracy of estimation of the correlation between obesity and bladder cancer risk. Nevertheless, several limitations in our analysis should be taken into consideration which could affect the final conclusion. Firstly, because our study failed to include unpublished observations and exclude studies with insufficient information, such as meeting abstracts, which might bring about a publication bias even though no statistically significant evidence of publication bias was observed in neither Egger's nor Begg's test. Secondly, various assessments of obesity were used in our analysis. Some studies used self-report as a method to assess obesity, which may lead to some misclassification of obese people as non-obese people. This underreporting might lead to an underestimate of the magnitude of the association between obesity and bladder cancer risk. Thirdly, unmeasured risk factors might bring out potential bias. Although the most studies included were adjusted for more than 3 confounders, we still couldn't exclude the possibility that the remaining factors could affect the final statistics. For example, most studies in our analysis failed to take physical activity into account, which might influence our results, for physical activity played an important role in the development of cancer.

In conclusion, our results supported that obesity was associated with the increased risk of bladder cancer. Further researches are needed to get a better understanding of the correlation and to provide more convincing evidence for clinical intervention in the prevention of bladder cancer.

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References

Begg CB, Mazumdar M (1994). Operating characteristics of a rank correlation test for publication bias. *Biometrics*, **50**, 1088-101.

Chen HS, Su LT, Lin SZ, et al (2012). Increased risk of urinary tract calculi among patients with diabetes mellitus--a

population-based cohort study. *Urology*, **79**, 86-92.

Chow WH, Lindblad P, Gridley G, et al (1997). Risk of urinary tract cancers following kidney or ureter stones. *J Natl Cancer Inst*, **89**, 1453-7.

DerSimonian R, Laird N(1986). Meta-analysis in clinical trials. *Control Clin Trials*, **7**, 177-88.

Dunn SE, Kari FW, French J, et al (1997). Dietary restriction reduces insulin-like growth factor I levels, which modulates apoptosis, cell proliferation, and tumor progression in p53-deficient mice. *Cancer Res*, **57**, 4667-72.

Egger M, Davey Smith G, Schneider M, Minder C (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ*, **315**, 629-34.

Flegal KM, Graubard BI, Williamson DF, Gail MH (2005). Excess deaths associated with underweight, overweight, and obesity. *JAMA*, **293**, 1861-7.

Funfstuck R, Nicolle LE, Hanefeld M, Naber KG (2012). Urinary tract infection in patients with diabetes mellitus. *Clin Nephrol*, **77**, 40-8.

Haggstrom C, Stocks T, Rapp K, et al (2011). Metabolic syndrome and risk of bladder cancer: prospective cohort study in the metabolic syndrome and cancer project (Me-Can). *Int J Cancer*, **128**, 1890-8.

Jankovic S, Radosavljevic V (2007). Risk factors for bladder cancer. *Tumori*, **93**, 4-12.

Jee SH, Yun JE, Park EJ, et al (2008). Body mass index and cancer risk in Korean men and women. *Int J Cancer*, **123**, 1892-6.

Jemal A, Bray F, Center MM, et al (2011). Global cancer statistics. *CA Cancer J Clin*, **61**, 69-90.

Jones ME, Swerdlow AJ (1998). Bias in the standardized mortality ratio when using general population rates to estimate expected number of deaths. *Am J Epidemiol*, **148**, 1012-7.

Key TJ, Appleby PN, Reeves GK, Roddam AW(2010). Insulin-like growth factor 1 (IGF1), IGF binding protein 3 (IGFBP3), and breast cancer risk: pooled individual data analysis of 17 prospective studies. *Lancet Oncol*, **11**, 530-42.

Koebnick C, Michaud D, Moore SC, et al (2008). Body mass index, physical activity, and bladder cancer in a large prospective study. *Cancer Epidemiol Biomarkers Prev*, **17**, 1214-21.

Larsson SC, Andersson SO, Johansson JE, Wolk A (2008). Diabetes mellitus, body size and bladder cancer risk in a prospective study of Swedish men. *Eur J Cancer*, **44**, 2655-60.

Mantel N, Haenszel W(1959). Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst*, **22**, 719-48.

Murta-Nascimento C, Schmitz-Drager BJ, Zeegers MP, et al (2007). Epidemiology of urinary bladder cancer: from tumor development to patient's death. *World J Urol*, **25**, 285-95.

Rinaldi S, Cleveland R, Norat T, et al (2010). Serum levels of IGF-I, IGFBP-3 and colorectal cancer risk: results from the EPIC cohort, plus a meta-analysis of prospective studies. *Int J Cancer*, **126**, 1702-15.

Siegel R, Naishadham D, Jemal A (2013). Cancer statistics, 2013. *CA Cancer J Clin*, **63**, 11-30.

Zhao H, Grossman HB, Spitz MR, et al (2003). Plasma levels of insulin-like growth factor-1 and binding protein-3, and their association with bladder cancer risk. *J Urol*, **169**, 714-7.