Metabolic Factors and Cancer Risk

Prospective Studies on Prostate Cancer, Colorectal Cancer, and Cancer Overall

Tanja Stocks

Department of Surgical and Perioperative Sciences
Urology and Andrology, Umeå University, Umeå
Sweden 2009
Learn from yesterday, live for today, hope for tomorrow. The important thing is not to stop questioning.

Albert Einstein
ABSTRACT

Background: A large number of prospective studies have shown that overweight and diabetes are related to an increased risk of many cancers, including colorectal cancer. In contrast, diabetes has been related to a decreased risk of prostate cancer, and overweight has been related to an increased risk of fatal, but not of incident, prostate cancer. Data from studies on metabolic factors related to overweight and diabetes, and the association with cancer risk, are limited.

Aim: The aim of this thesis was to study metabolic factors in relation to risk of prostate cancer (paper I and III), colorectal cancer (paper II and V), and cancer overall (paper VI).

Methods: Study designs were i) case-control studies, nested within the Northern Sweden Health and Disease Cohort (paper I and II), and ii) cohort studies of the Swedish Construction Workers cohort (paper III), and the Metabolic syndrome and Cancer project (Me-Can) comprising seven European cohorts (paper V and VI). Paper IV was a descriptive paper of Me-Can.

Results, prostate cancer: In paper I, increasing levels of several factors related to insulin resistance (insulin, insulin resistance index, leptin, HbA1c, and glucose) were associated with a decreased risk of overall incident prostate cancer, and the associations were stronger for non-aggressive tumours. In paper III, increasing levels of blood pressure was associated with a significant decreased risk of overall incident prostate cancer and of non-aggressive tumours. Body mass index (BMI) was significantly positively related to fatal prostate cancer.

Results, colorectal cancer: In paper II, obesity, hypertension, and hyperglycaemia, were associated with an increased risk of colorectal cancer, and presence of two or three of these factors was associated with a higher risk than the presence of one single factor. In paper V, BMI was associated with a significant linear positive association with risk of colorectal cancer in men and women, and significant positive associations were also found in men for blood pressure and triglycerides. A high metabolic syndrome score, based on levels of BMI, blood pressure, glucose, cholesterol, and triglycerides, was associated with a significant increased risk of colorectal cancer in men and women. The association was stronger than for any of the factors in single, but there was no evidence of a positive interaction between these metabolic factors.
**Results, cancer overall:** Blood glucose was significantly positively associated with risk of incident and fatal cancer overall, and at several specific sites. The associations were stronger in women than in men, and for fatal than for incident cancer.

**Conclusions:** Results from these studies indicate that elevated blood glucose is related to an increased risk of cancer overall and at several specific sites, and further, that overweight and metabolic aberrations increase the risk of colorectal cancer in an additive way. The association with prostate cancer seems to be more complex; insulin resistance and high blood pressure were in our studies related to a decreased risk of overall incident prostate cancer and of non-aggressive tumours, whereas overweight increased the risk of fatal prostate cancer.
CONTENTS

ABBREVIATIONS .................................................................................................................. 9

LIST OF PAPERS .................................................................................................................. 10

OVERVIEW OF PAPERS ....................................................................................................... 11

1 BACKGROUND .................................................................................................................. 12
   1.1 CANCER INCIDENCE AND MORTALITY ................................................................. 12
      1.1.1 Cancer overall ............................................................................................... 12
      1.1.2 Colorectal cancer .......................................................................................... 13
      1.1.3 Prostate cancer ............................................................................................. 15
   1.2 ETHNICITY, HEREDITY, ENVIRONMENT, AND CANCER RISK ..................... 17
      1.2.1 Cancer overall ............................................................................................... 17
      1.2.2 Colorectal cancer .......................................................................................... 19
      1.2.3 Prostate cancer ............................................................................................. 20
   1.3 OBESITY, DIABETES, METABOLIC FACTORS, AND CANCER RISK ............ 21
      1.3.1 Relationship between metabolic factors ......................................................................
      1.3.2 Cancer overall ............................................................................................... 24
      1.3.3 Colorectal cancer .......................................................................................... 25
      1.3.4 Prostate cancer ............................................................................................. 26
      1.3.5 Methodological aspects of studying metabolic factors ...............................................
      1.3.6 In summary, what is known and what is missing? ......................................................

2 AIMS .................................................................................................................................. 29

3 MATERIAL AND METHODS ........................................................................................... 30
   3.1 COHORTS .................................................................................................................. 30
      3.1.1 The Northern Sweden Health and Disease Cohort .............................................. 30
      3.1.2 The Swedish Construction Workers cohort ....................................................... 31
      3.1.3 The Metabolic syndrome and Cancer project ......................................................
   3.2 STUDY DESIGN AND SELECTION OF SUBJECTS ............................................. 34
      3.2.1 Paper I and II ................................................................................................. 34
      3.2.2 Paper III ......................................................................................................... 35
      3.2.3 Paper V and VI .............................................................................................. 36
   3.3 STATISTICAL ANALYSES ....................................................................................... 38
      3.3.1 Paper I and II ................................................................................................. 38
      3.3.2 Paper III, V and VI ......................................................................................... 39
   3.4 ETHICAL CONSIDERATIONS ...................................................................................... 42
4 MAIN RESULTS AND DISCUSSION ........................................... 43
  4.1 PROSTATE CANCER – PAPER I AND III .................................. 43
    4.1.1 Results ........................................................................ 43
    4.1.2 General discussion ...................................................... 46
    4.1.3 Interpretation .............................................................. 48
    4.1.4 Conclusions ............................................................... 50
  4.2 COLORECTAL CANCER – PAPER II AND V ............................ 51
    4.2.1 Results ........................................................................ 51
    4.2.2 General discussion ...................................................... 55
    4.2.3 Interpretation .............................................................. 57
    4.2.4 Conclusions ............................................................... 58
  4.3 CANCER OVERALL – PAPER VI ........................................... 58
    4.3.1 Results ........................................................................ 58
    4.3.2 General discussion ...................................................... 62
    4.3.3 Interpretation .............................................................. 63
    4.3.4 Conclusions ............................................................... 64

5 FUTURE PERSPECTIVES ......................................................... 65

6 SUMMARY ............................................................................. 68

7 SUMMERING .......................................................................... 70

8 ACKNOWLEDGEMENTS .......................................................... 72

9 REFERENCES ........................................................................... 75

PAPERS ..................................................................................... 91

I INSULIN RESISTANCE AND PROSTATE CANCER
II THE METABOLIC SYNDROME AND COLORECTAL CANCER RISK
III BLOOD PRESSURE, BODY SIZE AND PROSTATE CANCER RISK
IV COHORT PROFILE: THE METABOLIC SYNDROME AND CANCER PROJECT (ME-CAN)
V METABOLIC FACTORS AND COLORECTAL CANCER RISK
VI GLUCOSE AND CANCER RISK
ABBREVIATIONS

40-y  Age 40 programme
APC  Adenomatous polyposis coli
BMI  Body mass index
CI  Confidence interval
CONOR  Cohort of Norway
CV  Coefficient of variation
HbA1c  Glycated haemoglobin
HOMA-IR  Homeostatic model assessment of insulin resistance
IGFBP  Insulin-like growth factor binding protein
IGF-I  Insulin-like growth factor-I
Me-Can  Metabolic syndrome and Cancer project
MetS  Metabolic syndrome
MMR  Mismatch repair
MPP  Malmö Preventive Project
MSP  Mammography Screening Project
NCS  Norwegian Counties Study
NSAID  Non-steroidal anti-inflammatory drugs
OGTT  Oral glucose tolerance test
OR  Odds ratio
Oslo I  Oslo study I
PSA  Prostate specific antigen
RAS  Renin-angiotensin system
RC  Regression calibration
RDR  Regression dilution ratio
RR  Relative risk
SD  Standard deviation
VHM&PP  Vorarlberg Health Monitoring and Prevention Programme
VIP  Västerbotten Intervention Project
WHO  World Health Organization
LIST OF PAPERS


All publications, including tables and figures, were reproduced with permission from the publishers.
### OVERVIEW OF PAPERS

<table>
<thead>
<tr>
<th>Paper</th>
<th>Cohort, design</th>
<th>Main exposures</th>
<th>Endpoints</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>VIP, nested case-control</td>
<td>Fasting and post-load glucose, HbA1c, C-peptide (insulin), HOMA-IR, leptin</td>
<td>Incident PCa ($n=392$), non-aggressive ($n=278$) and aggressive ($n=114$) tumours</td>
<td>Exposures were inversely related to PCa risk, and the associations were stronger among men younger than 59 years at recruitment, and in the group of non-aggressive tumours.</td>
</tr>
<tr>
<td>II</td>
<td>VIP and MSP, nested case-control</td>
<td>BMI, blood pressure, fasting and post-load glucose, HbA1c, C-peptide, leptin, adiponectin</td>
<td>Incident CRCa ($n=306$)</td>
<td>No significant associations were found across quintiles. Obesity, hypertension, and impaired glucose were associated with increases in risk, and the risk was higher with presence of 2-3 of these factors.</td>
</tr>
<tr>
<td>III</td>
<td>Swedish Construction Workers cohort, cohort</td>
<td>BMI, height, blood pressure</td>
<td>Incident ($n=10,002$) and fatal ($n=2,601$) PCa. Non-aggressive ($n=2,817$) and aggressive ($n=2,402$) tumours</td>
<td>Blood pressure was significantly inversely related to risk of incident PCa and of non-aggressive tumours. BMI was significantly positively related to risk of fatal PCa.</td>
</tr>
<tr>
<td>IV</td>
<td>Me-Can, cohort profile paper</td>
<td>BMI, blood pressure, and fasting/non-fasting glucose, total cholesterol, and triglycerides</td>
<td>Incident ($n=4,695$) and fatal ($n=1,740$) CRCa</td>
<td>Metabolic syndrome score was significantly positively associated with risk of incident CRCa. Significant positive associations were also found for BMI, blood pressure and triglycerides in men, and for BMI in women.</td>
</tr>
<tr>
<td>V</td>
<td>Me-Can, cohort</td>
<td>Fasting/non-fasting glucose</td>
<td>Incident ($n=30,285$) and fatal ($n=10,061$) cancer of all sites</td>
<td>Glucose was significantly positively associated with risk of incident and fatal cancer, overall and at specific cancer sites.</td>
</tr>
</tbody>
</table>

VIP, Västerbotten Intervention Project; HbA1c, glycated haemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; PCa, prostate cancer; MSP, Mammography Screening Project; BMI, body mass index; CRCa, colorectal cancer; Me-Can, Metabolic syndrome and Cancer project.
1 BACKGROUND

1.1 Cancer incidence and mortality

Cancer is a major health problem, in particular in developed countries, and the incidence and prevalence of cancer is predicted to increase worldwide. In developed countries, the highest incidence rates of specific cancers are in men: 1) prostate, 2) lung and 3) colorectum, and in women: 1) breast, 2) colorectum, and 3) lung. Incidence of prostate cancer has increased dramatically in many Western countries since the 90ies, due to increased PSA testing in asymptomatic men.

1.1.1 Cancer overall

The global burden of cancer is high; in 2008, with an approximate world population of 6.7 billion people, around 12.4 million persons were diagnosed with cancer and 7.6 million died out of cancer. Overall, cancers with the highest incidence rates are cancer of the lung, colorectum and stomach, breast cancer and cervix cancer among women, and cancer of the prostate and liver among men (Figure 1). These cancers, except for prostate cancer, are also the most common cause for cancer death. Incidence and mortality rates of cancer overall are much higher in developed countries than in developing countries, where infectious diseases are the by far largest health problem in many areas. In developed countries, cardiovascular disease is the main cause of death, followed by death caused by cancer. The lifetime expectancy is increasing worldwide, particularly in developing countries, and as most cancers are more common at higher ages, higher incidence rates and prevalence, and death from cancer, is expected in the future.
1.1.2 Colorectal cancer

Incidence rates of colorectal cancer is somewhat higher in men than in women (ratio 1.2:1)\textsuperscript{3}. Compared to other cancers worldwide, incidence rates of colorectal cancer ranks fourth in men and three in women, and in developed countries, colorectal cancer ranks three in men, after prostate cancer and lung cancer, and two in women, after breast cancer\textsuperscript{1}. In Europe, colorectal cancer accounts for 13% of all new cases in men and women together, and the total number of new cases are similar to those for prostate cancer, lung cancer and breast cancer\textsuperscript{4}. The five-year survival in cases diagnosed between 1990 and 1994 was for men and women in the United States 59% and 60%, in Europe, 45% and 48%, and in the Nordic countries, approximately 50% and 55%,
Figure 2. Trends of incidence and mortality rates of colorectal cancer in the Nordic Countries. Figure from NORDCAN © 2007 Association of the Nordic Cancer Registries.

Figure 3. Cumulative risk of incidence and mortality of colorectal cancer in 2004 in the Nordic Countries. Figure from NORDCAN © 2007 Association of the Nordic Cancer Registries.
respectively. Cancer registries in the Nordic countries started between 1943 (Denmark) and 1958 (Sweden), and the registries are known for a high coverage of cancer cases and high quality of data. During the past decades, incidence rates of colorectal cancer have increased in the Nordic countries, whereas mortality rates have declined (Figure 2). In Finland, a nationwide screening programme started in 2004, and discussions about starting up organised screening is currently ongoing in the other Nordic countries (Lars Pålman, personal communication, April 15, 2009). The cumulative risk of diagnosis and death of colorectal cancer in the Nordic countries is shown in Figure 3.

1.1.3 Prostate cancer

There are large differences in incidence rates of prostate cancer between countries and regions in the world. Whereas incidence rates are low in most developing countries, incidence of prostate cancer is ranked number one in men in developed countries, accounting for 20-25% of new cancers in men. Prostate specific antigen (PSA) is a marker commonly used in the diagnosis and treatment of prostate cancer. PSA is produced in the prostate, and an elevation of PSA in plasma may indicate presence of prostate cancer, but it may also indicate e.g. inflammation or enlargement of the prostate. An increased PSA testing in asymptomatic men in many countries in the 90ies resulted in a dramatic increase of diagnosis of latent prostate cancers. Although PSA testing in the Nordic countries has been much less common than e.g. in the United States, the increased PSA testing resulted in a clear increase of incidence rates of prostate cancer in the 90ies, but no change in mortality rates of the disease (Figure 4). The prognosis of prostate cancer is overall good; the 5-year survival in men diagnosed with prostate cancer between 1990 and 1994 was in the United States 92%, in Europe, 57%, and in the Nordic countries, approximately 65%. The higher survival in the United States compared to the Nordic countries can largely be explained by a higher PSA testing in the United States and thus, a higher detection of low-risk prostate cancers. As survival from prostate cancer is good, mortality rates of prostate cancer in developed countries ranks only number three, as compared to the first rank for cancer incidence. The cumulative risk of diagnosis and death of prostate cancer in the Nordic countries is shown in Figure 5.
Figure 4. Trends of incidence and mortality rates of prostate cancer in the Nordic Countries. Figure from NORDCAN © 2007 Association of the Nordic Cancer Registries

Figure 5. Cumulative risk of incidence and mortality of prostate cancer in 2004 in the Nordic Countries. Figure from NORDCAN © 2007 Association of the Nordic Cancer Registries
1.2 Ethnicity, heredity, environment, and cancer risk

The main identified exposures causing cancer overall are tobacco smoking, which causes one third of all cancers in developed countries, and chronic infections, which causes one fourth of all cancers in developing countries. Heredity and lifestyle play an important role in the aetiology of colorectal cancer. The main known factors that have been associated with risk of prostate cancer are age, ethnicity and family history of prostate cancer.

1.2.1 Cancer overall

Genetic variants predisposing for cancer have been identified for a number of cancer sites; the most established genes associated with risk are the adenomatous polyposis coli (APC) and mismatch repair (MMR) genes for colorectal cancer and the BRCA1 and BRCA2 genes for breast and ovarian cancer. Mutations on the BRCA1 or BRCA2 genes are related to a 10 to 30-fold increased risk of breast cancer and 2-4% of breast cancers are estimated to be attributable to mutations in these genes. Numerous other genetic variants have been identified that are related to different types of cancer. Although few single gene mutations have been identified that confer an essential cancer risk, family history of cancer is an important risk factor for most cancer types. However, the vast majority of cancers are sporadic. Studies on immigrants, in particular of men and women moving from Asian countries to the United States, have shown that immigrants adopt cancer rates to become more similar to the population in the new country, whereas rates of cancers that are more common in the native country are lower in immigrants than in their native counterparts. These observations support a role for environmental factors in cancer development.

The most established environmental risk factor for cancer is tobacco smoking. Smoking has been most strongly related to lung cancer; smokers have a 15 to 30-fold increased risk of lung cancer compared to non-smokers, and 90% of all lung cancers in men are estimated to be attributable to smoking. The proportion is somewhat lower in women, due to a lower consumption of smoking tobacco in women. Tobacco smoking has also been related to several other cancer forms, such as cancers of the upper aerodigestive tract (oral cavity, pharynx, larynx, oesophagus), kidney, bladder, stomach, cervix and pancreas, as well as acute myeloid leukemia. Approximately 30% of all cancers in developed countries are caused by smoking, and as smoking...
increases in developing countries, the proportion of cancers attributable to tobacco use in these countries is increasing.

Chronic infections are the cause for approximately 26% of all cancers in developing countries, and 8% of cancers in developed countries. The most common infectious agents that have been related to cancer, which also cause a large number of new cases, are hepatitis B and C virus, associated with hepatocellular carcinoma, human papilloma virus (HPV), associated with cervix cancer, and helicobacter pylori, associated with gastric cancer.

A number of cancers in women, in particular breast and endometrial cancer, have been related to reproductive factors and sex-hormones. A low age at first pregnancy and high parity has been shown to decrease the risk of breast and endometrial cancer and a high lifetime exposure of sex-hormones increase the risk. Menarche at a low age, and late menopause - when oestrogen and progesterone production in women ceases, have been related to an increased risk of breast and endometrial cancer, and furthermore, hormone replacement therapy after menopause has also been related to an increased risk of these cancers.

Other identified factors related to cancer are ionising radiation, which is a risk factor for several cancers, in particular of thyroid cancer, leukemia, and breast cancer, and ultraviolet radiation, which is the strongest risk factor for skin cancer, in particular in people of white ethnicity with high sun exposure. Occupational exposures have been related to cancer risk, such as asbestos for lung cancer and benzene for leukemia. Chronic inflammation has been related to an increased risk of a number of cancers, including cancer of the lung, prostate, colorectum and the pancreas, the latter for which chronic inflammation (chronic pancreatitis) is a strong risk factor, commonly caused by heavy alcohol consumption.

In a recent extensive report on nutrition, physical activity and cancer, a number of nutritional factors, food items, and also physical activity were concluded to be related to risk of various types of cancers. Of common food types and nutrients, the evidence was estimated to be convincing of a positive association between consumption of red or processed meat and colorectal cancer, alcohol and cancer of the mouth, pharynx and larynx, oesophagus, breast, and colorectal cancer in men, and between beta-carotene and risk of lung cancer. There was no convincing evidence of a reduced risk of cancers by a high intake of particular foods, but the evidence was concluded to be strong that a high intake of vegetables and legumes decreases risk of cancer of the mouth, pharynx and larynx, oesophagus and stomach. A diet high in dietary fibre, milk and calcium was found to be related to a decreased risk of colorectal cancer. There was also relatively strong evidence of a decreased risk of some cancers by high intake of micro-nutrients, such as lycopene and selenium for
prostate cancer. Physical activity was concluded to be directly linked to a reduced risk of colorectal cancer, and probably also of postmenopausal breast cancer and endometrial cancer.

1.2.2 Colorectal cancer

Two well-defined hereditary syndromes account for around 5-10% of colorectal cancers, familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC). FAP is caused by mutations of the APC gene and HNPCC is caused by mutations in the MMR gene. Around 5% of colorectal cancers are estimated to be attributable to APC and MMR mutations, and up to 20% of colorectal cancers are familial.

Ulcerative colitis and Crohn’s disease are inflammatory bowel diseases that have been related to an increased risk of colorectal cancer. Persons with ulcerative colitis have an approximately 1.1 to 2.8-fold increased risk of colorectal cancer, and risk increases with duration of the disease. Crohn’s disease has been associated with and approximately 2-fold increased risk. The use of non-steroidal anti-inflammatory drugs (NSAID) has been shown to reduce the risk of colorectal cancer.

Insulin-like growth factor-I (IGF-I) is a growth stimulating hormone which peaks in puberty and declines thereafter. In vitro and in vivo studies have further shown that IGF-I stimulate tumour growth, which has raised an interest to further study the association with cancer. Bioactivity of IGF-I is regulated by IGF-binding proteins (IGFBP). Only 1% of IGF-I circulates in its free form, and 99% of IGF-I is bound to IGFBPs, of which IGFBP-3 is the most common type. Free IGF-I - the more potent form of IGF-I - has rarely been studied on the association with cancer risk, but total IGF-I, and also IGFBP-3, is strongly related to free IGF-I. Elevated IGF-I has been related to a significant increased risk of colorectal cancer, and IGFBP-3 has overall not been related to risk.

Compared to other cancers of the gastrointestinal tract, the association between tobacco smoking and risk of colorectal cancer has been modest. However, a recent meta-analysis showed that current and ex-smokers had a significant 15-20% higher risk of colorectal cancer than never smokers and the risk increased with duration and dose of smoking.

Lifestyle factors and its outcome is largely involved in the aetiology of colorectal cancer, as was described previously for overall cancer, and as will be further described in section “Obesity, diabetes, metabolic factors, and cancer risk”.
1.2.3 Prostate cancer

The large variation in prostate cancer incidence worldwide may for some regions be explained by differences in diagnostic practice and life expectancy, but these factors are unlikely to explain e.g. the large differences of approximately ten times higher rates of prostate cancer in the United States than in Asia, including more developed Asian countries. Emigration and twin studies have shown that environmental as well as genetic factors play important roles in prostate cancer. One of the most important factors seems to be ethnical belonging. African-American men have an approximately 25-fold higher incidence rate than populations in Asia, and a 1.5-fold higher rate than Americans of white ethnicity. Furthermore, a family history of prostate cancer increases risk up to 2.2-fold in men with a first-degree relative with prostate cancer, and in twin studies, the heritability has been estimated to 42%. These studies indicate that genetic factors are important in prostate cancer aetiology, but whilst many risk modifying genetic variants have been identified recently, they can only explain a small part of the heritability of the disease. Age at diagnosis is high; the cumulative risk of prostate cancer in the Nordic countries is only around 2% at the age of 55 years, but increases up to 17% at 75 years of age (Figure 5). Except for age, ethnicity, and familial aggregation, relatively little is known about the aetiology of prostate cancer.

IGF-I has been more consistently related to risk of prostate cancer than of colorectal cancer. A recent meta-analysis, including data from 12 studies, showed that men with top quintile levels of IGF-I had a significant 1.4-fold increased risk of prostate cancer compared to men in the lowest quintile. A positive association with risk was also found for IGFBP-3, but this association was explained by its correlation with IGF-I levels. Genetic association studies have given further support for the causal role of IGF-I along the lines of Mendelian randomisation, by identifying genetic variants in the IGF-I gene associated with both elevated levels of IGF-I, and with an increased risk of prostate cancer.

Androgens are important for normal function of the prostate, and animal studies have further shown that androgens stimulate prostate tumour growth. Moreover, a large randomised clinical trial showed that treatment with finasteride, a drug that reduces intraprostatic levels of dihydrotestosterone, the most active form of testosterone, was related to a decreased risk of prostate cancer. Suppression of androgens in locally advanced prostate cancer and in metastatic disease reduces progression of the disease initially, but at a later stage, progression continues independent of androgens. In contrast to data from animal and clinical studies, observational studies on blood concentrations of androgens and prostate cancer risk do not support a role for androgens in prostate cancer; a recent meta-analysis showed no significant association. The
lack of association in observational studies has been speculated to be due to that circulating concentrations of androgens may not reflect androgen activity in the prostate. Chronic inflammation may have a role in prostate cancer. Factors related to inflammatory states, such as sexually transmitted diseases and proinflammatory cytokines have been related to an increased risk. A potential link between chronic inflammation and prostate cancer is that reactive oxygen species in inflammation cause DNA damage. Long-term use of NSAIDs has been shown to reduce the risk of prostate cancer.

1.3 Obesity, diabetes, metabolic factors, and cancer risk

A large number of studies on body weight, diabetes and cancer risk, have shown that obesity and diabetes increase the risk of cancer overall, and of several cancer sites, including cancer of the colorectum. Obesity has been differently related to risk of prostate cancer according to disease aggressiveness, and diabetes has been related to a decreased risk of prostate cancer. Few studies exist on metabolic factors and cancer risk, and studies have been relatively small.

1.3.1 Relationship between metabolic factors

Obesity is a key factor underlying other metabolic disturbances, and is caused by genetic susceptibility to weight gain in combination with overeating, i.e. too little physical activity in proportion to energy intake. Amongst other effects of adipose tissue, it releases free fatty acids and proinflammatory cytokines, such as tumour necrosis factor-α, and interleukin-6. These cytokines promote development of insulin resistance, defined as a condition when the blood glucose lowering response to insulin is insufficient. Adipose tissue also secretes leptin – associated with obesity and insulin resistance, and adiponectin, which is negatively related to obesity and has insulin sensitising effects. Abdominal fat mass, often assessed by waist or waist-to-hip ratio, has been related to a higher risk of diabetes and of cardiovascular and overall mortality than has general obesity, assessed by body mass index (BMI, kg/ m²). This might be explained by that abdominal fat is more metabolically active and less sensitive to insulin than is subcutaneous fat, and BMI neither
distinguishes between localisation of fat mass, nor between fat mass and muscle mass.

At insulin resistant states when glucose levels tend to rise, insulin secretion by pancreatic β-cells increase to maintain normal glucose levels\textsuperscript{55}. After many years of increasing circulating levels of glucose and insulin, insulin resistance may proceed into type 2 diabetes\textsuperscript{55}, for which the diagnostic criteria by the World Health Organization (WHO) is fasting plasma glucose of 7.0 mmol/l or higher, or post-load plasma glucose of 11.1 mmol/l or higher\textsuperscript{59}. Risk of type 2 diabetes increases with excess weight\textsuperscript{60}, and between 60-90% of diabetics are obese\textsuperscript{61,62}; however, genetic susceptibility for diabetes and failure of pancreatic β-cells, is required for progression into diabetes\textsuperscript{55}. After β-cell failure, insulin levels decline, and glucose levels increase. Insulin is a key hormone not only for glucose control, but also for regulation of fat metabolism, and thus, insulin resistance also includes disturbed fat metabolism, including increased free fatty acids in the circulation and an increase of triglycerides in the liver and in circulation\textsuperscript{63-65}.

The metabolic syndrome (MetS) is a constellation of factors that tend to cluster and increase the risk of type 2 diabetes and cardiovascular disease\textsuperscript{66}. Several definitions are currently in use; the most frequently used definitions are those by the WHO and the National Cholesterol Education Program/Adult Treatment Panel III, which include obesity, insulin resistance or hyperglycaemia, hypertension, and dyslipidaemia in their definitions\textsuperscript{66}. Studies in this thesis have included the definition of the MetS and categories of factors, as defined by the WHO\textsuperscript{59,67-69} (Table 1). Despite the original idea of the MetS to describe a constellation of factors that often occur jointly in an individual\textsuperscript{70}, factors are only moderately associated with each other. For instance, although obesity is one of the main causes of insulin resistance, only around 50% of obese persons are insulin resistant\textsuperscript{63}. The relation between factors in the MetS have commonly been investigated by the use of factor analysis, which aim at grouping factors together that seem to cluster\textsuperscript{71}. A number of studies have been performed on the topic, and in most studies, more than one group of factors were identified\textsuperscript{71}. An example is a study of the Framingham Offspring Study, in which three groups of metabolic factors were identified (Figure 6). The central factor was identified as central or general obesity, insulin, and lipids. A second factor was blood pressure and BMI, and a third consisted of glucose and insulin\textsuperscript{72}. The picture of several clusters of factors in the MetS, and not one entity, indicates that not only one underlying physiological feature causes the MetS as a whole\textsuperscript{71,73}. The MetS is widely debated regarding the additional value of a syndrome to the individual factors included, and regarding how the MetS should be defined\textsuperscript{71,73}. 
Table 1. Categories for glucose, blood pressure and BMI, and definition of the metabolic syndrome, by the World Health Organization\textsuperscript{59,67-69}

<table>
<thead>
<tr>
<th>Factor</th>
<th>Categories</th>
<th>Metabolic syndrome</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose, mmol/l</td>
<td>Normal: plasma&lt;6.1, blood&lt;5.6</td>
<td>Glucose level of IFG, IGT or higher, or insulin resistance defined as glucose uptake in the lowest quartile under hyperinsulinaemic euglycaemic conditions +2 of the following:</td>
<td>Plasma is standard measurement. Whole blood was used in the MPP cohort (paper V and VI)</td>
</tr>
<tr>
<td></td>
<td>IFG: plasma 6.1-6.9, blood 5.6-6.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DM: plasma≥7.0, blood≥6.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-load glucose, mmol/l</td>
<td>Normal: venous plasma&lt;7.8, capillary plasma&lt;8.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IGT: venous plasma 7.8-11.0, capillary plasma 8.9-12.1</td>
<td></td>
<td>Venous plasma is standard measurement. Capillary plasma was used in the VIP cohort (paper I and II)</td>
</tr>
<tr>
<td></td>
<td>DM: venous plasma≥11.1, capillary plasma≥12.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td>Normal: &lt;140/90, Hispanic hypertension grade I: 140/90, &lt;160/100</td>
<td>≥140/90</td>
<td>Grade II and III were combined in studies (paper II and III)</td>
</tr>
<tr>
<td></td>
<td>Grade II: ≥160/100, &lt;180/110, Grade III: ≥180/110</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>Underweight: &lt;18.5, Normal: 18.5-24.9, Overweight: Preobese: 25-29.9</td>
<td>&gt;30 or waist-to-hip ratio &gt;0.9 in men and &gt;0.85 in women</td>
<td>Underweight was added to normal weight category, and obese categories were combined in studies (paper II and III)</td>
</tr>
<tr>
<td></td>
<td>Obese class I: 30-34.9, Obese class II: 35-39.9, Obese class III: ≥40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipids, mmol/l</td>
<td>Triglycerides ≥1.7 or HDL-cholesterol &lt;0.9 in men and &lt;1.0 women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>Urinary albumin≥20 µg/min or albumin/creatinin ratio≥30 mg/g</td>
<td></td>
<td>Rarely used in studies</td>
</tr>
</tbody>
</table>

BMI, body mass index; IFG, impaired fasting glucose; DM, diabetes mellitus; IGT, impaired glucose tolerance; MPP, Malmö Preventive Project; VIP, Västerbotten Intervention Project.
1.3.2 Cancer overall

Excess body weight has in observational studies commonly been measured by BMI and has in women been related to an increased risk of overall incident cancer\textsuperscript{57,75-79}. The association in men has generally been weak at BMI levels lower than obesity (>30 kg/m\textsuperscript{2})\textsuperscript{57,76-80}. High BMI has been related to no risk or a decreased risk of cancer of the prostate and lung, which has largely driven the weak association between BMI and overall cancer among men in European populations\textsuperscript{57,76,77}, where these cancers dominate among men, and also in Asian populations\textsuperscript{79,80}, where lung cancer is a common cancer form among men. Increased BMI has been related to an increased risk of a number of specific cancer sites. In a recent meta-analysis, the strongest associations were found for oesophagus (adenocarcinoma) and renal cell cancer in both men and women, and for colorectal and thyroid cancer in men, and for cancer of the endometrium and gallbladder in women\textsuperscript{81}. A comparison for the most common cancers showed that results between geographical regions were largely coherent.

The by far largest study on BMI and risk of death from cancer, conducted in the United States, showed that, compared to those with normal weight (BMI 18.5-24.9 kg/m\textsuperscript{2}), men and women with obesity in the range 30-34.9 kg/m\textsuperscript{2} had a significantly increased risk of cancer by 23% and 9%, respectively\textsuperscript{82}. BMI was strongly positively associated with risk of a number of cancers, such as cancer of the colorectum, kidney and pancreas in men and women, for liver cancer in men, and for cancer of the endometrium and cervix uteri.

Type 2 diabetes, identified by medical records, self-report, or as measured diabetic glucose levels, has been related to a small increased risk of overall...
incident or fatal cancer in men and women\textsuperscript{83,84}. The association has been stronger for a number of specific sites, such as cancer of the colorectum, kidney, pancreas, liver and bladder in both sexes, and in women, also for cancer of the endometrium and breast\textsuperscript{83-94}. These data, mainly from populations in Europe and the United States, but also from Asia, including a very large study of more than one million men and women in Korea\textsuperscript{92}, have been fairly consistent between populations of white ethnicity and Asian populations. The Korean study included data on fasting glucose, and showed that not only diabetes was related to an increased risk of incident and fatal cancer overall and at many separate sites, but that glucose was linearly associated with risk of several specific cancers among men and women, also at levels of impaired fasting glucose or lower\textsuperscript{92}. Studies on glucose and cancer risk in Western populations have suggested an increased risk of incident cancer overall, but have been too small in size to fully explore the strength of association for separate cancers, other than the most common cancers\textsuperscript{95,96}.

1.3.3 Colorectal cancer

BMI has generally been more strongly related to colorectal cancer risk in men than in women, and associations have been stronger for colon than for rectal cancer\textsuperscript{81,82,97,98}. A 5 kg/m\textsuperscript{2} increment in BMI ranges between a relative risk of 1.24 for colon cancer in men and a relative risk of 1.02 for rectal cancer in women. For diabetes, the association with colorectal cancer has shown similar results in men as compared to women, and for colon versus rectal cancer\textsuperscript{86}. In a summary estimate from a meta-analysis performed in 2005, diabetics compared to non-diabetics had a 30% increased risk of incident colorectal cancer\textsuperscript{86}. The Korean study of blood glucose and cancer risk reported a modest but significant positive association between increasing glucose and risk of fatal colorectal cancer in men, whereas no association was observed in women, or for incident colorectal cancer. Other much smaller studies on fasting or post-prandial glucose or of glycated haemoglobin (HbA1c) – a measure of average glucose level during the past two months\textsuperscript{99} – have generally shown no significant association with incident or fatal colorectal cancer\textsuperscript{95,96,100-106}.

The positive relation between obesity and diabetes and colorectal cancer has been followed up by analytical studies on hormonal factors related to insulin resistance, such as insulin or C-peptide (a marker of insulin secretion), leptin, and adiponectin. Data from prospective studies suggest that elevated insulin is related to an increased risk of colorectal cancer\textsuperscript{101,102,105,107-112}; however, in most studies the association was non-significant\textsuperscript{101,105,108,110,112}, and in one study, no association was found\textsuperscript{106}. Studies on leptin and adiponectin are few and small and have provided inconsistent results\textsuperscript{110,113-116}. The largest study on
leptin and colorectal cancer risk \((n \text{ cases}=378)\) showed a significant positive association for colon cancer in men\(^{110}\), and the largest study on adiponectin and risk \((n \text{ cases}=381)\) showed no association\(^{116}\). There are some indications of that high blood pressure is related to an increased risk of colorectal cancer, but no conclusions can yet be drawn on the basis from previous studies\(^{117-123}\).

The MetS has been related to an increased risk of colorectal cancer\(^{109,117,120,121,123,124}\). Various MetS factors have been included in studies and the cut-off for presence versus no presence of factors has also varied e.g. by using standard cut-off points or top quantile levels among subjects, or defining hyperglycaemia or hypertension based on self-reports of existing diabetes or hypertension, or by reported medical treatment for these conditions. Nevertheless, presence of three or more factors has generally been related to an increased risk of colorectal cancer, but as definitions and cut-off points have been divergent, results are difficult to compare between studies and it is difficult to compare the strength of association between factors.

1.3.4 Prostate cancer

A possible link between a Western lifestyle, including overweight and insulin resistance, as a cause for the high incidence rates of prostate cancer in Western countries, has found no support in prospective epidemiological studies. There is consistent evidence that overweight is not related to risk of incident prostate cancer\(^{81}\), and diabetes has been associated with a significant 15-30% decreased risk of incident or fatal prostate cancer\(^{125-128}\), and moreover, plasma glucose has not been related to prostate cancer risk\(^{92,95,96}\).

Interestingly, a meta-analysis of studies that had been published up to October 2004, suggested a diverse association between BMI and risk of incident prostate cancer according to tumour characteristics at diagnosis\(^{129}\). Whilst there was no significant association between BMI and non-aggressive tumours, a 5 kg/m\(^2\) increment of BMI was related to a significant 12% increased risk of aggressive prostate cancer. A number of large studies published during the last few years, have provided further support to previous findings, and have also suggested that overweight or obesity may even decrease the risk of non-aggressive tumours\(^{130-135}\). In contrast, large cohort studies from Sweden and the United States that used prostate cancer death as endpoint have consistently shown an increased risk in overweight and obese men\(^{82,136,137}\).

In comparison to existing data on BMI, diabetes, and blood glucose, the influence of other metabolic factors on prostate cancer risk has rarely been studied. Studies on insulin/ C-peptide or leptin \((n \text{ cases}<400 \text{ in all studies})\) have shown inconsistent results\(^{138-145}\), and in only two studies, associations were stratified into tumour subgroups\(^{141,144}\). Previous studies on blood pressure and
prostate cancer risk showed no significant association with risk, and none included information of tumour characteristics.  

1.3.5 Methodological aspects of studying metabolic factors

The simple reason to that many studies have been performed on BMI and diabetes is that the information is often easily accessible. But is BMI accurate enough to assess obesity as a metabolic risk factor as it is only a marker of general adiposity, and not of abdominal adiposity? Some studies on colon or colorectal cancer have included measures of waist-to-hip ratio or waist, and in the two largest studies to date, the positive association with risk in women was found to be stronger for abdominal obesity than for BMI, whereas both BMI and abdominal measures were positively associated with risk in men. This may reflect that high BMI is more strongly related to abdominal obesity in men than in women. However, the strength of BMI as a marker in large-scale observational studies is that measurement error is very low, because error in height and weight measures is low, and because BMI in individuals changes relatively little over time. As the key question in observational studies commonly is whether the “usual” level of an exposure, rather than the level at a specific time-point, is related to risk, the use of a marker with low measurement error and thus high regression dilution ratio (RDR) between repeated measurements is an advantage. In contrast to BMI, metabolic factors such as blood pressure, glucose, insulin and triglycerides have low RDR. Thus, a single measurement of these factors will cause an imprecise estimate of the usual level and this causes an attenuation of the association with outcome. If several measurements are available, these can be used to assess a more precise exposure level, and if repeated measurement is available for at least a subset of subjects, random error can be calculated and be used to calculate more correct associations with outcome. HbA1c is naturally a better measure of usual glucose level than glucose, as it reflects average glucose concentration, and leptin has been shown to have a relatively high RDR of 0.79 for measurements performed four years apart, which is higher than what has been reported for other exposure factors in studies in this thesis, except for BMI.

1.3.6 In summary, what is known and what is missing?

Cancer is a large health problem, in particular in developed countries, and the economical costs and individual suffering from cancer are large. The prevalence of obesity and type 2 diabetes are increasing worldwide; approximately 9.8% of adults in the world were obese in 2005, and the number
has been predicted to increase up to 20% in 2030\textsuperscript{156}, and for diabetes, a prevalence of 5.9% worldwide in 2007 is predicted to increase to 7.1% in 2025\textsuperscript{157}. In addition to that obesity and diabetes increase the risk of cardiovascular disease\textsuperscript{57,58,158,159}, obesity and diabetes have also been related to an increased risk of many types of cancer\textsuperscript{81,83,84}. An increasing westernisation of lifestyle, including an increased use of tobacco, and overeating together with less physical activity leading to an increasing prevalence of obesity worldwide, is predicted to cause an increased burden of cancer\textsuperscript{1}. We already know that a large proportion of cancer could be prevented by promoting a healthy lifestyle, such as keeping normal weight, being physical active, eating adequate portions and little energy-dense foods, and not to smoke, so what more is there to know?

Although the public health message is unlikely to change much through further epidemiological studies on metabolic factors and cancer risk, there is much more to learn about the aetiology of cancer. The association between obesity, diabetes, and cancer in total and for the most common cancer forms, is becoming clearer, but less is known about rarer cancers. Furthermore, new data from the past few years on obesity and prostate cancer risk have pointed out the importance of distinguishing low-risk prostate cancers from more aggressive forms or prostate cancer death when assessing the association with obesity\textsuperscript{129}, and thus such differentiation is also of interest for other metabolic factors. The grouping of prostate cancers is of particular interest because of this cancer's heterogeneity, ranging from patients living a good life for many years after diagnosis and without any treatment, to patients with fast growing prostate tumours leading to early cancer death\textsuperscript{47}. Even though prostate cancer is the most common cancer form among men in developed countries in terms of incidence and prevalence\textsuperscript{1,3} and one may expect that many questions have been sorted out, little is known about the influence of metabolic factors other than obesity. In comparison to prostate cancer, the relation between obesity, diabetes, and metabolic factors with colorectal cancer is much more straightforward; the positive associations in studies has been very consistent\textsuperscript{81,86,117}. Still, due to a small number of cases in published studies and inconsistencies between studies, there is not enough data to determine an association between the MetS and included factors, and colorectal cancer. The strength and pattern of association between factors other than obesity and diabetes is unclear, and it is unknown whether some factors interact on the association with colorectal cancer or if instead, the risk increase for each factor is additive. Furthermore, it is also unclear if associations differ between men and women, and for incident versus fatal colorectal cancer.
2 AIMS

The aim of this thesis was to study metabolic factors in relation to cancer risk.

Specific aims were to investigate the association between:

- factors related to insulin resistance and prostate cancer risk (paper I).
- BMI and blood pressure, and prostate cancer risk (paper III).
- metabolic factors and prostate cancer risk according to disease aggressiveness:
  - in subgroups according to tumour characteristics at diagnosis (paper I and III)
  - for incident and fatal outcome (paper III).
- metabolic factors, in single and combined, and colorectal cancer risk (paper II and V).
- metabolic factors and colorectal cancer risk in men and women separately, and for incident and fatal outcome (paper V).
- blood glucose and risk of incident and fatal cancer, overall and at specific cancer sites (paper VI).
3 MATERIAL AND METHODS

3.1 Cohorts

3.1.1 The Northern Sweden Health and Disease Cohort

The Northern Sweden Health and Disease Cohort consists of three subcohorts: The Västerbotten Intervention Project (VIP), the Northern Sweden WHO Monitoring of Trends of Cardiovascular disease study (MONICA), and the Mammography Screening Project (MSP). Participants in these projects undergo a health examination and are asked to leave a blood sample for research purposes. In participants who give their approval, the blood sample is fractioned into plasma, buffy coat and erythrocyte samples, which are stored in -80°C for future research. Data from the cohorts are stored at the Medical Biobank, Umeå, Sweden, and as of December 31, 2008, data had been collected for a total of 106,740 unique individuals, of which a blood sample had been stored for 97,914 individuals. Data from the VIP and the MSP have been used for studies in this thesis.

3.1.1.1 The Västerbotten Intervention Project

The VIP has been ongoing since 1985. The start was a pilot project in Norsjö municipality that aimed at improving the health in the population. Amongst other activities, health examinations were implemented, which were later on implemented in primary health care and these examinations covered the entire Västerbotten county in 1991. Residents of Västerbotten are invited to a health examination at the age of 40, 50, and 60 years, and before 1996, residents were also invited at the age of 30. During the first years, participants were asked to fast for a minimum of four hours before the examination, which was changed into an eight hours’ fast in 1992. Height and weight are measured without shoes and with light indoor clothing. Blood pressure is measured with a mercury sphygmanometer after five minutes rest in supine position. A blood sample is drawn, and plasma levels of glucose, total cholesterol and triglycerides is measured; however triglycerides was not measured consequently in all participants at all health care centres throughout the years. Before 2001, data on triglycerides is available from approximately 80% of health examinations, and thereafter, the coverage is virtually complete. An oral glucose tolerance test (OGTT) is performed in participants without known diabetes mellitus and with a fasting glucose level below 7.0 mmol/l. Participants are asked to fill in a
questionnaire in connection with the health examination, which includes questions on e.g. physical activity, food habits, tobacco use and medication.

3.1.1.2 The Mammo graphy Screening Project
Since 1995, all women between 50 and 70 years of age in Västerbotten county are invited every 2-3 years to undergo breast cancer screening\textsuperscript{163}. Participants are not asked to fast before the examination, but in participants who leave a blood sample, fasting time before the blood draw is recorded. Participants fill in a questionnaire that covers questions on e.g. height, weight, menstruation, reproductive history and medical use. Height and weight has been measured in the MSP since September 1998.

3.1.2 The Swedish Construction Workers cohort
Between 1969 and 1993, the Construction Industry’s Organisation for Working Environment, Safety and Health offered medical services to all employed construction workers in Sweden\textsuperscript{164}. The employees were invited to a health examination every 2-3 years, and data from the examinations were stored from 1971. The examination included measurement of height, weight and blood pressure, which was measured with a mercury manometer after five minutes rest in supine position. Participants answered a questionnaire that included health-related questions such as work environment and tobacco use. The attendance rate has been estimated to 70-80\%. Data from health examinations is available for 361,280 construction workers.

3.1.3 The Metabolic syndrome and Cancer project
The Metabolic syndrome and Cancer project (Me-Can) was initiated in 2006; details about the project are described in paper IV. The aim of the project was to pool data from several cohorts in order to have large statistical power to study the association between factors in the MetS and cancer risk. The large data set facilitated the possibility to study a large number of cancers, including rare cancers, and to, in addition to risk of incident cancer, study the association with cancer death. The seven cohorts included in Me-Can are: from Norway, the Oslo study I (Oslo), the Norwegian Counties Study (NCS), the Cohort of Norway (CONOR), and the Age 40 programme (40-y); from Austria, the Vorarlberg Health Monitoring and Prevention Programme (VHM&PP); and from Sweden, the VIP, and the Malmö Preventive Project (MPP) (Figure 7).
Figure 7. Map with location of subcohorts included in Me-Can. The 40-year cohort includes all counties in Norway (all grey and black marked areas in Norway), the Norwegian Counties Study (NCS) includes areas ■ and △, the Cohort of Norway (CONOR) includes areas ■ and △, and further cohorts (marked in black) are; the Oslo study I (Oslo I), the Vorarlberg Health Monitoring and Prevention Programme (VHM&PP), the Västerbotten Intervention Project (VIP) and the Malmö Preventive Project (MPP). Figure reproduced from Stocks et al., paper IV165.
Table 2. Description of Me-Can cohorts

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Purpose</th>
<th>Participants</th>
<th>Year</th>
<th>Att. rate</th>
<th>N subj/obs in raw files</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oslo</td>
<td>To study risk factors of CVD and to prevent CVD</td>
<td>Men in Oslo, Norway, aged 40-49 years and a subset of men aged 20-39 years</td>
<td>1972-1973</td>
<td>60%</td>
<td>17,973/17,973</td>
</tr>
<tr>
<td>NCS</td>
<td>To prevent CVD</td>
<td>Men and women in the counties Finnmark, Sogn og Fjordane, and Oppland, aged 35-49 years, and in 1974-1978, a subset of inhabitants aged 20-34 years</td>
<td>1974-1978</td>
<td>78-90%</td>
<td>91,847/188,536</td>
</tr>
<tr>
<td>CONOR</td>
<td>To collect data for research on the aetiology of various diseases</td>
<td>Men and women in different regions all over Norway within different age-groups</td>
<td>1994-2003</td>
<td>Average 56%, range 30-76% in surveys</td>
<td>169,355/176,464³</td>
</tr>
<tr>
<td>40-y</td>
<td>To study risk factors of CVD and to prevent CVD</td>
<td>Men and women aged 40-42 years, in all Norwegian counties</td>
<td>1985-1999</td>
<td>69%</td>
<td>415,045/426,768³</td>
</tr>
<tr>
<td>VHM&amp;PP</td>
<td>To prevent chronic diseases, particularly CVD and cancer</td>
<td>Men and women, 19 years of age or older in the Vorarlberg province</td>
<td>1985-2005</td>
<td>66%</td>
<td>175,618/638,906</td>
</tr>
<tr>
<td>VIP</td>
<td>To prevent diabetes and CVD</td>
<td>Men and women aged 30 (before 1996), 40, 50, and 60 years in the Västerbotten county</td>
<td>1985-ongoing</td>
<td>60%</td>
<td>85,692/112,300</td>
</tr>
</tbody>
</table>

Me-Can, Metabolic syndrome and Cancer project; Att. rate, attendance rate; subj, subjects; obs, observations; Oslo, Oslo study I; CVD, cardiovascular disease; NCS, Norwegian Counties Study; CONOR, Cohort of Norway; 40-y, Age 40 programme; VHM&PP, Vorarlberg Health Monitoring and Prevention Programme; VIP, Västerbotten Intervention Project; MPP, Malmö Preventive Project.

³There was an overlap of subjects between Norwegian cohorts; the total number of subjects was 645,406 and the total number of observations was 809,637.
The coordinating centre of the project is at the Department of Surgical and Perioperative sciences, Urology and Andrology, Umeå University, Sweden.

All cohorts are population-based and include data from health examinations, to which people of a predefined sex and age were invited during a period of years, summarised in Table 2.

Data on height, weight, blood pressure, and blood/plasma/serum levels of glucose, total cholesterol and triglycerides are available in all cohorts. Height and weight were measured in a similar fashion in all cohorts; without shoes and with light indoor clothing. Blood pressure was measured with a mercury sphygmomanometer in all cohorts except for in the CONOR and the 40-y cohort, where an automatic device was used. Resting time before the measurement varied between 2-10 minutes between the cohorts, and measurements were performed in a sitting position in all cohorts, except for in the VIP and the MPP where a supine position was standard procedure. Participants in the Norwegian cohorts were not required to be fasting at the examination, whereas participants in the MPP were asked to fast overnight before the examination, which was also implemented in 1988 in the VHM&PP. Before that year in the VHM&PP, an OGTT was performed instead of measuring fasting glucose. Glucose was measured in serum in the Norwegian cohorts, in plasma in the VHM&PP and the VIP, and in whole blood in the MPP. Cholesterol and triglycerides were measured in serum in all cohorts. Determination of glucose and lipid levels were performed by enzymatic methods in all cohorts, except for in the Oslo cohort and in the NCS (before 1980), where enzymatic methods were used. In the Norwegian cohorts, glucose levels measured with the non-enzymatic method yielded 0.8-1.1 mmol/l higher levels compared to levels measured with the enzymatic method.

In all cohorts, except for in the VHM&PP, participants were asked to fill in a questionnaire that covered questions on lifestyle issues, and also questions of particular interest for the study, e.g. questions on history or symptoms of specific diseases, such as diabetes or cardiovascular disease, and questions on medications. In the VHM&PP, the examining physician asked about lifestyle and other issues, and answers were recorded.

3.2 Study design and selection of subjects

3.2.1 Paper I and II

In February, 2004, the VIP was linked to the regional cancer register (paper I), and in September, 2004, the VIP and the MSP were linked to the regional
cancer register (paper II), which covers around 99% of prostate cancers and colorectal cancers in the region. Incident cases with a blood sample available, and without any cancer diagnosis (except non-melanoma skin cancer) before the health examination or before the diagnosis of prostate and colorectal cancer, respectively, were included, resulting in a total of 392 prostate cancer cases (paper I) and 306 colorectal cancer cases (paper II). For each prostate cancer case, one control was randomly selected among participants in the VIP, and for each colorectal cancer case, two controls were randomly selected among participants in the VIP and the MSP. Of participants who were alive and who had no cancer diagnosis (except non-melanoma skin cancer) at the date of cancer diagnosis of the index case, matching was performed for cohort, sex, date (±2 months) and age (±6 months) at the health examination, and in paper II, due to inclusion of the MSP, also for fasting time before the examination. In paper II, if no control fulfilled the matching criteria, the criteria were broadened into ±3 months for date and ±1 year for age. For 17 cases, only one control fulfilled the matching or broadened criteria.

For subjects included in paper I and II, a fraction of the stored plasma samples was thawed for measurement of C-peptide, leptin, and in paper II, of adiponectin concentration. HbA1c was measured in erythrocyte fractions. Cases were analysed in the same batch as the matched control and laboratory staff were blinded to case-control status. In paper I, all intrabatch coefficients of variation (CV) were below 7% and all interbatch CVs were below 8%, and in paper II, intrabatch CVs were below 12% and interbatch CVs were below 13%.

In paper I, record linkages were performed by use of the National registration number, a unique number for each resident in Sweden. Prostate cancer cases were linked to the Northern part of the National Prostate Cancer Register, and to the National Cause of Death Register, and these data, together with data from medical records, were used to classify cases into having a non-aggressive or aggressive tumour at diagnosis. The tumour was classified as aggressive if the case had a non-localised tumour (T3-4), or a high grade tumour, defined as Gleason score 8-10 or WHO grade 3, or had lymph node metastasis (N1), or bone metastasis (M1), or had a serum PSA level higher than 50 ng/ml, or if the case had died of prostate cancer up to October 2005. If none of these criteria were fulfilled, the tumour was classified as non-aggressive.

3.2.2 Paper III
Through linkages of the Swedish Construction Workers cohort to the National Population Register, the National Cancer Register, and the National Cause of Death Register, information for each subject was obtained for migration, cancer diagnoses and vital status up to December 31, 2004, and for cause of death up
to December, 2003. Of 361,280 subjects in the cohort, we excluded: 17,458 women, 388 subjects with an incorrect National registration number, 30 subjects that had been registered as dead and 2,765 subjects that had emigrated before the date of baseline examination. Further, 1,232 subjects were excluded that had a cancer diagnosis before the baseline examination, as were 3,248 subjects with missing data for height, weight, or blood pressure. A total of 336,159 subjects were included in the study.

The study population was also linked to the National Prostate Cancer Register, which started in 1996. For 97% of cases diagnosed in the year 1996 and later, data on tumour characteristics was sufficient to categorise tumours as non-aggressive or aggressive. The definition of aggressive tumours was identical to the definition used in paper I, except for that fatal disease was not included in the criteria.

3.2.3 Paper V and VI

Cohorts in Me-Can were linked to respective National registers; the Cancer Register, the Cause of Death Register, and in Sweden and Norway, to the Population Register. The last year of data coverage was for cancer diagnoses/migration/vital status/cause of death: in Norway, 2005/2005/2005/2004; in Austria, 2003/ no information/2003/2003; and in Sweden, 2006/2006/2006/2004. As the Eurostat European shortlist for cause of death had been used for categorisation of death cause in the Norwegian cohorts, the same categorisation for cause of death was used in the other cohorts. These groups, and a more detailed categorisation for incident cancers, were used in paper VI.

Data cleaning and exclusions from the original 940,060 subjects with data from 1,600,296 health examinations were similar, but not identical, in paper V and VI (Figure 8). In order to reduce the possibility of reverse causation, it had been decided that prevalent cancers should not be included in Me-Can studies of cancer risk, and follow-up of subjects should always start one year after the baseline examination. Thus, for the first part of exclusions that were identical in paper V and VI, we excluded examinations (observations) at which a subject had a previous cancer diagnosis, or at which the follow-up time until end of follow-up for incident cancer was less than one year. Another exclusion criteria was extreme values for exposure factors, which were set to: height <100 or >250 cm, weight <35 or >250 kg, BMI <15 or >60 kg/m², systolic blood pressure <75 mm Hg, diastolic blood pressure <40 mm Hg, systolic blood pressure <diastolic blood pressure, glucose <1 mmol/l, cholesterol <0.5 or >20 mmol/l, and triglycerides <0.05 or >35 mmol/l. Data on BMI had been decided to be required for inclusion in Me-Can studies as it was considered as
Figure 8. Description of data cleaning and selection of subjects/observations in paper V and VI. OGTT, oral glucose tolerance test; ← exclusions; → selected baseline observation.
the main possible confounder to the other key exposures, and thus, observations with data missing for height and weight were excluded. After the main exclusions, subjects with a total of 1,440,411 observations were eligible in paper V, and after further exclusions of observations with data missing for glucose, 1,025,940 observations were eligible in paper VI. For each study, the first observation for a subject was selected, and if data from a fasting state and for smoking status was available, the first of these observations was selected. Restrictions from the Norwegian Institute of Public Health were that the proportion of Norwegian subjects in Me-Can studies should not exceed approximately 50% of all subjects. Therefore, we further excluded: in paper V, subjects from Norway with data missing for any of the exposure factors or for smoking status, and in paper VI, subjects from Norway with data missing for smoking status, and also the full NCS cohort. The total number of subjects was 578,700 in paper V and 549,944 in paper VI.

### 3.3 Statistical analyses

P-values lower than 0.05 were considered statistically significant, except for the evaluation of proportionality of hazards (paper III, V and VI), for which a more approximate approach was used, based on statistical testing, subgroup analyses, and graphs. Odds ratios (OR) and relative risks (RR) were considered statistically significant if the 95% confidence interval (CI) did not include unity.

#### 3.3.1 Paper I and II

In paper I, the association with prostate cancer risk was calculated for C-peptide, leptin, HbA1c, fasting glucose, and post-load glucose and also for an insulin resistance index - homeostatic model assessment of insulin resistance (HOMA-IR) - calculated from levels of fasting glucose and C-peptide. These exposures, except for HOMA-IR, were also included in paper II, which further included leptin/adiponectin ratio, BMI and blood pressure.

The association between exposure factors and cancer in paper I and II was assessed for quartiles, or for tertiles in subgroup analyses, and in paper I, associations were also assessed for per one unit increase of exposures. Quantile cut-off levels were calculated by the distribution among controls, and in paper II, due to differences in levels between groups, cut-offs for C-peptide were also calculated separately in groups according to fasting time before the blood draw, and cut-offs for leptin and adiponectin were calculated separately among men.
and women. In paper II, associations were also assessed for WHO categories of BMI, blood pressure and plasma glucose, in three categories, and as binary MetS factors, and further for the number of MetS factors present. Cut-off level for obesity and hyperglycaemia was approximately at the 90th percentile among controls, and for comparison, the association with colorectal cancer risk for C-peptide, HbA1c, leptin, adiponectin, and the leptin/adiponectin ratio, was assessed for decile ten versus deciles 1-9.

Conditional regression analysis was used to calculate OR of disease. Due to the matched case-control design, models were automatically adjusted for matching criteria, and analyses were performed with and without additional adjustment for leptin in paper I, and for BMI in paper II. Linearity of associations in quantiles or categories was assessed by likelihood ratio tests, assigning subjects the mean exposure level in the category (paper I), or assigning subjects the score level of the category, i.e. 1, 2, 3 etc. (paper II). Heterogeneity between ORs in subgroups was tested with \( \chi^2 \) statistics.

### 3.3.2 Paper III, V and VI

Cox proportional hazards regression was used to calculate RRs of cancer for exposure factors. In these analyses, subjects contributed person-years from the date of baseline examination in paper III, and from one year after baseline in paper V and VI, until the date of cancer diagnosis, or until the date of censoring by another cancer diagnosis, death or emigration, or until end of follow-up, whichever occurred first. In analyses with fatal cancer as endpoint, date of cancer diagnosis as endpoint was replaced with date of cancer death, and censoring by another cancer was performed for cancer death and not for cancer diagnosis. In paper III, non-censored subjects that had no previous cancer diagnosis by January 1, 1996, were included in analyses of non-aggressive and aggressive incident prostate cancer. As the incidence and mortality of cancer is highly age-dependent, attained age was used as time variable in Cox analyses in paper III, V and VI. The trend for associations in quantiles or categories were assessed by the Wald test, assigning subjects the median exposure level in the category in paper III, and assigning subjects the mean exposure level in the category in paper V and VI. Cox proportional hazards assumption was tested by the use of Schoenfeld’s residuals, and if there was an indication of violation of the proportionality, further analyses (graphs, stratification, subgroup analyses, and time-dependent analyses) were performed. Violations of the proportionality were handled as described in the papers.
3.3.2.1 Paper III

In paper III, the association with prostate cancer risk was studied for quintile levels of systolic and diastolic blood pressure, BMI, and height, and blood pressure and BMI were also analysed in WHO defined categories. Analyses included adjustment for birth year, and BMI was additionally adjusted for smoking status, and the association for blood pressure was further adjusted for BMI.

3.3.2.2 Paper V

In paper V, the association with colorectal cancer risk was assessed for BMI, systolic and diastolic blood pressure, and for blood/plasma/serum levels of glucose, cholesterol and triglycerides. The relative risk for these factors was studied for quintile levels, and for Z score factors. Quintile cut-offs were calculated separately within each cohort and sex, and for glucose, cholesterol and triglycerides, also within categories of fasting time. The Z score factors were derived by standardising the exposures within the same groups that were used for quintile cut-off calculation, by (level-mean)/standard deviation (SD), resulting in variables with the mean value zero and a SD of one. For blood pressure, (systolic+diastolic)/2 was used, and as glucose and triglycerides were skewed and had outliers, these factors were log-transformed (base e) before standardisation. A MetS Z score was calculated by summing the five individual Z score factors, and the sum was standardised within cohort, sex and fasting time. Standardisation of the MetS factor was performed in order to have the same distribution as the single factors, and thereby enable a direct comparison of relative risk with colorectal cancer.

All Cox regression models were stratified by cohort, and included adjustment for birth year, baseline age, and smoking status. Quintile analyses of all factors but BMI, were further adjusted for BMI. Analyses of the individual Z score factors were performed with inclusion of all these factors in the model.

Risk estimates were adjusted for random error in exposure measurements, calculated from repeated measurements in 133,820 subjects, in total including 406,364 observations. RRs in quintiles were corrected directly by dividing the regression coefficient in the Cox model by the estimated regression dilution ratio (RDR) of exposure. RRs of Z scores were corrected indirectly by replacing each original Z score in the Cox model with its conditional expected value, i.e. regression calibration (RC). As RRs of Z scores were adjusted for all metabolic factors, which all except BMI have substantial random error, the RC method that allows for correction for random error also for covariates.
in the model was used in these analyses. Analyses of RDR and RC were based on linear mixed effect models, similar to those described by Wood et al.\textsuperscript{169,170}. In order to obtain a “usual value” of exposures, RDR and RC were predicted for the time point at approximately half the follow-up time\textsuperscript{152}.

For each separate factor, and for the MetS score, we tested if a model dichotomising levels into top versus quintile 1-4 or into top versus decile 1-9, respectively, differed significantly from a linear risk estimate on the association with incident or fatal colorectal cancer risk. We used likelihood ratio test, comparing a linear model of the Z score factor with a model that additionally included a dichotomised variable. Interaction between BMI, blood pressure, glucose, cholesterol, and triglycerides, was tested for all pair-combinations of Z score factors by the use of likelihood ratio test, comparing the additive model with a model that additionally included a product term of two standardised factors. Heterogeneity between risk estimates for incident colon versus rectal cancer, and between incident versus fatal colorectal cancer, were tested by the use of $\chi^2$ statistics.

\subsection*{3.3.2.3 Paper VI}

The association between blood/serum/plasma levels of glucose and risk of all cancers in paper VI was assessed for glucose levels in quintiles, deciles and per 1 mmol/l increment. Quantile cut-offs were calculated separately within cohort, sex and category of fasting time. Analyses of relative risk per 1 mmol/l increment were restricted to the 99\% of subjects with levels lower than 10 mmol/l (subjects with glucose lower than 1 mmol/l had already been excluded during data cleaning). All analyses were stratified for cohort and birth year, and also for sex in analyses of men and women combined, and were adjusted for baseline age, smoking status and BMI, and analyses of per one mmol/l increment were also adjusted for fasting status.

RDR of glucose was estimated from 406,364 health examinations in 133,820 subjects, using a similar model as was used for RDR calculation in paper V. RDR was estimated from subjects in the full Me-Can cohort and estimates were predicted for subjects included in the actual study. The average predicted RDR among subjects were used to correct relative risks in quantiles, and per 1 mmol/l increment of glucose.
3.4 Ethical considerations

Written informed consent was obtained from all study participants, and all studies were approved by research ethical committees; in paper I-III, at Umeå University Hospital, Umeå, Sweden, and in paper V and VI, by ethical committees in the respective countries.
4 MAIN RESULTS AND DISCUSSION

4.1 Prostate cancer - paper I and III

4.1.1 Results

Characteristics of study subjects and prostate cancer cases in paper I and III is shown in Table 3. Mean BMI was 26.3 (SD=3.2) kg/m² among cases and controls in the VIP-based study (paper I), and 24.2 (SD=3.2) kg/m² among men in the Construction Workers cohort (paper III). Cases in paper I were much younger at diagnosis than were cases in paper III, and a higher proportion of cases in paper I had a non-aggressive tumour.

<table>
<thead>
<tr>
<th></th>
<th>Paper I</th>
<th>Paper III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>392 cases, 392 controls</td>
<td>336,159 subjects</td>
</tr>
<tr>
<td>Age at baseline, years, mean (SD)</td>
<td>57.1 (4.5)</td>
<td>34.7 (13.1) (52.7 [8.8] in incident cases)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>26.3 (3.2)</td>
<td>24.2 (3.2)</td>
</tr>
<tr>
<td>Years of follow-up, mean (SD)</td>
<td>6.2 (3.3)</td>
<td>22.2 (7.5)</td>
</tr>
<tr>
<td>Age at diagnosis, years, mean (SD)</td>
<td>63.3 (5.0)</td>
<td>70.1 (8.4)</td>
</tr>
<tr>
<td>Incident cases, n</td>
<td>392</td>
<td>10,002</td>
</tr>
<tr>
<td>Not classified, n</td>
<td>-</td>
<td>4,783</td>
</tr>
<tr>
<td>Non-aggressive, n (% of classified)</td>
<td>278 (71)</td>
<td>2,817 (54)</td>
</tr>
<tr>
<td>Aggressive, n (% of classified)</td>
<td>114 (29)</td>
<td>2,402 (46)</td>
</tr>
<tr>
<td>Fatal cases, n</td>
<td>46 cases included in aggressive tumour group</td>
<td>2,601</td>
</tr>
</tbody>
</table>

SD, standard deviation; BMI, body mass index.

\textsuperscript{a}Aggressive cancer defined as: T3-4, or lymph node metastasis, or bone metastasis, or Gleason score \geq 8/WHO grade 3, or serum prostate specific antigen \geq 50 ng/ml, or in paper I, if the case had died due to prostate cancer up to October 2005. If none of these criteria were fulfilled, cases were classified as having a non-aggressive cancer.

In paper I, 12% of men were obese and 18% of men had impaired fasting glucose level or higher. All factors related to insulin resistance were inversely related to prostate cancer risk, and significant trends for increasing quintiles were found for C-peptide, HOMA-IR, leptin, and HbA1c (Table 4). The associations for C-peptide, HOMA-IR and HbA1c were not significant after adjustment for leptin. For all exposure factors, the inverse associations observed in the full study group were stronger in men younger than 59 years at
recruitment and in the group of non-aggressive tumours, whereas no significant associations were observed in men 59 years or older, or in the group of aggressive tumours. Top tertile levels of C-peptide, HOMA-IR, leptin and HbA1c were associated with a significant approximately 50% decreased risk of non-aggressive tumours (Figure 9).

Table 4. Odds ratios (95% CI) of prostate cancer for quartiles and per one unit increase of factors. Table reproduced from Stocks et al., paper I171.

<table>
<thead>
<tr>
<th>C-peptide</th>
<th>Quartiles</th>
<th>Per one unit increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutoffs, ng/ml</td>
<td>1 (ref) 2 3 4</td>
<td>P_trend Odds Ratio P</td>
</tr>
<tr>
<td>Case/control</td>
<td>134/98 97/98 82/98 79/98</td>
<td>&gt;2.6</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.00 0.76 (0.53-1.10) 0.63 (0.43-0.93) 0.59 (0.40-0.89) .008 0.82 (0.70-0.97) .02</td>
<td></td>
</tr>
<tr>
<td>OR adjusted^a (95% CI)</td>
<td>1.00 0.87 (0.59-1.28) 0.79 (0.52-1.20) 0.89 (0.55-1.44) .59 0.96 (0.79-1.16) .65</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HOMA-IR</th>
<th>Quartiles</th>
<th>Per one unit increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutoffs</td>
<td>&lt;1.1 1.1-1.5 1.5-2.0 &gt;2.0</td>
<td></td>
</tr>
<tr>
<td>Case/control</td>
<td>97/70 98/98 93/106 78/92</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.00 0.73 (0.48-1.09) 0.63 (0.42-0.96) 0.60 (0.38-0.94) .03 0.82 (0.67-1.02) .07</td>
<td></td>
</tr>
<tr>
<td>OR adjusted^a (95% CI)</td>
<td>1.00 0.84 (0.55-1.28) 0.81 (0.52-1.27) 0.89 (0.53-1.52) .78 1.00 (0.78-1.29) .98</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Leptin</th>
<th>Quartiles</th>
<th>Per one unit increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutoffs, ng/ml</td>
<td>&lt;3.0 3.0-4.5 4.5-6.9 &gt;6.9</td>
<td></td>
</tr>
<tr>
<td>Case/control</td>
<td>117/91 98/92 87/92 67/92</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.00 0.81 (0.54-1.21) 0.73 (0.49-1.09) 0.55 (0.36-0.84) .006 0.93 (0.89-0.97) .002</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>Quartiles</th>
<th>Per one unit increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutoffs, %</td>
<td>&lt;4.2 4.2-4.5 4.5-4.7 &gt;4.7</td>
<td></td>
</tr>
<tr>
<td>Case/control</td>
<td>100/74 118/111 61/82 97/109</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.00 0.71 (0.46-1.08) 0.50 (0.31-0.81) 0.56 (0.35-0.91) .02 0.87 (0.68-1.12) .28</td>
<td></td>
</tr>
<tr>
<td>OR adjusted^a (95% CI)</td>
<td>1.00 0.77 (0.49-1.19) 0.58 (0.36-0.95) 0.67 (0.41-1.10) .12 0.95 (0.74-1.23) .70</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fasting glucose</th>
<th>Quartiles</th>
<th>Per one unit increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutoffs, mmol/l</td>
<td>&lt;5.0 5.0-5.5 5.5-5.9 &gt;5.9</td>
<td></td>
</tr>
<tr>
<td>Case/control</td>
<td>85/82 107/90 99/102 75/92</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.00 1.14 (0.75-1.73) 0.93 (0.61-1.43) 0.74 (0.47-1.18) .15 1.00 (0.87-1.15) .95</td>
<td></td>
</tr>
<tr>
<td>OR adjusted^a (95% CI)</td>
<td>1.00 0.96 (0.62-1.49) 0.83 (0.54-1.29) 0.70 (0.44-1.14) .12 1.01 (0.88-1.17) .85</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Postload glucose</th>
<th>Quartiles</th>
<th>Per one unit increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutoffs, mmol/l</td>
<td>&lt;5.6 5.6-6.4 6.4-7.3 &gt;7.3</td>
<td></td>
</tr>
<tr>
<td>Case/control</td>
<td>107/83 81/83 54/77 90/89</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.00 0.75 (0.49-1.15) 0.51 (0.32-0.83) 0.75 (0.50-1.14) .21 0.95 (0.68-1.03) .23</td>
<td></td>
</tr>
<tr>
<td>OR adjusted^a (95% CI)</td>
<td>1.00 0.79 (0.51-1.23) 0.52 (0.31-0.85) 0.85 (0.55-1.31) .46 0.97 (0.89-1.05) .47</td>
<td></td>
</tr>
</tbody>
</table>

ref, reference group; HOMA-IR, homeostatic model assessment of insulin resistance; HbA1c, glycated haemoglobin.

^aAdjusted for leptin.
Figure 9. Odds ratios of prostate cancer for tertiles in men with non-aggressive (n_cases=278) and aggressive (n_cases=114) cancer, respectively. OR, odds ratio; HOMA-IR, homeostatic model assessment of insulin resistance; HbA1c, glycated haemoglobin. Figure reproduced from Stocks et al., paper I. In paper III, 5% of men were obese and 37% of men had hypertension. Increasing quintile levels of systolic and diastolic blood pressure were associated with a significant decreased risk of incident prostate cancer; men in the top quintile of systolic blood pressure had a 16% lower risk of prostate cancer compared to men in the lowest quintile, and men in the top quintile of diastolic blood pressure had a 18% lower risk (Figure 10). The association for
systolic blood pressure was stronger in the group of non-aggressive tumours, whereas no significant trend for blood pressure was observed in the group of aggressive tumours. BMI was not significantly related to risk of incident prostate cancer, but increasing BMI was associated with a significant increased risk of fatal prostate cancer. Top versus bottom quintile of BMI was related to a 28% increased risk, and a similar pattern, although not significant, was observed for aggressive tumours.

![Figure 10. Relative risks for prostate cancer in the four endpoint groups in paper III ordered by disease severity, by quintile levels of systolic and diastolic blood pressure, BMI and height. BP, blood pressure; BMI, body mass index.](image)

### 4.1.2 General discussion

Findings from paper I and III are in line with data from previous studies on BMI and diabetes, and our studies further contribute with new insights about the relation between metabolic factors and risk of prostate cancer. Obesity or overweight have overall not been related to risk of incident prostate cancer, but have been related to an increased risk of fatal disease, as was also found in paper III. No significant association was found for BMI and risk in tumour subgroups, but the pattern of association in our study are in line with
findings from recent studies that have shown no association or an inverse association with risk of non-aggressive tumours, and no association or a positive association with risk of aggressive tumours.\textsuperscript{129-135}

Diabetes has been consistently associated with a decreased risk of prostate cancer\textsuperscript{125-128}, and accordingly, insulin resistance related factors in paper I were associated with a decreased risk of incident prostate cancer. Data on diabetes and fatal prostate cancer are limited\textsuperscript{85,126,172}, and data from studies on diabetes in which subgroup analyses of tumour characteristics were performed have shown mixed results\textsuperscript{126,128,134,173-176}, possibly partly explained by that the definition of aggressive tumours has varied between studies, or because of other differences between study subjects, e.g. age. A meta-analysis of diabetes and prostate cancer risk that included 20,373 cases showed a stronger inverse association in studies performed in the year 1990 or later\textsuperscript{125}, i.e. when PSA testing had increased and more low-risk prostate cancers were detected, which support our findings of a stronger inverse association between insulin resistance and non-aggressive prostate cancer. Insulin resistance or related factors may underlie the decreased risk of prostate cancer in diabetics, although further mechanisms included in the pathogenesis of diabetes may also play a role that is not relevant to non-diabetic insulin resistant men. Most\textsuperscript{128,175-178}, but not all\textsuperscript{174}, prospective studies have shown that risk decreases further with a long diabetes duration, and overweight or obesity in combination with diabetes may also further decrease the risk.\textsuperscript{127,128,173}

Of exposure factors in paper I, strong associations were found for C-peptide, HOMA-IR, leptin, and HbA1c, whereas associations for fasting and post-load glucose levels were weaker and non-significant in the full study group, in accordance with other studies on glucose and cancer risk.\textsuperscript{92,95,96} The stronger association found for HbA1c than for glucose, may reflect the stability of HbA1c as a marker, as it is a measure of glucose level during the approximately past two months,\textsuperscript{99} and as the analytical method used in our study has shown very low intra-individual CVs.\textsuperscript{179} Leptin is another very stable marker; levels are neither influenced by meals\textsuperscript{180} nor by freeze-thaw cycles\textsuperscript{181}, and in addition, random error of measurements within individuals over a longer time-period of at least four years, is low.\textsuperscript{155} Adjustment for leptin substantially weakened the associations for C-peptide, HOMA-IR and HbA1c, which may relate to that leptin is a more stable marker than at least C-peptide and HOMA-IR, or that leptin is more strongly related to other factors associated with risk, e.g. fat mass. A few previous studies on leptin and prostate cancer risk have shown inconsistent results.\textsuperscript{138-141} Studies on insulin or C-peptide have shown no association with risk,\textsuperscript{139,142-145} except for one smaller case-control study that showed a significant positive association in a Chinese population with a large proportion of non-localised and high grade prostate cancers.\textsuperscript{140}
In paper III, we examined the association between blood pressure and prostate cancer risk, which in previous much smaller studies showed no significant association with incident or fatal prostate cancer\textsuperscript{118,119,122,142,146-149}. Our study is the first to report a small, but significant, decreased risk of overall incident prostate cancer and of non-aggressive tumours in high blood pressure, whereas high blood pressure was non-significantly related to an increased risk of fatal prostate cancer. However, antihypertensive drugs is a possible confounder\textsuperscript{182} and was not controlled for in our or in most previous studies\textsuperscript{119,122,142,146,148,149}.

4.1.3 Interpretation

Competing risks, i.e. that an event removes a subject from being at risk for another event\textsuperscript{183,184}, is often not accounted for in survival analysis; however, it may possibly have influenced results in our and previous studies of metabolic factors and prostate cancer risk. As prostate cancer is diagnosed at a high age, a substantial proportion of men may die before they could have been diagnosed with prostate cancer, and death from these competing risks, e.g. cardiovascular diseases, is likely to be higher among men who are obese, have high blood pressure, or who are insulin resistant, than among men without these conditions. If bias by competing risks plays a role in our and in previous studies, some of the inverse associations between metabolic factors and risk may in reality be weaker than what has been shown, and positive associations may be stronger.

The divergent findings for overweight and prostate cancer risk according to endpoint has resulted in a hypothesis that biological mechanisms involved in prostate tumour initiation may be different from those that promote prostate tumour growth and progression\textsuperscript{185,186}. However, detection bias has been proposed to possibly be involved, such that obese men might be diagnosed at a later stage because of lower PSA levels and a larger prostate gland compared to normal weight men, and because digital rectal examination is more difficult to evaluate in obese men. A later detection and more advanced tumours at diagnosis in obese men could partly explain the lower risk of non-aggressive prostate cancer, but a higher risk of prostate cancer death\textsuperscript{185,186}. However, results from studies on BMI and PSA level are not consistent\textsuperscript{187}, and it is unlikely that e.g. a 0.1 ng/ ml lower PSA level in obese (BMI 30-34.9 kg/ m\textsuperscript{2}) compared to normal weight (BMI<25 kg/ m\textsuperscript{2}) men, as was found in a study of almost 3,000 men without prostate cancer\textsuperscript{188}, explains the lower prostate cancer risk in obese men. Furthermore, contrary to what may be believed, PSA testing in the United States has been shown to be more common in obese men than in normal weight men\textsuperscript{189,190}, which further refutes an explanation by detection
bias. Whether a difference in PSA testing exists between diabetic versus non-diabetic men is unclear\textsuperscript{127,176}; however, possible differences in screening behaviour and lower PSA levels in diabetic compared to non-diabetic men has been estimated to explain at the most 20% of the lower prostate cancer risk in diabetics\textsuperscript{127}.

It is unlikely that metabolic factors in obesity and insulin resistance per se cause a lower risk of non-aggressive prostate cancer, and it is unlikely that a lifestyle related to obesity and insulin resistance causes a decreased risk. A genetic variant in the TCF2 gene has been identified that has opposite effects on risk of diabetes and prostate cancer\textsuperscript{191,192}, and this and other genetic variants could partly underlie the inverse association between diabetes and prostate cancer risk.

It has been proposed that lower testosterone concentrations in obese and diabetic men compared to men without these conditions may explain the lower risk of prostate cancer in obesity and diabetes\textsuperscript{125,185}. Lower testosterone levels in men with hypertension\textsuperscript{193,194} and with other metabolic disturbances\textsuperscript{195} may also explain our findings of an inverse association between these factors and risk of incident prostate cancer. However, there is a discrepancy between results from experimental and clinical studies on one hand which have shown that androgens play an important role in prostate cancer\textsuperscript{45,46}, and on the other hand, observational studies of plasma androgen levels and prostate cancer risk which have shown no association\textsuperscript{48}. This discrepancy may be explained by that androgen levels in plasma does not fully reflect androgen action in the prostate\textsuperscript{45}, and therefore, the putative link of androgens between metabolic factors and a decreased risk of prostate cancer needs further investigation.

Insulin stimulates tumour growth\textsuperscript{196} and the decline in insulin production in diabetes has further been proposed to explain the decreased prostate cancer risk in diabetes, which is also supported by that risk further decreases after a long diabetes duration\textsuperscript{125,126}. The decline in leptin levels - another mitogen\textsuperscript{197} in hypoinsulinaemia, has also been speculated to be involved\textsuperscript{125}. These hypotheses would though not explain our findings of a decreased risk of prostate cancer in insulin resistance, which includes high levels of insulin and leptin. Possibly, insulin and IGF-I actions are altered in insulin resistance. Insulin and IGF-I have similar signalling pathways, but under normal circumstances, insulin has mainly metabolic effects and IGF-I acts primarily mitogenic\textsuperscript{198}. In insulin resistance, however, the reduced effect of insulin may result in a compensating increase of the metabolic properties of IGF-I, whereas its mitogenic and tumour growth promoting effect may decrease\textsuperscript{33,198}. Indicative of a glucose lowering response to IGF-I in insulin resistance is that treatment with IGF-I improves glycaemic control in diabetics\textsuperscript{199-201}. However, in the context of the insulin-IGF-I system, it is confusing that elevated IGF-I has
been related to an increased risk of prostate cancer and colorectal cancer\textsuperscript{34}, whereas in contrast to prostate cancer, obesity and diabetes have been related to an increased risk of colorectal cancer\textsuperscript{61,86}. Although insulin and the IGF-I system are thought to play an important role in cancer, neither the relationships between IGF/IGFBP compounds, nor the action of IGF-I and its binding proteins on cancer cells, are fully elucidated\textsuperscript{202}.

Data from our and previous studies suggest that insulin and leptin do not play a key role in the initiation of prostate cancer, but these factors have been implicated as putative mechanisms explaining the increased risk of prostate cancer death in overweight and obese men\textsuperscript{185,203}. An increase in insulin levels in obesity and thereby higher levels of free IGF-I, has further been suggested as possible mediators in the association\textsuperscript{185,203}. A recent study of prostate cancer cases showed that prostate cancer specific survival was poorer in obese and overweight men than in normal weight men, and was poorer in men with high C-peptide (insulin) levels than in men with lower levels of C-peptide\textsuperscript{204}, which supports that insulin may be involved in prostate cancer progression.

We found a non-significant association between high blood pressure and an increased risk of prostate cancer death, and such an association could be caused by activation of the renin-angiotensin system (RAS) in hypertension. Angiotensin II is the biologically active peptide in RAS and has been identified as a potential mitogen in the prostate\textsuperscript{205}, and activation of the RAS might stimulate progression of prostate cancer into an aggressive tumour\textsuperscript{206,207}.

4.1.4 Conclusions
Data from paper III confirms findings from a large number of studies that overweight is related to an increased risk of fatal prostate cancer, but is not associated with incident prostate cancer. Overweight may decrease the risk of non-aggressive tumours, which however was not found in our study. Previous data on blood pressure and prostate cancer risk is limited, and we found a similar pattern for blood pressure as for overweight, such that high blood pressure was related to a decreased risk of incident prostate cancer and of non-aggressive tumours, but was related to a non-significant increased risk of fatal disease. Furthermore, diabetes is related to a decreased risk of prostate cancer, and results from paper I showed that several factors related to insulin resistance were strongly inversely related to overall incident prostate cancer and of non-aggressive tumours, but not of aggressive tumours.

Results from our and previous studies may indicate that different factors are involved in initiation versus progression of the tumour; androgens may have a key role in initiation, whereas e.g. insulin and leptin may further stimulate tumour growth and spread.
4.2 Colorectal cancer - paper II and V

4.2.1 Results

Cases and controls in paper II were recruited from the VIP and the MSP, and subjects in paper V were from the Me-Can cohort. Characteristics of subjects and colorectal cancer cases in paper II and V are presented in Table 5. In paper II, the main results were presented for men and women combined, whereas in paper V, the large sample size enabled us to explore the association separately among men and women.

<table>
<thead>
<tr>
<th></th>
<th>Paper II</th>
<th>Paper V</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subjects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects</td>
<td>VIP</td>
<td>220 cases, 427 controls</td>
</tr>
<tr>
<td></td>
<td>MSP</td>
<td>86 cases, 168 controls</td>
</tr>
<tr>
<td></td>
<td></td>
<td>578,700 subjects; 289,866 men,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>288,834 women</td>
</tr>
<tr>
<td><strong>Age at baseline, years, mean (SD)</strong></td>
<td>54.8 (6.6)</td>
<td>61.7 (6.2)</td>
</tr>
<tr>
<td><strong>BMI, mean (SD)</strong></td>
<td>26.3 (3.8)</td>
<td>25.3 (4.0)</td>
</tr>
<tr>
<td>Men</td>
<td>26.3 (3.3)</td>
<td>25.7 (3.5)</td>
</tr>
<tr>
<td>Women</td>
<td>26.2 (4.3)</td>
<td>24.9 (4.4)</td>
</tr>
<tr>
<td><strong>Years of follow-up, mean (SD)</strong></td>
<td>6.3 (3.5)</td>
<td>3.8 (2.4)</td>
</tr>
<tr>
<td><strong>Age at diagnosis, years, mean (SD)</strong></td>
<td>61.2 (7.2)</td>
<td>65.5 (6.3)</td>
</tr>
<tr>
<td><strong>Incident cases, n</strong></td>
<td>220</td>
<td>-</td>
</tr>
<tr>
<td>Men</td>
<td>125</td>
<td>-</td>
</tr>
<tr>
<td>Women</td>
<td>95</td>
<td>86</td>
</tr>
<tr>
<td><strong>Fatal cases, n</strong></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Men</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Women</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

VIP, Västerbotten Intervention Project; MSP, Mammography Screening Project; SD, standard deviation; BMI, body mass index.

*Height and weight had not been measured in all subjects in the MSP, and therefore, information on BMI was not used in the study for MSP subjects.

In paper II, concentrations of C-peptide, HbA1c, leptin, and adiponectin were measured in stored blood samples from subjects, and data on BMI, blood pressure and fasting and post-load glucose levels were available in subjects from the VIP. None of the studied exposures were significantly related to risk of colorectal cancer across quartile levels. A borderline significant association was found for diastolic blood pressure; OR for top versus bottom quartile was 1.59 (95% CI, 0.94-2.70, p for trend=0.07).

In subjects from the VIP, the association between BMI, blood pressure, and glucose was further explored in categories and as MetS factors, as defined...
by the WHO. The proportion of subjects in the VIP with obesity was 15%, hypertension 50%, and hyperglycaemia, 20%. Presence of obesity and hyperglycaemia, versus no presence, was related to a significant 70-80% increased risk of colorectal cancer, and hypertension was related to a 30% non-significant increased risk (Figure 11). Presence of three MetS factors was, compared to no factor, related to a 2.5-fold increased risk of colorectal cancer (p for trend = 0.002).

<table>
<thead>
<tr>
<th>MetS factor</th>
<th>Presence</th>
<th>Cases/controls</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Obesity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI &gt;30</td>
<td>No</td>
<td>175/366</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>43/55</td>
<td>1.77 (1.11-2.82)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = .016</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure ≥140/90 or use of anti-hypertensive drugs</td>
<td>No</td>
<td>98/214</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>118/195</td>
<td>1.30 (0.90-1.86)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = .16</td>
</tr>
<tr>
<td><strong>Hyperglycaemia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting glucose ≥6.1 (IFG) or post-load glucose ≥8.9 (IGT)</td>
<td>No</td>
<td>159/341</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>55/70</td>
<td>1.70 (1.09-2.63)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = .018</td>
</tr>
<tr>
<td><strong>Combined presence</strong></td>
<td>0</td>
<td>75/167</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>79/171</td>
<td>1.09 (0.74-1.60)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>40/44</td>
<td>2.40 (1.36-4.25)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>17/19</td>
<td>2.57 (1.20-5.52)</td>
</tr>
</tbody>
</table>

*Figure 11. Odds ratios for colorectal cancer for presence of the MetS factors obesity, hypertension and hyperglycaemia, respectively, and for an increasing number present. Odds ratios for hypertension and hyperglycaemia are adjusted for BMI. Figure reproduced from Stocks et al., paper II (208).*
For comparison with the high cut-off levels for obesity and hyperglycaemia at approximately the 90th percentile among controls in the study group, risk was assessed for top decile levels of C-peptide, HbA1c, leptin, adiponectin and leptin/adiponectin ratio in VIP subjects. ORs in top deciles were substantially higher than in the top quartile of factors. Top versus bottom decile of factors were related to 40-90% increases in risk of colorectal cancer, but, except for adiponectin, the associations were not significant.

In paper V, 11% of men and 12% of women were obese. Except for BMI, absolute levels of exposure factors were not totally comparable between MeCan cohorts, as different measurement methods had been used.

Analyses of repeated measurements in 133,820 subjects in the study showed that random error for measurements of BMI was low (high RDR), but was high for all other exposure factors. RDR was for BMI 0.90, and ranged between 0.31 (glucose) and 0.68 (cholesterol) for the other exposures. RRs were adjusted for random error of exposure measurements.

Quintile analyses showed significant linear positive associations between BMI, blood pressure, cholesterol, and triglycerides, and risk of incident colorectal cancer in men (Table 6). In women, significant linear positive associations were found for BMI and cholesterol.

In men, a one unit increment of Z score for BMI, blood pressure, and triglycerides was associated with a significant increased risk of incident colorectal cancer (Table 7). The association between the MetS Z score was stronger than for any of the factors in single, but there was no significant positive interaction between any combinations of two single factors. In women, a one unit increment of Z score for BMI was significantly positively related to risk of incident colorectal cancer. As in men, there was a stronger positive association between the MetS Z score than for any single factor, but there was no significant positive interaction between factors. However, a significant negative interaction was found for blood pressure and cholesterol, such that women with high levels of blood pressure and cholesterol had a decreased risk of colorectal cancer. The RR of incident colorectal cancer for calibrated Z score of cholesterol was 1.44 (95% CI, 0.99-2.12) in women with blood pressure levels below -1 SD of calibrated Z score levels, and was 0.94 (95% CI, 0.83-1.07) in women with blood pressure higher than 1 SD. Such a pattern was also observed in men, but there was no significant interaction between blood pressure and cholesterol in men.
Table 6. Relative risk\(^a\) of incident colorectal cancer in paper V, by quintiles of metabolic factors

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Quintile</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n cases</td>
<td>RR (95% CI)</td>
<td>n cases</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>1</td>
<td>399 1.00 (referent)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>484 1.08 (0.93-1.26)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>588 1.22 (1.06-1.41)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>642 1.27 (1.10-1.46)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>721 1.51 (1.32-1.73)</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(P_{\text{trend}}&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>1</td>
<td>403 1.00 (referent)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>408 0.89 (0.69-1.15)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>577 1.02 (0.81-1.30)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>545 1.04 (0.82-1.34)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>898 1.25 (1.00-1.58)</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(P_{\text{trend}}=0.004)</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>1</td>
<td>387 1.00 (referent)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>447 0.96 (0.75-1.26)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>595 0.92 (0.73-1.20)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>651 1.12 (0.87-1.44)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>751 1.40 (1.08-1.78)</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(P_{\text{trend}}=0.001)</td>
<td></td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>1</td>
<td>376 1.00 (referent)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>503 1.00 (0.66-1.48)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>537 1.17 (0.79-1.75)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>630 1.10 (0.76-1.61)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>668 1.13 (0.76-1.66)</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(P_{\text{trend}}=0.89)</td>
<td></td>
</tr>
<tr>
<td>Cholesterol, mmol/l</td>
<td>1</td>
<td>376 1.00 (referent)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>489 1.00 (0.83-1.23)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>581 1.09 (0.90-1.32)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>653 1.18 (0.97-1.42)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>730 1.21 (1.00-1.45)</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(P_{\text{trend}}=0.009)</td>
<td></td>
</tr>
<tr>
<td>Triglycerides, mmol/l</td>
<td>1</td>
<td>396 1.00 (referent)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>520 1.29 (0.98-1.70)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>568 1.36 (1.04-1.78)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>634 1.62 (1.22-2.11)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>649 1.70 (1.29-2.23)</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(P_{\text{trend}}=0.001)</td>
<td></td>
</tr>
</tbody>
</table>

RR, relative risk; CI, confidence interval; BMI, body mass index.

\(^a\)Relative risks (RR) from Cox regression models, with attained age as time scale, stratified by cohort, and adjusted for baseline age, birth year, smoking status, and all factors except BMI, were further adjusted for BMI. RRs are corrected for regression dilution ratio (RDR); conversion into uncorrected RR=exp(\log(RR)*RDR). RDR: BMI, 0.90; systolic blood pressure, 0.54; diastolic blood pressure, 0.52; glucose, 0.31; cholesterol, 0.68; triglycerides, 0.48.
Table 7. Relative risk (95% CI)\(^a\) of incident colorectal cancer in paper V, by Z scores of metabolic factors, in single and combined (MetS)

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Men (n cases=2,761)</th>
<th>Women (n cases=1,815)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Z score, original values(^b)</td>
<td>Calibrated Z score(^c)</td>
</tr>
<tr>
<td>BMI</td>
<td>1.09 (1.05-1.14)</td>
<td>1.07 (1.02-1.13)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>1.06 (1.02-1.10)</td>
<td>1.10 (1.02-1.18)</td>
</tr>
<tr>
<td>Log(glucose)</td>
<td>1.01 (0.97-1.04)</td>
<td>1.02 (0.89-1.16)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>1.01 (0.97-1.05)</td>
<td>1.00 (0.94-1.07)</td>
</tr>
<tr>
<td>Log(triglycerides)</td>
<td>1.09 (1.04-1.13)</td>
<td>1.17 (1.06-1.28)</td>
</tr>
<tr>
<td>MetS</td>
<td>1.17 (1.12-1.21)</td>
<td>1.24 (1.18-1.31)</td>
</tr>
</tbody>
</table>

CI, confidence interval; MetS, metabolic syndrome; BMI, body mass index.

\(^a\)Relative risks from Cox regression models, with attained age as time scale, stratified by cohort, and adjusted for baseline age, birth year, and smoking status. Relative risks of single factors include all single factors in the model.

\(^b\)Z scores for original values (mean=0, standard deviation (SD)=1) were derived by (level-mean)/SD. BMI and blood pressure (systolic+diastolic blood pressure)/2 were standardised within subcohort and sex, and log(glucose), cholesterol and log(triglycerides) were additionally standardised within groups of fasting time. Z score of MetS was derived by standardisation, within subcohort, sex and fasting time, of the sum of Z scores for the five single factors.

\(^c\)Z scores, derived from original values, were calibrated. Calibrated Z scores have the mean value zero and the SD ranges between 0.39 for log(glucose) and 0.89 for BMI.

There were no significant differences in risk estimates between incident and fatal colorectal cancer for any of the single factors or for the MetS. Risk estimates for colon versus rectal cancer were generally similar, except for BMI, which was more strongly related to colon than to rectal cancer, and the difference was borderline significant in women (p=0.05).

A dichotomised model of high levels versus low to normal levels of exposure factors, including the MetS score, was not significantly different from a linear model, except for triglycerides in women. Only very high triglyceride levels were associated with an increased risk in women, the RR of incident colorectal cancer for top versus decile 1-9 was 1.41 (95% CI, 1.09-1.87).

4.2.2 General discussion

In paper II, a similar approach as in previous studies\(^{17,120,121,123,124}\) was used to investigate the association between the MetS and risk of colorectal cancer. We calculated ORs for exposures in increasing categorical levels, and dichotomised exposures into MetS factors to further assess risk with the number of MetS factors present. We found weak associations for exposures in quartiles, except for diastolic blood pressure which by definition reached hypertensive levels in the top quartile, but found significant positive associations for obesity and hyperglycaemia, and also stronger associations for other metabolic factors in the top decile than in the top quartile. Thus, we concluded that factors in the MetS might only be related to an increased colorectal cancer risk at very high
levels. In accordance with previous studies\textsuperscript{117,120,121,123,124}, we found that the combination of MetS factors was related to an increased risk of colorectal cancer, and the association with two or three factors – obesity, hypertension and hyperglycaemia – was stronger than if only one factor was present. Some previous studies showed a similar increased risk for single factors as for the combination of factors\textsuperscript{117,120,121}. However, the magnitude of effect by single factors and by the MetS is difficult to evaluate on the basis of results from previous studies, including paper II, as different cut-points has been used for metabolic factors.

Paper V included more than ten times as many cases compared to the largest of previous studies\textsuperscript{121} which facilitated a much more detailed investigation of associations than in previous studies, and moreover, the correction for random error in exposure measurements included in paper V was another big advantage to previous studies\textsuperscript{117,120,121,123,124}. In quintile analyses, we found significant linear positive associations with incident colorectal cancer in men for BMI, blood pressure, cholesterol, and triglycerides, and in women for BMI and cholesterol. Except for triglycerides in women, there was no indication that risk by metabolic factors and the continuous MetS score only increased at high levels, which would support the use of high cut-off levels of MetS factors and the MetS, as has been used in previous studies. Results from paper V support the use of metabolic factors on a continuous scale to assess the association with colorectal cancer risk.

The strength of association between single factors and the MetS score and colorectal cancer risk in our population was directly comparable due to the standardisation of factors into the same scale, and because random error in exposures was corrected for. As regression dilution ratio of BMI is very high\textsuperscript{152,153}, 0.90 in our study, associations for BMI with risk did not change much by the correction. RDR for other factors was low, and consequently, associations with risk became stronger after correction. Analyses of a continuous risk estimate (Z score) with all exposures included in a model, showed that in men, after correction for random error, blood pressure and triglycerides were more strongly related to risk than was BMI. In women, BMI was most strongly related to risk also after correction.

Although in paper V there was a stronger association between the combined MetS score than for any single factor, we found no evidence of a positive interaction between metabolic factors, and thus an additive effect between these factors can be assumed. There was, however, a negative interaction between cholesterol and blood pressure in women, and suggestively also in men. These findings are intriguing, and have also been observed on the association with stroke, in particular of haemorrhagic stroke, in several large studies\textsuperscript{209-212}. These findings for colorectal cancer need to be confirmed in
further studies, and further investigation is needed in order to explain a cholesterol–blood pressure interaction on colorectal cancer and stroke.

4.2.3 Interpretation

The main biological explanation for an increased colorectal cancer risk in obesity, the MetS, and also in diabetes, and colorectal cancer has been ascribed to the effects of insulin resistance in these conditions. Insulin has been shown to promote growth of normal and neoplastic colorectal epithelial cells and has been shown to have mitogenic actions in vitro. Insulin may also act indirectly by decreasing IGFBPs, resulting in an increase in biologically active free IGF-I, which stimulates tumour growth through proliferative and antiapoptotic actions. In support of the insulin-IGF-I hypothesis, high plasma IGF-I has been related to an increased risk of colorectal cancer, and, although no association was found for insulin in our study (Paper II) and in another previous study, there is some support of an increased risk of colorectal cancer in men and women with elevated insulin levels.

BMI has generally been more strongly related to risk of colorectal cancer in men than in women. Because waist measures have been positively associated with risk in both sexes, it has been speculated that a stronger correlation between BMI and abdominal obesity in men than in women explains the stronger association between BMI and risk in men. In our study, the association between BMI and risk was similar in women and men in analyses of Z score of BMI which included adjustment for metabolic factors, whereas exclusion of these factors in analyses displayed stronger associations in men than in women. Inclusion of metabolic factors in analysis of BMI might possibly result in associations that more closely reflect abdominal obesity and its metabolic aberrations, including insulin resistance and its effect on colorectal cancer.

We found a strong linear association between triglycerides and colorectal cancer in men, and risk was also increased among women in the top decile of triglyceride levels. Previous prospective studies showed no significant association with risk, but these studies were relatively small and did not correct for random error in triglyceride measurements. Hypertriglyceridaemia is related to insulin resistance, and the link to colorectal cancer may be through the insulin-IGF-I pathway. Another putative mechanism may be increased bile acids, associated with high triglycerides and also with colorectal cancer. Blood pressure was related to an increased risk of colorectal cancer in men, which was also indicated in some previous studies of men or of men and women combined. As is also hypothesised for
prostate cancer, activation of the RAS may stimulate tumour growth in the colorectum\textsuperscript{218,219}. Obesity and the metabolic disturbances investigated in paper II and V are caused by lifestyle and by genetic predisposition for these conditions\textsuperscript{53,220}. Colorectal cancer is one of the cancers that have been most strongly related to lifestyle\textsuperscript{1,24}; physical activity decreases risk of colorectal cancer, as does foods containing dietary fibre and calcium\textsuperscript{24}. High intake of red and processed meat and alcohol have been related to an increased risk of colorectal cancer, and further nutritional factors have been indicated to be related to risk\textsuperscript{24}. An increased risk of colorectal cancer in men and women with a high metabolic risk score is likely to reflect the strong lifestyle-colorectal cancer connection. Genetics is also likely to be involved in the findings for metabolic factors, either by predisposing for metabolic aberrations and thereby influencing risk of colorectal cancer, or by being directly linked to metabolic factors and to colorectal cancer. However, despite a possible direct involvement of genetics in the associations, it seems likely that a healthy diet and increased physical activity, which are known to decrease risk of cardiovascular diseases\textsuperscript{221}, would also decrease the risk of colorectal cancer.

4.2.4 Conclusions
Data from our and previous studies show that a cluster of metabolic risk factors is related to an increased risk of incident and fatal colorectal cancer. The effect by single factors appears to be additive rather than multiplicative. Of components in the MetS, the strongest single risk factor is excess weight in men and women, and in our large study (paper V), elevated levels of blood pressure and triglycerides were further identified as strong risk factors in men. Lifestyle is strongly related to colorectal cancer and to factors in the MetS, and a healthy lifestyle is likely to prevent against colorectal cancer.

4.3 Cancer overall - paper VI
4.3.1 Results
Paper VI included 274,126 men and 275,818 women in the Me-Can cohort. Mean age at baseline was 44.7 (SD=11.6) years in men and 45.0 (SD=12.8) years in women. Mean BMI was 25.8 (SD=3.5) kg/m\textsupersquare{} in men and 25.0 (SD=4.5) kg/m\textsupersquare{} in women, and 11\% of men and 13\% of women were obese. All participants in the VHM&PP and the MPP and 90\% of participants in the
VIP had fasted more than eight hours before the health examination, whereas in the Norwegian cohorts, only 5% of subjects had fasted more than eight hours. Of the 50% of men and women in the full cohort who had fasted more than eight hours, 8% of men and 6% of women had impaired glucose level, and 4% of men and 3% of women had a glucose level in the diabetic range.

During follow-up, not counting the first year which was excluded in analyses, 18,621 men and 11,664 women were diagnosed with cancer, and 6,973 men and 3,088 women died out of cancer.

All risk estimates were corrected for RDR of glucose, which was found to be low; 0.40 in men and 0.43 in women for glucose levels in the range 1-9.9 mmol/l. The 1% of subjects outside the range 1-9.9 mmol/l were excluded in analyses of cancer risk per 1 mmol/l increment of glucose. Table 8 shows the RR for incident and fatal cancer overall, and for separate cancers for which significant associations were found.

Table 8. Relative risk (95% CI) of incident and fatal cancer overall, and for separate cancers for which significant associations were found, per 1 mmol/l increment of glucose. Cancers are ranked by relative risk for incident cancer.

<table>
<thead>
<tr>
<th>Sex, cancer</th>
<th>Incident cancer</th>
<th>Fatal cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cancer</td>
<td>1.05 (1.01-1.10)</td>
<td>1.15 (1.07-1.22)</td>
</tr>
<tr>
<td>Gallbladder, biliary tract</td>
<td>2.01 (1.14-3.53)</td>
<td>1.15 (1.07-1.22)</td>
</tr>
<tr>
<td>Thyroid gland</td>
<td>1.88 (1.16-3.07)</td>
<td>1.00-1.00</td>
</tr>
<tr>
<td>Liver, intrahepatic bile ducts</td>
<td>1.76 (1.21-2.56)</td>
<td>2.12 (1.37-3.30)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>1.59 (1.13-2.23)</td>
<td>1.00-1.00</td>
</tr>
<tr>
<td>Larynx, trachea/bronchus/lung</td>
<td>1.15 (1.02-1.29)</td>
<td>1.21 (1.06-1.37)</td>
</tr>
<tr>
<td>Rectum, anus</td>
<td>1.14 (0.94-1.37)</td>
<td>1.44 (1.08-1.92)</td>
</tr>
<tr>
<td>Brain, nervous tissue</td>
<td>0.59 (0.42-0.84)</td>
<td>1.00-1.00</td>
</tr>
</tbody>
</table>

| **Women**   |                 |              |
| Total cancer| 1.11 (1.05-1.16)| 1.21 (1.11-1.33) |
| Pancreas    | 1.55 (1.12-2.13)| 1.70 (1.29-2.24) |
| Urinary bladder | 1.45 (1.05-2.01) | 0.99 (0.44-2.18) |
| Stomach     | 1.31 (1.00-1.73) | 1.56 (1.13-2.14) |
| Uterine corpus and other parts of uterus | 1.14 (0.95-1.38) | 1.69 (1.05-2.73) |
| Cervix uteri | 0.85 (0.59-1.21) | 2.26 (1.20-4.28) |

| **Men and women** |                 |              |
| Liver, intrahepatic bile ducts | 1.75 (1.28-2.39) | 1.77 (1.19-2.62) |
| Oesophagus | 1.29 (0.92-1.80) | 1.73 (1.19-2.53) |

CI, confidence interval.

*Estimated from Cox models with attained age as time scale, stratified by cohort, and adjusted for baseline age, birth year, body mass index, smoking status, and fasting time. RRs are corrected for regression dilution ratio (RDR); conversion into uncorrected RRs = \( \exp(\log(\text{RR}) \times \text{RDR}) \). RDR: men, 0.40; women, 0.43; all, 0.41.

**No fatal endpoint.

*Not presented in paper.
A 1 mmol/l increment of glucose was in men associated with a significant increased risk of overall incident (RR, 1.05, 95% CI, 1.01-1.10) and fatal cancer (RR, 1.15, 95% CI, 1.07-1.22). Significant positive associations for incident and fatal cancer at specific sites were found for cancer of the liver, gallbladder, and the respiratory tract, and for incident thyroid cancer and multiple myeloma, and for fatal rectal cancer. Glucose was significantly inversely related to risk of brain tumours in men.

The association between glucose and risk of cancer overall was somewhat stronger in women than in men; the RR per 1 mmol/l increment was in women for overall incident cancer 1.11 (95% CI, 1.05-1.16), and for fatal cancer 1.21 (95% CI, 1.11-1.33). A 1 mmol/l increment of glucose was in women associated with significant increases in risk of incident and fatal cancer of the stomach (borderline significant for incidence) and pancreas, and for incident urinary bladder cancer, and for fatal cancer of the cervix uteri and uterine corpus. In contrast to men, glucose per 1 mmol/l increment was related to a non-significant increased risk of brain tumours in women (RR, 1.34 [95% CI, 0.92-1.94]), and was related to a non-significant decreased risk of incident thyroid cancer (RR, 0.72 [95% CI, 0.47-1.10]).

Of rare cancers that were analysed in men and women combined, a significant increased risk per 1 mmol/l increment of glucose was observed for fatal cancer of the liver and the oesophagus.

The association between glucose and cancer risk, and for death from all causes, was further explored for glucose in deciles (Figure 12), using the lowest 40% of glucose levels as the referent group. In men, there was no significant association between increasing deciles and risk of incident cancer, whereas for fatal cancer and overall death, a strong risk increase was observed between decile nine and ten. The RR for top versus decile 1-4 in men for incident cancer was 1.14 (95% CI, 0.97-1.33, p for trend=0.09), for fatal cancer 1.84 (95% CI, 1.46-2.40, p for trend<0.001), and for overall death 3.29 (95% CI, 2.86-3.78, p for trend<0.001). Exclusion of prostate cancer in analyses resulted in stronger and significant associations for overall incident and fatal cancer in men.

In women, increasing deciles was linearly and significantly related to risk of overall incident and fatal cancer, and for overall death; the RR for top versus decile 1-4 for overall incident cancer was 1.42 (95% CI, 1.18-1.74, p for trend<0.001), for fatal cancer 2.05 (95% CI, 1.42-2.93, p for trend<0.001), and for overall death 3.69 (95% CI, 3.00-4.59, p for trend<0.001).
Figure 12. Relative risks (95% CI) in A, men, and B, women, of incident cancer (n cases: men, 18,621; women, 11,664), fatal cancer (n cases: men, 6,973; women, 3,088), and of death from all causes (n cases: men, 21,445; women, 8,424) by deciles of glucose. RRs are corrected for regression dilution ratio (RDR); conversion into uncorrected RR = \exp(\log(\text{RR}) \times 0.3). IFG indicates the range of impaired fasting glucose in the cohorts among subjects that had fasted more than eight hours before the blood draw, and DM indicates the range of diabetic glucose levels. Glucose levels in the Oslo study I were recalculated (level-0.95) to correspond with enzymatic levels measured in the other Norwegian cohorts.
4.3.2 General discussion

Our study is the largest study to date on glucose and cancer risk in a population of white ethnicity; the largest of previous studies were from the VHM&PP\textsuperscript{96} and the VIP\textsuperscript{95}, included in our Me-Can study. Jee \textit{et al.} reported the association between fasting glucose and cancer risk in 1.3 million Korean men and women\textsuperscript{92}, and results from our and the Korean study are largely coherent. Both studies showed an increased risk of overall cancer in men and women with elevated glucose levels, and associations were somewhat stronger for fatal than for incident cancer. Furthermore, strong associations were found in both studies for several specific cancers, such as pancreas cancer, particularly in women, liver cancer, and fatal cancer of the oesophagus and cervix uteri. Glucose was not related to risk of prostate cancer in our study or in the Korean study, and consequently, exclusion of prostate cancers in our study, which constituted 31\% of incident and 12\% of fatal cancers among men, resulted in substantially stronger associations for overall cancer in men. In the Korean study, in which rates of prostate cancer were low as in other Asian countries\textsuperscript{3}, strong associations between glucose and overall incident and fatal cancer was found in men at levels of impaired fasting glucose or lower, whereas in women, risk of overall cancer was only increased at diabetic glucose levels. Although in our study absolute glucose levels were approximated from subjects with glucose measured in a fasting state, our data suggested an increased risk of cancer among women already at glucose levels in the upper normal range. Diabetes has been associated with an increased risk of cancer overall and at specific cancer sites, in men and women\textsuperscript{83-94}. Findings from our and the Korean study suggest that glucose at levels lower than diabetic levels, and possibly also below that of impaired glucose, are related to an increased cancer risk.

Lung cancer and gastric cancer are common cancers worldwide and although a relatively large number of cases with these cancers were included in our and the Korean study\textsuperscript{92}, different results were found between the studies. Whereas we found a significant positive association between glucose and incident and fatal cancer of the stomach in women, and of the lung in men and a non-significant association in women, glucose was not related to risk of these cancers in the Korean study. The explanation for these inconsistencies is unclear. Lung cancer, and also stomach cancer, is related to tobacco smoking\textsuperscript{16,17}, and there were large differences in the proportion of smokers between the two studies; smoking was twice as common in Korean men (59\%) than in men in our study (29\%), whereas much fewer Korean women smoked (4\%) than did women in our study (23\%). An imprecise or incorrect classification of smoking status might mask a possible confounding or interaction effect in the association between glucose and risk, or alternatively, other factors, such as differences in genetics or e.g. nutrition, may be at play.
Furthermore, the increased risk of stomach cancer in our study only in women with elevated glucose, but not in men, is intriguing. In support of our findings, a study of diabetes and cancer risk in the United States showed the same pattern\textsuperscript{85}, whereas in a large Danish study of diabetics, a small increase in risk of stomach cancer was found in both men and women\textsuperscript{83}. We found opposite associations for glucose and risk between men and women for thyroid cancer and brain tumours. These suggested differences between men and women need to be further investigated in detail, e.g. by including further covariates of importance for the specific cancers that might interact with glucose, such as sex hormones, which may play a role in the observed differences between men and women for thyroid cancer\textsuperscript{222,223}.

As in our study, other studies have reported large random error of glucose measurements\textsuperscript{95,153,154}, which shows that studies that do not include correction for glucose variation are likely to substantially underestimate the association with outcome. Without correction, the RR of fatal cancer among men and women in the top decile was approximately 1.2, which after correction increased up to an approximately 2-fold increased risk, and the risk of death from all causes was even stronger, in accordance with the study by Jee et al.\textsuperscript{92}.

4.3.3 Interpretation

The association between elevated glucose and an increased cancer risk may be causal or some uncontrolled factors may confound the associations, such as e.g. genetics and nutrition. Genetics that relate to glucose control may also be directly related to cancer\textsuperscript{192}, and as regards to nutrition, various factors have been identified as risk factors for cancer\textsuperscript{24}, and it is possible that some of these components that are related to glucose control, act through a different pathway to cancer than through glucose. However, for most cancers, it is unlikely that a substantial confounding effect by nutritional factors remains after taking body weight into account, which was adjusted for in our study.

Insulin and IGF-I have been shown to promote tumour growth by stimulating cell proliferation and inhibiting apoptosis\textsuperscript{33,196,224}. Hyperglycaemia causes an elevation of insulin and free IGF-I, and the insulin-IGF-I pathway has been proposed as the key link between diabetes or insulin resistance and cancer\textsuperscript{84,85}. Possibly, glucose is also directly linked to cancer, as glucose is the main energy substrate in tumour cells, in particular in fast-growing tumours\textsuperscript{225-227}. The stronger association between glucose and risk of fatal cancer than of incident cancer in our and in the study by Jee et al.\textsuperscript{92} may be resulted by that glucose and related factors are more strongly involved in the progression of an existing tumour, than in the initiating phase. Other explanations may be that more “healthy” people, with normal glucose levels, are more prone to seek
health care than people with poor health, and thus will be diagnosed with cancer at an early stage and have a better prognosis. Alternatively, for some cancers, inconsistencies in registration of cancer diagnosis versus cancer death may exist that cause a difference in association\textsuperscript{228,229}.

4.3.4 Conclusions

In conclusion, paper VI showed that elevated glucose was related to an increased risk of cancer overall and at several separate sites, and stronger associations were found in women than in men, and for fatal than for incident cancer. Results from our study and from another large study in Korea are largely similar and show that glucose levels also in the upper range of normal levels may be related to an increased cancer risk. Glucose control is not only beneficial for prevention of diabetes and cardiovascular diseases, but is likely to also prevent cancer.
5 FUTURE PERSPECTIVES

Observational studies have consistently shown that obesity, diabetes, and metabolic factors related to these conditions increase the risk of several cancer forms, including colorectal cancer, and also death of prostate cancer. However, confounding and reverse causation remains a concern in observational studies, and thus, causality needs to be confirmed in studies with other design. Randomised controlled trials are considered the gold standard of studying causality in epidemiology, as it reduces possible effects of known, and importantly also for any unknown confounders. However, conducting such a trial is expensive and time consuming, and often not possible because of ethical concerns. Furthermore, as it takes many years to develop cancer, only surrogate markers for cancer are generally feasible to use in randomised trials. Another method is to adopt the concept of Mendelian randomisation, in which a genetic variant with a known association with the exposure of interest is studied with regards to the disease outcome. An association between the genotype and disease that is mediated only through the exposure of interest supports a causal association between exposure and disease. Several studies applying a Mendelian randomisation method have supported or refuted causality of associations found in observational studies. One example is that an u-shaped association between alcohol intake and hypertension has been reported in observational studies, i.e. such that moderate alcohol consumption was found to be beneficial for blood pressure, whereas studies of the ALDH2 genotype – strongly related to alcohol intake – have shown that the increase in blood pressure by alcohol intake is likely to be linear. The ALDH2 genotype has also been investigated in oesophagus cancer, and these studies have confirmed findings from observational studies that alcohol is a risk factor for oesophagus cancer. In order to investigate causality in future studies of lifestyle, metabolic factors, and cancer risk, inclusion of genetic analyses in future studies can give additional important information.

Future studies on metabolic factors and cancer risk should preferably include data on nutritional factors and physical activity, as this information could further elucidate possible pathways to cancer. A dilemma is the difficulties involved in assessing food intake and its nutritional compounds. The validity of food frequency questionnaires used in large scale studies is poor, including random and systematic error in dietary intake, and more accurate assessment of diet is time consuming and expensive. Furthermore, as nutrients are not eaten in isolation, a change in one nutrient will also result in other nutritional changes, which restricts the dietary assessment of nutrition at least in larger studies to rather identify dietary patterns than to accurately assess
micronutrient intake in detail. Dietary biomarkers measured in biological samples can add further information to such studies\textsuperscript{233}. Some biomarkers exist that highly reflect intake of a particular nutrient, such as urinary nitrogen for protein intake, but identification of further biomarkers is needed for optimal use in epidemiological studies. The use of nutritional biomarkers, which do not include biases associated with dietary assessment methods, would be a big step forward in diet-disease association studies. Another field to further expand in the lifestyle-metabolic syndrome aspect is to investigate gene-environment interactions, and to thereby answer questions such as whether cancer risk by metabolic aberrations is confined to people with a specific genetic trait.

Over the past few years, a number of studies on prostate cancer with different endpoints have been published, which altogether show a pattern that obesity, and possibly also further metabolic disturbances, increase the risk of aggressive prostate cancer and of death from prostate cancer, but not of non-aggressive disease. It has been speculated that factors related to obesity may stimulate prostate cancer progression, and in addition to plausible mechanistic explanations, there are some data from clinical studies in support of such a hypothesis. Recurrence rates after radical prostatectomy has been found to be higher in obese than in normal weight men\textsuperscript{234,235}; however, these data could also be explained by a direct link between a radical excision with negative margins in lean men compared to in obese men. Further clinical studies with detailed information on clinical predictors are needed to investigate the effect of obesity and metabolic factors on prostate cancer progression. Data from large cohorts could also be useful to assess survival in cases with a baseline observation preferably dated to a restricted time period in relation to diagnosis, e.g. five to one years before diagnosis. In such analysis, additional information on tumour characteristics and treatment is of great value. For prostate cancer and other cancers diagnosed at a high age it would also be of interest to study if associations from observational studies hold in analyses accounting for competing risks by other diseases.

Cohort studies are extremely valuable when studying different aspects of cancer aetiology, but they are expensive and a long follow-up is needed for a sufficient number of cancer cases to develop. Nevertheless, once a cohort is "mature", a variety of aspects can be investigated with relatively little effort. In order to gain high statistical power, several large collaborative projects are currently being started to study various aspects of cancer, e.g. the international Cohort Consortium formed by the National Cancer Institute in the United States\textsuperscript{236}, and the European Cohort Consortium, which is an extension of the already existing European Prospective Investigation into Cancer and Nutrition (EPIC) project\textsuperscript{237}. These collaborative initiatives are likely to yield more conclusive evidence on various relations in cancer epidemiology. Besides
increasing the study size, quality aspects should also be given priority in future observational studies. The inclusion of correction for random error in exposure measurements is already being used frequently in cardiovascular disease research and is likely to become more common also in studies of cancer. Furthermore, exposures can be investigated into more detail, for example, studies from the EPIC project have suggested that measures of fat distribution in addition to BMI may better characterise the association between obesity and risk of colorectal cancer\textsuperscript{150}, and possibly also of prostate cancer\textsuperscript{133} and renal cell cancer\textsuperscript{238}.

An even bigger challenge than finding ways to further investigate the relation between metabolic factors and cancer is to find ways to reverse the obesity and diabetes epidemic. Lifestyle changes are difficult to continue in long term; even in well controlled intervention trials in which good support for behavioural changes is provided, adherence is low. For example, in a randomised controlled trial comparing weight loss with different diets during two years, recently published in the New England Journal of Medicine, it was shown that regardless of diet, subjects started to regain weight after one year\textsuperscript{239}. It may well be that individual changes require action also from the environment, e.g. family, friends, or larger groups, and even the whole community\textsuperscript{240}. 
6 SUMMARY

Overweight and diabetes have been related to an increased risk of many cancer forms in men and women, including colorectal cancer, which is one of the cancers that have been most strongly related to lifestyle factors. For prostate cancer, overweight has been differently related to risk according to disease severity. Whereas overweight is not related to risk or may even decrease the risk of non-aggressive prostate cancer, an increased risk of aggressive prostate cancer and of prostate cancer death has been observed in overweight men. Diabetes has been related to a decreased risk of prostate cancer. Few studies have examined metabolic factors related to overweight and diabetes, on the association with cancer risk. In studies included in this thesis, we investigated the association between metabolic factors and risk of prostate cancer, colorectal cancer, and of cancer overall.

In paper I, we found that high levels of factors related to insulin resistance were associated with a decreased risk of prostate cancer, and the associations were stronger in the group of non-aggressive tumours. Paper III showed that whereas overweight was not related to risk of incident prostate cancer, overweight men had an increased risk of death of prostate cancer. High blood pressure was related to a decreased risk of incident prostate cancer and of non-aggressive disease, but was related to a non-significant increased risk of prostate cancer death.

In paper II, we found that obesity, hypertension, and hyperglycaemia, were related to an increased risk of colorectal cancer, and presence of two or three of these factors was related to a higher risk than the presence of the factors in single. In paper V, a high metabolic syndrome score, based on levels of BMI, blood pressure, glucose, cholesterol, and triglycerides, was related to an increased risk of colorectal cancer. Factors in the metabolic syndrome increased the risk of colorectal cancer in an additive, and not multiplicative, way. Significant positive associations for single factors were found for BMI in men and women, and for blood pressure and triglycerides in men.

Paper VI showed that high levels of blood glucose were related to an increased risk of cancer overall and of several specific cancer sites. We found that the association for overall cancer was stronger in women than in men, and for fatal than for incident cancer.

Conclusions:

- Insulin resistance and high blood pressure are related to a decreased risk of incident prostate cancer, but overweight is related to an
increased risk of prostate cancer death. As regards to blood pressure, further studies are needed before any conclusions can be drawn. Data from our and previous studies suggest that factors involved in prostate tumour initiation may be different from those that stimulate progression.

- Factors in the metabolic syndrome are related to an increased risk of colorectal cancer in an additive way, i.e. the risk increase by addition of each factor corresponds to what can be expected, as no interaction between factors appears to be present. Several mechanisms have been identified that may explain the associations between metabolic factors and colorectal cancer.

- Elevated blood glucose is related to an increased risk of cancer overall, and at several specific sites.
7 SUMMERING

Övervikt och diabetes har i studier relaterats till en ökad risk av flertalet cancerformer bland män och kvinnor, inklusive kolorektalcancer, som är en av de cancerformer som varit starkast relaterat till livsstil. Övervikt har påfunnits vara olika relaterat till risk för prostatacancer beroende på cancernoens aggressivitet. Medan övervikt inte är relaterat till risk, eller t.o.m. kan minska risken för en icke-aggressiv prostatacancer, har män med övervikt funnits ha en ökad risk för aggressiv prostatacancer och prostatacancerdöd. Diabetes har relaterats till en minskad risk för prostatacancer. Få studier har undersökt metabola faktorer relaterade till övervikt och diabetes, och dess association med cancerrisk.


I delarbete II fann vi att fetma, hypertoni och hyperglykemi utgjorde en ökad risk för kolorektalcancer, och förekomst av två eller tre av dessa faktorer var relaterat till en högre risk än för faktorerna var för sig. I delarbete V observerades att en hög nivå av metabola syndromet, vilket baserades på nivåer av BMI, blodtryck, glukos, kolesterol och triglycerider, var relaterat till en ökad risk för kolorektalcancer. Faktorer i det metabola syndromet ökade risken additivt och inte multiplikativt. Enskilda faktorer som var signifikant relaterade till kolorektalcancerrisk bland män och kvinnor var höga nivåer av BMI, och bland män även höga nivåer av blodtryck och triglycerider.

I delarbete VI observerades att höga nivåer av blodglukos var relaterat till en ökad risk för alla cancercr sammanslagna, samt för flertalet specifika cancerformer. Vi fann att associationen mellan glukos och total cancer var starkare bland kvinnor än bland män, och för cancerdöd än för cancerincidens.

Slutsatser:

- Insulinresistens och högt blodtryck är relaterade till en minskad risk för incident prostatacancer, men övervikt är relaterat till en ökad risk för prostatacancerdöd. Fler studier behövs innan någon säker slutsats kan dras avseende blodtryck och risk för prostatacancer. Resultat från våra
och tidigare studier kan tyda på att de faktorer som stimulerar initiering av prostatacancer inte är desamma som de som stimulerar tillväxt av prostatacancer.

- Faktorer i det metabola syndromet ökar risken av kolorektalcancer additivt, d.v.s. riskökningen för varje ytterligare faktor motsvarar den förväntade summerade effekten, eftersom ingen multiplikativ effekt mellan faktorer kunde påvisas. Flera möjliga mekanismer har identifierats som skulle kunna förklara relationen mellan metabola faktorer och kolorektalcancer.

- Förhöjt blodglukos är relaterat till en ökad risk för alla cancrar sammanslagna, och för flertalet specifika cancerformer.
I am grateful to the many persons who have contributed to this work and who have supported me during these four years. I especially want to thank:

**Pär Stattin** - my main supervisor. Thanks for giving me the chance without knowing much more about me than that I could read and write. Thanks for all the support, for always taking the time for conversations, for being picky, for being cheerful when I needed it the most (or the least), for giving me a lot of responsibility, and for really making an effort for me to have a good education. You are such a smart, respectable, and good person.

**Håkan Jonsson** - my co-supervisor. Thanks for all the valuable conversations about statistics and methods and for bringing down the statistical language to my level. Thanks for almost always taking the time when I called you or, often without any warning, showed up at your door, thanks for being so positive and interested in our work.

**Annie Lukanova** - my co-supervisor. Thanks for the personal and open conversations about work and life, for sharing your epidemiological and writing skills, and thanks for your encouragement in work and to me in person.

**Mattias Johansson** and **Christel Häggström** - my PhD friends during the first and last episode, respectively. Mattias, thanks for your company and help in work, and in particular, I am glad to have you as my friend. As a reply to your thesis, I also enjoyed having you as my cooking student. Christel, how nice it is to have a friend at work who is working on the same topic! Thanks for your support, for all the breaks in-between, and for trying to make me more social.

All the people at the Urology department - the university and clinical part, thanks for counting me as one of you even though I was not taking part in your daily work. Thank you **Solveig** for all kinds of things that you have helped me with during these years, and **Börje**, thanks for showing interest in my progress.

Collaborators in Me-Can, my main project, my “baby”. This was the most fun project throughout, thanks to the nice and easy going people involved in it, in particular: **Kilian Rapp, Hanno Ulmer, Tone Bjørge**, and **Jonas Manjer**.

**Göran Hallmans** - founder of the Medical Biobank in Umeå. Without data - no thesis, thank you much for that, and also for helping me out with making new contacts for my future. Thanks also to **Åsa Ågren** for your positive and service minded way to co-ordinate and help out with any data queries.
Thanks also to all other co-authors of my papers, especially Maria-Pia Hergens, for long-lasting patience with paper III, Rudolf Kaaks, for your involvement in paper I and II, Bernt Lindahl, for your expert opinion in paper I and also thereafter if I had any questions, Anders Engelund and Randi Selmer, for sorting out divergent queries about the extensive Norwegian data, and although not included in this thesis, Anne Cust and Eva Lundin, for pleasant collaboration in the breast cancer study.

Thank you Anders Ödin, for sorting out all kinds of problems with my PC. Thanks to people at the Oncological centre: Lena Nathanaelsson, Ove Björ, Björn Tavelin, and others at the OC who helped me sorting out different issues, or who were just friendly the many times that I was around, and to people at the biobank: John Hutilainen, Hubert Sjödin, Sara Nilsson, Veronica Hellström, and Sören Holmgren, and thanks also to: Anders Berg, Richard Palmqvist, Kjell Grankvist, Karin Hjertkvist, and Sabina Rinaldi – all contributing in different ways to this work.

I would also like to express my feelings and gratitude to the people I like the most:

I am so impressed by two persons who give more to others than they will ever get in return, Micke in Nyköping, and Wiebke. Micke, thanks for having been such a good boss and friend; introducing me to sports activities I had never tried before, and for just being welcoming and positive to me and to anyone. Wiebke, I´ve had so much fun with you because you don´t like to (Wiebke cite) “den Fischen im Aquarium zuzugucken”. Your energy to make things happen seems to be endless, you´re just great!

Sture. You made it possible for me and Mikael to spend time together with our father in your home, not only once, but year after year, every Christmas, for weeks. You must be crazy, and I am so grateful.

All my uncles, aunts and cousins around Sweden – the Johansson gene must be quite strong, because even if I don´t see any of you often, there is some kind of understanding and recognition when we meet.

Isn´t it great with friends? I have the best ones, I especially want to mention: Lumpan, my dear friend for deep talking, Camilla, always up for sports or to analyse life, Jonas, there is no one more cozy, kind and patient, and thanks for the front page!, Katti, almost too nice to be good for herself, Åsa, makes the most fun parties, Julia, when will you understand that you are the courageous one?, Nils, my newfound friend who knows how to have fun, and Raphael, I´ll send you the 90% for the AH with nuts in return.
Jenny - my cousin and very close friend. We have known each other forever, and have had a lot of fun together. I always feel welcome to your family, and it feels so good to know that you will always be there (as will I).

Sonja - my best friend. You are invaluable. So encouraging, so good to talk to about anything, so sparkling, and such a true friend - the first one to be there to support or to have fun with. I still keep a sms from you, one example of your encouragement, dated to September 30, 2004: “Hej! Ville bara säga att du är en jättebra kompis! Jag tycker om digjätemycket! Jag åker till min bror nu. Ha en bra kväll! Kram Sonja”

Ingemar - my “plastic daddy”, always glad, singing, teasing, kind, and a real original. You can be my plastic daddy forever (even though I nowadays take more care of you than the other way around). I love you.

My dad Josef. You are missing all the fun! Thanks for giving me and Mikael truly compromiseless love, for being so goodhearted, and for showing me that if you really believe in something, that is what you´ve got to do. I will miss you at all big moments in life. I love you.

My mum Kristina. You treat me like a princess when I visit, and if you can’t find out where I am, the police almost gets involved, just like a real mum. Thanks for your support and care. I love you. Lasse, thanks for making my mum happy, and for being so friendly.

Mikael and Jonas - my brothers. I love you both. Even if our contact is sporadic, you mean so much to me. The moments hanging in the sofa and arguing about whose turn it is to brew coffee, it doesn’t have to be more complicated than that. Mikael, I am so glad that you exist, for all the years we have shared - I don’t know how I would have managed without you. Jonas, to me you are almost an angel, so kind and calm. But I’ve heard that I don’t have all the facts, but don’t worry, I don’t believe in what they say 😊.

Last but not least, many thanks to all study participants for your contribution to research!

This work was supported by the World Cancer Research Fund, the Swedish Cancer Society, the Research Foundation in Northern Sweden, and by the Västerbotten County Council.
9 REFERENCES


