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Relationship of Body Mass Index to Cancer Incidence in Young and Middle Aged Men and Women followed over 24 years: The Tromsø Study

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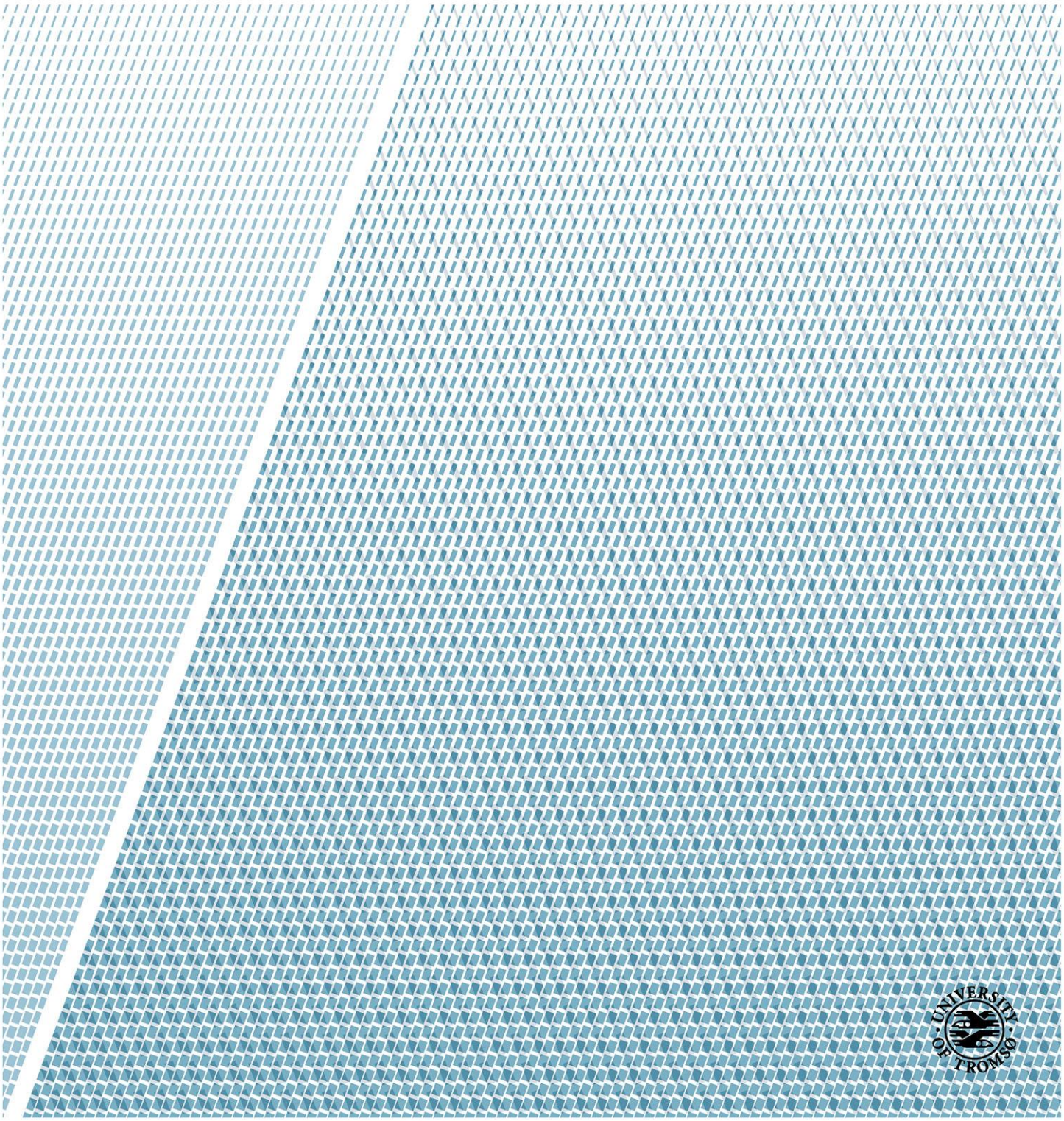

DEDICATION

To my father, William Folorunso Oyeyemi,

the man who created in me the need to be a better person,

…rest in peace.

ACKNOWLEDGEMENTS

The theme of this thesis was chosen as a result of personal interest in cancer research and a humble wish to contribution to medical knowledge. I thank the Data and Publication Committee for granting me access to the needed dataset and the University Library for providing unlimited access to countless high profile academic resources.

The thesis started as a vague conception in my mind and I was only able to bring it into reality through the assistance and expertise of my supervisor, Professor Bjarne Koster Jacobsen. I lost count of the number of cups of coffee we went through to actualise this piece of work, but I remember vividly those times he had to rescue me when I stubbornly get lost in the deep labyrinth of data and statistics. I thank you most sincerely for your wealth of knowledge and experience you brought to bear, your enthusiasm in my work, your sense of humour, and your friendly-styled superlative supervision. I also appreciate the course co-ordinator, Tor Gisle, for his ever ready attitude to assist and resolve issues. I thank all my fellow co-travellers in the quest for knowledge for all the delightful fun we had together. With Felix on my left, Susan on my right, and Nils and his gang behind me, those long hours of lectures and coursework were always exciting and full of ingenious humours.

I am profoundly grateful to my mother for her supports and prayers; I can never thank you enough. I am forever grateful to my wife, the rainbow in my sky and my own jewel of inestimable value. Thank you for your enormous tolerance and understanding. Soon, I shall be fully home with you. To my awesome God, for the gift of life and the opportunities therein, I remain eternally grateful.

Oyeyemi, Sunday Oluwafemi

July 2014

ABSTRACTS

Background: Obesity remains a serious but preventable challenge of our time, and it has been linked to many comorbidities. This study uses body mass index (BMI) as a measure of obesity to investigate the relationship between low and high BMI and total cancer incidence, as well as some common specific cancers. These relationships were explored in relatively young subjects who may lose more life years to cancer.

Method: A population-based cohort study was carried out using the third Tromsø survey of 1986-87 (Tromsø 3) with the Norwegian Cancer Registry (up to December 2010). The cohorts, which were year of birth based, were aged 20-61 years (men) and 20-56 years (women) in 1986. A total of 19,943 subjects (10,219 men and 9,724 women) were followed up for a mean period of 22.41 years. During the follow-up period, a total of 2,248 incident cancers were identified with 1,252 (55.7%) in men, and 996 (44.3%) in women. The relationship of the subjects' BMI to the cancer incidence was explored using Cox proportional hazards regression to compute the hazard ratios (HR). In most of the analyses, subjects with BMI 20.0-24.9 kg/m^2 were the reference category.

Results: In men, a U-shaped relationship between BMI and total cancer incidence was observed, with men of BMI 20.0-24.9 kg/m^2 having the lowest risk of cancer occurrence (BMI < 20.0 kg/m^2: HR=1.41 [95% CI: 1.03-1.93]; BMI ≥ 30.0 kg/m^2: HR=1.30 [95% CI: 1.03-1.63]). Unlike in men, there was essentially no relationship between BMI and the total cancer incidence observed in women. BMI appeared indifferent to prostate cancer risk, while BMI < 20.0 kg/m^2 and ≥ 30.0 kg/m^2 were associated with increased risk of lung cancer. In men, BMI may be a strong risk factor in colon cancer, with BMI < 25.0 kg/m^2 having the lowest risk (BMI 25.0-29.9 kg/m^2: HR=1.81 [95% CI: 1.19-2.74]; BMI ≥ 30.0 kg/m^2: HR=1.83

[95% CI: 0.88-4.07]). In women, a null relationship was observed. However, when the women cohort were stratified into 2 by their mean age at baseline, 36 years, a relatively strong positive linear relationship was found between BMI and colon cancer risk in those younger than 36 years at the study baseline (BMI 25.0-29.9 kg/m^2: HR=2.09 [95% CI=0.57-7.58]; BMI ≥ 30.0 kg/m^2: HR=5.26 [95% CI: 1.15-24.06]). In men, a positive linear relationship was found between BMI and the risk of colorectal cancer (BMI < 20.0 kg/m^2: HR=0.67 [95% CI: 0.16-2.74]; BMI ≥ 30.0 kg/m^2: HR=1.81 [95% CI=1.01-3.22]). No marked fluctuation in the risk of colorectal cancer was observed in women.

Conclusion: Low and high BMI have impacts on the total cancer risk in the relatively young and the middle aged population, as well as the risk of some of the other specific cancers studied. Therefore, any public health policies directed at reducing cancer incidents should address both ends of the BMI spectrum in the community.

Keywords: obesity, body mass index, cancer incidence, cohort study, Tromsø study, prostate cancer, lung cancer, colon cancer, cancer of the rectum, colorectal cancer.

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CHAPTER 1: INTRODUCTION

1.1 Background

Obesity is one of the most serious and preventable public health challenges of the 21st century (1). It is a condition in which there is excess accumulation of body fat. The World Health Organization (WHO) defined obesity as abnormal or excessive fat accumulation that may impair health (2), and this is traditionally regarded as a weight of at least 20% above the recommended for a specific height (3).

In simple terms, obesity occurs as a result of intake of more calories through diet than is burnt through active living or physical activities. This caloric imbalance may be caused singularly or in combination with genetic, environmental or and behavioral factors (1, 2). Some medications and disease conditions are also known to cause weight gain (4). In 2013, the American Medical Association classified obesity as a disease (5).

There are some accurate methods of measuring obesity, such as magnetic resonance imaging (MRI), computerized tomography (CT), dual-energy X-ray absorptiometry, underwater weighing, air-displacement plethysmography, and bioelectric impedance analysis. However, these measurement methods are not suitable for large population studies (6). There is no absolutely flawless population-based method of measuring obesity, nevertheless, the most commonly used methods are anthropometric, and are body mass index (BMI), waist circumference, waist-to-hip ratio, waist-to-height ratio and skinfold thickness. This research work shall make use of the BMI method. This provides a very useful population-level measure of obesity because it is the same for both male and female adults

of all ages (2, 6). BMI is calculated by dividing the weight (in kilograms) by the square of the height (in metres) of the individual.

1.2 How common is obesity?

The prevalence of obesity is reportedly rising rapidly throughout the world, and has been described as one of the fastest developing global public health challenges of the present day (6, 7).

In the United States, the National Health and Nutrition Examination Survey (NHANES) carried out a study between 1988 and 1994 and revealed that about 56 per cent of adult age 20 and above were either overweight or obese. By 2007-2008, about 68 per cent of same group were overweight or obese (8). In a population-based study carried out in Tromsø, Norway, the BMI of the participants was found to have increased during a 15 to 20 year follow-up (1974-1994) in all the examined birth cohorts of the population (9). This same trend was also found in another study, the Nord-Trøndelag Health Study (HUNT Study) where a large representative of adult Norwegian population was followed over 22 years (10). Findings from the HUNT Study indicate rising prevalence of obesity in Norway, as do unpublished recent results from the Tromsø Study shown (10, 11).

In 2008, the WHO estimated over 1.4 million adults age 20 and above to be overweight, out of which about 500 million were obese. This means more than 10% of the world's adult population was obese (2). And going by the WHO projection, it is estimated that by the year 2015, about 2.3 million adults will be overweight of which more than 700 million will be obese (6). It follows then that any disease conditions associated with obesity will most likely increase just as those who are obese increase in number.

1.3 Cancer and the link to obesity

WHO describes cancer as an uncontrolled growth and spread of cells which can affect almost any parts of the body (12). Cancer is one of the leading causes of death worldwide. In 2012, it accounted for about 8.2 million deaths globally (12, 13). The common types of cancer differ from males to females, and may also differ from one part of the world to another. The 5 leading behavior and dietary risks account for about 30% of cancer deaths, and these risks, as cited by the WHO, are: tobacco use, obesity, low fruit and vegetable intake, lack of physical activity, and alcohol use (12). Obesity is second only to smoking as an avoidable risk of cancer death. Sadly, it is projected that the annual cancer occurrence will increase from about 14 million in 2012 to about 22 million within the next 20 years (12, 13), and this may not be unconnected with the epidemic rise of overweight and obese population in the world.

The association between obesity and some disease conditions such as heart diseases and diabetes have consistently been demonstrated and often with good public awareness (14, 15). However, it appears there is still relatively insufficient public and political acceptance and precise perception of the ties between obesity and cancer.

This may be partly due to the fact that most studies addressing the issue of the association between obesity and cancer usually make use of heterogeneous population including many cities and diverse people of different cultural values, societal mores, and urbanity. Such is the widely cited prospective cohort study conducted in the United States by Calle et al. (2003) whereby participants were from all 50 states, the District of Columbia, and Puerto Rico (16). While this may be of statistical advantage, individuals and each city may not fully identify with the findings and conclusions.

On the other hand, a prospective cohort study involving only a city and followed up for decades may be relatively easily brought to that specific public (or city's) awareness. The findings may also be easy to identify with, and the population-based desired associated behavioral or dietary changes effected. This is the ultimate goal of public health service - to effect positive changes in the community. Such special opportunity is offered by the data of the Tromsø study when merged with the Norwegian Cancer Registry.

1.4 Cancer and the link to low weight

In most Western populations, underweight is much less prevalent than obesity, and most studies have concentrated their investigations on the relationship between obesity and cancer risk. Nevertheless, there are findings that are strongly suggestive that underweight may be a cancer risk factor in some specific organs or sites (17, 18).

1.5 The Tromsø Study

The Tromsø Study originally started in 1974 in an attempt to fight the high mortality of cardiovascular diseases in Norway (19). The first survey was denoted as Tromsø 1, and since then, there have been 5 other Tromsø study surveys conducted at intervals of 5-8 years, representing Tromsø 1-6.

This research work shall make use of Tromsø 3 survey initiated in 1986-87 because of the available dataset therein and the corresponding length of follow-up. When this is merged with the matching Cancer Registry, all other needed information shall be captured.

1.6 Purpose of the Study

There is a strong relationship between age and cancer risk, and the impact (in terms of relative risk) of most other risk factors tends to attenuate with age. Cancer at a relatively

early age may be much more important than in the old age because of more years of life that may be lost to cancer. Therefore, it is of interest to study the BMI-cancer relationship in the relatively young and middle aged people as we intend to do in this study.

Thus, the overall purpose of this study is to explore the relationship between BMI and cancer in the relatively young and middle-aged adults in Tromsø municipality, Norway. This study is envisaged to expand the literature and add to the body of knowledge in this area. This work is also expected to serve as an important material for other similar cities in Norway and Europe.

1.7 Research Hypotheses

1. Low and high body mass indexes increase the risk of total cancer incidence.
2. Low and high body mass indexes increase the risk of incidence of some common cancers.

1.8 Research Questions

The primary aim of this study was to answer the following questions:

1. What is the relationship of BMI to the total cancer incidence?
2. What is the relationship of BMI to the most common incident cancers in Tromsø?

This research work shall follow a quantitative research approach with a prospective study methodology. The needed dataset shall be obtained from the Data and Publication Committee of the Department of Community Medicine of UiT-The Arctic University of Norway.

1.9 Outline of the Study

This thesis is organized in six chapters:

Chapter 1 is the introduction to the study. It gives the foretaste to the study.

Chapter 2 presents the literature review, highlighting relevant previous researches conducted in the area of the current study and the pertinent theoretical or biological framework.

Chapter 3 describes the details of the methodology guiding the study.

Chapter 4 contains the key findings of the study.

Chapter 5 discusses these key findings, their scientific consonance with the previous researches, theoretical framework, and clinical or public health relevance.

Chapter 6 presents the conclusion drawn from the study with highlights on the implications.

CHAPTER 2: LITERATURE REVIEW

2.1 Database search

The literature was first searched in October 2013 (and updated till June 2014) to find previous relevant studies conducted in the area of the current study. A broad initial search was conducted in Cochrane, PubMed, Thomson ISI's Web of Science, and Google Scholar. The keywords and or Medical Subject Heading (MeSH) terms used were: obesity, overweight, excess body weight, body mass index, and Cancer. The search was later focused on some specific cancer sites such as prostate, lungs, colon and rectum (breast cancer was not a special focus for reasons given on page 13). The references of the relevant articles so found were further searched to identify more articles related to the study subject matter.

2.2 Obesity and cancer

The awareness of the health problems associated with obesity has long been known to man. This was portrayed by Hippocrates when he reportedly wrote that "Corpulence is not only a disease itself, but the harbinger of others" (20, 21), thereby acknowledging that obesity leads to other comorbidities.

There is large amount of scientific evidence from the laboratory that fat animals are more likely to develop cancer than the lean ones. When this happens, the cancers grow large, faster and spread more quickly in the fat experimental animals (22). This same corollary has been observed in humans by different studies. One of such was a study conducted by Daling et al (2001) on invasive ductal breast cancer in 1,177 women. They found that those in the uppermost range of excess body weight developed cancers of higher histological grade and relatively larger cancer size compared with normal weight individuals (23).

In the European Union, Bergstrom et al (2001) estimated that about 5% of all incident cancers were due to obesity (24), with about 3.5% in males and 6.5% in females. This translates to approximately 72,000 additional cases each year (25). In a more recent article by Wolin, Carson and Colditz (2010), obesity was said to be responsible for about 20% of all cancers in humans (26). However, excess weight does not increase the risk of cancer by the same amounts or measures in different tissues (26-30). These measures (or associations) may also be sex-specific over a range of cancers (28). Calle et al (2003) found a dose-response relationship between excess body weight as measured by BMI and all cancers combined, and this relationship differed by gender (16). They used BMI of 18.5-24.9 kg/m^2 as the reference category, and for women of BMI 25.0-29.9 kg/m^2, 30.0-34.9 kg/m^2, 35.0-39.9 kg/m^2, and 40.0 kg/m^2 and above, the risks of developing cancer were 8%, 23%, 32%, and 62% higher, respectively. For men, only BMI 30.0 kg/m^2 and above carried increased risk of cancer. For BMI 30.0-34.9 kg/m^2, 35.0-39.9 kg/m^2, and 40.0 $kg/m^2$and above, the risks of developing cancer were 9%, 20%, and 52% higher, respectively (16).

There is also ethnic variations and affinity in obesity-cancer risk. In a meta-analysis conducted by Renehan et al (2008), they found a particularly strong association between increased BMI and breast cancer in the Asia-Pacific women population (28). The African American also show relative susceptibility to cancer compared to the Hispanic who are somewhat protected (31).

2.3 Obesity and Some Specific Cancers

The International Agency for Research on Cancer (IARC) in 2002 concluded that there was ample scientific evidence linking obesity and some specific cancers. These cancers include that of the colon, post-menopausal breast, endometrial, kidney and esophageal (32). About

11% of colon cancer was ascribed to obesity, while it was 9% in post-menopausal breast cancer. About 39% of endometrial cancer, 25% of kidney cancer, and 37% of esophageal cancer, were attributed to excess body weight (32).

Following the prospective study of Calle et al (2003), more obesity-linked cancers were observed and added to the list. They were: liver, pancreatic, non-Hodgkin lymphoma, and myeloma (16, 33). Some of these cancers are strongly related to obesity with apparently convincing evidence while others are only weakly linked with probable evidence, and also with gender influence (31, 33).

2.4 Pathophysiological and biological framework linking obesity to cancer

In the attempt to further ascertain the link between excess body weight and cancer risks, there have been many studies directed at understanding the possible mechanisms involved in the linkage. A detailed summary of all the possible mechanisms is beyond the scope of this thesis. Howbeit, these mechanisms linking excess body weight and cancer risk are yet to be completely understood (30). Nevertheless, the three most studied mechanisms or postulations shall be discussed briefly.

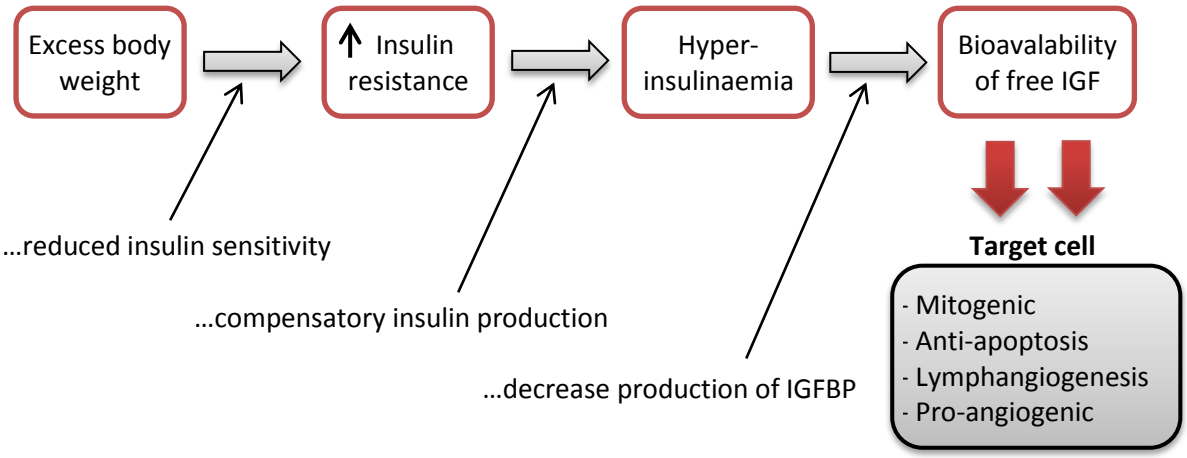
2.4.1 Insulin and insulin-like growth factors (IGFs)

It has been established that excess body weight is associated with reduced insulin sensitivity. In other words, obesity correlates positively with insulin resistance (31). This situation triggers a compensatory stimulation of the pancreas for more insulin which usually leads to persistent hyper-insulinaemia (30, 31, 33).

The “insulin-cancer hypothesis” proposed that persistent hyper-insulinaemia decreases the production of *insulin-like growth factors binding proteins -1* and *-2* (IGFBP-1 and IGFBP-2).

These IGFBPs are supposed to bind with *insulin-like growth factors -1* and *-2* (IGF -1 and -2) and thus inhibit the actions of the growth factors (IGF). When there is decreased production of IGFBPs it results into bioavailability of free IGF. IGF-1 attributably changes the cellular environment in favour of cancer development (27, 30, 31, 33-36) (Figure 1). The attributes of IGF favouring cancer development include, but not limited to: mitogenic (induce cell division); anti-apoptotic (prevent necessary or programmed cell death); pro-angiogenic (support formation of new blood vessels); stimulate cancer-related lymphangiogenesis; increase cell migration; and enhanced the effectiveness of other cell growth stimulants such as oestrogens (30, 31, 34).

Figure 1 - Obesity, free IGF and carcinogenesis



Studies and subsequent meta-analysis have demonstrated that the total circulatory IGF consistently associate positively with increased risk of colorectal (37), prostate (38) and pre-menopausal breast cancer (30, 33, 34).

In spite of all these, the *insulin-IGF hypothesis* has 2 major fundamental discrepancies (30). The blood levels of total circulating IGF increase linearly with increasing BMI up to about BMI 27 kg/m^2 and subsequent decrease with increasing BMI (36). Secondly, the total IGF

levels of obese people who intentionally lose weight tend to increase in value despite their decreasing weight (30). These are key inconsistencies in this biological framework.

2.4.2 Sex Hormones

Some cancers, such as endometrial, uterine, ovarian, breast and prostate cancers are considered to be hormone dependent (33). There are evidences that obesity affects the production of the sex hormones which have been implicated in the development of cancer (33). These endogenous hormones include oestrogens (such as oestradiol), androgens (such as testosterone) and progestogens (such as progesterone). The increased breast cancer risk in obese post-menopausal women may be explained by increased aromatase enzyme activity in the adipose tissue resulting in faster conversion of androgenic precursors to oestradiol (34). There are consistent indications that increase circulating oestrogens increase the risk of breast cancer in women after menopause (34). The implicative attributes of oestrogens in causing breast cancer development may be via increasing DNA damage, genetic instability and mutation (34). However, Renehan et al (2008) posit that oestrogens' proliferative effects may be the most important (34).

Androgens levels (such as testosterone) are inversely related to BMI in men while it directly correlated in women (39, 40). Elevated levels of androgens have been associated with both pre and post-menopausal breast and endometrial cancers, thus linking excess body weight and cancers (31).

2.4.3 Adipokines

Adipokines are polypeptide hormones derived from adipose tissue (or adipocytes). There are more than 50 types of adipokines, but the most well-known and studied is leptin (33, 34). This may be because it is one of the most abundantly produced adipokines in the body,

and its levels in the circulation correlate directly with BMI (34). Vona-Davis and Rose (2007) observed that leptin may be mitogenic, pro-angiogenic, pro-inflammatory, and anti-apoptotic (41). Some studies have demonstrated associations between serum leptin and colorectal cancer, breast cancers, but the association with prostate cancer has been inconsistent (34).

2.5 Pathophysiological and biological framework linking underweight to cancer

The biologic mechanism and evidence linking underweight to increased cancer risk is less known (17). Nevertheless, central to the underweight-cancer hypothesis is the oxidative DNA stress, which has been implicated in the initiation and promotion of carcinogenesis (42). Decreasing levels of BMI are associated with significantly increased levels of DNA oxidative damage. The oxidative damage is measured by 8-hydroxydeoxyguanosine, which is a biomarker of oxidative injury (42). Likewise, lower BMI has been shown to correlate with increased risk of lung cancer (18).

The BMI-related cancers are diverse and apparently there is no single mechanism or pathway to explain all (34). Many studies have been conducted in the area of obesity and cancer, but more are still required because there are still many inconsistencies and knowledge gaps. This was recently reiterated by Boeing (2013) who suggested that analyses of cohort studies was still needed to evaluate the risk for specific cancer sites (43).

CHAPTER 3: RESEARCH METHODOLOGY

3.1 Ethical Consideration and Permission

Application was made for the data of the 3rd Tromsø Study of 1986-87 (hereafter referred to as Tromsø 3). Access to the relevant data file with the required variables was granted by the Data & Publication Committee of the Department of Community Medicine of UiT-The Arctic University of Norway. The research study was found to be covered by the existing approvals and concessions from the Regional Committee for Medical Research Ethics (REK) and the Norwegian Data Inspectorate. However, we were, unfortunately restrained by the Data & Publication Committee from using the given dataset for the study of breast cancer to prevent conflict of interest with another larger on-going research project.

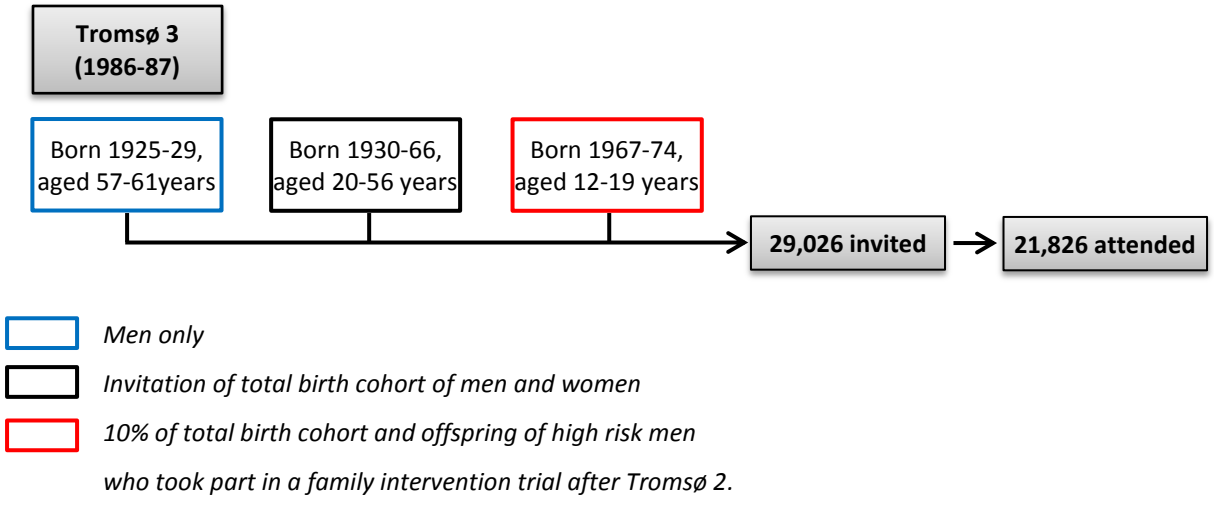
The national 11-digit personal identification number enables thorough follow-up of participants concerning cancer, death, emigration and so on, by linkage to the official national registries, and in this case cancer register. The data quality of the Norwegian Cancer Registry is of high standard because it is made compulsory by law (19, 44).

3.2 The Third Survey of the Tromsø Study - Tromsø 3

This research work made use of Tromsø 3 which took place following the successful conduct of the first and the second Tromsø survey. Tromsø 3 was initiated in 1986. It was a prospective population-based cohort study in the municipality of Tromsø. Tromsø is geographically located about 350 kilometres north of the Arctic Circle, and it is the largest city in the Northern Norway with population of about 67,000 inhabitants. The population studied is almost exclusively Caucasian, and the enrolment was based on the official population registry of the Tromsø municipality. Through this, the residents were invited on

the basis of their year of birth at the time of the survey (19). All men aged 20-61 years (born 1925-1966) and all women aged 20-56 years (born 1930-1966) were invited. An additional small numbers of individuals younger and older than the above-mentioned cohorts were also invited. These individuals were not, however, random samples of the population and were therefore not included in the analytical sample which this present analyses are based on. Only men were invited for the birth cohort born in 1925-29 (Figure 2). This was reportedly because the Tromsø Study was originally aimed at middle-aged men and this group of men was being followed from the first survey of the Tromsø Study (Tromsø 1) in 1974 (19).

Figure 2 - The Tromsø Study: Invitation by birth cohort and attained age in Tromsø 3



(Adapted from Jacobsen et al., 2012 (19))

Personal invitation which included information about the survey, the examination, and a questionnaire were sent to the potential participants by mail about a couple of week before the proposed date of appointment for each person. However, each individual could attend at any other more convenient time within the lifespan of the study which was about one year (1986-87) (19).

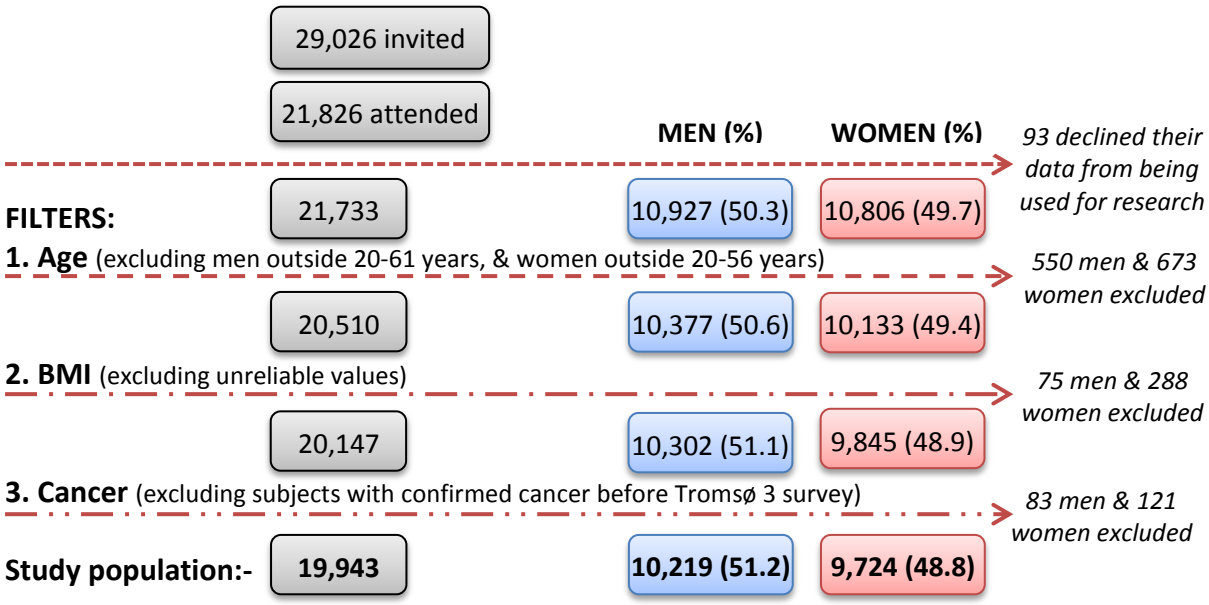
3.3 Study Population

The men and women in this study were selected from the 21,826 who attended Tromsø 3 survey in 1986-87. 93 participants refused their data from being used for research. Thus, the remaining 21,733 participants were subjected to inclusion and exclusion criteria.

3.4 Inclusion and Exclusion Criteria

Men aged between 20 and 61 years, and women aged between 20 and 56 years were included in the analysis, as all subjects in these age groups were invited. This age bracket excluded 550 men and 673 women leaving us with 20,510 attending subjects. We excluded subjects with missing value for BMI or unreliable BMI (such as in denial of height or weight measurement, pregnancy, disability, measured with shoes, limping or bent individuals). This criterion excluded 75 men and 288 women. Also excluded were those who had been diagnosed with cancer before they attended Tromsø 3 survey (prevalent cancer cases). This criterion excluded 204 subjects of which 83 were men and 121 were women. The eligible participants for the current analysis included 10,219 men and 9,724 women (Figure 3).

Figure 3 - Application of inclusion and exclusion criteria and study population



3.5 Body Mass Index

The body mass index (BMI) which is a measure of adiposity, was categorized into: less than 20.0 kg/m^2 ("underweight", "low-weight" or "thin"); 20.0 to 24.9 kg/m^2 ("healthy", "normal", "recommended" or "acceptable" weight); 25.0 to 29.9 kg/m^2 ("overweight"); and 30.0 kg/m^2 and above ("obese"). These categories are exactly the same as used in some previous studies (9), and closely similar to those proposed by the WHO (6).

In all the analyses, BMI category of 20.0 to 24.9 kg/m^2 was made the reference group. For the analyses of some cancers in specific sites, a slight modification was made by combining the lower 2 categories of the BMI. This was done because of the limited numbers of events.

3.6 Cancer Endpoints

The end points in the analyses were cancers from all sites, following the *International Classification of Diseases, 10th Revision* (ICD-10) and as grouped together by the Norwegian Cancer Registry. The endpoint was considered to occur if the subject had tumor degree of malignance and reliability of tumor origin equals to 3 and above, on a scale of 1 to 5. Only the first cancer cases were considered. We assumed that the second cancer cases may be influenced by the first and may have profound effect on the BMI. During the follow-up period, a total of 2,248 incident cancers were identified (1,252 in men and 996 in women). Analyses were run for all cancers combined, separately for the 2 genders, and then for the first four commonest cancer sites (breast cancer was left out to prevent conflict of interest of another on-going research project (see page 13)).

3.7 Follow-up

Follow-up was from the date the participants attended the survey (in 1986-1987) to the first of the following dates: date of diagnosis of cancer (2,248 incident cancers); death (2,503

deaths); emigration from Norway (331 emigrants); or end of follow-up (December 31, 2010). End of follow-up was end of 2010 as this was the latest available data from the Cancer Registry of Norway as at the time of writing this thesis.

3.8 Information on the Covariates

The 5 potential confounders taken into consideration were age (*in single years*); smoking status (*current smoker; ex-smoker; and never smoker*); physical activity (lasting at least 20 minutes into: *rarely or never, weekly, several times a week, and daily*); alcohol consumption (*yes or no*); and level of education (*less than high school; high school; bachelor degree; and master degree and above*). Only the first 2 were used in the final analyses (see section 3.9).

3.9 Statistical Analysis

The software package IBM SPSS Statistics for Windows (Version 21.0. Armonk NY: IBM Corp) was used for all analyses. Men and women were analyzed separately, but together when necessary. The covariates were tested for normal distribution by visual inspection of the distribution curves. Frequencies and cross-tabulation were made for the categorical data.

The crude incidence rate of all cancers combined and some specific cancer sites in men and women were estimated as the number of cases per 100,000 person-years. The persons-time (or men- and women-years) were calculated as the sum of cancer-free follow-up time (in years). Cox proportional hazards regression modeling was used to compute the hazard ratio. The hazard ratio was assumed to be very close to the relative risk, and thus used interchangeably. *P*-values less than 0.05 were considered statistically significant. We adjusted for age and smoking status (*current smoker, ex-smoker or never smoker*). Variables such as physical activity, alcohol consumption, and levels of education were initially adjusted for in the analyses. However, adjusting for these 3 variables had little or no impact

on the results with regard to the relationship between BMI and cancer incidence. This was true for total cancer incidence as well as the specific cancer sites considered. Hence they were not included in the final statistical model presented here. Furthermore, when interactions terms *BMI and age*, *BMI and smoking*, as well as *smoking and age* were included in the model for total cancer incidence, there were no significant interaction for the two former interaction terms (including information about BMI), but the interaction term *smoking and age* was statistically significant ($p = 0.04$ in both men and women). However, including this interaction term in the model did not change the point estimates for the effect of BMI more than marginally. Thus, we did not include these interaction terms in the model presented.

A test of linear trend in risk of cancer according to BMI categories was done by scoring the BMI categories 1 to 4 and entering the scores as continuous term in the Cox regression model. Likewise, the p-value for non-linear relationship was computed by including a second order term in the model.

3.10 Assumptions of proportional hazards in models

The proportional hazards model assumes that the hazard under investigation is consistent and do not vary differently over time. This was assessed visually by checking the log minus log plots made for the different cancer types. The curves in each plot were not perfectly, but approximately parallel, except in few plots where minimal crossings were observed towards the ends of the curves. In addition, the plots of the residuals (Schoenfeld residuals) were horizontal and close to zero, meaning that the assumption of proportional hazards was true.

The results of all cancers combined and the specific cancer sites analyzed were presented based on the study population.

CHAPTER 4: RESULTS

4.1 Baseline characteristics

Following the application of inclusion and exclusion criteria (see Methodology section and Figure 3), the eligible study population was 19,943 subjects. 10,219 (51.2%) of them were men while 9,724 (48.8%) were women.

The mean age of men in the study at the start of the follow-up was 38.61 years, while 20 and 61 years were, by design, the minimum and maximum age, respectively. The mean age of women was 36.31 years, and 20 and 56 years were, by design, the minimum and maximum age, respectively. The men had a mean BMI of 24.61 kg/m^2, while 14.50 kg/m^2 and 47.30 kg/m^2 were the minimum and maximum BMI respectively. The women had a mean BMI of 23.09 kg/m^2, and 13.30 kg/m^2 and 45.00 kg/m^2 were their minimum and maximum BMI, respectively.

4.1.1 All cancers combined

During the 446,821 person-years of the follow-up period (average follow-up: 22.41 years), a total of 2,248 cancer incidents were identified. 1,252 (55.7%) of the cancers were found in men while 996 (44.3%) were in women. However, it should be noted that the age range of men in the study was 20-61 years while that of women was 20-56 years.

The mean BMI of men who had cancer during the follow-up period was 25.11 kg/$m^2$and that of those who did not have cancer throughout was 24.54 kg/m^2. For women, the mean BMI of those who had cancer during the follow-up period was 23.61 kg/m^2while that of those who did not have cancer was 23.03 kg/m^2. Thus, the difference in the means BMI between

those who had cancer and those who did not have cancer was 0.57 kg/m^2 for men and 0.58 kg/m^2 for women (p-values of the differences < 0.001 in both genders) (Table 1).

Table 1 - The Tromsø Study (Tromsø 3): Characteristics of the Study Population - numbers, percentages, means and standard deviations (SD)

CHARACTERISTICS	MEN	WOMEN
Study population	10,219	9,724
Person-years of follow-up	224,648	222,173
Mean follow-up period in years	21.98	22.85
Number of cancers identified	1,252	996
Percentage of population with cancer	12.3	10.2
Follow-up time [in person-years]	224,648	222,173
Crude incidence rate [per 100,000 person-years]	557	448
Mean age in years (SD)	38.61 (11.06)	36.31 (9.63)
Mean BMI in kg/m^2 (SD)	24.61 (3.04)	23.09 (3.48)
Mean BMI in kg/m^{2}of people with *no cancers* (SD)	24.54 (3.01)	23.03 (3.47)
Mean BMI in kg/m^{2}of people with *cancers* (SD)	25.11 (3.16)	23.61 (3.56)
Difference in kg/m^2 between mean BMI for *cancer* and *no cancer* population (p-value)	0.57 (<0.001)	0.58 (<0.001)

4.1.2 Cancer by primary sites

Prostate cancer was the most common cancer in the follow-up period. This was followed by breast cancer; lung and tracheal cancer; and colon cancer, in that order. Table 2 shows the 12 most common cancers in the study population during the follow-up period.

Table 2 - The Tromsø Study (Tromsø 3): Incident Cancers by Primary Site (using *International Classification of Diseases, 10th edition (ICD 10)*) in Men and Women

CANCERS	ICD 10 CODES	NUMBER (%)	MEN	WOMEN
Prostate	C61	346 (15.4)	346	NA
Breast	C50	315 (14.0)	2	313
Lung, Trachea	C33-34	264 (11.7)	176	88
Colon	C18	181 (8.1)	102	79
Bladder, Ureter, Urethra	C66-68	108 (4.8)	86	22
Rectum, Recto-sigmoid, Anus	C19-21	101 (4.5)	69	32
Melanoma (Skin)	C43	87 (3.9)	47	40
Non-Hodgkin Lymphoma	C82-85, C96	82 (3.6)	48	34
Stomach	C16	74 (3.3)	50	24
Pancreas	C25	62 (2.8)	40	22
Ovary	C56	58 (2.6)	NA	58
Leukaemia	C91-95, D45-47	56 (2.5)	34	22
Other cancers		514 (22.9)	252	262
TOTAL		**2,248 (100.0)**	**1,252**	**996**

4.2 Body Mass Index (BMI) and Total Cancer Incidence

In the unadjusted analyses, the percentages of the population with cancer incident in the four BMI categories generally increase with increasing BMI. For the men, it was 10.8%, 10.6%, 14.3% and 16.5% for low weight, normal weight, overweight and obese people, respectively, and for the women, it was 7.1%, 10.2%, 12.3% and 12.7% for women with low weight, normal weight, overweight and obese, respectively. The crude incidence rate of cancer in men was 557 per 100,000 men-years while that of women was 448 per 100,000 women-years (Table 1 and 3).

Table 3 - The Tromsø Study (Tromsø 3): Distribution of all cancers (combined) according to the four BMI categories in Men and Women

MEN				
BMI categories *(in kg/m^2)*	**Population**	**Cancer (%)**	**Person-years**	***Crude IR**
Low weight *(BMI < 20.0)*	389	42 (10.8)	8,588	489
Normal Weight *(BMI 20.0-24.9)*	5,685	605 (10.6)	127,100	476
Overweight *(BMI 25.0-29.9)*	3,636	521 (14.3)	78,397	665
Obese *(BMI ≥ 30.0)*	509	84 (16.5)	10,562	795
TOTAL	**10,219**	**1,252 (12.3)**	**224,648**	**557**
WOMEN				
Low weight *(BMI < 20.0)*	1,410	100 (7.1)	32,749	305
Normal Weight *(BMI 20.0-24.9)*	6,117	624 (10.2)	140,187	445
Overweight *(BMI 25.0-29.9)*	1,740	214 (12.3)	39,011	549
Obese *(BMI ≥ 30.0)*	457	58 (12.7)	10,226	567
TOTAL	**9,724**	**996 (10.2)**	**222,173**	**448**

*Crude IR = Crude incidence rate per 100,000 person-years

4.3 Relationships between BMI and total cancer incidence

The relative risk of the total cancer incidence (all cancers combined) according to the BMI grouping was estimated using the Cox proportional hazard regression model, with normal weight (BMI of 20.0-24.9 kg/m^2) as the reference, and adjusted for age and smoking status.

After adjusting for age and smoking, both the low weight and obese were associated with increased risk of cancer in men, whereas no relationship was found in women (Table 4).

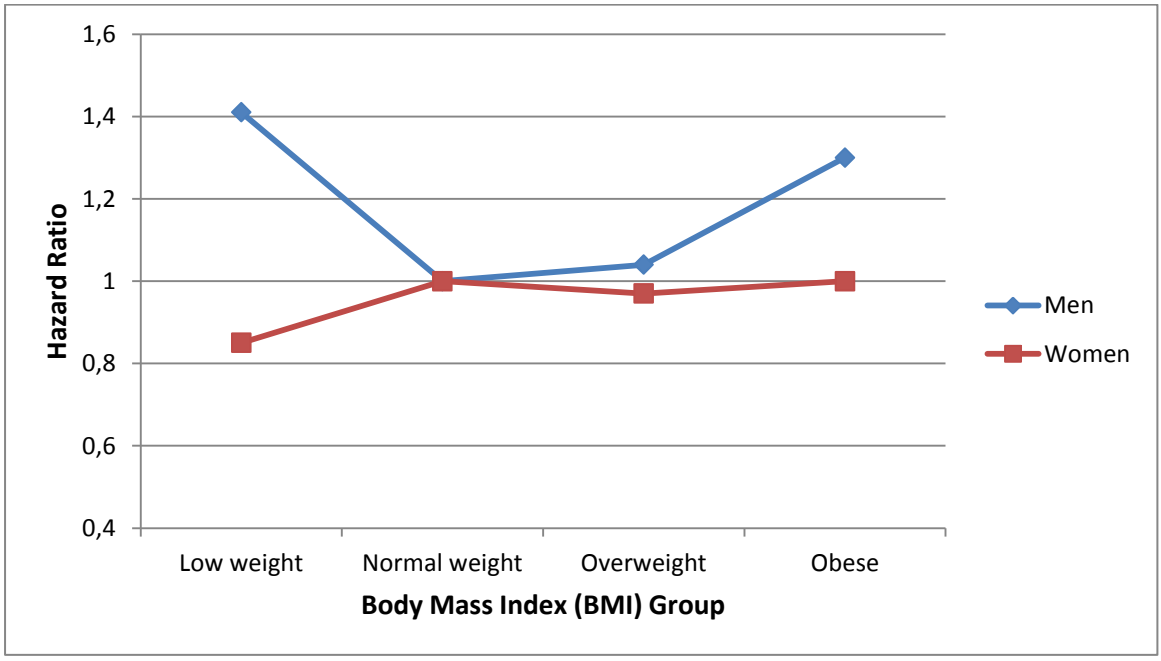
Table 4 - The Tromsø Study (Tromsø 3): Relationship between BMI and total cancer incidence with Hazard Ratios (HR 95% confidence limits) in Men and Women

MEN		
BMI categories *(in kg/m^2)*	***Age adjusted* HR (95% CI)**	***Age and smoking adjusted* HR (95% CI)**
Low weight *(BMI < 20.0)*	1.54 (1.12-2.10)	1.41 (1.03-1.93)
Normal Weight *(BMI 20.0-24.9) *ref. cat.*	1.00	1.00
Overweight *(BMI 25.0-29.9)*	1.00 (0.89-1.13)	1.04 (0.93-1.18)
Obese *(BMI ≥ 30.0)*	1.21 (0.96-1.52)	1.30 (1.03-1.63)
P-value for homogeneity	*0.020*	*0.032*
P-value for linear trend	*0.97*	*0.34*
WOMEN		
Low weight *(BMI < 20.0)*	0.87 (0.71-1.08)	0.85 (0.69-1.05)
Normal Weight *(BMI 20.0-24.9) *ref. cat.*	1.00	1.00
Overweight *(BMI 25.0-29.9)*	0.96 (0.82-1.12)	0.97 (0.83-1.14)
Obese *(BMI ≥ 30.0)*	0.97 (0.74-1.27)	1.00 (0.76-1.31)
P-value for homogeneity	*0.64*	*0.52*
P-value for linear trend	*0.76*	*0.49*

HR = hazard ratio; 95% CI = 95% confidence interval; *ref. cat. = reference category

Furthermore, the data from the two genders were merged and additional adjustment for sex and interaction term - *sex and BMI* were included in the model. This was to assess whether the effects of BMI on total cancer incidence were statistically different by sex. The p-value for interaction by sex was 0.043, which shows the effects were significantly different by sex. Figure 1 illustrates the relationships found in men and women.

Figure 4 - The Tromsø Study (Tromsø 3): Relative risks of all cancers combined in men and women according to BMI categories



The above relationship did not change in both genders even when the first 5 years of the study was excluded from the analyses.

4.4 Analyses of Cancers by Primary sites

4.4.1 Prostate Cancer

Prostate cancer was the most common cancer in the study with 346 incident cases. It accounted for 27.6% of all the cancers in men. The crude incidence rate of prostate cancer in the study population was 153 per 100,000 men-years (Table 5).

Table 5 - The Tromsø Study (Tromsø 3): Distribution of Prostate cancer according to the four BMI categories

MEN				
BMI categories *(in kg/m^2)*	**Population of men**	**Prostate cancer (%)**	**Person-years**	***Crude IR**
Low weight *(BMI < 20.0)*	389	7 (1.8)	8,612	81
Normal Weight *(BMI 20.0-24.9)*	5,685	175 (3.1)	127,610	137
Overweight *(BMI 25.0-29.9)*	3,636	146 (4.0)	78,874	185
Obese *(BMI ≥ 30.0)*	509	18 (3.5)	10,646	169
TOTAL	10,219	346 (3.4)	225,742	153

*Crude IR = Crude incidence rate per 100,000 person-years

The mean BMI of men with incident prostate cancer was 25.03 kg/m^2, whereas those with *no* prostate cancer had mean BMI of 24.60 kg/m^2. The difference in the means BMI was 0.43 kg/m^2 (p-value = 0.009). However, when adjusted for age and smoking status, and normal weight (BMI between 20.0 and 24.9 kg/m^2) used as the reference category, essentially, no relationship was found between BMI and the risk of prostate cancer (Table 6 and Figure 5).

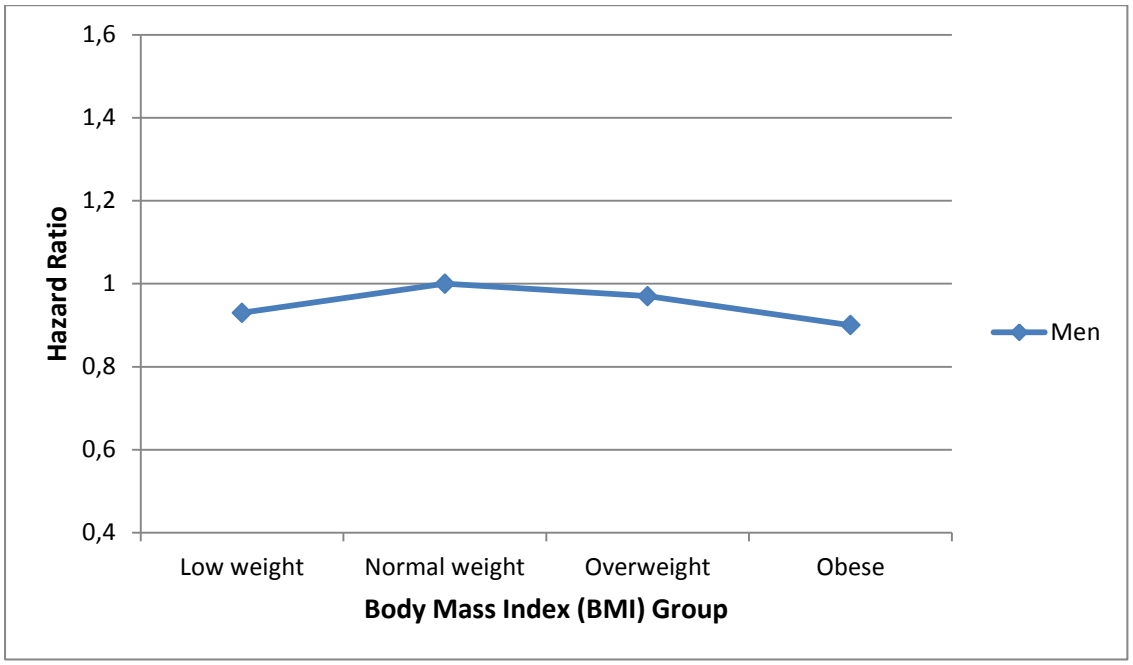
Table 6 - The Tromsø Study (Tromsø 3): Relationships between BMI and prostate cancer incidence with Hazard ratios (95% confidence limits)

MEN		
BMI categories *(in kg/m^2)*	***Age adjusted* HR (95% CI)**	***Age & smoking adjusted* HR (95% CI)**
Low weight *(BMI < 20.0)*	0.94 (0.44-2.00)	0.93 (0.44-2.00)
Normal Weight *(BMI 20.0-24.9) *ref. cat.*	1.00	1.00
Overweight *(BMI 25.0-29.9)*	0.96 (0.77-1.20)	0.97 (0.77-1.21)
Obese *(BMI ≥ 30.0)*	0.90 (0.55-1.46)	0.90 (0.56-1.47)
P-value for homogeneity	*0.96*	*0.97*
P-value for linear trend	*0.66*	*0.70*

HR = hazard ratio; 95% CI = 95% confidence interval; *ref. cat. = reference category

When men diagnosed within 3 years from baseline (start of follow-up) were excluded from the analyses, we observed no material change in the estimates of the relative risk associated with the BMI categories.

Figure 5 - The Tromsø Study (Tromsø 3): Relative risks of prostate cancers in men according to BMI categories



4.4.2 Lung and Tracheal Cancers

Lung and tracheal cancers were the third most common cancer after prostate and breast cancers in the study population. As there were no cases of tracheal cancer, the results essentially reflect relationships with lung cancers and we hereafter referred to them as such. Lung cancer was the second most common in men (after prostate cancer) and the second most common in women (after breast cancer). It accounted for 264 cancer cases which was 11.7% of all the cancer incidents within the follow-up period. There were 176 cases in men with the crude incidence rate of 78 per 100,000 men-years, and 88 cases in women with the crude incidence rate of 40 per 100,000 women-years.

Table 7 - The Tromsø Study (Tromsø 3): Distribution of Lung cancers according to the BMI categories in Men and Women

MEN				
BMI categories *(in kg/m^2)*	**Population**	**Cancer (%)**	**Person-years**	***Crude IR**
Low weight *(BMI < 20.0)*	389	9 (2.3)	8,626	104
Normal Weight *(BMI 20.0-24.9)*	5,685	83 (1.5)	127,702	165
Overweight *(BMI 25.0-29.9)*	3,636	69 (1.9)	78,960	87
Obese *(BMI ≥ 30.0)*	509	15 (2.9)	10,663	141
TOTAL	**10,219**	**176 (1.7)**	**225,951**	**78**
WOMEN				
Low weight *(BMI < 20.0)*	1,410	13 (0.9)	32,830	40
Normal Weight *(BMI 20.0-24.9)*	6,117	55 (0.9)	140,682	40
Overweight *(BMI 25.0-29.9)*	1,740	14 (0.8)	39,268	36
Obese *(BMI ≥ 30.0)*	457	6 (1.3)	10,314	58
TOTAL	**9,724**	**88 (0.9)**	**223,094**	**40**

*Crude IR = Crude incidence rate per 100,000 person-years

The mean BMI of men who had lung cancer was 24.93 kg/m^2, whereas that of men who did not was 24.61 kg/m^2. The mean BMI of women who had lung cancer was 23.14 kg/m^2 while that of women who did not have the cancer was 23.09 kg/m^2. The difference in the means BMI between those who had cancer and those who did not was 0.32 kg/m^2 for men and 0.05 kg/m^2 for women, and the corresponding p-values for these differences were 0.16 and 0.90 respectively.

As expected, the highest percentage of the lung cancers were found in the current smokers (compared to ex- and never-smokers). However, the current smokers in the low weight category bear the highest proportion of the lung cancer in both men and women (Table 8). Almost all the people who had lung cancers in the low weight category are current smokers (8 out of 9 in men and 12 out of 13 in women) (Table 8).

Table 8 - The Tromsø Study (Tromsø 3): Distribution of Lung Cancer according to BMI Categories and Smoking Status in Men and Women

SEX	BMI CATEGORIES	SMOKING STATUS	NO LUNG CANCER	LUNG CANCER (%)	TOTAL
MEN	**Low weight**	Current-smoker	252	8 (88.9)	260
		Ex-smoker	47	0 (0.0)	47
		Never-smoker	81	1 (11.1)	82
		Sub-total	**380**	**9 (100.0)**	**389**
	Normal weight	Current-smoker	2697	69 (83.1)	2766
		Ex-smoker	1147	11 (13.3)	1158
		Never-smoker	1758	3 (3.6)	1761
		Sub-total	**5602**	**83** (100.0)	**5685**
	Overweight	Current-smoker	1419	54 (78.3)	1473
		Ex-smoker	1137	14 (20.3)	1151
		Never-smoker	1011	1 (1.4)	1012
		Sub-total	3567	69 (100.0)	3636
	Obese	Current-smoker	177	10 (66.7)	187
		Ex-smoker	170	5 (33.3)	175
		Never-smoker	147	0 (0.0)	147
		Sub-total	**494**	**15** (100.0)	**509**
WOMEN	**Low weight**	Current-smoker	805	12 (92.3)	817
		Ex-smoker	199	1 (7.7)	200
		Never-smoker	393	0 (0.0)	393
		Sub-total	**1397**	**13** (100.0)	**1410**
	Normal weight	Current-smoker	2802	40 (72.7)	2842
		Ex-smoker	1196	6 (10.9)	1202
		Never-smoker	2064	9 (16.4)	2073
		Sub-total	**6062**	**55** (100.0)	**6117**
	Overweight	Current-smoker	706	11 (78.6)	717
		Ex-smoker	341	1 (7.1)	342
		Never-smoker	679	2 (14.3)	681
		Sub-total	**1726**	**14** (100.0)	**1740**
	Obese	Current-smoker	167	4 (66.7)	171
		Ex-smoker	92	0 (0.0)	92
		Never-smoker	192	2 (33.3)	194
		Sub-total	**451**	**6** (100.0)	**457**

Table 9 - The Tromsø Study (Tromsø 3): Relationship between BMI and Lung Cancer incidence with the Hazard Ratios (HR 95% confidence limits) in Men and Women

MEN		
BMI categories *(in kg/m^2)*	**Age adjusted HR (95% CI)**	**Age & smoking adjusted HR (95% CI)**
Low weight *(BMI < 20.0)*	2.50 (1.26-4.99)	1.82 (0.91-3.62)
Normal Weight *(BMI 20.0-24.9) *ref. cat.*	1.00	1.00
Overweight *(BMI 25.0-29.9)*	0.92 (0.67-1.27)	1.09 (0.79-1.50)
Obese *(BMI ≥ 30.0)*	1.46 (0.84-2.53)	2.03 (1.17-3.53)
P-value for homogeneity	*0.021*	*0.037*
P-value for linear trend	*0.63*	*0.30*
WOMEN		
Low weight *(BMI < 20.0)*	1.54 (0.83-2.83)	1.32 (0.72-2.43)
Normal Weight *(BMI 20.0-24.9) *ref. cat.*	1.00	1.00
Overweight *(BMI 25.0-29.9)*	0.60 (0.33-1.07)	0.67 (0.37-1.21)
Obese *(BMI ≥ 30.0)*	0.94 (0.40-2.18)	1.13 (0.48-2.63)
P-value for homogeneity	*0.12*	*0.36*
P-value for linear trend	*0.063*	*0.25*

HR = hazard ratio; 95% CI = 95% confidence interval; *ref. cat. = reference category

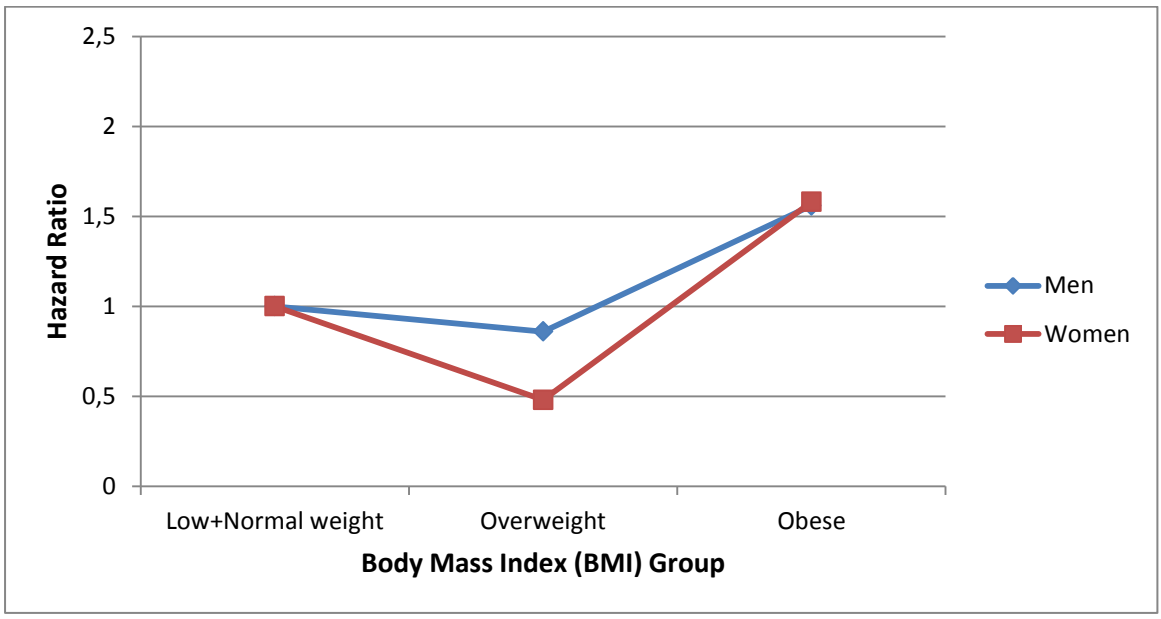
Table 9 (above) gives the results for lung cancer stratified by gender.

To assess whether the effect of BMI on lung cancer incidence were statistically different by sex, the data from the two genders were merged and additional adjustment for sex and interaction term - *sex and BMI* were included in the model. The p-value for interaction by sex was 0.45, which shows the effects were not significantly different by sex. Therefore, the data from men and women were merged to increase power. In the age and smoking status adjusted analyses of the merged data, normal weight was used as the reference category, and the hazard ratios and 95% confidence intervals were: low weight 1.55 (0.98-2.45); overweight 0.96 (0.73-1.26); and obese 1.67 (1.05-2.65). The p-values for homogeneity and linear trend were 0.036 and 0.89 respectively. This is a U-shaped relationship similar to the one observed in men (alone) (Figure 6). The U-shaped relationship was statistically confirmed (p-value of second order term = 0.004).

Figure 6 - The Tromsø Study (Tromsø 3): Relative Risks of Lungs in Men and Women according to the BMI categories

In a separate analysis, we merged the data of the never- and ex-smokers (of more than 5 years), and used the low and normal weight categories as the reference (because of the small numbers). The hazard ratios and 95% confidence intervals in men were: overweight 0.86 (0.37-2.00); obese 1.56 (0.43-5.66); and in women: overweight 0.48 (0.10-2.20); obese 1.58 (0.34-7.34). The p-value for linear trend was 0.79 in men and 0.98 in women, while the p-value for homogeneity was 0.65 in men and 0.48 in women (Figure 7).

Figure 7 - The Tromsø Study (Tromsø 3): Relative Risks of Lungs Cancers in Never- and Ex-smokers (of more than 5 years) in Men and Women according to the BMI categories



4.4.3 Colon Cancer

Colon cancer was the third commonest cancer in both men and women in the study population. It accounted for 8% of all the cancers in the follow-up period with a total of 181 incident cases. There were 102 cases in the men with the crude incidence rate of 45 per 100,000 men-years, and 79 cases in women with the crude incidence rate of 35 per 100,000 women-years.

As there were no incident colon cancer in men with low weight and few in women with low weight, subjects in low and normal weight categories were merged for all the analyses done for colon cancer incidents. Nevertheless, we noted that there were 389 men with low weight among the 6,074 low/normal weight category. For the women, there were 1,410 with low weight among the 7,527 low/normal weight category, and there were 6 colon cancer incidents among the 1,410 low weight women.

Table 10 - The Tromsø Study (Tromsø 3): Distribution of Colon cancers according to the BMI categories

MEN				
BMI categories *(in kg/m^2)*	**Population**	**Cancer (%)**	**Person-years**	***Crude IR**
Low/normal weight *(BMI <25.0)*	6,074	37 (0.6)	136,383	27
Overweight *(BMI 25.0-29.9)*	3,636	57 (1.6)	78,972	72
Obese *(BMI ≥ 30.0)*	509	8 (1.6)	10,660	75
TOTAL	**10,219**	**102 (1.0)**	**226,015**	**45**
WOMEN				
Low/ Normal weight *(BMI <25.0)*	7,527	56 (0.7)	173,526	32
Overweight *(BMI 25.0-29.9)*	1,740	18 (1.0)	39,257	46
Obese *(BMI ≥ 30.0)*	457	5 (1.1)	10,314	49
TOTAL	**9,724**	**79 (0.8)**	**223,097**	**35**

*Crude IR = Crude incidence rate per 100,000 person-years

The mean BMI of men who had colon cancer was 26.10 kg/m^2, whereas that of men who did not have colon cancer was 24.60 kg/m^2. For women, the mean BMI of those who had colon cancer was 23.83 kg/m^2 while that of those who did not have was 23.09 kg/m^2. The difference in the means BMI between those who had cancer and those who did not was 1.50 kg/m^2 for men and 0.74 kg/m^2 for women, and the corresponding p-values for the differences were <0.001 and 0.057 respectively.

When adjusted for age and smoking status, and low and normal weight (BMI less than 25.0 kg/m^2) used as the reference category, a linear relationship was found between BMI and the risk of colon cancer in men, while it was null in women (Table 11 and Figure 8). The p-value

for linear trend was 0.010 in men and 0.84 in women, indicating an association in men but not in women (Table 11 and Figure 8).

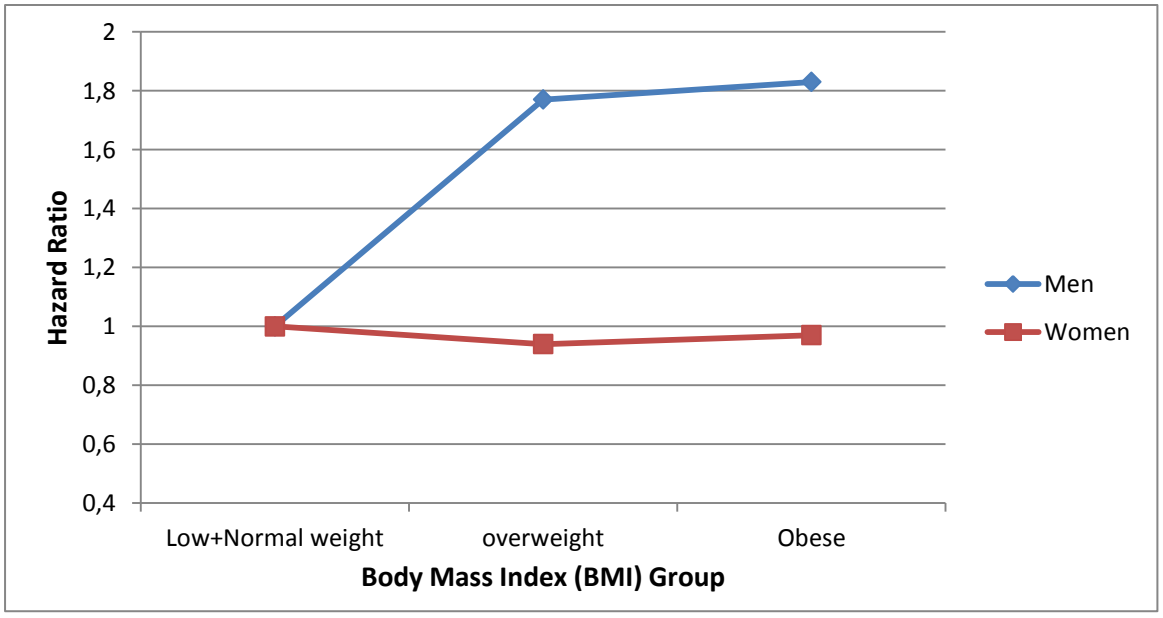
The relationship did not attenuate after the first 3 years of the follow-up period was excluded from the analyses.

Table 11 - The Tromsø Study (Tromsø 3): Relationship between BMI and Colon cancer incidence with the Hazard Ratios (HR 95% confidence limits)

MEN		
BMI categories *(in kg/m^2)*	**Age adjusted HR (95% CI)**	**Age & smoking adjusted HR (95% CI)**
Low/normal weight *(BMI<25.0) *ref. cat.*	1.00	1.00
Overweight *(BMI 25.0-29.9)*	1.81 (1.19-2.74)	1.77 (1.16-2.70)
Obese *(BMI ≥ 30.0)*	1.89 (0.88-4.07)	1.83 (0.85-3.95)
P-homogeneity	*0.016*	*0.023*
P-value for linear trend	*0.006*	*0.010*
WOMEN		
Low/normal weight *(BMI<25.0) *ref. cat.*	1.00	1.00
Overweight *(BMI 25.0-29.9)*	0.94 (0.55-1.61)	0.94 (0.54-1.61)
Obese *(BMI ≥ 30.0)*	0.95 (0.38-2.40)	0.97 (0.38-2.43)
P-value for homogeneity	*0.97*	*0.97*
P-value for linear trend	*0.83*	*0.84*

HR = hazard ratio; 95% CI = 95% confidence interval; *ref. cat. = reference category

Figure 8 - The Tromsø Study (Tromsø 3): Relative risks of Colon Cancer in Men and Women according to BMI categories



When the BMI was entered as a continuous variable (that is, in single unit BMI increment), and age and smoking status corrected, the relative risk for men was 1.10 (95% CI 1.04-1.17) with the p-value of 0.002. For women, no relationship was indicated (p-value = 0.96).

The data of the women was then stratified into 2 by age 36 years at baseline (36.31 years was the mean age of the women cohort at the study baseline), thus having 2 groups of women: those below 36 years and those above 36 years. The results from the stratified analyses are given in Table 12 and Figure 9.

Table 12 - The Tromsø Study (Tromsø 3): Relationship between BMI and Colon cancer incidence with the Hazard Ratios (HR 95% confidence limits) stratified by mean age (36 years)

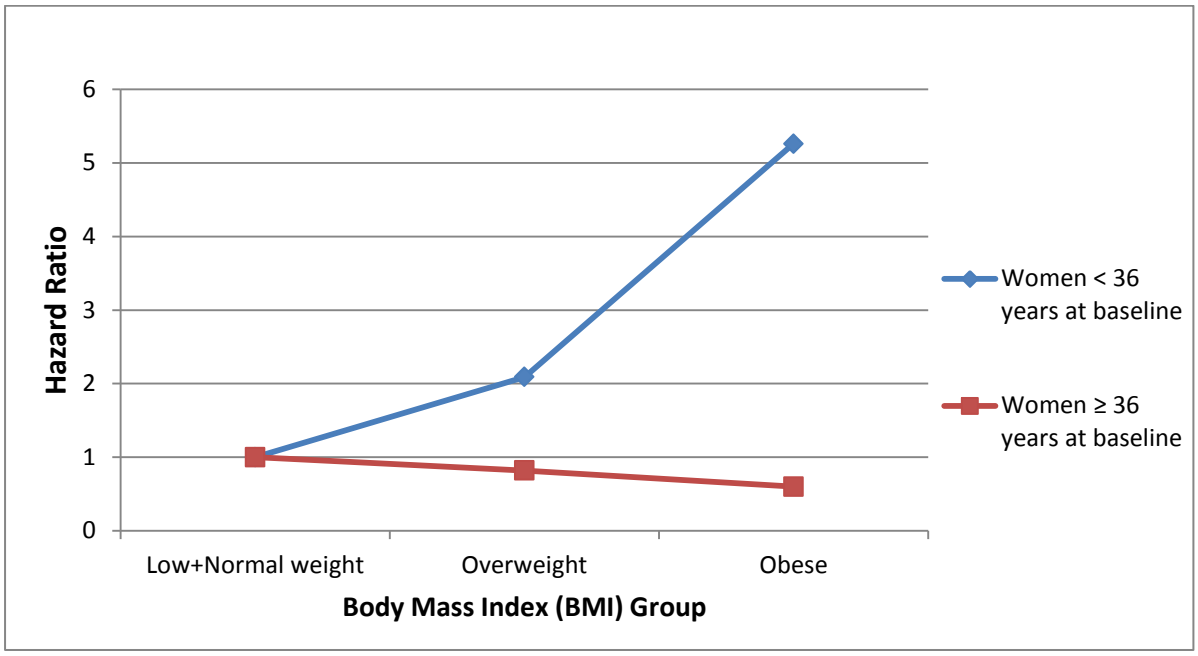
	Women < 36 years at baseline	**Women ≥ 36 years at baseline**
BMI Categories *(in kg/m^2)*	***HR (95% CI)**	***HR (95% CI)**
Low/normal weight *(BMI<25.0) *ref. cat.*	1.00	1.00
Overweight *(BMI 25.0-29.9)*	2.09 (0.57-7.58)	0.82 (0.46-1.48)
Obese *(BMI ≥ 30.0)*	5.26(1.15-24.06)	0.60 (0.19-1.95)
P-value for homogeneity	*0.078*	*0.61*
P-value for linear trend	*0.026*	*0.32*
WHEN THE FIRST 3 YEARS OF BASELINE WAS EXCLUDED		
Low/normal weight *(BMI<25.0) *ref. cat.*	1.00	1.00
Overweight *(BMI 25.0-29.9)*	2.09 (0.57-7.58)	0.83 (0.45-1.52)
Obese *(BMI ≥ 30.0)*	5.26 (1.15-24.06)	0.65 (0.20-2.11)
P-value for homogeneity	*0.078*	*0.68*
P-value for linear trend	*0.026*	*0.38*

*HR = Age and smoking adjusted hazard ratio; 95% CI = 95% confidence interval; *ref. cat. = reference category

A positive linear relationship was found in the relatively young women.

When the BMI was entered as a continuous variable (in single unit increment), the relative risk for women below 36 years (at baseline) was 1.13 (95% CI 1.00-1.26) with the p-value of 0.044. For women of 36 years and above, it was 0.97 (95% CI 0.90-1.04) with p-value of 0.4, indicating no relationship for these older women.

Figure 9 - The Tromsø Study (Tromsø 3): Relative risks of Colon Cancer in Women < 36 year and Women ≥ 36 years (at baseline) according to BMI categories



In another analysis, we considered the age at colon cancer diagnosis and used data of women who had cancer at 55 years and below for the model. The results showed a similarly positive association between increased BMI and risk of colon cancer in this group. (Low/normal weight as the reference category, overweight: HR=1.13, 95% CI=0.37-3.44, obese: HR=2.15, 95% CI=0.49-9.50). However, the relationship was not statistically significant.

4.4.4 Cancers of the Rectum, Recto-sigmoid and Anus

There were 101 incident cancers of the rectum, recto-sigmoid and the anus. As there were only 3 cases of anal cancer, the results basically reflect relationships with cancers of the rectum and recto-sigmoid, and we therefore refer to them as such hereafter. Rectal and recto-sigmoidal cancers accounted for 4.5% of all the cancers in the follow-up period. There were 69 cases in the men with the crude incidence rate of 31 per 100,000 men-years, and 32 cases in women with the crude incidence rate of 14 per 100,000 women-years.

Table 13 - The Tromsø Study (Tromsø 3): Distribution of Cancers of Rectum and Recto-sigmoid according to the BMI categories

MEN				
BMI categories *(in kg/m^2)*	**Population**	**Cancer (%)**	**Person-years**	***Crude IR**
Low weight *(BMI < 20.0)*	389	2 (0.5)	8,627	23
Normal Weight *(BMI 20.0-24.9)*	5,685	30 (0.5)	127,755	24
Overweight *(BMI 25.0-29.9)*	3,636	31 (0.9)	78,994	39
Obese *(BMI ≥ 30.0)*	509	6 (1.2)	10,672	56
TOTAL	**10,219**	**69 (0.7)**	**226,046**	**31**
WOMEN				
Low weight *(BMI < 20.0)*	1,410	5 (0.4)	32,842	15
Normal Weight *(BMI 20.0-24.9)*	6,117	18 (0.3)	140,717	13
Overweight *(BMI 25.0-29.9)*	1,740	6 (0.3)	39,271	15
Obese *(BMI ≥ 30.0)*	457	3 (0.7)	10,317	29
TOTAL	**9,724**	**32 (0.3)**	**223,147**	**14**

*Crude IR = Crude incidence rate per 100,000 person-years

The mean BMI of men who had cancer of the rectum and recto-sigmoid was 25.54 kg/m^2, whereas that of men who did not was 24.60 kg/m^2. For women, the mean BMI of those who had the cancer was 23.53 kg/m^2 while that of those who did not was 23.09 kg/m^2. The difference in the means BMI between those who had the cancer and those who did not was 0.94 kg/m^2 for men and 0.44 kg/m^2 for women, and the corresponding p-values for the differences were 0.01 and 0.48 respectively.

Table 14 - The Tromsø Study (Tromsø 3): Relationship between BMI and incidence of the Cancer of the Rectum and Recto-sigmoid with the Hazard Ratios (HR 95% confidence limits)

MEN		
BMI categories *(in kg/m^2)*	**Age adjusted HR (95% CI)**	**Age & smoking adjusted HR (95% CI)**
Low weight *(BMI < 20.0)*	1.41 (0.34-5.92)	1.32 (0.31-5.57)
Normal weight *(BMI 20.0-24.9) *ref. cat.*	1.00	1.00
Overweight *(BMI 25.0-29.9)*	1.25 (0.75-2.07)	1.30 (0.78-2.16)
Obese *(BMI ≥ 30.0)*	1.80 (0.75-4.35)	1.92 (0.79-4.65)
P-value for homogeneity	*0.57*	*0.48*
P-value for linear trend	*0.25*	*0.18*
WOMEN		
Low weight *(BMI < 20.0)*	1.43	1.43 (0.52-3.91)
Normal weight *(BMI 20.0-24.9) *ref. cat.*	1.00	1.00
Overweight *(BMI 25.0-29.9)*	0.99	1.00 (0.39-2.55)
Obese *(BMI ≥ 30.0)*	1.84	1.89 (0.55-6.51)
P-value for homogeneity	*0.72*	*0.70*
P-value for linear trend	*0.87*	*0.84*

HR = hazard ratio; 95% CI = 95% confidence interval; *ref. cat. = reference category

Figure 10 - The Tromsø Study (Tromsø 3): Relative risks of Cancer of Rectum and Recto-sigmoid in Men and Women according to BMI categories

The relationships between BMI and the risk of rectal and recto-sigmoid cancers appeared U-shaped (Figure 10), however, the p-value for the second order term was 0.51 in men and 0.25 in women.

Unlike in colon cancer, stratification by the mean age of the women cohort (36 years) has no new profound effect modification on the risk of the cancers in the women.

4.4.5 Colorectal Cancers

There were 101 incident cancers in the rectum, recto-sigmoid colon and the anus. This constituted 4.5% of all the cancer incidents in the study population. When these were added to the colon cancers, there were 282 cases which represented 12.6 per cent of all the cancers identified in the follow-up period. 171 cases of these cancers were found in men, with the crude incidence rate of 76 per 100,000 men-years, while 111 cases occurred in women with the crude incidence rate of 50 per 100,000 women-years (Table 15).

Table 15 - The Tromsø Study (Tromsø 3): Distribution of Colorectal Cancer according to the BMI categories

MEN				
BMI categories *(in kg/m^2)*	**Population**	**Cancer (%)**	**Person-years**	***Crude IR**
Low weight *(BMI < 20.0)*	389	2 (0.5)	8,627	23
Normal Weight *(BMI 20.0-24.9)*	5685	67 (1.2)	127,726	53
Overweight *(BMI 25.0-29.9)*	3636	88 (2.4)	78,922	112
Obese *(BMI ≥ 30.0)*	509	14 (2.8)	10,659	131
TOTAL	**10,219**	**171 (1.7)**	**225,934**	**76**
WOMEN				
Low weight *(BMI < 20.0)*	1,410	11 (0.8)	32,838	34
Normal Weight *(BMI 20.0-24.9)*	6,117	68 (1.1)	140,664	48
Overweight *(BMI 25.0-29.9)*	1,740	24 (1.4)	39,250	61
Obese *(BMI ≥ 30.0)*	457	8 (1.8)	10,314	78
TOTAL	**9,724**	**111 (1.1)**	**223,065**	**50**

*Crude IR = Crude incidence rate per 100,000 person-years

The mean BMI of men with colorectal cancer was 25.87 kg/m^2 whereas men with no such cancer had mean BMI of 24.59 kg/m^2. Women with colorectal cancer had mean BMI of 23.74 kg/m^2 while women with no such cancer had 23.08 kg/m^2 as their mean BMI value. The difference in the means BMI between those who had colorectal cancer and those who did not was 1.28 kg/m^2 for men and 0.65 kg/m^2 for women, and the corresponding p-values were <0.001 and 0.047 respectively.

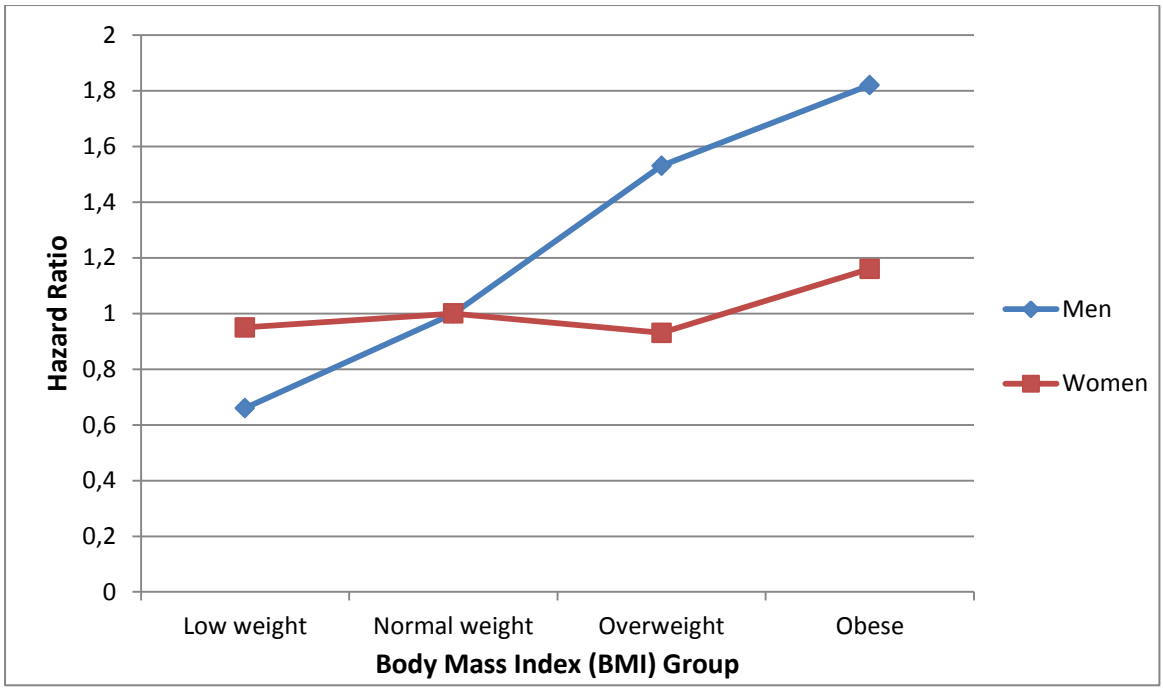
Table 16 - The Tromsø Study (Tromsø 3): Relationship between BMI and Colorectal Cancer incidence with the Hazard Ratios (HR 95% confidence limits)

MEN		
BMI categories *(in kg/m^2)*	**Age adjusted HR (95% CI)**	**Age & smoking adjusted HR (95% CI)**
Low weight *(BMI < 20.0)*	0.67 (0.16-2.74)	0.66 (0.16-2.72)
Normal weight *(BMI 20.0-24.9) *ref. cat.*	1.00	1.00
Overweight *(BMI 25.0-29.9)*	1.52 (1.10-2.10)	1.53 (1.11-2.11)
Obese *(BMI ≥ 30.0)*	1.81 (1.01-3.22)	1.82 (1.02-3.26)
P-value for homogeneity	*0.030*	*0.028*
P-value for linear trend	*0.003*	*0.003*
WOMEN		
Low weight *(BMI < 20.0)*	0.94 (0.49-1.78)	0.95 (0.50-1.80)
Normal weight *(BMI 20.0-24.9) *ref. cat.*	1.00	1.00
Overweight *(BMI 25.0-29.9)*	0.93 (0.58-1.49)	0.93 (0.58-1.50)
Obese *(BMI ≥ 30.0)*	1.14 (0.55-2.39)	1.16 (0.57-2.44)
P-value for homogeneity	*0.96*	*0.96*
P-value for linear trend	*0.86*	*0.84*

HR = hazard ratio; 95% CI = 95% confidence interval; ref. cat. = reference category

In the age and smoking status adjusted analyses, the p-value for linear trend was 0.003 for men and 0.84 for women, indicating a relationship in men, but not in women.

Figure 11 - The Tromsø Study (Tromsø 3): Relative Risks of Colorectal Cancers in Men and Women according to BMI categories



When the BMI was entered into the Cox regression model as a continuous variable (in single unit increment), the resulting relative risk for men was 1.09 (95% CI 1.04-1.14) with a p-value of 0.001. For women, the p-value was 0.98, thus, no relationship was found in women.

In a separate analyses and as done in the colon cancer, we limit the analyses in women to those aged 36 years and below (at baseline), we found a linear relationship between BMI and the risk of colorectal cancer, though not statistically significant (HR=1.31, 95% CI = 0.73-2.36, p-value of linear trend = 0.37). When women aged 36 years and above (at baseline) were analysed, no relationship was found (HR=0.97, 95% CI=0.72-1.31, p-value of linear trend = 0.86)

CHAPTER 5: DISCUSSION

5.1 All cancers combined

In this population based prospective study, we found a U-shaped relationship between BMI and total cancer incidence in men during a mean of 21.98 years of follow-up. The U-shaped relationship did not change even when the first 5 years of the follow-up period was excluded from the analyses. This means that it is unlikely that the increased risk in the low weight and obese men is due to preclinical disease. Unlike in men, there was essentially no relationship between BMI and the total incident cancers in women (Table 4 and Figure 4).

The findings are similar to the results of a study conducted by Inove, Sobne and Tsugane (2004) in Japan where they also observed a U-shaped increased risk of cancer occurrence according to the BMI categories in men and little or no fluctuation in the risk in women of different BMI categories (45). On the contrary, Calle et al (2003) found increased BMI associated with increased risk of incident cancers in both men and women. However, they did not explore the relationship in the underweight subjects (16).

There are possibilities of several mechanisms for the effects of a low or high BMI on the risk of cancer, and attempts have been made to explain the U-shaped risk variation according to BMI categories seen in men. It was suggested that the increased risk of all cancers combined in the low weight BMI category may be caused by “oxidative DNA stress” or mild inflammations common in the underweights. The immune system may be damaged by these inflammations, thus allowing cancer cells to proliferate (42, 46). Malnutrition may also reduce immune responses and weaken resistance to infection which may also increase risk of cancer occurrence (45, 47). The increased risk in the overweight and obesity may

however, be explained by different mechanisms of insulin-like growth factor-1 (IGF-1), sex steroids and abdominal obesity. These mechanisms, described earlier in this thesis (see literature review section) may explain the increase in cancer risk with increasing adiposity. Animal studies have also revealed that over-nutrition may also reduce immunity which may lead to increased risk of cancer (45, 48). However, obesity has no substantial effects on the total cancer occurrence in women. The mechanism(s) responsible for the observed different cancer risk patterns according to genders (for all cancers combined) remained largely unclear (45).

The public health implication of these findings is that very low or high BMI in otherwise healthy population may have critical association for future development of cancers (45), and health policies may hence be to encourage reduction of body weight as low as possible but above the low weight category, particularly in men.

5.2 Prostate Cancer

We found no marked variation in the risk of prostate cancer in relation to BMI. However, there was a slight reduction in the risk in the obese, although not statistically significant (Table 6 and Figure 5).

The epidemiologic evidence linking BMI and prostate cancer is rather controversial. Some studies have revealed increased BMI to be associated with decreased risk of prostate cancer (49, 50), others found increased risk (51, 50), while some studies found no clear association of risk (50, 52, 53). In a 21-year follow-up of 950,000 Norwegian men, obese men were found to have 9% increased risk of prostate cancer, while the obese men aged 50 to 59 years at the end of the follow-up had a 58% increased risk (54). Therefore, some

interactions between age and obesity may account for why some studies found increased risk and others no relationship between increasing BMI and prostate cancer risk (50).

Our study investigated men aged 61 years and younger (at baseline). In a similar study by Giovannucci et al (2003) where men younger than 60 years were studied, they found increased BMI to be associated with decreased risk of prostate cancer (55). However, Renehan (2011) considered that this may only be apparent as he opined that "there is an inherent bias in a clinician's ability to detect prostate cancer in obese men as larger sized prostates make biopsy less accurate for finding an existing cancer" (30).

The mechanism for decrease risk of prostate cancer in obese individuals is unclear but thought to be associated with hormones (55). The raised circulating level of leptin in obese men may decrease the androgen (such as testosterone) in them (55, 56), and the lowered testosterone level associated with obesity may account for the decreased risk of prostate cancer (55).

The public health implication of this is, even if obesity slightly decreases the risk of prostate cancer, the overall effects of obesity are overwhelmingly detrimental to the general health status (55).

5.3 Lung Cancer

We found a U-shaped relationship between BMI and the risk of lung cancer. Thus, the underweight and the obese are at higher risk of lung cancer compared to the normal weight category. From the unadjusted descriptive statistics (Table 8), almost all the people who had lung cancers in the low weight category are current smokers. Therefore, low weight subjects who smoke may be at higher risk of lung cancer. It is an established observation that

smokers have lower mean BMI (30). But then, whatever is the cause of the low BMI, either due to the current smoking status, or it predates smoking, a low BMI correlates with an increased risk of lung cancer. As we have adjusted for smoking, the impact of smoking on BMI-lung cancer relationship should be minimized. However, it is rather difficult to fully adjust for this strong risk factor for the disease, and we would expect residual confounding by smoking.

This finding re-echoes the result of the prospective study of Koh et al (2009) conducted in Singapore Chinese Health Study which concluded that smokers with low BMI may be at higher risk of lung cancer (18).

The other (right) half side of the U-shaped relationship in our findings (Figure 6) shows increased BMI with increased risk of lung cancer in men, whereas the relationship approximately fluctuates around the null in women. Most of the risk observed seems to be for men in the highest BMI category (Table 9).

In the exclusive analysis of never- and former smokers of more than 5 years (in an attempt to minimize the smoking factor and explore the BMI-lung cancer relationship more), both obese men and women show increased risk of lung cancer (Figure 7). However, this is not statistically significant in both genders. Even then, 5 years post smoking cessation also may not be long enough time to completely exclude the smoking factor.

Our findings here is analogous to Rauscher, Mayne and Janerich (2000) in a case-control study where they found 2.6 fold increased odds ratio for lung cancer in never- and former-smokers (of more than 10 years) when they compared the highest octile of BMI to the lowest (38).

The results of studies in this area, especially the relationship between BMI and never-smokers, have been conflicting (57). While some studies have reported positive association (58), many have given evidence of inverse association (59), and others have shown no association at all (60). Nevertheless, the results of the current analyses are consistent with BMI-cancer association found in some other cancer sites, and similar biological mechanism or theories have been used to provisionally explain the association.

In the case of low BMI and its association with increased risk of lung cancer, studies have shown that decrease in BMI inversely relate with the level of marker in the urine called 8-hydroxydeoxyguanosine, which is a marker of oxidative DNA damage in smokers (61.) Thus, BMI may act as an independent indicator for vulnerability to smoking-related cancer (62). Furtherance to this, smoking may also cause decrease in BMI via weight loss by enhancing metabolic rate, which also bring about a carcinogenic pathway through higher production of cellular reactive biological substances (62).

The public health implications of our findings are the possible increased lung cancer risk in smokers in the low weight population who may usually be predominantly young adults, and also the increased risk in the obese. These important implications further highlight the imperativeness of keeping healthy body weight

5.4 Colon Cancer

Our results confirm that increased BMI is a strong risk factor for colon cancer in men. No association was found in women (Table 11 and Figure 8).

Our findings in men are consistent with several studies where increased BMI have been reported for increased risk of colon cancer in men (63-67). Meanwhile, other studies have

either found weak or null association between BMI and risk of colon cancer in women (63, 67). However, when the analyses were restricted to the women aged 36 years and below at baseline (36 years is the mean age of the female cohort), we observed a relatively strong positive association between BMI and the risk of colon cancer (Figure 9). This association was not altered even when the first 3 years of the follow-up period was excluded from the analyses (Table 12), which means the relationship is not as a result of preclinical disease. Conversely, when data of women aged 36 years and above (at baseline) were alternatively used for the analyses, the association was, as expected, negative, but not statistically significant (Table 12).

These findings suggest that BMI may be an important predictor of colon cancer occurrence in relatively young women, but its effects weaken by age, or probably by menopausal status as Giovannucci (2001) suggested, (68). Thus, menopausal status is a possible effect modifier of BMI and colon cancer risk relationship.

Our findings in women are similar to the results of the study conducted by Terry, Miller and Rohan (2002) in Canada where a cohort aged 40-76 years at baseline were investigated. When they confined their analyses to women below 55 years at baseline (the mean age of their women cohort was 55 years), they found strong association between BMI and colon cancer risk, but no association was found among women aged 55 years and above at baseline (69). Nevertheless, there are divergent findings in some studies where increased body size in older women was reportedly associated with colon cancer risk (70).

The exact biological mechanism responsible for our observation is not fully understood (71), but it is believed to be closely related to insulin, insulin-like growth factor (IGF), sex hormones and possibly adipokines (see literature review section). The risk of colon cancer

may particularly be increased by obesity through the insulin/IGF axis (68), and in women, the high levels of oestrogen (sex hormone) associated with increased BMI in post-menopausal women may produce opposing effects (68, 21). The opposing effects of oestrogens and the insulin/IGF axis may about balance or offset each other and consequently resulting into little or no substantial association left between BMI and colon cancer risk as seen in older or post-menopausal women (68). This may speculatively account for the negative, albeit not statistically significant association we observed in the older women in our study. In the pre-menopausal women, obesity tends to increase insulin level but it is a negligible means of oestrogen (due to higher ovarian production). Hence, the adverse effects of the high level of insulin may hold sway (68). This may speculatively explain the increased BMI associated with increased colon cancer risk in the pre-menopausal women observed in our study.

If these submissions are apposite, it further means that increased BMI would remain a risk factor in post-menopausal women on oestrogens replacement therapy (68), even if oestrogen replacement therapy by itself may reduce colon cancer risk (73).

The public health relevance of these findings further underscores the importance of keeping healthy body weight in men, young women, and probably as well as in older women on oestrogen replacement therapy.

5.5 Cancer of the Rectum, Recto-sigmoid and Anus

As mentioned earlier, there were only 3 cases of cancer of the anus in our study, thus, our findings basically reflect relationships between BMI and cancer of the rectum and recto-sigmoid. Our results suggest that increase BMI is associated with increased risk of this type of cancers. This is observed in both men and women, but is slightly stronger in men than in

women. However, the observed associations are neither statistical significant in men nor women (Table 14). Unlike in colon cancer, menopausal status appeared to have no effect modification on the risk of rectal and recto-sigmoid cancers.

The positive association between obesity and the risk of rectal and recto-sigmoid cancers was also found in similar other studies. Some studies reported that the association was stronger in men than in women (74, 75), while others reported it was limited to only men (76-78), and some found no association in both genders (79).

The tentative biological mechanism involving insulin, IGF, sex hormones and adipokines earlier expounded in respect of colon cancer may also be tenable for the relationship observed here. Furtherance to that, that increased BMI and cancer risk is stronger for colon than rectal cancer may mean that these or other mechanisms related to obesity are stronger for colon than for rectal cancer (78), and several studies have reported that the level of C-peptide and leptin (an adipokine) were more strongly and positively associated with risk of colon cancer than rectal cancer (78).

5.6 Colorectal Cancers

Our results suggest that increase BMI is associated with increased risk of colorectal cancers in men, whereas there are no substantial changes in the risk in women, except a relatively small (but statistically not significant) increased risk in the obese (Table 16 and Figure 11). The findings were grossly similar to what were observed in the BMI-colon cancer relationship, especially in men.

The relatively small increased risk in obese women becomes more profound when the analyses are limited to women less than 36 years old at baseline. Moreover, the linear

relationship between BMI and the risk of colorectal cancer in the women less than 36 years in age, though not statistically significant, may also indicate the possible modifying effect of the menopausal status in women regarding the risk of colorectal cancer, or may actually be a reflection of the colon cancers present in the analyses.

Meta-analyses have indicated that BMI may be more strongly associated with colon cancer than rectal (81, 82) cancer incidence. Our findings were consistent with previous studies where stronger positive relationship for BMI and colorectal cancer risk were found in men compared to women (83, 84). When we restricted the analyses in women to those aged 36 years and below, our results were similar to that of Terry et al (2001) conducted in Sweden (72).

The biological mechanism by which increased BMI increases colorectal cancer risks are largely unclear (71), but the speculative explanations previous provided under colon cancer may equally be accountable here. In addition, the possible mechanism(s) for gender difference is thought to be probably related to testosterone concentration. Studies have shown that increased BMI is inversely related to testosterone concentration in men (39) while it is directly related in women (80). Therefore, a reduction in testosterone concentration caused by obesity may be one reason for stronger association of increased BMI with colon and rectal cancer risk in men than in women (78). However, as recently argued by Kitachara et al (2013), additional studies are needed for better understanding of the biologic mechanism(s) underpinning these associations (71).

Our findings further highlighted the importance of early adulthood weight control in both men and women.

5.7 Limitations and Strengths of the Study

We need to acknowledge some limitations in this study. Some invited participants within the stipulated birth cohorts did not attend Tromsø 3 survey; we do not have knowledge of the BMI of these non-attendees. Even though the participants were at liberty to attend at suitable time within the timeframe of about a year, non-attendees were 25 per cent of the total invitees. This estimate is lower (approximately 20 per cent) if people who gave reasons for not attending are taken in to consideration (19). This may be a possible source of selection bias in the study. However, Montgomery et al (2010) posited in their study that the differences between participants and non-participants in prospective cohort study are generally small, and they did not find significant evidence of selection bias (85). In another study by Knudsen et al (2010), they also opined that non-participation in the study of association between exposure and outcome may not have any serious threat to the validity of the results (86). Thus, we do not consider that the 25 per cent non-attendees in Tromsø 3 survey would have introduced any substantial selection bias into our results. Moreover, prospective studies like ours, where the outcome is unknown at the time of enrolment are less susceptible to selection bias (87).

BMI is a surrogate measure of body fat and the measurement relies solely on the weight and height. Accordingly, BMI usually overestimates the adipose tissue (body fat) in people with more lean body mass, such as muscular people and athletes (88), while it underestimates the body fats in people with less lean body mass such as the elderly and people having eating disorder like in anorexia nervosa and bulimia nervosa (88). Therefore, some group of people who are fit and athletic or body builders could have been misclassified as overweight, while some old individuals or in muscle wasting disorders may

have also been misclassified as low weight. This may potentially lead to bias of misclassification of exposure (87). There were, however, no elderly (65 years and above) and probably very few muscular subjects and patients with eating or muscle wasting disorders in the sample.

Other anthropometric measures reflecting the body fat (such as waist circumference, waist-to-height ratio, and waist-to-hip ratio) have been suggested and used in some studies. Unfortunately we do not have any of these in Tromsø 3 survey either as alternatives or for comparison to BMI measurement. Howbeit, studies have shown that BMI correlates sufficiently high enough with body fat (89) to minimise misclassification mentioned above, and therefore, we do not suppose this could have compromised our results.

Measurement of BMI close to the time of diagnosis of cancer may be lower than the preclinical values, and may also have led to misclassification. To assess the possibility of this effect (if any), each BMI-cancer analysis was further verified by excluding cases diagnosed within the first 3 or 5 years of the follow-up (as deemed appropriate), and we checked for attenuation or complete alteration of the results or patterns previously observed. Our results did not suggest that the preclinical disease had any significant impact on our results or on the conclusions.

Changes in BMI after the study began were not factored in in the study. However, even though BMI tends to increase with age, and more strongly in relatively young adults than older subjects, there is a strong tracking with regards to BMI; the correlation between BMI at baseline and after, for instance after 10 years, is high (92). Furthermore, the classification with regards to confounders (such as smoking) may have changed during follow-up period. These changes may have had effects on the possible outcome of the participants (having

incident cancer or not), and some residual confounding is likely. In addition, we did control for smoking status in all our analyses, but, we could not assess the contribution of environmental tobacco smoke (ETS) exposure in these BMI-cancer relationships. The amount of ETS exposure in never-smokers may be essential for ascertaining the cancer risks related to ETS exposure (90).

The possible effects of family history of obesity and cancer were not explored in this study. Both obesity and cancer are known to correlate within families (91), but we do not have adequate information suitable for analyses for both in our study. Likewise, information on dietary intake (such as red or processed meat) was also not available. As BMI and dietary habits are linked in different (and sometimes quite complicated) ways, this may be a weakness in our study.

Regardless of the above, our study had the evident strength of a population-based prospective design, with a comparatively long follow-up time (1986 to 2010). There was relatively high attendance rate (about 75%) and minimal loss to follow-up (19). Baseline information including weight and height of participants were collected beforehand, thus avoiding the exposure-recall bias which is an integral of case-control studies. The cohorts used in the study were based on birth-year and not based on professional affiliation (e.g. nurses) or church membership (e.g. Adventist) as in some studies, which could introduce possibilities of bias. The study also enjoyed the advantage of measured (not self-reported) values of height and weight, and the reliability of the connected Norwegian registries for cancer diagnosis, death, and emigration. Thus, body mass index at baseline was measured with high validity and the follow-up of deaths and incident cancers with histologic confirmations were mostly assured and complete.

5.8 External Validity

The findings in this study may be generalizable to cities similar to Tromsø municipality in population homogeneity, and to the rest of Norway, Europe or any similar population that is predominantly Caucasian. However, the generalizability may not extend to Asia and Africa because, for instance, Asians have more body fat at any given BMI compared to Caucasians (93). Increased risks of diabetes and cardiovascular diseases may thus start at lower BMI in Asian population compared to Caucasians and this may extend to cancer risks as well (84). Therefore, the BMI cut-offs for overweight and obesity may be expected to be different in Asians.

5.9 Recommendation for Future Studies

Obesity-related cancers are diverse and there still exist much knowledge gaps in the mechanism(s) underpinning the association between obesity and cancers, and what is actually responsible for the gender difference observed in some cancer incidents. More studies are still required in this area for better understanding. A better understanding may lead to improved or development of new public health approach to the prevention and treatment of BMI-related cancers.

It has also been implied that waist circumference, waist-hip-ratio and waist-to-height ratio (as measure of obesity) may be better predictors of future health risk than BMI (94). However, there is need for big cohort studies to evaluate these measures alongside BMI as regards the risk of cancers, and the associated gender variations in some of the cancer incidents.

CHAPTER 6: CONCLUSION

The purpose of this current study was to determine the relationship between BMI and the total cancer incidence as well as its relationships with some common specific cancers. This was done in relatively young subjects (in cancer research perspective).

The findings demonstrated that both the underweight and obese men were at increased risk of total incident cancer while the women were not. Thus, our **first hypothesis** that low and high BMIs increase the risk of total incident cancers holds in men but not in women. For specific cancers, adiposity may be a threat to the men as regards colon and colorectal cancers, and similarly to the relatively young premenopausal women, but not to the older women. Low weight and obese subjects may be at increased risk of lung cancer, whereas prostate cancer appeared to be indifferent to adiposity. Thus, our **second hypothesis** that low and high BMIs increase the risks of common cancers is gender specific and holds for some specific cancers (such as lungs and colon), but fell for others (such as prostate).

Our findings confirmed previous studies and contributed additional evidence in respect of BMI and total incident cancer risk, colon and colorectal cancer risks, and the possible modifying effect of menopausal status in the risk of colon cancer in women. Our study also supported the existing knowledge that underweight individuals who smoke may be at higher risk of lung cancer.

These results suggested that the safest body weight in respect of reducing ones cancer risks may be the “normal” weight, as both ends of the BMI spectrum may be at increased risk of future cancer development. Therefore, public health policies directed at reducing incidence of cancers should address both the obese and the underweights in the community.

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