Obesity and Oesophageal Cancer

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Abstract

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 (BMI) 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 gastroesophageal 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

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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.

Keywords
Obesity · Oesophageal cancer · Oesophageal adenocarcinoma · Gastro-oesophageal reflux disease

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 aetiology 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 (RR) are weaker. Gastrooesophageal 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 aetiologic 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 $\geq$ 25 kg/m^2) 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 $\geq$ 30 kg/m^2) was associated with a significantly higher risk of

oesophageal adenocarcinoma in all studies [6], with 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 (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

Table 1 Summary of pooled analyses and meta-analyses on the association between overweight and obesity and risk of oesophageal adenocarcinoma

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

Abbreviations: *RR* relative risk; *CI* confidence interval

oesophageal adenocarcinoma associated with 5 kg/m^2 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 fivefold risk for a BMI $\geq$ 40 kg/m^2 (compared with BMI < 25 m/^{2}). 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 twofold higher (RR 2.32, 95 % CI 1.51, 3.57) and obesity with more than threefold (RR 3.29, 95 % CI 1.82, 5.95) higher risk of oesophageal adenocarcinoma compared with normal weight.

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 gastroesophageal junction adenocarcinomas by data linkage with the National Cancer Registry [21]. Adolescent overweight (BMI $\geq$ 25 kg/m^2; mean age at examination was 17 years) was associated with more than twofold higher combined risk of oesophageal and gastroesophageal 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/m^2 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 $\geq$ 25 vs. 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 tumour 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 clinicopathologic 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 tumour stage, residual confounding by clinicopathological 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 Gastroesophageal Reflux Disease (GERD)

GERD is more common in obese individuals due to 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 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 gastroesophageal 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 is 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.

References

1. Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, MacIntyre MF, Allen C, Hansen G, Woodbrook R, Wolfe C, Hamadeh RR, Moore A, Werdecker A, Gessner BD, Te Ao B, McMahon B, Karimkhani C, Yu C, Cooke GS, Schwebel DC, Carpenter DO, Pereira DM, Nash D, Kazi DS, De Leo D, Plass D, Ukwaja KN, Thurston GD, Yun Jin K, Simard EP, Mills E, Park EK, Catala-Lopez F, deVeber G, Gotay C, Khan G, Hosgood HD 3rd, Santos IS, Leasher JL, Singh J, Leigh J, Jonas JB, Sanabria J, Beardsley J, Jacobsen KH, Takahashi K, Franklin RC, Ronfani L, Montico M, Naldi L, Tonelli M, Geleijnse J, Petzold M, Shrime MG, Younis M, Yonemoto N, Breitborde N, Yip P, Pourmalek F, Lotufo PA, Esteghamati A, Hankey GJ, Ali R, Lunevicius R, Malekzadeh R, Dellavalle R, Weintraub R, Lucas R, Hay R, Rojas-Rueda D, Westerman R, Sepanlou SG, Nolte S, Patten S, Weichenthal S, Abera SF, Fereshtehnejad SM, Shiue I, Driscoll T, Vasankari T, Alsharif U, Rahimi-Movaghar V, Vlassov VV, Marcenes WS, Mekonnen W, Melaku YA, Yano Y, Artaman A, Campos I, MacLachlan J, Mueller U, Kim D, Trillini M, Eshrati B, Williams HC, Shibuya K, Dandona R, Murthy K, Cowie B, Amare AT, Antonio CA, Castaneda-Orjuela C, van Gool CH, Violante F, Oh IH, Deribe K, Soreide K, Knibbs L, Kereselidze M, Green M, Cardenas R, Roy N, Tillmann T, Li Y, Krueger H, Monasta L, Dey S, Sheikhbahaei S, Hafezi-Nejad N, Kumar GA, Sreeramareddy CT, Dandona L, Wang H, Vollset SE, Mokdad A, Salomon JA, Lozano R, Vos T, Forouzanfar M, Lopez A, Murray C, Naghavi M (2015) The global burden of cancer 2013. JAMA Oncol 1(4):505–527. doi:10.1001/jamaoncol.2015.0735

2. Pennathur A, Gibson MK, Jobe BA, Luketich JD (2013) Oesophageal carcinoma. Lancet 381 (9864):400–412. doi:10.1016/S0140-6736(12)60643-6
3. Domper Arnal MJ, Ferrandez Arenas A, Lanas Arbeloa A (2015) Esophageal cancer: risk factors, screening and endoscopic treatment in Western and Eastern countries. World J Gastroenterol (WJG) 21(26):7933–7943. doi:10.3748/wjg.v21.i26.7933
4. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136(5):E359–E386. doi:10.1002/ijc.29210
5. Vizcaino AP, Moreno V, Lambert R, Parkin DM (2002) Time trends incidence of both major histologic types of esophageal carcinomas in selected countries, 1973–1995. Int J Cancer 99 (6):860–868. doi:10.1002/ijc.10427
6. Ryan AM, Duong M, Healy L, Ryan SA, Parekh N, Reynolds JV, Power DG (2011) Obesity, metabolic syndrome and esophageal adenocarcinoma: epidemiology, etiology and new targets. Cancer Epidemiol 35(4):309–319. doi:10.1016/j.canep.2011.03.001
7. Pandeya N, Olsen CM, Whiteman DC (2013) Sex differences in the proportion of esophageal squamous cell carcinoma cases attributable to tobacco smoking and alcohol consumption. Cancer Epidemiol 37(5):579–584. doi:10.1016/j.canep.2013.05.011
8. Adami HO, Hunter D, Trichopoulos D (2008) Textbook of cancer epidemiology. Oxford University Press, Oxford
9. Hoyo C, Cook MB, Kamangar F, Freedman ND, Whiteman DC, Bernstein L, Brown LM, Risch HA, Ye W, Sharp L, Wu AH, Ward MH, Casson AG, Murray LJ, Corley DA, Nyren O, Pandeya N, Vaughan TL, Chow WH, Gammon MD (2012) Body mass index in relation to oesophageal and oesophagogastric junction adenocarcinomas: a pooled analysis from the International BEACON Consortium. Int J Epidemiol 41(6):1706–1718. doi:10.1093/ije/dys176
10. Kubo A, Corley DA (2006) Body mass index and adenocarcinomas of the esophagus or gastric cardia: a systematic review and meta-analysis. Cancer Epidemiol Biomark Prev 15 (5):872–878. doi:10.1158/1055-9965.EPI-05-0860
11. Turati F, Tramacere I, La Vecchia C, Negri E (2013) A meta-analysis of body mass index and esophageal and gastric cardia adenocarcinoma. Ann Oncol (Official Journal of the European Society for Medical Oncology/ESMO) 24(3):609–617. doi:10.1093/annonc/mds244
12. Lindkvist B, Johansen D, Stocks T, Concin H, Bjorge T, Almquist M, Haggstrom C, Engeland A, Hallmans G, Nagel G, Jonsson H, Selmer R, Ulmer H, Tretli S, Stattin P, Manjer J (2014) Metabolic risk factors for esophageal squamous cell carcinoma and adenocarcinoma: a prospective study of 580,000 subjects within the Me-Can project. BMC Cancer 14:103. doi:10.1186/1471-2407-14-103
13. Lagergren J (2011) Influence of obesity on the risk of esophageal disorders. Nat Rev Gastroenterol Hepatol 8(6):340–347. doi:10.1038/nrgastro.2011.73
14. Singh S, Sharma AN, Murad MH, Buttar NS, El-Serag HB, Katzka DA, Iyer PG (2013) Central adiposity is associated with increased risk of esophageal inflammation, metaplasia, and adenocarcinoma: a systematic review and meta-analysis. Clin Gastroenterol Hepatol (The Official Clinical Practice Journal of the American Gastroenterological Association) 11 (11):1399–1412 e1397. doi:10.1016/j.cgh.2013.05.009
15. Steffen A, Huerta JM, Weiderpass E, Bueno-de-Mesquita HB, May AM, Siersema PD, Kaaks R, Neamat-Allah J, Pala V, Panico S, Saieva C, Tumino R, Naccarati A, Dorronsoro M, Sanchez-Cantalejo E, Ardanaz E, Quiros JR, Ohlsson B, Johansson M, Wallner B, Overvad K, Halkjaer J, Tjonneland A, Fagherazzi G, Racine A, Clavel-Chapelon F, Key TJ, Khaw KT, Wareham N, Lagiou P, Bamia C, Trichopoulou A, Ferrari P, Freisling H, Lu Y, Riboli E, Cross AJ, Gonzalez CA, Boeing H (2015) General and abdominal obesity and risk of esophageal and gastric adenocarcinoma in the European prospective investigation into cancer and nutrition. Int J Cancer 137(3):646–657. doi:10.1002/ijc.29432

16. O'Doherty MG, Freedman ND, Hollenbeck AR, Schatzkin A, Abnet CC (2012) A prospective cohort study of obesity and risk of oesophageal and gastric adenocarcinoma in the NIH-AARP diet and health study. Gut 61(9):1261–1268. doi:10.1136/gutjnl-2011-300551
17. Steffen A, Schulze MB, Pischon T, Dietrich T, Molina E, Chirlaque MD, Barricarte A, Amiano P, Quiros JR, Tumino R, Mattiello A, Palli D, Vineis P, Agnoli C, Misirli G, Boffetta P, Kaaks R, Rohrmann S, Bueno-de-Mesquita HB, Peeters PH, May AM, Spencer EA, Allen NE, Bingham S, Tjonneland A, Halkjaer J, Overvad K, Stegger J, Manjer J, Lindkvist B, Hallmanns G, Stenling R, Lund E, Riboli E, Gonzalez CA, Boeing H (2009) Anthropometry and esophageal cancer risk in the European prospective investigation into cancer and nutrition. Cancer Epidemiol Biomark Prev 18(7):2079–2089. doi:10.1158/1055-9965.EPI-09-0265
18. Zhang X, Wu K, Giovannucci EL, Ma J, Colditz GA, Fuchs CS, Willett WC, Stampfer MJ, Nimptsch K, Ogino S, Wei EK (2015) Early life body fatness and risk of colorectal cancer in u.s. Women and men-results from two large cohort studies. Cancer Epidemiol Biomark Prev 24(4):690–697. doi:10.1158/1055-9965.EPI-14-0909-T
19. Nimptsch K, Giovannucci E, Willett WC, Fuchs CS, Wei EK, Wu K (2011) Body fatness during childhood and adolescence, adult height, and risk of colorectal adenoma in women. Cancer Prev Res 4(10):1710–1718. doi:10.1158/1940-6207.CAPR-11-0272
20. Koebnick C, Getahun D, Smith N, Porter AH, Der-Sarkissian JK, Jacobsen SJ (2011) Extreme childhood obesity is associated with increased risk for gastroesophageal reflux disease in a large population-based study. Int J Pediatr Obes: IJPO (An Official Journal of the International Association for the Study of Obesity) 6(2–2):e257–e263. doi:10.3109/17477166.2010.491118
21. Levi Z, Kark JD, Shamiss A, Derazne E, Tzur D, Keinan-Boker L, Liphshitz I, Niv Y, Furman M, Afek A (2013) Body mass index and socioeconomic status measured in adolescence, country of origin, and the incidence of gastroesophageal adenocarcinoma in a cohort of 1 million men. Cancer 119(23):4086–4093. doi:10.1002/cncr.28241
22. Cook MB, Freedman ND, Gamborg M, Sorensen TI, Baker JL (2015) Childhood body mass index in relation to future risk of oesophageal adenocarcinoma. Br J Cancer 112(3):601–607. doi:10.1038/bjc.2014.646
23. Aarestrup J, Bjerregaard LG, Gamborg M, Angquist L, Tjonneland A, Overvad K, Linneberg A, Osler M, Mortensen EL, Gyntelberg F, Lund R, Tia S, Baker JL (2016) Tracking of body mass index from 7 to 69 years of age. Int J Obes (2005). doi:10.1038/ijo.2016.88
24. Smith M, Zhou M, Whitlock G, Yang G, Offer A, Hui G, Peto R, Huang Z, Chen Z (2008) Esophageal cancer and body mass index: results from a prospective study of 220,000 men in China and a meta-analysis of published studies. Int J Cancer 122(7):1604–1610. doi:10.1002/ijc.23198
25. Enzinger PC, Mayer RJ (2003) Esophageal cancer. N Engl J Med 349(23):2241–2252. doi:10.1056/NEJMra035010
26. Fahey PP, Mallitt KA, Astell-Burt T, Stone G, Whiteman DC (2015) Impact of pre-diagnosis behavior on risk of death from esophageal cancer: a systematic review and meta-analysis. Cancer Causes Control 26(10):1365–1373. doi:10.1007/s10552-015-0635-z
27. Trivers KF, De Roos AJ, Gammon MD, Vaughan TL, Risch HA, Olshan AF, Schoenberg JB, Mayne ST, Dubrow R, Stanford JL, Abrahamson P, Rotterdam H, West AB, Fraumeni JF, Chow WH (2005) Demographic and lifestyle predictors of survival in patients with esophageal or gastric cancers. Clin Gastroenterol Hepatol (The Official Clinical Practice Journal of the American Gastroenterological Association) 3(3):225–230
28. Thrift AP, Nagle CM, Fahey PP, Smithers BM, Watson DI, Whiteman DC (2012) Predictors of survival among patients diagnosed with adenocarcinoma of the esophagus and gastroesophageal junction. Cancer Causes Control 23(4):555–564. doi:10.1007/s10552-012-9913-1

29. Sundelof M, Lagergren J, Ye W (2008) Patient demographics and lifestyle factors influencing long-term survival of oesophageal cancer and gastric cardia cancer in a nationwide study in Sweden. Eur J Cancer 44(11):1566–1571. doi:10.1016/j.ejca.2008.04.002
30. Chan DS, Vieira AR, Aune D, Bandera EV, Greenwood DC, McTiernan A, Navarro Rosenblatt D, Thune I, Vieira R, Norat T (2014) Body mass index and survival in women with breast cancer-systematic literature review and meta-analysis of 82 follow-up studies. Ann Oncol (Official Journal of the European Society for Medical Oncology/ESMO) 25 (10):1901–1914. doi:10.1093/annonc/mdu042
31. Lee J, Meyerhardt JA, Giovannucci E, Jeon JY (2015) Association between body mass index and prognosis of colorectal cancer: a meta-analysis of prospective cohort studies. PLoS ONE 10(3):e0120706. doi:10.1371/journal.pone.0120706
32. Renehan AG, Sperrin M (2016) The obesity paradox and mortality after colorectal cancer: a causal conundrum. JAMA Oncol. doi:10.1001/jamaoncol.2016.0868
33. Lagergren J, Bergstrom R, Nyren O (1999) Association between body mass and adenocarcinoma of the esophagus and gastric cardia. Ann Intern Med 130(11):883–890
34. Chow WH, Blot WJ, Vaughan TL, Risch HA, Gammon MD, Stanford JL, Dubrow R, Schoenberg JB, Mayne ST, Farrow DC, Ahsan H, West AB, Rotterdam H, Niwa S, Fraumeni JF Jr (1998) Body mass index and risk of adenocarcinomas of the esophagus and gastric cardia. J Natl Cancer Inst 90(2):150–155
35. Thrift AP, Shaheen NJ, Gammon MD, Bernstein L, Reid BJ, Onstad L, Risch HA, Liu G, Bird NC, Wu AH, Corley DA, Romero Y, Chanock SJ, Chow WH, Casson AG, Levine DM, Zhang R, Ek WE, MacGregor S, Ye W, Hardie LJ, Vaughan TL, Whiteman DC (2014) Obesity and risk of esophageal adenocarcinoma and Barrett's esophagus: a Mendelian randomization study. J Natl Cancer Inst 106(11). doi:10.1093/jnci/dju252
36. Calle EE, Kaaks R (2004) Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev 4(8):579–591. doi:10.1038/nrc1408
37. Tilg H, Moschen AR (2006) Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol 6(10):772–783. doi:10.1038/nri1937
38. Garcia JM, Splenser AE, Kramer J, Alsarraj A, Fitzgerald S, Ramsey D, El-Serag HB (2014) Circulating inflammatory cytokines and adipokines are associated with increased risk of Barrett's esophagus: a case-control study. Clin Gastroenterol Hepatol (The Official Clinical Practice Journal of the American Gastroenterological Association) 12(2):229–238 e223. doi:10.1016/j.cgh.2013.07.038
39. Rubenstein JH, Kao JY, Madanick RD, Zhang M, Wang M, Spacek MB, Donovan JL, Bright SD, Shaheen NJ (2009) Association of adiponectin multimers with Barrett's oesophagus. Gut 58(12):1583–1589. doi:10.1136/gut.2008.171553
40. Thompson OM, Beresford SA, Kirk EA, Bronner MP, Vaughan TL (2010) Serum leptin and adiponectin levels and risk of Barrett's esophagus and intestinal metaplasia of the gastroesophageal junction. Obesity 18(11):2204–2211. doi:10.1038/oby.2009.508
41. Doyle SL, Donohoe CL, Finn SP, Howard JM, Lithander FE, Reynolds JV, Pidgeon GP, Lysaght J (2012) IGF-1 and its receptor in esophageal cancer: association with adenocarcinoma and visceral obesity. Am J Gastroenterol 107(2):196–204. doi:10.1038/ajg.2011.417
42. Donohoe CL, Doyle SL, McGarrigle S, Cathcart MC, Daly E, O'Grady A, Lysaght J, Pidgeon GP, Reynolds JV (2012) Role of the insulin-like growth factor 1 axis and visceral adiposity in oesophageal adenocarcinoma. Br J Surg 99(3):387–396. doi:10.1002/bjs.8658
43. Greer KB, Thompson CL, Brenner L, Bednarchik B, Dawson D, Willis J, Grady WM, Falk GW, Cooper GS, Li L, Chak A (2012) Association of insulin and insulin-like growth factors with Barrett's oesophagus. Gut 61(5):665–672. doi:10.1136/gutjnl-2011-300641
44. WCRF World Cancer Research Fund/American Institute for Cancer Research (2007) Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington DC