Risk of Cancer in the Digestive System in Adult Obese Norwegians: An Unselected Population-Based Study

Master thesis by

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Risk of cancer in the digestive organs in the obese Norwegian population

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At last, my deepest gratitude to my husband. Thank you for reviewing my work and always love and support me. Now I am looking forward to spending the summer with you, waiting for our baby girl to make her announcement. Throughout the writing process, baby kicks have also been very motivating.

Oslo, May 2019

Marlene Fritsch Kielland
Abstract

Background: Obesity is one the most challenging health burden during the last decades and the incidence of obesity is still increasing, not just in the western countries but also among the middle class in developing countries. Obesity is a risk factor for several “life-style” diseases like diabetes mellitus, hypertension, cardiovascular disease, and osteoarthritis. During recent years an increasing focus on risk of cancer development in the obese population has also emerged.

Objective: To investigate the association between obesity (BMI ≥ 30 kg/m^2) and cancer risk in the digestive system in the Norwegian adult population.

Methods: Data from nation-wide tuberculosis screening program in Norway in the period 1963 – 1975 was used to obtain weight and height to calculate BMI. The data from this unselected population-based cohort was linked with the Cancer Registry of Norway to investigate the total incidence of cancer and specifically the hazard ratio (HR) of esophageal, gastric, colorectal, liver, gallbladder and pancreatic cancer was estimated by using Cox proportional hazard regression analysis.

Results: In total 1,911,598 persons were included in the tuberculosis screening program. After exclusion, the total cohort counted 1,649,931 persons, of these were 157,435 (10 %) measured to be obese (BMI ≥ 30 kg/m^2). During the follow-up, 468,238 cancer cases were registered. There was an 8% increased incidence of total cancer among obese women HR 1.08 (95% confidence interval 1.06-1.09, p<0.005). Compared with normal weight (BMI 18.5-24.9 kg/m^2) an increased risk for several cancers in the digestive system was observed in obese men and women. Obese men and women had an increased risk for esophageal adenocarcinoma, HR 2.12 (95% CI 1.59-2.28) and HR 2.43 (95% CI 1.72-3.44), respectively. Obese men were observed to have an increased risk for gastric cancer of cardia and colorectal cancer, HR 1.80 (95% CI 1.35-2.38) HR 1.31 (95% CI 1.25-1.38), respectively. Both obese men and women were found to have an increased risk for hepatocellular carcinoma (HCC), HR 2.37 (95% CI 1.91-2.95) and HR 1.28 (95% CI 1.03-1.59), respectively. Increased risk of gallbladder cancer was observed in obese women, HR 2.13 (95% CI 1.76-2.59). Obesity in
men and women increased the risk for pancreatic cancer, HR 1.22 (95% CI 1.11- 1.35) and
HR 1.16 (95% CI 1.08, 1.24), respectively. Further, the risk of regional- and distant
metastasis was increased only among obese women HR 1.13 (95% CI 1.09-1.16) and HR 1.09
(95% CI 1.06-1.12), respectively. Finally, obese men and women had an increased risk of
death by cancer, HR 1.27 (95% CI 1.24-1.31) and HR 1.31 (95% CI 1.29-1.33), respectively.

**Conclusion:** This large unselected population-based cohort study from Norway shows a
significant higher risk of cancer development, metastatic disease, and cancer related death
among the obese population.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>DEXA</td>
<td>Due-energy X-ray absorptiometry</td>
</tr>
<tr>
<td>MR</td>
<td>Magnetic resonance</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>Kg</td>
<td>Kilograms</td>
</tr>
<tr>
<td>IARC</td>
<td>International Agency for Research in Cancer</td>
</tr>
<tr>
<td>WCRF</td>
<td>World Cancer Research Fund</td>
</tr>
<tr>
<td>CUP</td>
<td>Continuous Update Project</td>
</tr>
<tr>
<td>IGF-s</td>
<td>Insulin-like growth factors</td>
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<tr>
<td>FFA</td>
<td>Free fatty acids</td>
</tr>
<tr>
<td>IGF-1</td>
<td>Insulin-like growth factor-1</td>
</tr>
<tr>
<td>IGFBPs</td>
<td>IGF binding proteins</td>
</tr>
<tr>
<td>IP3</td>
<td>phosphatidylinositol-3 kinase</td>
</tr>
<tr>
<td>TNFα</td>
<td>Tumor necrosis factor α</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular endothelial growth factor</td>
</tr>
<tr>
<td>AMPK</td>
<td>AMP-activated protein kinase</td>
</tr>
<tr>
<td>NF-κB</td>
<td>Nuclear factor κ-light chain enhancer of activated B-cells</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>COX2</td>
<td>Cyclooxygenase-2</td>
</tr>
<tr>
<td>GERD</td>
<td>Gastroesophageal reflux disease</td>
</tr>
<tr>
<td>NAFLD</td>
<td>non-alcoholic fatty liver disease</td>
</tr>
<tr>
<td>NASH</td>
<td>non-alcoholic steatohepatitis</td>
</tr>
<tr>
<td>HCC</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard rate ratio</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International Classification of Diseases, 10th revision</td>
</tr>
<tr>
<td>SD</td>
<td>Standard derivation</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>REK</td>
<td>The Regional Committee for Medical and Health Research</td>
</tr>
<tr>
<td>GDPR</td>
<td>General Data Protection Regulation</td>
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1 Background

1.1 Overweight and Obesity

For more than 30 years, obesity has been a major cause of disease and death in the United States (US), secondary to tobacco (1). However, since the 1960s, tobacco consumes in the US has declined by one-third, whereas a decrease in physical activity combined with an unhealthy diet has been contributing to a doubling of obesity rate. According to the World Health Organization (WHO), more than 1.9 billion adults were estimated to be overweight globally in 2016, of which 650 million were obese (2). Consequently, the relative contributions of obesity and tobacco consume have changed (3).

Today, most of the world population lives in countries where overweight and obesity kill more people than underweight (4). Already in 2013, 4.5 million death worldwide were estimated to be caused by overweight and obesity, and the prevalence of overweight and obesity is rapidly increasing (5, 6). The Norwegian population is no exception. In the end of the 1960s approximately 5 % of middle-aged men were obese (7). Further, since the 1970s there has been an increase in the occurrence of overweight and obesity in Norway (7). Today, according to the Tromsø study and the Nord-Trøndelag Health Study (HUNT) a substantial subset of the Norwegian population are either overweight or obese (8, 9). This is a warning sign as excess body fatness has been linked to increased risk of cardiovascular disease, hypertension, type 2 diabetes, dyslipidemia, sleep apnea and musculoskeletal disorders (10, 11). Moreover, Epidemiological studies also indicate that excess body fatness contributes to the increased risk of different types of cancer and death by cancer (12, 13). Further, the tumor-promoting effect evoked by obesity seems to be tissue-specific and gender-specific and thus the risk of cancer is dissimilar for different organs and between gender.

At last, to our knowledge, no one has investigated the association between obesity and the risk of cancer in the digestive system in the Norwegian population. In this study, we will mainly focus on cancers in the digestive organs in an unselected Norwegian population.
1.1.1 Methods for assessing overweight and obesity

Overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health (14). Adipose tissue in humans store energy in the form of fat and triglycerides are the main storage lipid. We differ between subcutaneous and visceral adipose tissue, whereas subcutaneous adipose tissue is defined as fat tissue between the skin and muscle and visceral adipose tissue is found within the main cavities of the body, primarily in the abdominal cavity (15). The abdominal visceral adipose tissue has a high lipolytic activity and is more metabolically active compared to abdominal subcutaneous adipose tissue (16). Ideal measurements of adiposity would consider both the amount and site of deposition of the adipose.

There are several methods available to an estimation of total body fat mass. Due -energy X-ray absorptiometry (DEXA), underwater weighing (hydrodensitometry), dilution methods (hydrometry), bioimpedance analysis, measurement of skinfolds, and imaging methods including magnetic resonance imaging (MRI) and computed tomography (CT) are some.

However, due to its simplicity and low costs, body mass index (BMI) is the most commonly applied measure for body fatness. Different studies have found moderate to strong correlations between the BMI scale and densitometry estimates of body fat composition in adults (17). The validity of BMI as a measure of adiposity is further supported by its association with obesity related risk factors such as blood triglycerides, total cholesterol, blood pressure and fasting glucose levels (17). BMI is calculated as weight in kilograms (kg) divided by height in meters (m) squared (kg/m²) (18). According to the criteria of the WHO, BMI < 18.5 kg/m² is defined as underweight, between 18-25 kg/m² is defined as normal weight, between 25-30 kg/m² is defined as overweight, and BMI ≥ 30 kg/m² is defined as obesity (19). Furthermore, morbid obesity defined as BMI > 35 kg/m² with obesity related comorbidities or BMI > 40 kg/m². The risk of obesity associated comorbidity is associated with the degree of obesity (Table 1)
Table 1: Body mass index classification and risk of comorbidities

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m²)</th>
<th>Risk of comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
<td>Low (but risk of) other clinical problems increased</td>
</tr>
<tr>
<td>Normal range</td>
<td>18.5-24.9</td>
<td>Average</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0 – 29.9</td>
<td>Mildly increased</td>
</tr>
<tr>
<td>Obese</td>
<td>≥ 30.0</td>
<td></td>
</tr>
<tr>
<td>Class 1</td>
<td>30.0 – 34.9</td>
<td>Moderate</td>
</tr>
<tr>
<td>Class 2</td>
<td>35.0 – 39.9</td>
<td>Severe</td>
</tr>
<tr>
<td>Class 3</td>
<td>≥ 40.0</td>
<td>Very severe</td>
</tr>
</tbody>
</table>

WHO BMI Classification (19)

1.2 Obesity and Cancer

The hypothesis that obesity may be a risk factor for certain kinds of cancer goes back to the 1930s when speculations that excessive food consumption and overnutrition may be a cause of cancer (20). Today, several epidemiological studies support the hypothesis and show a strong relationship between overweight and the risk of different forms of cancer (21). In 2016, the International Agency for Research in Cancer (IARC) reported that 16 types of cancer probably or convincingly are associated with excess adiposity (21).

Cancer develops when cellular changes in normal cell regulation cause uncontrolled growth, proliferation, and differentiation (22). Genetic mutations or epigenetic factors can lead to altered cellular phenotype and disordered gene expression by activating oncogenes and/or deactivates tumor suppressor genes (22). Further, it is well documented that excess adiposity leads to chronic low-grade inflammation and metabolic disorders. These pathophysiological effects have been associated with cancer development and progression (23-25).
Overweight and obesity occur due to an imbalance between energy intake and energy expenditure. Excess energy from food and drinks is stored in the body as fat in adipose tissue. Further, adipose tissue is the body’s largest endocrine organ, capable of secreting chemokines, cytokines and, adipokines (26, 27) (Figure 1). Larger volumes of adipose tissue can potentially lead to higher production of hormones that can affect cell growth. Consequently, obesity leads to endocrine, metabolic, immunologic and inflammatory-like changes that in part, may explain the link between obesity and cancer (27). However, cancer development associated with overweight and obesity may be included by complex interactions of several pathophysiological mechanisms.

**Figure 1:** Endocrine signals from adipose tissue

A chronic increase in energy intake leads to metabolic stress and adipocyte dysfunction. Altered secretion of adipokines, increased inflammatory cytokines, dysregulation of lipid and glucose metabolism and disturbance of hormonal regulation affect the whole body and lead to systemic changes of metabolism. This results in hyperlipidemia, hyperglycemia and, hyperinsulinemia, which further leads to insulin resistance, chronic inflammation and circulating adipokines. All being potential risk factors for cancer development and progression. The figure is retrieved from Park et al “Paracrine and endocrine effects of adipose tissue on cancer development and progression.” (27)
1.2.1 Diet and physical activity and cancer risk

1.2.1.1 Diet

It is well documented from animal experiments and epidemiological studies that the quality of diet and alterations in calorie intake significantly influence the risk of cancer (28). The most recent report coordinated by the World Cancer Research Fund (WCRF)/AICR and the Continuous Update Project (CUP) concluded that there is strong evidence that consumption of red- and processed meat can lead to colorectal cancer (29). Both red- and processed meat are rich in fat, protein and haem iron which can promote tumorigenesis. When red- and processed meat are exposed to high temperatures over time it can result in the development of heterocyclic amines and polycyclic aromatic hydrocarbons. This has been linked to colorectal cancer development in experimental studies (29). Low intake of non-starchy vegetables and low intake of fruits seems to respectively increase the risk of colorectal cancer and stomach cancer (30). Further, the consumption of non-starchy vegetables and fruits can decrease the risk of several types of cancer (30). There is also strong evidence that dietary products, such as milk, cheese and, yogurt, probably protect against colorectal cancer (29).

1.2.1.2 Physical activity

Regular physical activity helps maintain a healthy body weight by balancing caloric intake with energy expenditure which, in turn, may prevent certain cancers by regulating insulin, sex hormones and prostaglandin (31). Most studies show that regular physical activity impact the immune system and reduces the risk of infections (32). Further, in their report, WCRF/AICR found strong evidences that being physical active decreases the risk of cancers in the colon, post menopause breast, and endometrium. Physical activity also seems to decrease the risk of cancer in the lungs, liver, breast (premenopausal), and esophagus. Nevertheless, the evidence for these associations is more limited (33).
1.2.2 Biological mechanisms linking obesity to cancer

In addition to diet and physical activity, there are several pathophysiological and biological mechanisms linking excess body weight and risk of cancer. Three of the most studied mechanisms are insulin and insulin-like growth factors (IGFs), sex steroids, and adipokines (34). Each of these three factors is intimately associated with endocrine and paracrine dysregulation of adipose tissue in obesity. The homeostasis of these hormones has been observed to be influenced by overweight and obesity (35).

1.2.2.1 Insulin resistance and insulin-like growth factors

Insulin is a peptide hormone produced by pancreatic β-cells and released in response to elevated blood glucose. In addition to its importance in glucose homeostasis, insulin is a central hormone in anabolic processes involved in early growth and development. Under normal physiologic conditions, insulin suppresses lipolysis (36). However, this latter function is impaired in the obese state (37).

Excess body fat and obesity are characterized by increased lipolysis leading to the excessive release of free fatty acids (FFA) into the circulation (36). Increased levels of FFAs may lead to excessive lipid accumulation in organs such as, pancreas, liver, and kidneys, which further promotes insulin resistance, hyperglycemia, dyslipidemia and hypertension (38). This group of conditions is collectively part of the metabolic syndrome.

Insulin like growth factor 1 (IGF-1) is a growth factor peptide produced by the liver after stimulated by the growth hormone (GH). IGF-1 plays an important role in regulating growth and development in many tissues (39). Under normal conditions, circulating IGF-1 is typically bound to IGF binding proteins (IGFBPs) which inhibit IGF-1 from binging to the IGF-1 receptor, and consequently regulates cell growth and survival (39).

The amount of bioavailable IGF-1 is increased by metabolic syndrome, possibly via hyperglycemia-induced suppression of IGFBPs synthesis or, hyperinsulinemia induced promotion of hepatic growth hormone receptor expression and IGF-1 synthesis (40). Binding of IGF-1 to its receptor, IGFR-1 leads to activation of the phosphatidylinositol-3 kinase (PI3)/AKT/mTOR pathway which regulates cell growth, cell proliferation, and survival.
through downstream mediators. Elevated circulating IGF-1 is an established risk factor for many cancer types (39, 41).

1.2.2.2 Sex steroids

Epidemiological studies have provided a substantial amount of evidence for altered levels of sex steroids in obesity (42, 43). This alteration can explain some of the associations observed between anthropometric incidences of excess body weight and the risk of some cancer types.

For men and premenopausal women, the gonads are the main source for circulating sex steroids. Testosterone and androstenedione are the primary androgens, and these are converted to estradiol and estrone, respectively, in a reaction catalyzed by aromatase enzyme (44). Aromatase is found at high levels in the ovaries in women and in the testis in men, and for both genders, at lower levels in peripheral tissues, such as brain, breast, muscle and adipose tissue (45).

After menopause, where ovarian estrogen production ceases, estrogen production continues to a much lesser degree through peripheral tissues, mainly adipose tissue (46). Compared to normal-weight postmenopausal women, obese postmenopausal women are known to have higher levels of total and circulating estrogen (47). Excessive local production of estrogens in adipose tissue is a potential risk factor for breast cancer, endometrial and colon cancer in postmenopausal women (48, 49). The Million Woman Study followed 1.2 million UK women age 50 to 64 years for a mean of 5.4 years, including 45,037 women with breast cancer, and identified a nearly 30% higher risk of developing postmenopausal breast cancer with obesity (49). Estrogen may promote tumor development and progression through several complex mechanisms. Direct effects of estrogens include the stimulation of cellular proliferation and inhibition of apoptosis, as well as the induction of vascular endothelial growth factor and angiogenesis (50, 51).

However, the connection between other steroid hormones and obesity is less clear. Research shows that the androgen receptor has been found to be activated by IL-6 and IGF-1, which both are elevated in obese state and can potentially lead to prostate cancer cell survival and proliferation (52).
1.2.2.3 Adipokines

Much endocrine and metabolic activity take place in adipose tissue. Polypeptide hormones derived from adipocytes are known as adipokines. Leptin and adiponectin are the most abundantly produced adipokines and the level of these peptides in the circulation largely reflects the amount and distribution of adipose tissue in the body (53). Leptin and adiponectin are the most studies adipokines in cancer development (34).

Leptin

Leptin acts centrally via the hypothalamus to regulate food intake and energy expenditure, and also on peripheral organs. Its main function is to mediate satiety, stimulate lipolysis, and suppress lipogenesis (54). The level of serum leptin correlates with fat mass, as leptin secretion increases in conjunction with adipocyte size (53). In the obese state, adipose tissue overproduces leptin, and the brain no longer responds to the signal. The release of leptin is stimulated by glucocorticoids, estrogen, tumor necrosis factor α (TNFα) and Insulin (55).

Leptin can modulate biological processes, including cytokine production, immune function, angiogenesis and carcinogenesis (54, 55). It has further been found to induce pro-tumor effects in several cancers (56, 57). Leptin can signal directly to cancer cells through the OB-R leptin receptor and downstream activation of the PI3K and MAPK pathways. Furthermore, leptin promotes angiogenesis through vascular endothelial growth factor (VEGF) (58).

Adiponectin

Adiponectin is secreted by adipocytes and can act on other tissues to increase insulin sensitivity (59) and has anti-inflammatory properties (60). In contrast to leptin, levels of adiponectin are reduced in the obese state (53) and are inversely correlated with the progression of several cancers (61). Additionally, adiponectin directly signals to cancer cells that express the adiponectin receptor, reducing cellular proliferation and inducing apoptosis (62). The possible mechanisms that may enable adiponectin to exert anticancer effects may include activation of AMP-activated protein kinase (AMPK) and inhibition of the nuclear factor κ- light chain enhancer of activated B-cells (NF- κ-B). Activated AMPK leads to increased insulin sensitivity and mTOR signaling. Activation of NF- κ-B reduces pro-inflammatory cytokine expression (63-65).
Results from in vitro, animal and epidemiological studies, linking leptin (65-67) or adiponectin (63, 68-70) individually to cancer risk is mixed. However, associations among the adiponectin-to-leptin ratio and the metabolic syndrome (71-73) and some cancers have been reported (74-76).

1.3 Obesity and Inflammation

When energy intake outpaces energy expenditure the adipose tissue expands by either enhancing adipocyte proliferation (hyperplasia) or enlarging adipocyte size (hypertrophy). Acute changes in energy intake are easily handled. However, a chronic increase in energy forces substantial metabolic stress. Indeed, chronic and excessive expansion of adipose tissue is associated with low-grade inflammatory response (26). Inflamed adipose tissue is characterized by elevated expression of pro-inflammatory factors, such as IL-6, TNFα, leptin, and VEGF (16) (Figure 3). Further, excess body fat is associated with increased levels of the pro-inflammatory marker C-reactive protein (CRP) in the blood (77).

In addition to adipocytes, adipose tissue is comprised of various stromal and vascular cells, including fibroblast, preadipocytes at various stages of differentiation, vascular endothelial cells and immune cells (78, 79). Macrophages that also produce inflammatory mediators (80-82) are the most abundant among the immune cells, and their number increases concurrently with adipose tissue mass (78).

Adipose tissue hypertrophy may lead to hypoxia, adipocyte necrotic death, and increased secretion of cytokines, chemokines, hormones and growth factors, as well as the dysregulated release of free fatty acids (FFAs) (26).

1.3.1 Inflammation and cancer

Inflammation is a recognized hallmark of cancer development (83). There is growing evidence that indicates that chronic inflammation is associated with an increased risk of cancer (84-87) (Figure 3).
Several tissue–specific inflammatory lesions are established neoplastic precursors for invasive cancer, including inflammatory bowel disease for colon cancer, gastritis for gastric cancer, and pancreatitis for pancreatic cancer (88, 89). Tumor microenvironments are composed of multiple cell types including epithelial cells, fibroblasts, mast cells, and cells of the innate and adaptive immune system (89, 90). As previously discussed, macrophages, which are activated in the obese state, infiltrate tumors and amplify the inflammatory tumor microenvironment, often through NF-κB–dependent production of cytokines and angiogenic factors (89).

Cyclooxygenase-2 (COX2) is one of several pro-inflammatory mediators induced by activation of NF-κB and is another important cancer-related inflammatory mediator (91). COX2 is an enzyme that is upregulated in several tumors and catalyzes the synthesis of the potent inflammatory lipid metabolite, prostaglandin E2. COX2 overexpression is an indicator of poor prognosis in multiple cancer types (92).

**Figure 2:** Mechanisms linking obesity to cancers

Obesity related inflamed adipose tissue has several effects that impact cancer development. The figure is retrieved from Deng et al “Obesity, inflammation, and Cancer” (26)

### 1.4 Cancer in the Digestive System

The digestive system is a group of organs working together to convert food into energy and basic nutrient to feed the entire body. Foods and drinks pass through the gastrointestinal tract made up of the oral cavity, pharynx, esophagus, stomach, small intestines and large intestines. In addition to the alimentary canal, the liver, gallbladder, and pancreas are all important accessory organs that help the body to digest food. According to the WCRF/IARC CUP,
adiposity is a probable risk factor for cancer in the digestive system, including the esophagus, colon, stomach, gallbladder, and pancreas (93, 94).

### 1.4.1 Esophageal cancer

Overweight and obesity may promote chronic gastroesophageal reflux disease (GERD). Research has shown that individuals with BMI > 25 kg/m² were shown to have 40-90 % higher risk of the symptoms of GERD, compared to normal weight (95, 96). Further, symptoms of GERD have been found to increase the risk of esophageal carcinoma with a fivefold-to-sevenfold (97, 98).

More than 90 % of esophageal cancers are either squamous-cell carcinomas or adenocarcinomas. Overweight and obesity are associated with decreased risk of esophagus squamous cell carcinoma compared to normal weight, but increased risk of esophageal adenocarcinoma (99). Both in Europe, North America and Norway, an increase in the incidence of esophageal adenocarcinoma have been observed in the last decades (100), (Figure 3).

![Figure 3: The incidence of esophageal cancer in Norway](Image)

(The figure is retrieved from the cancer registry of Norway’s annual report (87))
1.4.2 Gastric cancer

Gastric cancer is a major health concern due to its combination of high incidences and poor survival rate (101). The stomach is divided into several anatomic subsites, including the cardia, fundus, corpus, pylorus and, the antrum. Obesity has been associated with gastric cancer in cardia. A higher level of body fatness promotes the development of GERD or inflammation of the esophagus. This increases the risk of developing cardia cancer (30). In comparison, with individuals having BMI under 25 kg/m², both overweight and obese have an increased risk of developing cardia cancer (102). However, overweight and obesity have not been found to be a risk factor for non-cardia stomach cancer (102).

1.4.3 Colorectal cancer

Colorectal cancer is any cancer of the colon or rectum (103). Worldwide, more than 1.8 million people were diagnosed with colorectal cancer in 2018 (104). This makes colorectal cancer the third most common cancer (105). In Norway, colorectal cancer is one of the most frequent cancer, accounting 4,332 cases annually (106). There exist convincing data supporting the association between body fatness and colorectal cancer (30). For instant, elevated levels of insulin, and changes in hormonal profiles in obese individuals have been shown to promote the growth of colon cancer cells and inhibit apoptosis (107).

1.4.4 Hepatocellular carcinoma and Intrahepatic cholangiocarcinoma

Higher levels of body fatness have been found to be a risk factor for the development of liver cancer (108). Still, the mechanisms linking obesity and liver cancer development are unclear (30). However, individuals who are overweight or obese are at increased risk of non-alcoholic fatty liver disease (NAFLD). NAFLD is caused by excess fat stored in the liver cells and is an umbrella term for a range of liver conditions affecting people who drink little to no alcohol. NAFLD is a potentially serious form of disease, marked by liver inflammation. It can
further lead to a spectrum of pathologies, including variable degrees of simple steatosis, non-alcoholic steatohepatitis (NASH), cirrhosis, and eventually liver failure (109). NASH is a major risk factor for liver fibrosis and can lead to hepatocellular carcinoma (HCC), directly or indirectly through cirrhosis (109, 110). HCC is the most common type of liver cancer, accounting for 90% of all registered liver cancers (111).

Chronic inflammation and insulin resistance, as a result of excessive body fat, may contribute to hepatic dysfunction. The resulting chronic liver injury can promote compensatory hepatocyte injury, cell death, tissue remodeling, and regeneration. This has been shown in animal models to be a necessary factor for liver cancer development (30).

### 1.4.5 Gallbladder cancer

Development of metabolic syndrome and its components, such as hyperinsulinemia, dyslipidemia, hyperglycemia, and hypertension may also be the mechanism underlying the association between body fatness and gallbladder cancer development (30). Body fatness and metabolic syndrome appear to be associated with increased risk of gallstones, which has been observed as a major risk factor for gallbladder cancer development, probably due to the promotion of increased chronic inflammation at this site (112).

### 1.4.6 Pancreatic cancer

Excess body fat may promote the development of pancreatic cancer. Chronic inflammation, with activation of NF-κB signaling and increased production of pro-inflammatory cytokines, has been proposed as a possible mechanism. Further, overweight and obese individuals have increased levels of insulin, which can promote cell growth and inhibit apoptosis, and consequently may support the development of cancer (30).

It has been estimated that for each 5 kg/m² increase in BMI the lifelong relative risk for pancreatic cancer simultaneously increases by 13-18% (94, 113). Furthermore, the relative
risk of pancreatic cancer in obese patients compared to people categorized as normal weight has been found to be 20 – 50 % (113).

### 1.5 Metastasis and Survival in Obese Cancer Patients

Several epidemiological studies suggest an association between obesity and both cancer incidence and mortality. Cancer is the second leading cause of death globally, with approximately 9.6 million deaths in 2018 (14). One of the main reasons that cancer is so serious is its ability to spread to other parts of the body through the bloodstream or the lymph system. Cancer cells can spread locally by moving into close healthy tissue, regionally to nearby lymph nodes, tissue or organs, or it can spread to distant parts of the body. When this happens, it is called metastatic cancer (114), and further increases the risk of mortality.

Obesity is associated with poor prognosis among cancer patients (115). Adipocytes in the tumor microenvironment have been suggested to play a crucial role in disease progression by providing fatty acids and pro-inflammatory cytokines (114). Cancer cells have the ability to utilize free fatty acids released from adipocytes for energy production through β-oxidation. In this way, an adequate supply of free fatty acids from adipocytes in the tumor microenvironment favors uncontrolled growth and progression of malignancy (114).

Abnormal accumulation of adipose tissue usually leads to unbalanced adipokine levels, especially increased leptin (116). In vitro studies have shown that leptin might have a mitogenic and anti-apoptotic effect in various cancer types. Increased levels of leptin may also influence cell migration and invasion, which are two important steps in tumor progression and metastasis (117-119).
2 Objective of the study

Obesity is an increasing challenge worldwide and in Norway due to both increased morbidity and mortality. The main objective of this thesis was to investigate whether the obese population in Norway has a higher risk of cancer development in the digestive system compared to the normal weight population.

2.1 Specific Aims

The primary aim of this study is to investigate the association between obesity (BMI $\geq$ 30kg/m$^2$) and cancer risk in the digestive system in the Norwegian population with regard to esophageal, gastric, colorectal, liver, gallbladder, and pancreas cancer.

2.1.1 Secondary aims

We also aimed to investigate the association between BMI and stage of cancer (locoregional versus metastatic) at the time of discovery, and whether BMI may influence the possibility of cancer survival.
3 Materials and Methods

3.1 Study Population

Data were obtained from individuals included in the national-wide tuberculosis screening program in Norway, carried out between 1943 and 1999. The screening program was set up by the National Mass Radiography Service and included all inhabitants over the age of 15 years in 17 out of 19 counties in Norway. Height- and weight measurement was first introduced as a part of the screening program in 1963 and was conducted until 1975. In total, 1,911,598 persons were measured. Height was measured to the nearest centimeter and weight to the nearest half kilogram on regularly calibrated scales (120).

According to the Norwegian Law, all cases of cancer have to be reported to the National Cancer Registry starting from 1952. Each person’s height and weight records were linked to data from the Cancer Registry of Norway and, further linked to the Norwegian Tax Administration. Norwegian Tax is responsible for keeping the National registry updated. The National Registry provides all citizens in Norway with a unique 11-digital person-number and registers all deaths, based on the death certificate issued by physicians. The linking of the different registers was possible due to the national system of 11-digit personal identification number.

3.1.1 Inclusion and exclusion criteria

Persons under the age of 18 years and above 75 years at measurement were excluded from the study, along with people missing values of either height or weight. Persons diagnosed with cancer prior to the measurement or within one year after measurement were excluded from the study, due to the risk of interference with total body weight. Only individuals where histologically had been diagnosed with cancer were included in the study.
3.2 Statistical Methods

In the present study, participants were followed from the time at measurement to either death, date of turning 85-year-old or until 30\textsuperscript{th} of June 2018, whichever came first. Cox proportional hazards regression models with attained age as time scale, were fitted to obtain Hazard rate ratios (HR) estimates for incidence of different cancers. Similar studies, using some of the same material, have performed adjusted analysis to explore whether BMI had a different impact on the incidence of cancer for different age at measurement (120). In the present analysis, categorized variables for age at measurement, the period of measurement, and BMI were included. BMI was categorized using the WHO- classification (19) BMI <18.5 (underweight), 18.5-24.9 (normal), 25.0-29.9 (overweight) and > 30.0 (obese).

Separate analysis was performed for each of the six cancers of interest (Cancer of the esophagus, gastric, colon, gallbladder, liver and, pancreas) and their subsites by using International Classification of Diseases, 10\textsuperscript{th} revision (ICD-10) (121). An exception was colorectal cancer that was run as one analysis (combining colon and rectal cancer). In addition, separate analysis was performed for squamous-cell carcinomas and adenocarcinomas for esophageal cancer, with the use of morphology codes (122). Sub-sites of the colon were merged into ascending- and transverse colon cancer and descending- and sigmoid colon cancer. Similar Cox proportional hazards regression models were fitted to obtain relative risk estimates of different stages of metastasis at time of cancer diagnosis.

Further, Cox proportional hazards regression models and Kaplan – Meier models with time since cancer diagnosis, were fitted to obtain HR estimates of the incidence of death by cancer. These analyses were adjusted for the period of measure and age at diagnosis.

Continuous data were described with means and standard deviations (SDs) if normally distributed. Cox regression models were used to estimate hazard ratios (HRs) with 95 % confidence intervals (CI) for different BMI categories for men and women. People with BMI defined as normal weight was used as referent. In all tests, p < 0.05 was considered statistically significant.

All statistical analysis was performed separately for men and women and performed by using the \textit{stset} and \textit{stcox} function in the statistical program STATA/SE version 15/SE (STATA, College Station, TX).
3.3 Ethics and Approval

This present study was approved by The Regional Committee for Medical and Health Research in South Eastern Norway (REK 2018/670) (Appendix 1) and the Oslo University Hospital for General Data Protection Regulation (GDPR). The project was also evaluated and approved by the Norwegian Cancer Registry, the Norwegian Institute of Public Health, and the Norwegian Tax Administration for releasing the data and linking them together for this project.
4 Results

4.1 Study population

In total 1,911,598 persons, 918,000 (48 %) men and 993,598 (52 %) women, participated in the tuberculosis screening program during 1963-1975. Of these were 261,668 persons excluded from the present study. See Table 2 for exclusion criteria.

Table 2: Exclusion criteria of the study population

<table>
<thead>
<tr>
<th>Exclusion Criteria’s</th>
<th>n¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age under 18 or over 75 years at measurement</td>
<td>227,258</td>
</tr>
<tr>
<td>Missing data on height or weight</td>
<td>3,429</td>
</tr>
<tr>
<td>Diagnosed with cancer prior to measurement</td>
<td>25,560</td>
</tr>
<tr>
<td>Uncertain cancer diagnosis</td>
<td>12,734</td>
</tr>
<tr>
<td><strong>Total²</strong></td>
<td><strong>261,668</strong></td>
</tr>
</tbody>
</table>

¹Number excluded
²Some participants had more than one exclusion criteria

After exclusion, the study population consisted of 1,649,930 people. Demographics of the study population are shown in Table 3. Individuals were followed for an average of 30 years (1-55 years) after measurement, comprising 49.5 million person-years. During the follow-up, 468,238 persons developed histologically verified cancers. 243,860 (52 %) cancer cases were diagnosed in men and 224,378 (48 %) in women. The mean age of those diagnosed with cancer was 71 and 70 years in men and women, respectively. The characteristics of the study population are presented in Table 3.
### Table 3: Characteristics of the study population.

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants in the screening program</strong></td>
<td>918,000 (48 %)</td>
<td>993,598 (52 %)</td>
<td>1,911,598</td>
</tr>
<tr>
<td>Excluded</td>
<td>127,457</td>
<td>134,211</td>
<td>261,668</td>
</tr>
<tr>
<td><strong>Study population</strong></td>
<td>790,543 (48%)</td>
<td>859,387 (52%)</td>
<td>1,649,930</td>
</tr>
</tbody>
</table>

**Age at entry (years)**

Mean (SD) 44.56 (15.6) 44.56 (15.7)

**BMI**

- Underweight: <18.5
  - Men: 7,583 (1 %) 19,492 (2 %) 27,075 (2 %)
  - Women: 19,492 (2 %)
- Normal weight: 18.5 - 24.9
  - Men: 458,993 (58 %) 458,886 (53 %) 917,879 (56 %)
  - Women: 917,879 (56 %)
- Overweight: 25.0-29.9
  - Men: 283,640 (36 %) 263,895 (31 %) 547,535 (33 %)
  - Women: 547,535 (33 %)
- Obese: ≥ 30
  - Class I: 30.0 – 34.9
    - Men: 40,322 (5 %) 117,113 (14 %) 157,435 (10 %)
    - Women: 157,435 (10 %)
  - Class II: 35.0 – 39.9
    - Men: 2,897 (0.5 %) 21,523 (2.5%) 24,420 (1.5 %)
    - Women: 24,420 (1.5 %)
  - Class III: ≥ 40.0
    - Men: 359 (0.05 %) 5,340 (1%) 5,699 (0.5 %)
    - Women: 5,699 (0.5 %)

**Number of cancer diagnosis**

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>243,860</td>
<td>224,378</td>
<td>468,238</td>
</tr>
</tbody>
</table>

**Age at cancer diagnosis (years)**

Mean (SD) 71 70 70.5

Range 19-105 19-107 19-107

Out of the men were 7,583 categorized as underweight, 458,993 were normal weight, 283,640 overweight and 40,322 obese at the time of measurement. Of the women 19,492 were underweight, 45,886 categorized as normal weight, 263,895 overweighted and 117,113 obese at the time of measurement. BMI ≥ 30 kg/m² was further categorized as class I, II and III (Table 3). However, due to very few individuals in class II and III, all obese people were joined as one group. Figure 4 illustrates the BMI distribution for men and women.
Figure 4: BMI distribution of the study-population

Bar-diagram illustrating the BMI distribution among A) men and, B) women
4.2 Total Incidence of Cancer

During follow-up, 243,860 men and 224,378 women were diagnosed with cancer. Results from our analysis showed an 8 % increased risk of cancer for obese women, compared to normal weight women (Table 4). Furthermore, overweight men and women were observed to have a decreased risk of cancer at 3 % and 1 %, respectively. However, underweight men and women were observed to have an increased risk of cancer at 5 % and 10 %, respectively (Table 4).

Table 4: Incidence of Cancer

Estimated Hazard ratio (HR) for incidence with 90 % confidence intervals*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Incidence</th>
<th></th>
<th>Women</th>
<th>Incidence</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR</td>
<td>95 % CI</td>
<td>P- value</td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 18.5</td>
<td>1.05</td>
<td>(1.01 1.11)</td>
<td>0.030</td>
<td>1,783</td>
<td>1.10</td>
<td>(1.07 1.14)</td>
</tr>
<tr>
<td>18.5 – 24.9</td>
<td>1</td>
<td>Referent</td>
<td>142,216</td>
<td>1</td>
<td>Referent</td>
<td>121,822</td>
</tr>
<tr>
<td>25.0 – 29.0</td>
<td>0.97</td>
<td>(0.97 0.99)</td>
<td>0.000</td>
<td>89,042</td>
<td>0.99</td>
<td>(0.98 0.99)</td>
</tr>
<tr>
<td>≥ 30</td>
<td>1.00</td>
<td>(0.98 1.02)</td>
<td>0.860</td>
<td>10,821</td>
<td>1.08</td>
<td>(1.06 1.09)</td>
</tr>
</tbody>
</table>

* Age at measurement and period were included in the model in addition to body mass index. The study population was a cohort of persons aged 18-75 years at inclusion.

4.3 Esophageal Cancer

During the follow-up time were 2,427 men and 1,022 women diagnosed with esophageal cancer. In men, 37 % of the cases were adenocarcinomas and 47,5 % were squamous cell carcinomas. In women, the corresponding findings were 22 % and 56 %. Overweighed and obese men had about the same risk of esophageal cancer as individuals with normal weight (Table 5). Overweighed women had an overall reduced risk of esophageal cancer than normal weight women.
However, breaking the data down to esophageal adenocarcinoma and esophageal squamous cell carcinoma, a different picture was drawn. Both overweighted and obese individuals had a significantly higher risk of adenocarcinoma, but a reduced risk of squamous cell carcinoma. These findings were similar in both men and women (Table 5).

**Table 5: Incidence of Esophageal cancer**

Estimated Hazard ratio (HR) for incidence, with 90 % confidence intervals*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence</td>
<td>Incidence</td>
</tr>
<tr>
<td></td>
<td>HR 95 % CI P-value n</td>
<td>HR 95 % CI P-value n</td>
</tr>
<tr>
<td><strong>BMI (kg/m^2)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.5 - 24.9</td>
<td>1 Referent 1,461</td>
<td>1 Referent 557</td>
</tr>
<tr>
<td>25.0 - 29.9</td>
<td>0.95 (0.88 1.04) 0.282 865</td>
<td>0.84 (0.72 0.97) 0.019 317</td>
</tr>
<tr>
<td>≥ 30.0</td>
<td>1.10 (0.91 1.33) 0.330 116</td>
<td>0.88 (0.74 1.09) 0.212 138</td>
</tr>
</tbody>
</table>

**Esophageal adenocarcinoma**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence</td>
<td>Incidence</td>
</tr>
<tr>
<td></td>
<td>HR 95 % CI P-value n</td>
<td>HR 95 % CI P-value n</td>
</tr>
<tr>
<td><strong>BMI (kg/m^2)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.5 - 24.9</td>
<td>1 Referent 757</td>
<td>1 Referent 366</td>
</tr>
<tr>
<td>25.0 - 29.9</td>
<td>1.46 (1.27 1.68) 0.000 362</td>
<td>1.69 (1.28 2.23) 0.000 147</td>
</tr>
<tr>
<td>≥ 30.0</td>
<td>2.12 (1.59 2.28) 0.000 46</td>
<td>2.43 (1.72 3.44) 0.000 50</td>
</tr>
</tbody>
</table>

**Squamous cell esophageal carcinoma**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence</td>
<td>Incidence</td>
</tr>
<tr>
<td></td>
<td>HR 95 % CI P-value n</td>
<td>HR 95 % CI P-value n</td>
</tr>
<tr>
<td><strong>BMI (kg/m^2)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.5 - 24.9</td>
<td>1 Referent 475</td>
<td>1 Referent 594</td>
</tr>
<tr>
<td>25.0 - 29.9</td>
<td>0.70 (0.63 0.80) 0.000 366</td>
<td>0.55 (0.45 0.67) 0.000 470</td>
</tr>
<tr>
<td>≥ 30.0</td>
<td>0.71 (0.52 0.95) 0.020 53</td>
<td>0.43 (0.32 0.58) 0.000 105</td>
</tr>
</tbody>
</table>

* Age at measurement and period were included in the model in addition to body mass index. The study population was a cohort of persons aged 18-75 years at inclusion.
4.4 Gastric Cancer

In total gastric cancer was diagnosed in 11,965 men and 7,970 women during the time of follow-up. The risk of gastric cancer was reduced in both obese and overweight group in both genders (Table 6). However, when analyzing only the cancers found in the cardia, there was an increased risk among both overweight and obese men. Men who were overweight and obese were observed to have an increased risk of 22 % and 80 % respectively. There was no increase in the risk of cancer in cardia in overweight and obese women (Table 6).

For other anatomical locations in the stomach, we did not find any associations with obesity and gastric cancer (data not shown).

**Table 6:** Incidence of Gastric cancer

Estimated Hazard ratio (HR) for incidence, with 90 % confidence intervals*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th></th>
<th></th>
<th></th>
<th>Women</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence</td>
<td></td>
<td></td>
<td></td>
<td>Incidence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>95 % CI</td>
<td>P-value</td>
<td>n</td>
<td>HR</td>
<td>95 % CI</td>
<td>P-value</td>
<td>n</td>
</tr>
<tr>
<td><strong>BMI (kg/m^2)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.5 - 24.9</td>
<td>1</td>
<td>Referent</td>
<td>7,128</td>
<td>1</td>
<td>Referent</td>
<td>3,771</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25.0 - 29.9</td>
<td>0.81</td>
<td>(0.78</td>
<td>0.88)</td>
<td>0.000</td>
<td>4,338</td>
<td>0.95</td>
<td>(0.90</td>
<td>0.99)</td>
</tr>
<tr>
<td>≥ 30.0</td>
<td>0.86</td>
<td>(0.80</td>
<td>0.94)</td>
<td>0.000</td>
<td>633</td>
<td>0.91</td>
<td>(0.85</td>
<td>0.97)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th></th>
<th></th>
<th></th>
<th>Women</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence</td>
<td></td>
<td></td>
<td></td>
<td>Incidence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>95 % CI</td>
<td>P-value</td>
<td>n</td>
<td>HR</td>
<td>95 % CI</td>
<td>P-value</td>
<td>n</td>
</tr>
<tr>
<td><strong>BMI (kg/m^2)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.5 - 24.9</td>
<td>1</td>
<td>Referent</td>
<td>592</td>
<td>1</td>
<td>Referent</td>
<td>240</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25.0 - 29.9</td>
<td>1.22</td>
<td>(1.07</td>
<td>1.39)</td>
<td>0.003</td>
<td>385</td>
<td>1.16</td>
<td>(0.93</td>
<td>1.44)</td>
</tr>
<tr>
<td>≥ 30.0</td>
<td>1.80</td>
<td>(1.35</td>
<td>2.38)</td>
<td>0.000</td>
<td>54</td>
<td>1.26</td>
<td>(0.92</td>
<td>1.74)</td>
</tr>
</tbody>
</table>

* Age at measurement and period were included in the model in addition to body mass index. The study population was a cohort of persons aged 18-75 years at inclusion.
4.5 Colorectal Cancer

During follow-up, 20,164 men and 25,947 women were diagnosed with colon cancer. As seen in Table 7, the risk of colon cancer was increased in both genders with increasing BMI. The risk of colon cancer was observed to be highest in overweight and obese men, 21% and 41% respectively.

When looking at colon sub-sites, we found a positive association between BMI and cancer incidence among men in ascending, transverse and descending colon. We did not observe the same strong association in women.

Finally, an increased risk for colorectal cancer was observed with increasing BMI in both genders (Table 7). Overweight and obesity in men increased the risk of colorectal cancer 14% and 31%, respectively. The risk of colorectal cancer was only slightly increasing for overweight and women (Table 7).
**Table 7:** Incidence of Colorectal cancer

Estimated Hazard ratio (HR) for incidence, with 90 % confidence intervals*

| Variable | Colorectal cancer (ICD10: C18, C19 & C20) | | Colon Cancer (ICD10: C18) | | Ascending - and transverse Colon (ICD10: C18.2, C18.4) | | Descending- and sigmoid colon (ICD10: C18.6, C18.7) | | Rectum (ICD10: C20) |
| --- | --- | --- | --- | --- | --- | --- | --- |
| | Men | Women | Men | Women | Men | Women | Men | Women |
| BMI (kg/m²) | | | | | | | | |
| 18.5 - 24.9 | 1 | Referent | 18,346 | 1 | Referent | 19,258 | | |
| 25.0 - 29.9 | 1.14 (1.11 1.17) | 0.000 | 13,505 | 1.05 (1.02 1.07) | 0.000 | 12,455 | | |
| ≥ 30.0 | 1.31 (1.25 1.38) | 0.000 | 1,815 | 1.06 (1.03 1.10) | 0.000 | 5,014 | | |
| BMI (kg/m²) | | | | | | | | |
| 18.5 - 24.9 | 1 | Referent | 10,740 | 1 | Referent | 24,253 | | |
| 25.0 - 29.9 | 1.21 (1.18 1.25) | 0.000 | 8,386 | 1.07 (1.04 1.10) | 0.000 | 17,262 | | |
| ≥ 30.0 | 1.41 (1.32 1.50) | 0.000 | 1,118 | 1.08 (1.04 1.12) | 0.000 | 4,646 | | |
| BMI (kg/m²) | | | | | | | | |
| 18.5 - 24.9 | 1 | Referent | 1,774 | 1 | Referent | 2,933 | | |
| 25.0 - 29.9 | 1.17 (1.08 1.26) | 0.000 | 1,182 | 1.08 (1.01 1.15) | 0.018 | 1,519 | | |
| ≥ 30.0 | 1.41 (1.18 1.69) | 0.000 | 132 | 1.09 (0.98 1.20) | 0.103 | 490 | | |
| BMI (kg/m²) | | | | | | | | |
| 18.5 - 24.9 | 1 | Referent | 4,469 | 1 | Referent | 8,968 | | |
| 25.0 - 29.9 | 1.23 (1.17 1.28) | 0.000 | 3,551 | 1.05 (0.99 1.10) | 0.074 | 6,412 | | |
| ≥ 30.0 | 1.35 (1.23 1.49) | 0.000 | 460 | 1.09 (1.02 1.17) | 0.009 | 1,650 | | |
| BMI (kg/m²) | | | | | | | | |
| 18.5 - 24.9 | 1 | Referent | 6,888 | 1 | Referent | 5,085 | | |
| 25.0 - 29.9 | 1.02 (0.98 1.06) | 0.327 | 4,589 | 1.01 (0.96 1.06) | 0.737 | 3,227 | | |
| ≥ 30.0 | 1.17 (1.08 1.27) | 0.000 | 634 | 1.04 (0.97 1.10) | 0.266 | 1,350 | | |

* Age at measurement and period were included in the model in addition to body mass index. The study population was a cohort of persons aged 18-75 years at inclusion.
4.6 Hepatocellular carcinoma and Intrahepatic cholangiocarcinoma

In total 2,574 out of the 1,620,769 persons included in the study were diagnosed with HCC and intrahepatic cholangiocarcinoma and intrahepatic cholangiocarcinoma during the follow-up time. 1,863 (72 %) out of the 2,574 people were diagnosed with HCC, 1,101 men and 762 women. Increasing BMI was found to increase the risk for HCC in men. Obese men had more than twice the risk of being diagnosed with HCC compared to normal weight men. Further, obese women had an increased risk of 28 %, compared to women defined as normal weight (Table 8).

However, in total 715 people were diagnosed with intrahepatic cholangiocarcinoma, 316 men and 399 women. Obese women were shown to have an 58 % increased risk of intrahepatic cholangiocarcinoma compared to normal weight women. However, no association between increasing BMI and intrahepatic cholangiocarcinoma was found in men (Table 8).

Table 8: Incidence of Hepatocellular carcinoma and Intrahepatic cholangiocarcinoma

Estimated Hazard ratio (HR) for incidence, with 90 % confidence intervals*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hepatocellular carcinoma (ICD10: C22.0)</th>
<th>Intrahepatic cholangiocarcinoma (ICD10: C22.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td></td>
<td>Incidence</td>
<td>Incidence</td>
</tr>
<tr>
<td></td>
<td>HR 95 % CI  P- value  n</td>
<td>HR 95 % CI  P- value  n</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.5 - 24.9</td>
<td>1 Referent</td>
<td>1 Referent</td>
</tr>
<tr>
<td>25.0 - 29.9</td>
<td>1.23 (0.98 1.42) 0.002 439</td>
<td>1.09 (0.92 1.28) 0.334 256</td>
</tr>
<tr>
<td>≥ 30.0</td>
<td>2.37 (0.91 2.62) 0.000 98</td>
<td>1.28 (1.03 1.53) 0.025 121</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| * Age at measurement and period were included in the model in addition to body mass index. The study population was a cohort of persons aged 18-75 years at inclusion.
4.7 Gallbladder Cancer

Out of the 1,020 individuals who developed gallbladder cancer, were 219 (21%) men and 801 (79%) women. Obese women were observed to have more than two-times-higher risk for gallbladder cancer compared to normal weight women (Table 9). Further, overweight women were also shown to have an increased risk of 45% for gallbladder cancer. Among men, there were no associations between BMI and the risk of gallbladder cancer (Table 9).

**Table 9: Incidence of Gallbladder Cancer**

Estimated Hazard ratio (HR) for incidence, with 90% confidence intervals*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence</td>
<td>Incidence</td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>95 % CI</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.5 - 24.9</td>
<td>1</td>
<td>Referent</td>
</tr>
<tr>
<td>25.0 - 29.9</td>
<td>1.10</td>
<td>(0.83, 1.45)</td>
</tr>
<tr>
<td>≥ 30.0</td>
<td>1.05</td>
<td>(0.56, 1.96)</td>
</tr>
</tbody>
</table>

* Age at measurement and period were included in the model in addition to body mass index. The study population was a cohort of persons aged 18-75 years at inclusion.

4.8 Pancreatic Cancer

During the follow-up period, a total of 15,035 individuals, 7,267 (48%) men and 7,768 (52%) women were diagnosed with pancreatic cancer during the follow-up time. Obesity increased the risk of pancreatic cancer in both men and women compared to normal weight. Both overweight and obese women had an increased risk of pancreatic cancer (Table 10).
Table 10: Incidence of pancreatic cancer

Estimated Hazard ratio (HR) for incidence, with 90% confidence intervals*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Incidence</th>
<th>Women</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>P- Value</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.5 - 24.9</td>
<td>1</td>
<td>Referent</td>
<td>4,087</td>
<td>1</td>
</tr>
<tr>
<td>25.0 - 29.9</td>
<td>1.01</td>
<td>(0.96 1.06)</td>
<td>0.754</td>
<td>2,801</td>
</tr>
<tr>
<td>≥ 30.0</td>
<td>1.22</td>
<td>(1.11 1.35)</td>
<td>0.000</td>
<td>419</td>
</tr>
</tbody>
</table>

* Age at measurement and period were included in the model in addition to body mass index. The study population was a cohort of persons aged 18-75 years at inclusion.

4.9 Metastatic Diseases

At the time of cancer diagnosis, we observed that 178,652 persons were diagnosed with either regional- or distant metastasis of cancer. The analysis showed that obese men had an increased risk of 6% for regional metastasis. Further, was both overweight and obese women showed an increased risk of 2% and 13% respectively (Table 11). Furthermore, overweight men and women were observed to have a decreased risk of distant metastasis. However, obese women were found to have a 9% increased risk for distant metastasis (Table 11).
Table 11: Incidence of Metastasis

Estimated Hazard ratio (HR) for incidence, with 90 % confidence intervals*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men Incidence</th>
<th></th>
<th></th>
<th>Women Incidence</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95 % CI</td>
<td>P- value</td>
<td>n</td>
<td>HR</td>
<td>95 % CI</td>
</tr>
<tr>
<td><strong>BMI (kg/m^2)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.5 - 24.9</td>
<td>1</td>
<td>Referent</td>
<td>55,629</td>
<td>1</td>
<td>Referent</td>
<td>46,229</td>
</tr>
<tr>
<td>25.0 - 29.9</td>
<td>0.98 (0.97 1.00)</td>
<td>0.023</td>
<td>35,499</td>
<td>0.97 (0.95 0.98)</td>
<td>0.000</td>
<td>24,708</td>
</tr>
<tr>
<td>≥ 30.0</td>
<td>0.97 (0.94 1.00)</td>
<td>0.039</td>
<td>4,291</td>
<td>1.01 (0.99 1.03)</td>
<td>0.414</td>
<td>10,079</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men Incidence</th>
<th></th>
<th></th>
<th>Women Incidence</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95 % CI</td>
<td>P- value</td>
<td>n</td>
<td>HR</td>
<td>95 % CI</td>
</tr>
<tr>
<td><strong>BMI (kg/m^2)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.5 - 24.9</td>
<td>1</td>
<td>Referent</td>
<td>24,882</td>
<td>1</td>
<td>Referent</td>
<td>25,751</td>
</tr>
<tr>
<td>25.0 - 29.9</td>
<td>0.98 (0.96 1.01)</td>
<td>0.153</td>
<td>14,606</td>
<td>1.02 (1.00 1.04)</td>
<td>0.042</td>
<td>14,355</td>
</tr>
<tr>
<td>≥ 30.0</td>
<td>1.06 (1.05 1.11)</td>
<td>0.014</td>
<td>1,765</td>
<td>1.13 (1.09 1.16)</td>
<td>0.000</td>
<td>6,045</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men Incidence</th>
<th></th>
<th></th>
<th>Women Incidence</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95 % CI</td>
<td>P- value</td>
<td>n</td>
<td>HR</td>
<td>95 % CI</td>
</tr>
<tr>
<td><strong>BMI (kg/m^2)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.5 - 24.9</td>
<td>1</td>
<td>Referent</td>
<td>28,423</td>
<td>1</td>
<td>Referent</td>
<td>22,925</td>
</tr>
<tr>
<td>25.0 - 29.9</td>
<td>0.93 (0.91 0.95)</td>
<td>0.000</td>
<td>14,606</td>
<td>0.98 (0.95 0.99)</td>
<td>0.004</td>
<td>13,148</td>
</tr>
<tr>
<td>≥ 30.0</td>
<td>1.00 (0.96 1.05)</td>
<td>0.848</td>
<td>1,765</td>
<td>1.09 (1.06 1.12)</td>
<td>0.000</td>
<td>5,928</td>
</tr>
</tbody>
</table>

* Age at measurement and period were included in the model in addition to body mass index. The study population was a cohort of persons aged 18-75 years at inclusion.
4.10 Cancer Survival

Out of the 468,238 people diagnosed with cancer 265,479 died of cancer during follow-up. Underweight, overweight and obesity in men were observed to increase the risk of death by cancer. In women, the increase of death by cancer was associated with increasing BMI. Compared to normal weight people, obesity increased the risk of death by cancer in both men and women with 27% and 37% respectively (Table 12).

A Kaplan–Meier model was used to estimate survival probability for cancer patients according to BMI classification. Underweight and normal weight individuals at baseline measures were observed to have better overall survival compared with the overweight and obese individuals.

**Table 12: Incidence of death by cancer**

Estimated Hazard ratio (HR) for incidence, with 90% confidence intervals*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th></th>
<th></th>
<th></th>
<th>Women</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence</td>
<td></td>
<td></td>
<td></td>
<td>Incidence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>HR</td>
<td>95% CI</td>
<td>P- value</td>
<td>n</td>
<td>HR</td>
<td>95% CI</td>
<td>P- value</td>
<td>n</td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>1.12</td>
<td>(1.05 1.20)</td>
<td>0.000</td>
<td>1,032</td>
<td>1.03</td>
<td>(0.98 1.07)</td>
<td>0.268</td>
<td>2,247</td>
</tr>
<tr>
<td>18.5 - 24.9</td>
<td>1</td>
<td>Referent</td>
<td>80,438</td>
<td>1</td>
<td>Referent</td>
<td>62,331</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25.0 - 29.9</td>
<td>1.08</td>
<td>(1.24 1.31)</td>
<td>0.000</td>
<td>53,831</td>
<td>1.16</td>
<td>(1.14 1.17)</td>
<td>0.000</td>
<td>40,337</td>
</tr>
<tr>
<td>≥ 30.0</td>
<td>1.27</td>
<td>(1.24 1.31)</td>
<td>0.000</td>
<td>6,954</td>
<td>1.31</td>
<td>(1.29 1.33)</td>
<td>0.000</td>
<td>18,310</td>
</tr>
</tbody>
</table>

* Age at measurement and period were included in the model in addition to body mass index. The study population was a cohort of persons aged 18-75 years at inclusion.
Figure 5: Kaplan-Meier Estimates of Survival of cancer

Kaplan-Meier estimates of survival of cancer among men and women diagnosed with cancer, adjusted for age at diagnosis.
5 Discussion

5.1 Data Material and Method

The study subjects were collected from a population-based unselected National Health study with high attendance in the period between 1936-1975. One of the greatest strengths of the present study is the large size of the study population and the longtime of follow-up. This unique opportunity made it possible to perform analysis of cancer sub-sites and to specific histology. The measurement of height and weight were performed in a standardized way, without knowledge of whether the person later developed cancer or not. Personalized identification numbers and population-based registers on cancer incidence and death, led to an almost complete follow-up of the study subjects.

The material used in the present study has previously been used to study the association between height and weight and the risk of other cancers, but with a shorter observation interval (99, 123, 124). The present analyses have been performed in similar methods as previous studies, in order to make estimates comparable across different cancer sites.

The following limitations warrant a remark. Our study was an observational retrospective cohort and the data were nonrandomized. Furthermore, we used baseline measures throughout a long follow-up period. During follow-up, some individuals might have changed their BMI markedly. However, there are strong evidence in the literature that body weight tends to increase rather than decrease over time. Hopman et al demonstrated that on average, men under the age of 45 and women under age 55 were gaining approximately 0.45 kg per year (125). These findings were further supported by Fildes et al when investigating 278,982 obese men and women over a 9-year period. The annual probability of patients with BMI 30-35 kg/m² attaining normal weight was only 1 in 124 for women and 1 in 210 for men. The likelihood for attaining normal weight declined with increasing BMI (126).

BMI is the most commonly applied measure for body fatness. BMI is highly correlated with fat mass in a range of populations and proven to reflect obesity related disease risk. However, there are some well-known important limitations. BMI does not reflect body composition or distribution of body fat. Muscular end lean people may have a relativel high BMI, even if they
have relatively little body fat distribution (127, 128). Visceral adipose tissue is more metabolic active and secrets more cytokines and hormones that can affect the progression of cancer, compared to subcutaneous adipose tissue. Previously studies have shown that some cancers are associated more with abdominal obesity than BMI (129-133).

Moreover, we did not have any measure of the waist size for any of the individuals in the study population. Consequently, it was impossible to understand if the differences in the associations between BMI and the risk of cancer could be due to the deposition of fat.

Another limitation of this study is the inability to evaluate possible confounders. Alcohol consumption, smoking habits, physical activity, and dietary factors are all known to affect the risk of cancer development to a greater or lesser degree. Two or more alcoholic drinks a day has been shown to increase the risk of colorectal cancer (134), and three or more alcoholic drinks a day increase the risk of stomach cancer and HCC (134). Further, smoking is inversely related to BMI and might be an important confounder in the relationship between obesity and cancer. In the present study, no information about smoking habits was available.

At last, individuals in the study population were measured between the period 1963-1975. It is thus a question of whether the population is representative of today's society.

5.2 Results

This large population-based cohort study strongly supports a higher risk of cancer incidence in the digestive system among the obese population. The study population was followed up for 43-55 years, an observation time longer than any other cohort studies of obesity and cancer in the literature that we are aware of. Our results show that BMI ≥ 30 kg/m² leads to increased risk for esophageal adenocarcinoma, gastric cancer of the cardia, colorectal cancer, HCC, cholangiocarcinoma, gallbladder, and pancreatic cancer. We also observed that obese cancer patients had an increased risk of cancer metastasis both regionally, and distant metastasis compared to cancer patients with normal weight. This may explain why we observed an increased for cancer-specific mortality in obese patients.
5.1.1 Total incidence of cancer

Of the 1,649,930 individuals in the study population a total of 243,860 men and 224,378 women were diagnosed with overall cancer. Results showed that underweight men and women had an increased risk of cancer development compared to the other groups. However, we do not have any information about smoking habits in our study. This can explain some of the differences between the BMI group as smoking is inversely related to BMI and are known to increase the risk of several cancers. Further, overweight men and women were found to have a decreased risk of cancer development. Nevertheless, our findings only showed a small decrease compared to normal weight. At last, our analysis show that obese women have increased risk of overall cancer development, but no significant results for obese men were found. This could be due to sex hormones, as they play a crucial role in the development of several cancers.

5.1.2 Cancer of esophagus

In our study, we found that the risk for adenocarcinoma esophagus was more than twice as big for both obese men and women compared with normal weight people. However, obese men and women were observed to have a decreased risk for squamous cell esophageal carcinoma. The association between BMI and esophagus cancers has been investigated in several epidemiological studies. Our results support the hypothesis that it is necessary to distinguish between squamous cell carcinoma and adenocarcinoma when investigating the association between esophageal cancer and BMI.

The increased risk of esophageal adenocarcinoma can in part be explained by increased gastro- esophageal reflux among obese individuals. Obesity may lead to increased abdominal pressure and thus increase the risk of hiatal hernia. Chronic reflux overtime can predispose to Barret’s esophagus, which may progress via dysplasia pathway to esophageal adenocarcinoma (30, 135).

Historically, squamous cell carcinoma esophagus has occurred more frequently than adenocarcinoma esophagus. The last decade this has changed. There have been observed an increased incidence of esophageal adenocarcinoma in both the US, Western Europe and a
decrease in squamous cell carcinoma (100). Today, about 80% of patients diagnosed with esophageal cancer in Norway are diagnosed with adenocarcinoma (136). This coincides with the increase in body weight in the same population.

5.1.3 Gastric Cancer

Previous studies have found an association between overweight and obesity and an increased risk for gastric cancer. Results from a Norwegian cohort study using waist circumferences as a measure for body fatness showed that participants with high waist circumferences (women < 80 cm and men < 94 cm) had a 50% higher risk of gastric cancer compared to participants with lower waist circumferences (137). Our study could not confirm this association. On the other hand, we observed overweight and obese persons to have a decreased risk of gastric cancer. However, our results showed an increased risk for obese men to be diagnosed with cardia gastric cancer. The CUP analysis for body fatness and overall gastric cancers, cardia and non-cardia cancers found similar results (101).

The same mechanisms that explain the relationships between obesity and esophageal adenocarcinoma may also explain some of the relationship between obesity and cardia gastric cancer. Other possible mechanisms like abnormal gastric motility, insulin resistance, altered levels of metabolic endogenous hormones and abnormally increased levels of IGF have also been proposed (138).

Recent evidence has revealed an increased prevalence of Helicobacter pylori in obese patients (139). Helicobacter pylori have been found to increase the risk of gastric cancer, providing another indication for the increase in gastric cancer in the obese population. However, helicobacter pylori are also associated with a decreased risk of esophageal adenocarcinoma (101).

5.1.4 Colorectal cancer

In this large cohort study, we further observed an increased risk of colorectal cancer with increasing BMI in both men and women. Our findings support previous studies investigating
the relations between BMI and the risk of colorectal cancer. Ma et al indicated that obesity increased colorectal cancer risk by 30% (140) and Moghaddam et al (132) established that a 2 kg/m² increase in BMI contributes to an increase in colorectal cancer risk of 7% (4-10%).

An IARC working group concluded that there is a positive association between the risk of colorectal cancer and BMI, although weaker in women than in men (141). In our study, we observed a noticeably higher risk of colorectal cancer among both overweighted and obese men compared to overweight and obese women and thus support IARC conclusion.

The reasons for the differences in the strength of the association of obesity with colon cancer risk between genders are unclear. One hypothesis is that the high blood levels of estrogen associated with post-menopausal obesity might be responsible for this gender difference.

Another potential reason is that women and men have different distributions of body fat (142). By using data from the Fremingham study Moore et al had access to data on waist circumference and observed that this measure was a stronger predictor for colon cancer risk than BMI (143). Compared with women, men are more likely to have abdominal obesity, also known as visceral adipose tissue within the abdominal cavity (144). Elevated levels of visceral fat have been associated with both hyperinsulinemia, insulin resistance and chronic inflammation (16). Increased levels of circulating insulin can promote cell growth and inhibit apoptosis and have been identified as a risk factor for the development of colon cancer (145-147).

In the present study, we did not have any measure of waist size. Hence, it was not possible to explore whether the differences in the associations between BMI and risk of colon cancer might be due to the deposition of fat. The distribution of body fat may be important for the risk of colon cancer.

5.1.5 Hepatocellular Carcinoma and intrahepatic Cholangiocarcinoma

In line with previous studies, our results also showed an increased risk of HCC in both genders. In 2007, Larsson and Wolk, indicated that overweight and obesity contribute to the more frequent occurrence of primary liver malignancy and that maintaining normal
bodyweight may partially reduce cancer risk (148). Worldwide, HCC accounts for 85-90 % of the total primary liver malignancy burden (149) and usually develops within a background of advanced chronic liver disease, mainly related to alcohol abuse or hepatitis B or C virus infection. However, in the near future, it has been predicted that obesity is likely to become the leading factor. Epidemiological studies have proposed that obesity is a large contributor to overall HCC burden, either alone or as a cofactor (150-153). In our study we observed the risk of HCC to be twice as high among obese men compared to normal weight men. The rapidly increasing prevalence of obesity all over the world may be one of the reasons why the incidence of HCC has been found to be growing from 1.5 to 4.9 per 100,000 individuals in the past 30 years (154).

Overweight or obese individuals are at increased risk of NAFLD. High leptin levels and low adiponectin levels are two hallmarks of obesity and are both involved in NAFLD progression and carcinogenesis (155). NAFLD has been identified as the underlying cause in 13-38 % of patients diagnosed with HCC unrelated to virus and alcohol (156).

Our results showed a clear difference between obese men and women with a higher risk of HCC among men. One recent meta-analysis which included 17 studies, found a relative risk of HCC incidence for obese men and women to be 2.04 (95 % CI:1.70, 2.44) and 1.56 (95 % CI: 1.37, 1.78), respectively (157). It has been suggested that stimulatory effects of androgens and protective effects of estrogens may cause this difference as high free estrogen levels in women have been shown to suppress liver cancer proliferations and growth (158, 159). Interestingly, results from our study showed that obese women had an increased risk of intrahepatic cholangiocarcinoma compared to normal weight women. However, the numbers of diagnoses were very few, only accounting 62 individuals.

5.1.6 Gallbladder cancer

According to WCRF is there strong evidence that being overweight or obese increases the risk of gallbladder cancer (160). Gallbladder cancer is known to be one of the few cancers that mostly affects women. Previous studies have calculated the risk ratio with an increase in BMI of 5 kg/m² to be at the level of 1.59 in women (161). Our results confirmed this as we found a stronger association between body fatness with gallbladder cancer in women compared to
men. The WCRF suggests that the difference between men and women may in part be due to the adverse effects of female sex hormones on hepatic bile secretion and gallbladder function (30).

The underlying mechanisms that link obesity with gallbladder cancer are still unclear. However, the association between obesity and gallbladder cancer may be indirect. Obese patients have increased frequency of gallstones (162) and gallstone disease has been considered as one of the risk factors for gallbladder cancer (112, 163).

5.1.7 Pancreatic Cancer

The WCRF/IARC classified “body fatness” as a convincing cause of pancreatic cancer (164). Previous studies have demonstrated that the risk of pancreatic cancer is about 50% greater for obese people, compared to normal weight (165). Our results support the association between obesity and pancreatic cancer, but we did not observe the same increase in risk. The most recent WCRF/IARC, CUP, reported a 10% statistically significant increase for pancreatic cancer per 5 BMI units, no differences were observed between men and women (164). However, we observed the risk of being diagnosed with pancreatic cancer to be higher among obese men than obese women. Previous studies with the same results propose that differences in sex hormones may explain this finding (166). Increased estrogen production from adipose tissue in obese women, may decrease the risk of pancreatic cancer (166). This hypothesis is not fully understood.

Glucose intolerance and hyperinsulinemia have been proposed to be directly involved in the onset of pancreatic cancer (167). Previous studies have reported a positive association between elevated blood glucose levels and pancreatic cancer (168, 169). Elevated levels of glycated hemoglobin (HbA1c), has also been associated with increased risk of pancreatic cancer in prospective cohort studies (170). In the EPIC cohort study, blood samples were collected prior to diagnosis, elevated levels of HbA1c was associated with a 65% higher risk of pancreatic cancer (171).

Insulin resistance is associated with alterations of numerous of metabolic pathways, it is still unclear in which way insulin resistance are involved in pancreatic cancer. Proinsulin itself has
been proposed to play a role in carcinogenesis due to its ability to bind to insulin receptor and thus can impact cell proliferation (172).

Abdominal obesity, measured by waist circumferences or weight-hip ratio, has also been associated with increased risk of pancreatic cancer (165, 173). The impact of abdominal obesity on risk of pancreatic cancer appeared to be independent of BMI as controlling for BMI did not remove the positive association observed by obesity (165).

5.1.8 Metastatic diseases

When investigating the association between obesity and metastasis, we observed that obese women had an increased risk for being diagnosed with regional and distant metastasis compared to normal weight women. Obese men were observed to have an increased risk for regional metastasis.

There are only a few epidemiological studies investigating the relationship between obesity and metastasis. However, several in vitro studies have demonstrated that leptin secreted from adipose tissue induces cell invasion and migration in different cancer cells, such as colorectal cancer (174), HCC (175, 176), and gastric cancer cells (177).

Currently, it is still unclear whether obesity leads to increased risk of metastatic disease or not. Although our results showed an increased risk for regional and distant metastasis in obese women, this finding may be due to other important factors. Obese individuals tend to be treated differently than normal- and underweight people. Both patient’s delay and doctor’s delay may affect the results. Obese people have also been shown to be less likely to participate in screening programs which could contribute to a delay in cancer diagnosis (178).

5.1.9 Survival

In our study, after adjusting for age at time of cancer diagnosis, we observed that increasing BMI also increased the risk of death by cancer for both genders (Figure 5). Hence, obesity is not only increasing the risk of cancer development, but also increase the risk of cancer-specific mortality. One reason for increased mortality may be that obese people have more
often metastatic disease and a delay in both diagnosis and start of treatment will then have a negative effect on survival.

5.3 Future Perspective

Norway is one of the countries in Europe were the incidence of obesity is rapidly increasing. In 1963-1975, when the study population was measured, 10 % of the cohort was defined as obese. Today, we assume that more than 23 % of Norwegians are considered obese. Obesity is one of the major health challenges as there is a strong association between obesity and several diseases including cancer, as our study also shows.

Furthermore, obesity also provides a challenge for the society. In a recent report, Menon Economics estimated that the obese people account for more than 68 billion NOK recent years (179), including loss of life-years due to obesity-associated morbidity and death.

This highlights the urge for public health politicians to develop programs to reverse this trend as well as encouraging the next generation to increase physical activity and restrict excess calorie intake. To accomplish this, we need to involve all institutions that we interface (schools, colleges etc.) as well as making organized training facilities affordable for the majority of the population. Finally, we need to help the obese persons with weight reductions and implementing a healthy lifestyle. However, whether weight reduction after decades with obesity reduces the risk of cancer development is still to be investigated.
6 Conclusion

Overweight and obesity constitute as a major health problem for the 21st century, both due to the increasing prevalence and the cause-effect relationship with a number of diseases. Several studies have shown a relationship between obesity and cancer development. In our unselected population-based cohort of 1,649,930 individuals were also demonstrate an increased risk of cancer in the digestive system among the obese population, higher risk for metastatic disease, and cancer related mortality.

Considering the increase in the number of obese people worldwide, it is necessary to promptly investigate the mechanism linking obesity with cancer development. Furthermore, action has to be taken to prevent obesity. Countering an unhealthy lifestyle in order to reduce overweight and obesity in society may have an essential impact on public health in general as well as reducing cancer incidence and cancer-related death.
7 References


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Appendix

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Oslo universitetssykehus HF

2018/70 Risiko for kreft hos overviktige

Forskningsansvarlig: Oslo universitetssykehus HF
Prosjektleder: Shara Yaqub


Prosjektleder: prosjektbeskrivelse

Flere studier har vist sammenheng mellom overvikt og skje risiko for kreft. Særleg kreft i spiser, magesskap, slik og endemier samt bakteriell parasitt. Ettersom ikke overvikt eller risikoen for kreft er like selvsagt som alvorlig, vil vi bruke data fra helseforskningsområdet for å vurdere overvikt og risikoen for kreft.

Vurdering

Det er nødvendig å vurdere risikoen for kreft i spiser, og det er nødvendig å vurdere risikoen for kreft i spiser, og det er nødvendig å vurdere risikoen for kreft i spiser.
Shereh Yaqub  
Øst universitetssykehus HF  

2018/079 Risiko for krev hos overviktige  
Forskningsansvarlig: Øst universitetssykehus HF  
Projektleder: Shereh Yaqub  

Vi viser til saknad om prosjektorlending datert 08.11.2018 for omsvarte forskningsprosjekt. Saknaden er behandlet av leder for REK sørs-vest D på fullmakt, med hensyn på helsetiltaksloven § 11.  

Endringene innebærer:  
- undersøk forbruket av alle krevligne i hals kobøten i hals perioden (1953 til 2017).  
- undersøk status og stasstevn til hele kobøten fra Folkesøknad, inkludert "Skjernslederensvaktten fra 1943 til 1989".  

Vurdering  
REK har vurdert saknaden og har ingen forskningsetiske innvendiger til endringen av prosjektet.  

Vedtak  
REK har gjort en forskningsetisk vurdering av endringene i prosjektet, og godkjennet prosjektet slik det nå finnes.  

Klageansvarelig  
REKs vedtak kan påtale, jf. forvaltningslovens § 28 f). Eventuell klage sendes til REK sørs-vest D.  

Klageretten til å rekviret av sak  
Vi ber om at alle henvendelser sendes inn på korrekt skjemma via vår søknadshjelp:  
http://helsetilfluktsistokkom.no. Dersom det ikke finnes passende skjemma kan henvendelsen rettes på e-post til: post@helseforfunksjon.stokkom.no.  

Vennligst oppgi vått referansenummer i korrrespondansen.  

Med vennlig hilsen  
Finn Winje  
Professor em. dr. med.  

Ledet