Obesity and oesophageal cancer

Nimptsch, K. and Steffen, A. and Pischon, T.

This is the final version of the accepted manuscript. The original article has been published in final edited form in:

Obesity and Cancer

Recent Results in Cancer Research
2016 DEC 02 ; 208: 67-80
Publisher: Springer Verlag

The final publication is available at Springer via: https://doi.org/10.1007/978-3-319-42542-9_4

© 2016, Springer International Publishing Switzerland
Published in accordance with the German Copyright Law
Obesity and oesophageal cancer

Katharina Nimptsch1*, Annika Steffen2, Tobias Pischon1

1 Molecular Epidemiology Research Group, Max Delbrück Center for Molecular Medicine (MDC), Berlin, Germany
2 Department of Epidemiology, German Institute of Human Nutrition Potsdam-Rehbrücke, Nuthetal, Germany
* katharina.nimptsch@mdc-berlin.de; +49 (0)30 9406 4573

Abstract (150-250 words)

A substantial increase in the incidence of oesophageal adenocarcinoma has been observed in western countries during the past 30 years, which may be related to the parallel rise of the obesity prevalence. On the other hand, incidence rates of oesophageal squamous cell carcinomas, the other major histological type of oesophageal cancer, have remained relatively stable. Epidemiological research of the past decades has identified obesity as risk factor for oesophageal adenocarcinoma. Studies investigating general obesity as assessed by body mass index provide evidence for a strong positive association with oesophageal adenocarcinoma. Studies investigating abdominal obesity in relation to oesophageal adenocarcinoma observed also positive associations, which may be independent of general obesity. Some studies indicate that early life obesity is also associated with higher risk of oesophageal adenocarcinoma, but it is as to date unclear whether these associations are independent of adult obesity. Part of the positive association between obesity and oesophageal adenocarcinoma may be explained through obesity-related mechanical promotion of gastrooesophageal reflux disease, which is one of the main risk factors for oesophageal adenocarcinoma. Other lines of evidence point to an independent role of metabolic pathways modulating cell proliferation, apoptosis and cell growth such as pro-inflammatory cytokines, adipokines and insulin resistance, the role of which in oesophageal carcinogenesis is, however, as to date insufficiently understood. Studies investigating obesity in
relation to squamous cell carcinoma observed inverse relationships, but the underlying mechanisms remain unclear.

1 Introduction

Oesophageal cancer is ranked as ninth most common incident cancer and sixth most common cancer death by the Global Burden of Disease Cancer Collaboration [1]. With a five-year survival rate between 15 and 25%, oesophageal cancer poses an immense burden of disease globally [2,3]. Unlike many other common types of cancer, oesophageal cancer occurs more frequently in developing countries than in developed countries. Global incidence rates differ up to 20-fold, with highest observed incidence rates in countries in east and central Asia and southern sub-Saharan Africa. There is a male predominance of oesophageal cancer, which occurs globally 2-3 times more often in men than in women [4]. Two major histopathological types of oesophageal cancer can be distinguished, i.e. squamous cell carcinoma and adenocarcinoma, which differ in etiology and risk factors. Worldwide, squamous cell carcinoma is the predominant type of oesophageal cancer while adenocarcinoma is less common [3]. During the last 30 years, a substantial increase in the incidence of oesophageal adenocarcinoma has been observed in western Europe, north America, and Australia, making it the most rapidly growing cancer in developed countries [5]. Although this rise may be partly related to better diagnostic techniques [6], the parallel rise in the obesity prevalence has been suggested as a possible explanation. Incidence rates of oesophageal squamous cell carcinomas on the other hand, did not face substantial changes in incidence rates [5]. Tobacco use and alcohol consumption are the main risk factors for squamous cell carcinoma of the oesophagus [3], which together may account for half of squamous cell carcinoma cases [7]. Tobacco use is also a risk factor for oesophageal adenocarcinomas, but observed relative risks are weaker. Gastro-oesophageal reflux disease (GERD) , Barrett’s oesophagus and obesity are the best-established and strongest risk factors for
oesophageal adenocarcinoma [8]. Barrett’s oesophagus is a pre-malignant lesion that may develop as a consequence of long-term GERD and is considered a precursor of oesophageal adenocarcinoma. Since GERD is more prevalent in obese than non-obese individuals, it has been suggested that obesity is positively related to Barrett’s oesophagus and oesophageal adenocarcinoma mainly through GERD. On the other hand, several lines of evidence also observed an association between obesity and oesophageal adenocarcinoma independent of GERD, suggesting that also indirect mechanisms such as alterations in obesity-related biomarkers may play an etiologic role [9].

In the following chapter, the current epidemiologic evidence on the association between obesity and risk of oesophageal adenocarcinoma will be summarized, with special emphasis on the distinction between general obesity and body fat distribution and the role of obesity during early life. We will further review current knowledge on the impact of pre-diagnostic obesity on survival among oesophageal cancer patients. Finally, we will give an overview on the current knowledge on the biological mechanisms underlying the positive association between obesity and oesophageal adenocarcinoma. Furthermore, we will give an overview on the current knowledge on the association of obesity and squamous cell carcinoma.

2 Association between obesity and oesophageal adenocarcinoma incidence

A number of epidemiological studies have investigated the association between obesity and risk of oesophageal adenocarcinoma. There are abundant studies investigating general obesity represented by body mass index (BMI) while fewer studies have investigated abdominal obesity, for instance represented by waist circumference or waist-to-hip ratio. The definition of the outcome varies from study to study: Some studies report results on oesophageal adenocarcinoma alone, while others report results for oesophageal adenocarcinoma and the anatomically related
gastric cardia adenocarcinoma combined.

2.1 General obesity

A positive association between BMI and risk of oesophageal adenocarcinoma has been observed in a number of case-control and cohort studies and several meta-analyses and pooled analyses have been conducted to summarize the existing evidence (Table 1). The first comprehensive meta-analysis was published in 2006 and investigated the association between BMI and adenocarcinomas of the oesophagus or gastric cardia [10] combining data from 2 cohort and 12 case-control studies. In this data synthesis, being overweight or obese (BMI ≥25 kg/m²) was associated with a 1.7-fold (odds ratio (OR) 1.7, 95% confidence interval (CI) 1.6, 1.9) higher risk of oesophageal adenocarcinoma (including studies that combined oesophageal and gastric cardia adenocarcinomas). When studies using a combined endpoint were excluded (leaving 1 cohort and 5 case-control studies for analysis), the association was slightly stronger (OR 2.1, 95% CI 1.7, 2.4) and indicated a linear relationship. In a systematic review summarizing the evidence from epidemiological studies published between this first meta-analysis and May 2010, obesity (BMI ≥30 kg/m²) was associated with a significantly higher risk of oesophageal adenocarcinoma in all studies [6], with relative risks (RR) ranging from 2.5 to 11.3. Another meta-analysis on the association of BMI with oesophageal and gastric adenocarcinoma was published in 2013 and included 22 studies (12 case-control, 10 cohort studies) [11]. The results of this meta-analysis are generally in line with the previous meta-analysis: A positive association between overweight and obesity and risk of oesophageal or gastric cardia adenocarcinoma combined was observed (relative risk (RR) for overweight 1.71, 95% CI 1.50, 1.96; RR for obesity 2.34, 95% CI 1.95, 2.81). Risk estimates were higher when pooling data from case-control as compared with cohort studies, but associations were statistically significant for both study designs. No substantial sex-
differences were observed. Similar to the previous meta-analysis, the positive association with BMI was stronger for oesophageal adenocarcinoma (RR for overweight 1.87, 95% CI 1.61, 2.17; RR for obesity 2.73, 95% CI 2.16, 3.46) than for gastric cardia adenocarcinoma. In this meta-analysis, also a dose-response meta-analysis was conducted, estimating a 13% higher risk of oesophageal adenocarcinoma associated with 5 kg/m² higher BMI. However, the meta-analysis also revealed potential publication bias, which may indicate an overestimation of the true association. Adjustment for publication bias resulted in lower, but still statistically significant estimates for overweight and obesity.

In a pooled analysis using individual participant data from 12 epidemiological studies (10 case-control and 2 cohort studies), the association between BMI and oesophageal and oesophagogastric junction adenocarcinoma was investigated with special regard to potential effect modification by GERD or sex [9]. With respect to oesophageal adenocarcinoma, a strong positive dose-response association with BMI was observed, with risk estimates increasing linearly across BMI-categories, up to an almost five-fold risk for a BMI ≥40 kg/m² (compared with BMI <25 m²). These findings were multivariable adjusted for age, sex, smoking and study-specific adjustment variables and remained unchanged after additional adjustment for GERD in the five studies that collected information on GERD symptoms. Furthermore, the positive association between BMI and risk of oesophageal adenocarcinoma was similar in individuals with and without history of GERD symptoms. These observations suggest that also indirect metabolic pathways may explain part of the association between obesity and risk of oesophageal adenocarcinoma beyond the pathway via GERD. However, an analysis testing for interaction found evidence for synergism between BMI and GERD with respect to oesophageal adenocarcinoma risk, i.e. the joint effect of both exposures had a greater effect on the risk than would be expected from their independent effects. Similar associations between BMI and
oesophageal adenocarcinoma were observed after stratification by sex, but there was some indication that sex may modify the association between BMI and oesophageal adenocarcinoma in individuals without GERD symptoms, which, considering the sex-specific differences in fat distribution, especially differences in the amount of metabolic active visceral fat, also points to a role of indirect metabolic pathways. BMI was also positively associated with adenocarcinoma of the oesophagogastric junction in a dose-response manner, but associations were less pronounced than with oesophageal adenocarcinoma. Compared with the study-level meta-analyses, this pooled analysis used individual-level data and harmonized variables and statistical models enabling targeted investigation of confounding, effect modification and interaction. However, the pooled studies had some limitations in common, which may also influence pooled findings. For instance, most of the pooled studies were case-control studies lacking the ability to investigate the time-sequence between obesity and oesophageal adenocarcinoma. In addition, BMI was derived from self-reported adult height and weight in all pooled studies, which may introduce misclassification bias. However, a positive association between BMI and risk of oesophageal adenocarcinoma was also observed in a consortium of seven prospective cohort studies from Austria, Norway and Sweden, in all of which weight and height weight were measured at baseline [12]. In the pooled analysis adjusted for sex, age and smoking status, overweight at baseline was associated with more than two-fold higher (RR 2.32, 95% CI 1.51, 3.57) and obesity with more than three-fold (RR 3.29, 95% CI 1.82, 5.95) higher risk of oesophageal adenocarcinoma compared with normal-weight.
Table 1. Summary of pooled analyses and meta-analyses on the association between overweight and obesity and risk of oesophageal adenocarcinoma

<table>
<thead>
<tr>
<th>Publication</th>
<th>Data synthesis type</th>
<th>Number and design of included studies</th>
<th>Findings for oesophageal adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindkvist et al. 2014</td>
<td>Pooled analysis</td>
<td>7 prospective cohorts</td>
<td>Compared with BMI 18.5-25.0 kg/m² BMI 25.0-29.9 kg/m²: RR 2.32 95% CI 1.51, 3.57 BMI ≥30 kg/m²: RR 3.29, 95% CI 1.82, 5.95</td>
</tr>
<tr>
<td>Hoyo et al. 2012</td>
<td>Pooled analysis</td>
<td>10 case-control studies, 2 prospective cohorts</td>
<td>Compared with BMI &lt;25.0 kg/m² BMI 25.0-29.9 kg/m², RR 1.54 95% CI 1.26, 1.88 BMI 30.0-34.9 kg/m², RR 2.39, 95% CI 1.86, 3.06 BMI 35.0-39.9 kg/m², RR 2.79, 95% CI 1.89, 4.12 BMI ≥40 kg/m²: RR 4.76, 95% CI 2.96, 7.66</td>
</tr>
<tr>
<td>Turati et al. 2013</td>
<td>Meta-analysis</td>
<td>12 case-control studies, 10 prospective cohorts</td>
<td>Compared with BMI &lt;25.0 kg/m² BMI 25.0-29.9 kg/m²: RR 1.87 95% CI 1.61, 2.17 BMI ≥30 kg/m²: RR 2.73, 95% CI 2.16, 3.46</td>
</tr>
<tr>
<td>Kubo et al. 2006</td>
<td>Meta-analysis</td>
<td>12 case-control studies, 2 prospective cohorts</td>
<td>Compared with BMI &lt;25.0 kg/m² BMI 25.0-29.9 kg/m²: RR 1.9 95% CI 1.5, 2.4 BMI ≥30 kg/m²: RR 2.4, 95% CI 2.0, 2.8</td>
</tr>
</tbody>
</table>

Abbreviations: RR, relative risk; CI, confidence interval

2.2 Abdominal obesity

It has been suggested that abdominal obesity, reflecting the amount of metabolically active visceral fat, may be more important for the risk of Barrett’s oesophagus and oesophageal adenocarcinoma than general obesity [13]. In particular, it has been proposed that abdominal obesity may be associated with Barrett’s oesophagus and oesophageal adenocarcinoma independent of BMI and GERD. In a meta-analysis from 2013, abdominal obesity measured by waist circumference, waist-to-hip ratio or visceral fat determined by abdominal computed tomography (CT) was associated with risk of Barrett’s oesophagus independent of BMI [14]. In addition, abdominal obesity was associated with risk of Barrett’s oesophagus independent of GERD, while no association was observed with general obesity after adjustment for GERD symptoms. The association between both general and abdominal obesity and risk of oesophageal and gastric adenocarcinoma was investigated in the EPIC study [15]. In this prospective study with measured anthropometry at baseline, general obesity represented by BMI as well as
abdominal obesity represented by waist circumference or waist-to-hip ratio were strongly positively associated with risk of oesophageal adenocarcinoma. After mutual adjustment, BMI was no longer associated with oesophageal adenocarcinoma, whereas both waist circumference and waist-to-hip ratio remained strongly positively associated (RR 3.76, 95% CI 1.72, 8.22 and RR 4.05, 95% CI 1.85, 8.87, respectively). On the other hand, in the large prospective NIH-AARP Diet and Health Study, where both general and abdominal obesity were associated with higher risk of oesophageal adenocarcinoma [16], the association with abdominal obesity (waist-to-hip ratio) was attenuated but not eliminated by simultaneous adjustment for BMI, while the association with BMI was only slightly attenuated. In a meta-analysis on the association between waist circumference and risk of oesophageal adenocarcinoma, five studies including findings from the NIH-AARP Study [16] and an earlier investigation of EPIC [17] were summarized [14]. This meta-analysis concluded that abdominal obesity is associated with higher risk of oesophageal adenocarcinoma, although substantial heterogeneity was present.

2.3 Association between obesity during early life and risk of oesophageal cancer

Because carcinogenesis is a long process that may take several decades, it is possible, that not only obesity during adulthood, but also earlier in life may impact cancer risk. There is some evidence from epidemiological studies that overweight and obesity during early childhood or adolescence are related to later risk of cancer, such as colorectal neoplasia [18,19], independent of adult obesity. Also for oesophageal adenocarcinoma, early life body fatness may be of importance, since there is epidemiologic evidence that high BMI in children is associated with GERD [20]. So far only few studies have investigated whether BMI during childhood or adolescence is related to later risk of oesophageal adenocarcinoma. In a study from Israel more
than one million men whose weight and height were measured during an obligatory medical board examination to assess their suitability for military service were followed for cancer incidence including oesophageal and gastrooesophageal junction adenocarcinomas by data linkage with the National Cancer Registry [21]. Adolescent overweight (BMI ≥ 25 kg/m²; mean age at examination was 17 years) was associated with more than two-fold higher combined risk of oesophageal and gastrooesophageal junction adenocarcinomas. In Denmark, the association between BMI during childhood (ages 7-13 years) and risk of oesophageal adenocarcinoma were investigated by linking the Copenhagen School Health Records Register with the Danish Cancer Registry [22]. Authors observed a linear positive association between childhood BMI and later risk of oesophageal adenocarcinoma, in particular for BMI from ages 10 years onwards. For example, per one unit higher BMI z-score at age 13 years, the risk of oesophageal adenocarcinoma during adulthood was 31% higher (RR 1.31, 95% CI 1.13, 1.51). It is a downside of both these studies, that follow-up measures of BMI were not available. Thus, it could not be evaluated whether these associations are independent of adult overweight or obesity. Although tracking rates of early life overweight into adulthood appear to be moderate [23], the distinct effect of obesity throughout the life course should be addressed in long-term cohort studies with repeated anthropometry measurement.

3 Association between obesity and squamous cell carcinoma

A number of studies have also investigated obesity in relation to squamous cell carcinoma, observing either no association or inverse relationships. A meta-analysis summarizing evidence from 7 case-control and 3 cohort studies estimated linear inverse associations (RR per 5 kg/m² higher BMI 0.49, 95% CI 0.44, 0.55 for case-control; RR 0.69, 95% CI 0.69, 0.75 for cohort studies) [24]. Overweight and obesity were also strongly inversely associated in a pooled analysis
of prospective studies (RR for BMI ≥25 versus 18.5-25.0 0.64, 95% CI 0.47, 0.87) [12]. It has been discussed whether the consistently observed inverse association with obesity may be real or due to residual confounding, for instance by smoking, which is a strong risk factor for squamous cell carcinoma. In line with this hypothesis, a significant inverse association with obesity was only observed in smokers, but not in former or never smokers in the pooled analysis [12]. The biological mechanisms that could explain the inverse association remain unclear.

4 Association between obesity and oesophageal cancer survival

Because oesophageal cancer is often diagnosed at advanced stages, the prognosis is generally poor with 5-year survival rates around 15% [3]. The predominant determinants of survival from oesophageal cancer are the pathologic stage and tumor grade at the time of diagnosis [25]. Some studies have investigated whether risk factors of oesophageal cancer including obesity are also associated with survival, independent of clinico-pathologic factors [26]. The studies investigating pre-diagnostic BMI in relation to survival among oesophageal cancer patients were heterogeneous, in particular with respect to the time of when BMI measures were determined or recalled: the definition of pre-diagnostic BMI varied from usual BMI [27] to BMI one year [28] or 20 years prior to diagnosis [29]. The first study investigated the association between usual BMI and survival in oesophageal adenocarcinoma patients and observed longer survival associated with usual overweight but not obesity [27]. In a nationwide Swedish study in oesophageal adenocarcinoma patients, overweight or obesity 20 years before diagnosis was associated with a tendency of better survival compared with normal-weight [26,29]. On the other hand, BMI one year prior to diagnosis was not associated with oesophageal adenocarcinoma survival in a study conducted in Australia [28]. A meta-analysis summarizing these studies concluded that pooled results were suggestive of pre-diagnostic overweight or obesity being
associated with longer survival in oesophageal adenocarcinoma patients, although there was substantial heterogeneity among studies [26]. Authors of the meta-analysis also observed a suggestive association between overweight or obesity and better survival among oesophageal squamous cell carcinoma patients, summarizing evidence from four studies that also showed heterogeneity. A better survival associated with pre-diagnostic overweight or obesity is contrary to what is observed for other obesity-related types of cancer such as breast cancer [30] and colorectal cancer [31]. Although most studies adjusted for tumor stage, residual confounding by clinico-pathological characteristics cannot be excluded. In addition, it could be speculated that the observed survival benefits are due to a higher likelihood of early diagnosis in obese individuals, since a higher BMI is associated with GERD and Barrett’s oesophagus, both of which increase the likelihood of undergoing endoscopic examination which increases the chance of early detection and better survival. Finally, the observed association between pre-diagnostic obesity and better survival among oesophageal cancer patients may be consistent with a phenomenon commonly termed the “obesity paradox”, which has also been observed for cardiovascular and metabolic diseases and may be related to reverse causation or a special form of selection bias, but could also indicate a true association [32].

5 Potential mechanisms for the association of obesity with oesophageal adenocarcinoma

The mechanisms underlying the positive association between obesity and higher risk of oesophageal adenocarcinoma are not fully elucidated. The major hypotheses include mechanical effects of (abdominal) obesity promoting GERD on the one hand, and GERD-independent metabolic pathways on the other hand.

5.1 Pathways related to gastrooesophageal reflux disease (GERD)

GERD is more common in obese individuals due to a mechanically increased intra-abdominal
pressure [6]. GERD is the main cause of Barrett’s oesophagus, which is considered a precursor of oesophageal adenocarcinoma. It has been hypothesized, that the obesity-related development of oesophageal adenocarcinoma follows a stepwise process from leading from obesity-related GERD to Barrett’s oesophagus and eventually to oesophageal adenocarcinoma [13]. Support for this hypothesis comes from the observation that BMI about two decades before cancer diagnosis is more strongly associated with risk of oesophageal adenocarcinoma than BMI closer to diagnosis [33,34]. On the other hand, studies showing that the positive association between obesity and risk of oesophageal adenocarcinoma persisted after adjustment for GERD symptoms, and was observed in individuals with and without GERD symptoms, are in favour of the hypothesis that obesity and GERD are independent risk factors [9]. Further support for a GERD-independent pathway comes from a Mendelian Randomization study showing that a genetic risk score for obesity was unrelated to gastrooesophageal reflux symptoms, but was associated with higher risk of Barrett’s oesophagus and oesophageal adenocarcinoma [35]. Taken together, these observations suggest that an indirect metabolic pathway may link obesity with oesophageal adenocarcinoma in addition to GERD-related mechanisms.

5.2 Metabolic pathways
Adipose tissue, in particular visceral adipose tissue, results in altered concentrations and/or bioavailability of a variety of endogenous hormones such as insulin, proinflammatory cytokines and adipokines such as leptin and adiponectin. These metabolic factors may influence carcinogenicity by modulating cell proliferation, apoptosis and cell growth [36]. In particular, obesity can be considered a state of chronic low-grade inflammation due to the production of pro-inflammatory cytokines such as TNF-alpha or IL-6, which may exert systemic as well as local mediating effects [37]. It has been suggested that these pro-inflammatory processes may promote oesophageal metaplasia and carcinogenesis independently or synergistically with GERD.
symptoms [14]. Such a synergistic effect may be explained by an exacerbating effect of a pro-
inflammatory environment on local inflammation due to reflux-related gastric acid exposure at
the oesophagogastric junction, which may then lead to metaplasia and development of
oesophageal adenocarcinoma [37].

Compared with other obesity-related types of cancer such as colorectal cancer or postmenopausal
breast cancer, high-quality epidemiologic evidence relating obesity-related metabolic markers to
risk of oesophageal adenocarcinoma are scarce. However, several studies have investigated the
association between metabolic biomarkers and risk of Barrett’s oesophagus, which is considered
a precursor lesion of oesophageal adenocarcinoma. For instance, a case-control study among
individuals undergoing oesophagogastroduodenoscopy showed that circulating leptin and pro-
inflammatory cytokines were positively associated with Barrett’s oesophagus [38]. In addition, it
has been observed that among individuals with GERD symptoms high concentrations of the anti-
inflammatory low-molecular weight adiponectin are associated with lower risk of Barrett’s
oesophagus [39]. Findings from another case-control study suggest that blood concentrations of
leptin and adiponectin mediate part of the positive association between obesity and risk of
Barrett’s oesophagus [40]. There is also some evidence for the insulin and insulin-like growth
factor-1 (IGF-1) axis playing a role in obesity-related development of oesophageal
adenocarcinoma [41-43]. However, there is an urgent need of well-designed epidemiological
studies, for instance nested case-control studies of prospective cohorts in order to clarify the role
of obesity-related metabolic biomarkers in the development of oesophageal adenocarcinoma.

6 Summary and outlook

Epidemiological research of the past decades has provided strong evidence for overweight and
obesity as risk factors for oesophageal adenocarcinoma. Thus, the latest scientific evidence up to
today remains in line with the 2007 report of the World Cancer Research Fund and the American Institute for Cancer Research, in which the evidence for body fatness as risk factor for oesophageal adenocarcinoma was judged as “convincing” [44]. Recent epidemiological studies have extended previous evidence by indicating the importance of abdominal obesity for oesophageal cancer risk. The association of abdominal obesity with oesophageal adenocarcinoma may be even independent of general obesity, as has been demonstrated in recent analyses from large prospective cohort studies.

Part of the positive association between obesity, in particular abdominal obesity, and oesophageal adenocarcinoma may be explained through obesity-related mechanical promotion of GERD, which is one of the main risk factors for oesophageal adenocarcinoma. On the other hand, the observed GERD-independent positive association between obesity and risk of oesophageal adenocarcinoma points to metabolic pathways modulating cell proliferation, apoptosis and cell growth such as pro-inflammatory cytokines, adipokines and insulin resistance. The specific role of obesity-related biomarkers in oesophageal cancer development, however, is as to date insufficiently understood and deserves further attention in future research. In particular, there is a need of prospective investigations of a large variety of obesity-related biomarkers, in order to study the complex interrelations of potentially mediating pathways in oesophageal adenocarcinoma risk. Furthermore, the role of overweight and obesity throughout the life course, and in particular the association between early life independent of adult overweight and obesity should be addressed in long-term prospective investigations monitoring anthropometric measures throughout the life course. Also a potentially protective role of weight loss in relation to oesophageal adenocarcinoma risk should be addressed in well-designed studies.

In conclusion, the state-of-the-art epidemiological knowledge suggests a strong association of
general obesity and in particular abdominal obesity with risk of oesophageal adenocarcinoma. These associations support the hypothesis that at least part of the increase in oesophageal adenocarcinoma incidence rates that has been observed particularly in western countries may be due to the parallel increase in obesity prevalence. On the other hand, incidence rates of squamous cell carcinoma of the oesophagus have remained relatively stable. There are still aspects in the role of obesity in relation to oesophageal cancer that remain to be elucidated in well-designed future epidemiological studies. These investigations may pave the way for targeted prevention of oesophageal cancer through lifestyle or medical interventions.
7 References


