Prospective studies of cancer risk in Nord-Trøndelag: the HUNT study

Associations with anthropometric, socioeconomic, and lifestyle risk factors

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Trondheim 2001

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Front page:
Illustration from F.G. Gade (1929) Kreftsykdommene: Deres vesen, utbredelse og bekjempelse. Stenske forlag, Oslo

To my daughters,
Vida and Eila

Contents

Acknowledgements

The work presented in this thesis was carried out while I have been receiving a research fellowship from the Norwegian Cancer Society, a financial support for which I am very grateful. The research is based on data made available by the National Health Screening Service, the Cancer Registry of Norway, and the National Institute of Public Health, Community Medicine Research Center in Verdal, Nord-Trøndelag (recently incorporated into the Faculty of Medicine at the Norwegian University of Science and Technology (NTNU) as HUNT Research Center, Verdal). I acknowledge the important work of many individuals from these institutions, and in particular the meticulous data management at the research center in Verdal.

I owe particular gratitude to Professor Lars J Vatten who introduced me to the field of epidemiology, and who has been my daily mentor throughout this work. His scientific standards, epidemiologic knowledge, and encouraging advice have been of invaluable importance for my research.

I also whish to express my gratitude to Professor Roar Johnsen for valuable contributions and kind support both as co-author and as colleague, and for providing excellent working facilities as chairman of the Department of Community Medicine and General Practice at NTNU. Furthermore, I want to thank Professor Steinar Tretli for epidemiological and statistical advice during the course of this work.

Sincere thanks are also given to all my colleagues at the Department of Community Medicine and General Practice for fruitful discussions and a friendly working environment, and especially to Henrik Døllner, Rønnaug Ødegård, Pål Romundstad, and Svein Arthur Jensen for informal small talk and scientific inputs during everyday work at "Vorta på ISM".

Last but not least, my special thanks go to my friend and partner, Sissel, for her warm and enduring support, and to our daughters, Vida and Eila, for being so joyful and amusing.

Trondheim, August 2001

Tom Ivar Lund Nilsen

List of papers

This thesis is based on the following five publications:

Paper I Nilsen TIL and Vatten LJ. Anthropometry and prostate cancer risk: a prospective study of 22,248 Norwegian men. *Cancer Causes Control* 1999;10(4): 269-75

Paper II Nilsen TIL, Johnsen R, Vatten LJ. Socio-economic and lifestyle factors associated with the risk of prostate cancer. *Br J Cancer* 2000;82(7): 1358-63

Paper III Nilsen TIL and Vatten LJ. A prospective study of lifestyle factors and the risk of pancreatic cancer in Nord-Trøndelag, Norway. *Cancer Causes Control* 2000;11(7): 645-52.

Paper IV Nilsen TIL and Vatten LJ. Prospective study of colorectal cancer risk and physical activity, diabetes, blood glucose and BMI: exploring the hyperinsuliaemia hypothesis. *Br J Cancer* 2001;84(3): 417-22

Paper V Nilsen TIL and Vatten LJ. Adult height and risk of breast cancer: a possible effect of early nutrition. *Br J Cancer* 2001;85(7): 959-61

1

Introduction

> He is a better physician that keeps diseases off us, than he that cures them being on us; prevention is so much better than healing because it saves the labour of being sick.
>
> *Thomas Adams, 1618*

Cancer control is the ultimate objective of cancer research, cancer medicine, and cancer health services. Both theoretical arguments and empirical evidence indicate that primary prevention represents the most promising strategy for effective cancer control at the population level. This requires the identification of carcinogenic agents and the conditions that favor individual exposure to these agents. Different agents may act at different stages in the carcinogenic process and probably by very different mechanisms. Therefore, an agent is considered to be carcinogenic when a change in the frequency or the exposure to this agent is accompanied by a predictable change in frequency or occurrence of a particular cancer [Saracci and Trichopoulos, 1995].

This involves the topic of causal inference, which has generated intense debate among philosophers and scientists [Rothman, 1988]. In theory, the best empirical evidence regarding causation should come from double-blind randomized trials in humans, but experimental studies of cancer causation cannot be readily performed in humans. Hence, consistent findings of epidemiologic studies, carefully conducted and with adequate analytic control of confounding, represent the best criteria of causality in human carcinogenesis [Saracci and Trichopoulos, 1995].

Cancer is a generic name that derives from the Greek *karkinos*, and in truth, the term refers to more than 100 forms of the disease. Almost every tissue in the body can spawn malignancies, and what is more, each cancer has unique features. Still, the basic processes that produce these diverse tumors appear to be quite similar; accumulation of mutations; inappropriate reproduction and uncontrolled proliferation; and finally, the insidious property of cell migration, subsequently invading nearby tissue and forming distant metastases [Weinberg, 1996]. However, it is necessary to consider the various forms of cancer separately

in terms of both epidemiology and other factors, such as biology and treatment [Boyle et al., 1995].

1.1 Epidemiology and natural history of prostate cancer

Prostate cancer is the most frequently diagnosed malignancy in Western societies, and a leading cause of male cancer deaths [Landis et al., 1998; Cancer Registry of Norway, 1998]. Incidence has increased steadily in Norway from 1960 to 1990, but after 1992 the increase has escalated (Figure 1). This could partly be explained by a decrease in competing causes of death among the elderly and by increased life expectancy [Haas and Sakr, 1997]. Also, use of serologic testing for prostate-specific antigen (PSA) is likely to have contributed to this dramatic increase.

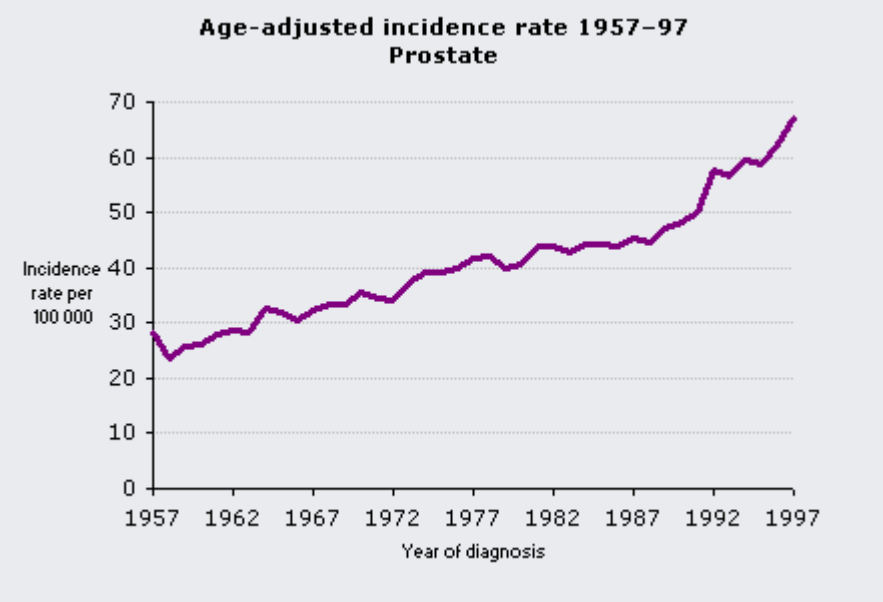

Figure 1: Age-adjusted incidence rate of prostate cancer in Norway between 1957 and 1997 [www.kreftregisteret.no]

Most of the established risk factors are constitutional, such as age, race, and family history. Prostate cancer is the most age-related of all epithelial cancers [Ross et al., 1979]; it rarely occurs prior to age 50, is infrequent for the next decade of life, but increases rapidly thereafter (Figure 2). African-American men have by far the highest prostate cancer rates in the world, followed by American and North-European whites, and the lowest rates are seen in Asian men [Muir et al., 1987]. Prostate cancer is also a familial disease; for an individual with

only one first-degree relative with prostate cancer, risk is elevated two-fold, increasing to five and 11-fold if two or three first-degree relatives are affected [Steinberg et al., 1990].

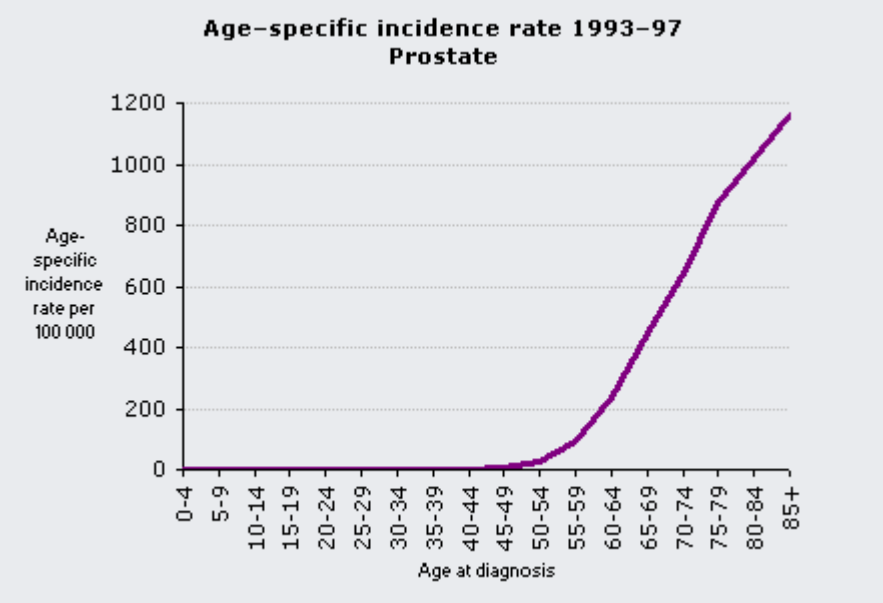

Figure 2: Age-specific incidence rate of prostate cancer in Norway in the period 1993 to 1997 [www.kreftregisteret.no]

However, the role of modifiable factors remains poorly understood, although the international variation [Muir et al., 1991; Parker et al., 1998], and especially that risk is modified by migration [Haenszel and Kurihara, 1968], indicates environmental mechanisms of causation. Dietary components have received great attention, both in epidemiologic and animal studies, and dietary fat is reported to be one of the most promising areas regarding prevention of prostate cancer [Giovannucci, 1996]. Cigarette smoking is generally not considered a risk factor for prostate cancer [Colditz, 1996], although a few studies have reported a positive association [Hsing et al., 1991; Cerhan et al., 1997]. Similarly, there are conflicting findings on the association between alcohol consumption and the risk of prostate cancer [Hiatt et al., 1994; Andersson et al., 1996; Hayes et al., 1996; Lumey et al., 1998]. Available results for physical activity and fitness are inconsistent [Le Marchand et al., 1991; Lee et al., 1992; Thune and Lund, 1994; Hartman et al., 1998], as are those considering marital status and socio-economic factors [Talamini et al., 1986; Severson et al., 1989; Hayes et al., 1992; Andersson et al., 1996; Harvei and Kravdal, 1997]. Considerable attention has been paid to patterns of sexual behaviour [Rotkin, 1977; Checkoway et al., 1987; Ross et al., 1987; Oishi et al., 1990; La Vecchia et al., 1993], and it has been suggested that both bacterial and viral infections may increase the risk of prostate cancer, but no causal relation has been established. There has also been a longstanding interest in the possible role of androgens in

the pathogenesis of prostate cancer, but studies on the association between plasma levels of testosterone or dihydrotestosterone and prostate cancer risk are conflicting [Gann et al., 1996; Signorello et al., 1997; Vatten et al., 1997].

Autopsy studies have shown a high prevalence of occult prostate cancer in the general male population; from 10% for men in their fifties to 70% for men in their seventies and eighties [Mettlin et al., 1993]. Hence, incidence data fail to provide adequate indication of the underlying burden of the disease; we only measure the "tip of the iceberg" and thus, many men die with prostate cancer but do not die from prostate cancer. However, the more we look for prostate cancer the more we will find, especially with abundant testing for PSA. Unfortunately we are not yet able to distinguish the significant (i.e. fast growing, metastasizing and potentially lethal) cancers from the more insignificant. The metaphor of the "barnyard pen" has been used to describe the different patterns of prostate cancer behavior [Pow-Sang, 1998]: In this pen there are turtles going nowhere (incidental, nonlethal cancers), rabbits ready to hop out at any time (potentially lethal cancers that might benefit from treatment), and free-flying birds (cancers that are beyond cure at diagnosis). Therefore, a major problem in diagnosing and treating prostate cancer is to identify tumors that will not grow, or grow very slowly, since "unnecessary" interventions may create worse problems for the patient than the cancer itself.

1.2 Epidemiology and natural history of pancreatic cancer

The incidence of pancreatic cancer has increased steadily in economically advanced populations, but the international variation is relatively small for pancreatic cancer compared to many other cancers [Parkin et al., 1992]. In the Nordic countries the age-adjusted incidence has been stable since the 1970s, and predictions until 2010 show only minor changes, but the predicted number of cases will increase with time due to the aging of the population [Engeland et al., 1993]. Although pancreatic cancer is relatively rare, the extraordinary bleak prognosis makes the disease a major cause of cancer mortality; it was the sixth leading cause of death from cancer in Norway in 1995 [Cancer Registry of Norway, 1999].

The majority of malignant pancreatic neoplasms are exocrine in origin, and 90% arise from the pancreatic ducts. Cancer arising at the head of the pancreas is more common than cancer that develop at the body and tail combined, but tumors at the latter locations are often larger at diagnosis because they are detected later than tumors at the head [DiMagno, 1995].

Signs and symptoms of pancreatic cancer are nonspecific and occur most often after advanced disease is present [DiMagno, 1995]. In most patients, the course of the disease is painful, and in about 70% of the patients, pain is the presenting symptom. Other clinical signs associated with pancreatic cancer are jaundice and weight loss [Raijman and Levin, 1993]. When first seen, 90 % of the patients have regional lymph node metastases and 80% have liver metastases [Ackerman and de Regato, 1962]. Case fatality rates for cancer of the pancreas are extremely high, with a 1-year relative survival of approximately 10% for both men and women (Figure 3).

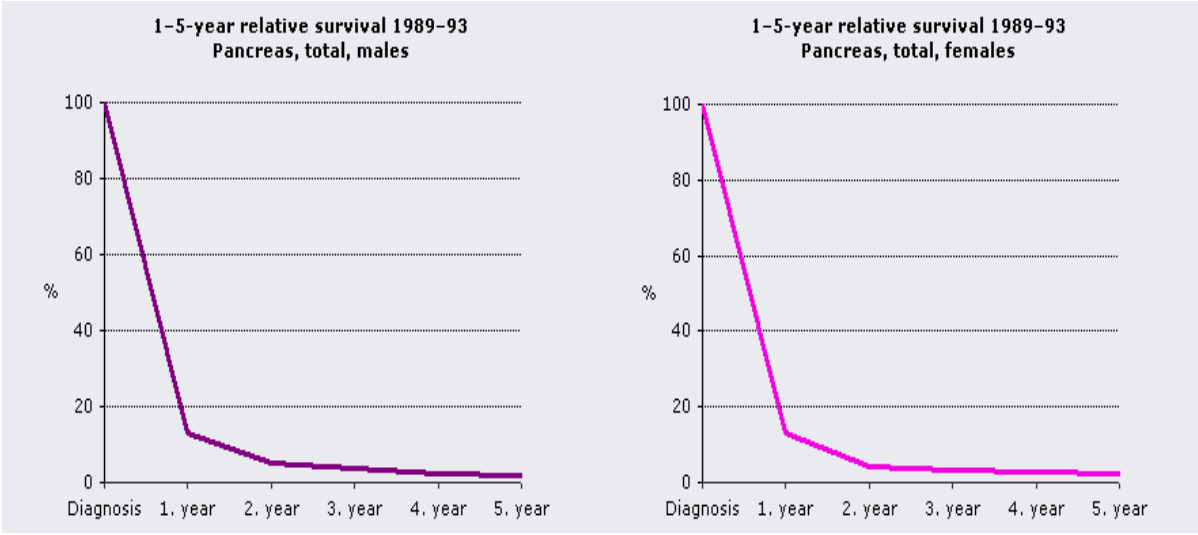

Figure 3: 5-year relative survival of pancreatic cancer for Norwegian males and females in the period 1989 to 1993 [www.kreftregisteret.no]

The incidence of pancreatic cancer varies with age, sex and race. Age-specific incidence rates (Figure 4) show that the disease is practically absent before age 40 years, then there is a slow increase in incidence between age 40 and 60 years, after which it rapidly escalates. Cancer of the pancreas is more common in men than in women. However, from the gender-specific incidence rates reported by the Cancer Registry of Norway, it appears that the increase in incidence of pancreatic cancer in men has leveled off, and maybe decreased, since the mid-1980s, while this trend is not evident for women (Figure 5). This is also reflected in a change in the age-adjusted male:female ratio over time; in the period 1963-67 the ratio was 1.9, between 1978 and 1982 it was 1.6, and between 1993 and 1997 the ratio had decreased to 1.3 [Cancer Registry of Norway, 2000]. In the United States, the highest incidence rates of pancreatic cancer is seen in nonwhite men, with the next highest rates in white men, followed by nonwhite women and white women [Gordis and Gold, 1993]. Worldwide, the highest incidence rates have been found in New Zealand Maoris and native Hawaiians, while India,

Singapore, and Kuwait all have low reported incidence [Muir et al., 1987]. It remains uncertain whether such geographical and racial differences reflect different genetic susceptibility to pancreatic cancer, or to what extent environmental exposures and lifestyle differences are involved [Carter, 1993].

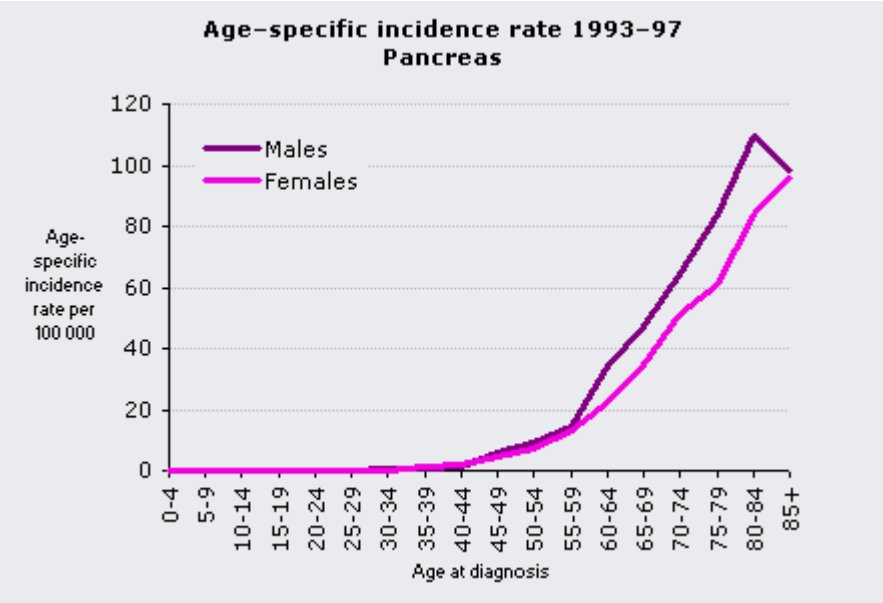

Figure 4: Age-specific incidence rate of pancreatic cancer in Norway in the period 1993 to 1997 [www.kreftregisteret.no]

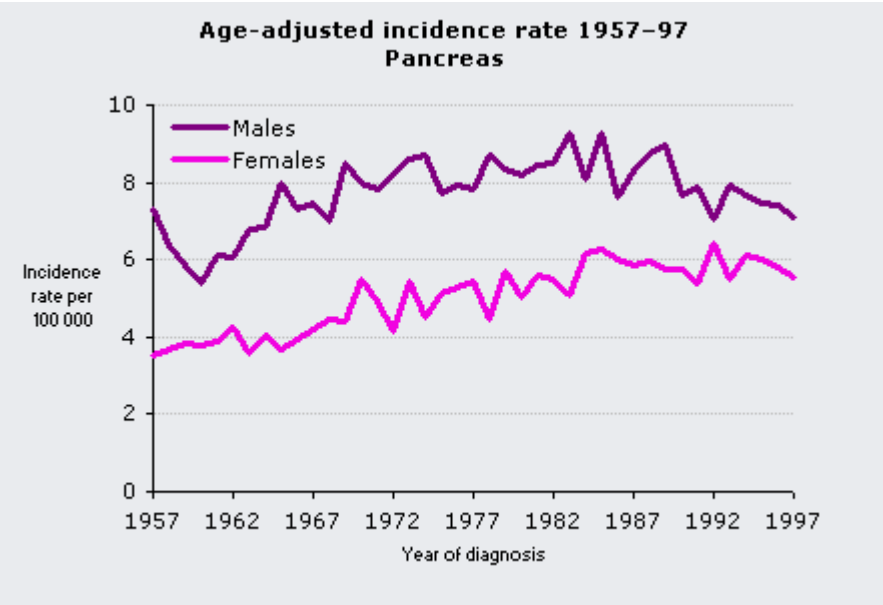

Figure 5: Age-adjusted incidence rate of pancreatic cancer in Norway between 1957 and 1997 [www.kreftregisteret.no]

Migration studies, especially of Japanese migrants to the United States, have not contributed to unravel the importance of modifiable risk factors in the etiology of pancreatic

cancer. Japanese migrants to the United States have a higher incidence than both native Americans and Japanese remaining in Japan [Buell and Dunn, 1968; Haenszel and Kurihara, 1968], but these apparent changes in incidence may be attributable to misclassification of pancreatic cancer as gastric cancer in Japan [Buell and Dunn, 1968]. Possible risk factors such as smoking [Howe et al., 1991; Boyle et al., 1996; Fuchs et al., 1996], alcohol consumption [Boyle et al., 1989], physical activity [Lee and Paffenbarger, 1994], diabetes mellitus [Hiatt et al., 1988; Calle et al., 1998], and anthropometry [Ji et al., 1996; Robsahm and Tretli, 1999] have been studied, but with the exception of cigarette smoking, which stands out as a plausible causative agent, no causal relations have been firmly established [Weiderpass et al., 1998].

1.3 Epidemiology and natural history of colorectal cancer

Colorectal cancer is the fourth commonest form of cancer occurring worldwide, with an estimated 783,000 new cases diagnosed in 1990, the most recent year for which international estimates are available [Boyle and Langman, 2000]. Colorectal cancer incidence rates vary approximately 20-fold around the world [Parkin et al., 1997]; the highest rates are seen largely in developed countries of North-America, Western Europe, and Australasia, while the lowest rates are seen in India and other Asian countries. In developed countries, colon cancer occurs at approximately twice the rate of rectal cancer, whereas in developing countries the incidence is similar for both these cancers. In Norway, the incidence of colon cancer has increased steadily the past 40 years, and has occurred with approximately equal frequency in men and women (Figure 6). Rectal cancer shows the same increase in incidence over the years as colon cancer, but it affects more men than women (Figure 7). In 1997 the age-adjusted male:female ratio for rectal cancer was 1.5 [Cancer Registry of Norway, 2000].

The importance of environmental factors in the etiology of colorectal cancer is suggested by migrants moving from low-incidence to high-incidence regions. For example, Japanese migrants moving to the USA and southern European migrants moving to Australia have higher mortality rates from colorectal cancer than the populations of their countries of origin [Haenszel and Kurihara, 1968; McMichael and Giles, 1988], and incidence rates of Japanese born in the USA exceed those of US whites [Shimizu et al., 1987]. Moreover, the incidence of colorectal cancer has increased rapidly in several populations previously considered to be at low risk for the disease [Parkin et al., 1997]. Hence, colorectal cancer has

been regarded as a predominantly lifestyle cancer associated with affluence, and especially with the "affluent diet" high in energy, fats and animal protein and low in dietary fiber, fresh fruits and vegetables. A follow-up of 88,751 women in the US Nurses' Health Study cohort showed that consumption of animal fat was associated with increased risk of colorectal cancer, with a relative risk of 1.89 (95% confidence interval 1.13 to 3.15) comparing extreme quintiles [Willett et al., 1990]. Several lifestyle factors apart from diet and nutrition have been studied in relation to colorectal cancer risk, but most promising for prevention is probably the observation of a protective effect of physical activity in colon cancer [Colditz et al., 1997].

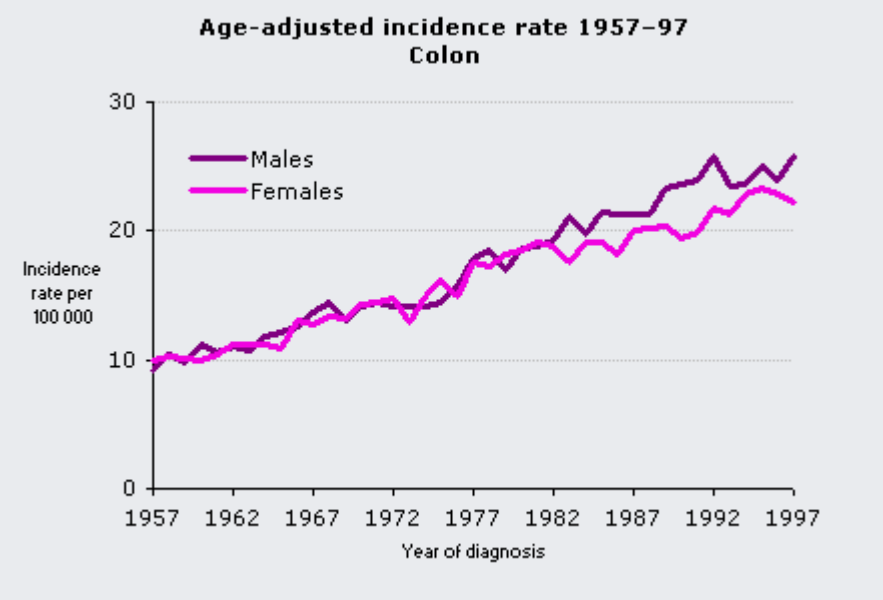

Figure 6: Age-adjusted incidence rate of colon cancer in Norway between 1957 and 1997 [www.kreftregisteret.no]

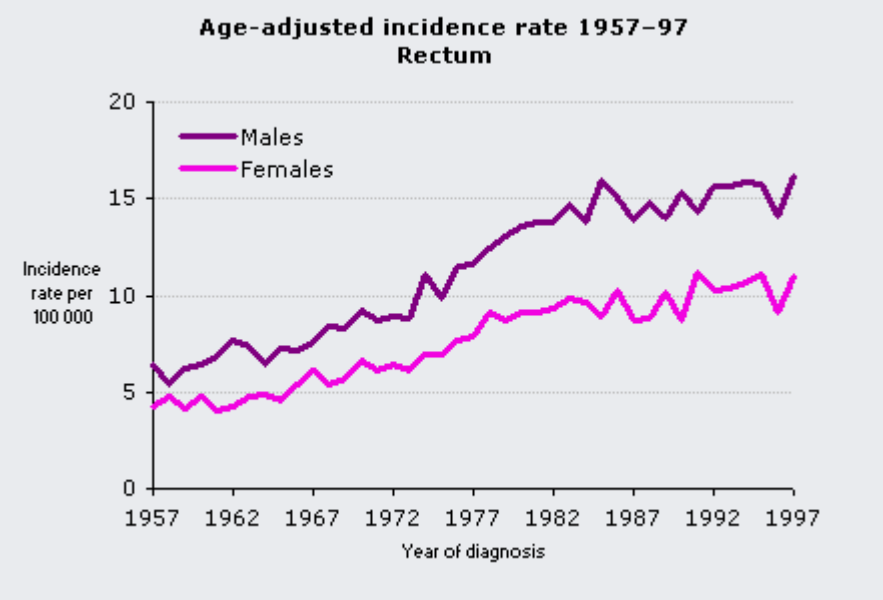

Figure 7: Age-adjusted incidence rate of rectal cancer in Norway between 1957 and 1997 [www.kreftregisteret.no]

Several genetically determined conditions predispose to colorectal cancer, for example familial adenomatous polyposis, a condition that carries an 80-100% risk of colorectal cancer by age 50 years, and hereditary non-polyposis colorectal cancer. Overall, however, these recognized syndromes account for relatively few colorectal cancers [McMichael and Giles, 1994]. A family history of colorectal cancer increases the risk for developing the disease, but an increased risk has also been observed among people with a family history of breast, ovarian and endometrial cancer [Potter et al., 1993].

The overwhelming majority of colorectal tumors are adenocarcinomas, and most cancers represent malignant conversion occurring in a preexisting adenomatous lesion. This yields a wide spectrum of lesions, ranging from small neoplasm with low-grade dysplasia and no immediate ability to invade or metastasize, at one end of the spectrum, to the poorly differentiated adenocarcinoma with an unlimited capacity for local and distant spread, at the other. Approximately 20% of adenocarcinomas are poorly differentiated or undifferentiated, and these tumors are associated with a poorer outcome. The aggressiveness of a colorectal tumor is reflected by its ability to invade, but there is no important relation between the apparent tumor size and the outcome. A large bulky tumor may neither penetrate the muscularis propria nor metastasize, while a small 2- to 3-cm tumor may invade and metastasize to distant sites. Hence, the best prognostic indicator is the depth of invasion, and this may be characterized according to the Duke-Turnbull classification that ranges from carcinoma in situ, via stage A, B, and C, to stage D, which is distant metastases [Boland, 1995].

1.4 Epidemiology and natural history of breast cancer

With one million new cases in the world each year, cancer of the breast is the most common form of cancer in women and comprises 18% of all female cancer [McPherson et al., 2000] The mortality rate from the disease has changed very little in the past 50 years, but its incidence has increased by 40 to 70% in the same period. In Norway, the incidence rate of breast cancer has increased from 40 cases per 100,000 in the early 1960s to more than 60 cases per 100,000 in the late 1990s (Figure 8). Moreover, in the 5-year period from 1993 to 1997 10,810 new cases of breast cancer were reported to the Cancer Registry of Norway, compared to 4,808 new cases in the 5-year period between 1958 and 1962 [Cancer Registry of Norway, 2000].

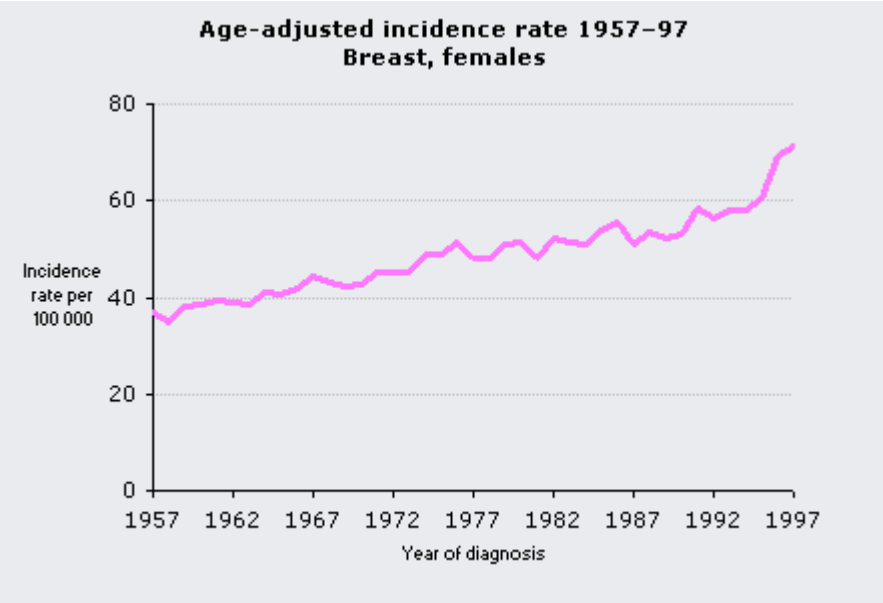

Figure 8: Age-adjusted incidence rate of female breast cancer in Norway between 1957 and 1997 [www.kreftregisteret.no]

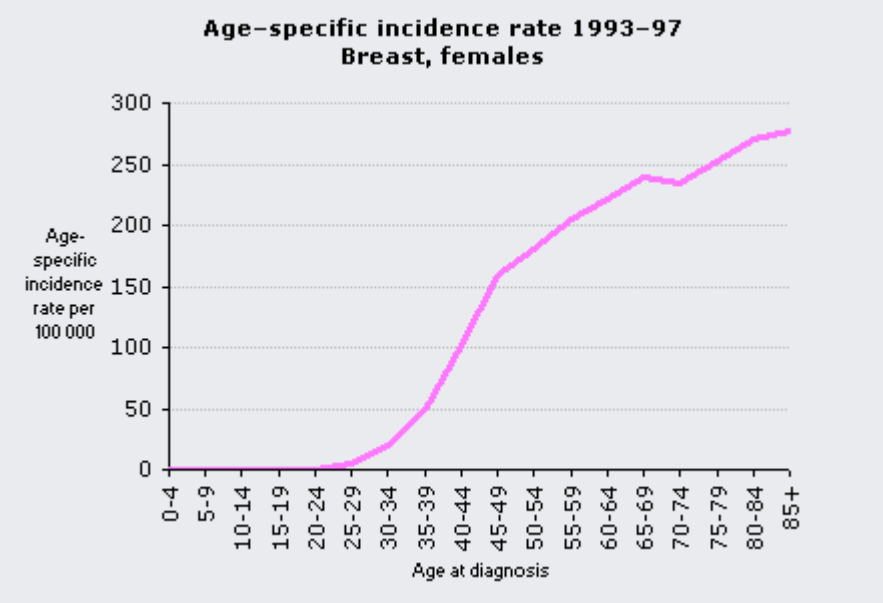

Figure 9: Age-specific incidence rate of breast cancer in Norway in the period 1993 to 1997 [www.kreftregisteret.no]

If we look at the age-specific incidence of breast cancer (Figure 9) we find that it already starts to increase among women in their late twenties, and continues to increase exponentially up to age 50 years (i.e. menopause), when there is a distinct slowing of the rate of increase. Epidemiologic studies on the effect of age at menopause on breast cancer risk have shown that a 10 year earlier age at menopause is associated with a halving of risk [Kelsey et al., 1993]. Compared to the slowed rate of increase in breast cancer incidence after menopause in Norway and other high risk countries of the Western world, the incidence rate in low risk Asian countries has been observed to remain almost constant after menopause

[Pike et al., 1983]. This lack of further increase in breast cancer incidence after menopause may be explained by very low levels of endogenous estrogen in postmenopausal Asian women [Bernstein and Ross, 1993].

The epidemiology of breast cancer is only partially understood, despite an enormous research activity. Major attention has been directed towards reproductive factors, and early menarche and late menopause have been associated with increased risk, pointing to a potential role of ovarian hormones in the etiology of the disease [Hsieh et al., 1990]. A late age at first birth is an important determinant of breast cancer risk, and MacMahon and colleagues first demonstrated that women with a fist birth after age 30 years had twice the risk of women who gave birth before age 20 years [MacMahon et al., 1970]. Lifetime risk is also reduced among women who report multiple births [Hsieh et al., 1990]. However, the protective effect of pregnancy appears only after some delay, with a transient increase in risk for some time after delivery [Lambe et al., 1994].

The incidence of breast cancer differs strongly across cultures, where the rate in highly developed countries of the western world may be five or more times higher than the rate in most Asian countries [Parkin et al., 1997]. However, since migration studies have shown that people who move from low incidence to high incidence areas, and assimilate the new culture, develop similar risk of breast cancer as natives of their new country [Buell, 1973; Ziegler et al., 1993], differences in breast cancer rates among different geographical areas do not appear to be based on genetic differences. Hence, the importance of dietary factors has been intensely studied; however, after several decades of research, the role of diet in breast cancer causation remains unclear [Hunter and Willett, 1996]. Studies of diet have primarily focused on nutrition during adult life, and it is not known whether dietary influences during periods of rapid growth (i.e. infancy and adolescence) may affect future risk of breast cancer. Height and other measures of frame size may reflect an influence of diet in the remote past that may be difficult to measure in any other way [Willett, 1998]. Adult body height has been positively associated with breast cancer risk in several studies [de Waard, 1975; Tretli, 1989; Vatten and Kvinnsland, 1990], suggesting that nutrition and somatic growth during childhood and adolescence may be of importance for the risk of breast cancer.

Recent interest has focused on the role of intrauterine factors and prenatal exposures on subsequent breast cancer risk, and some studies have reported a positive association with birth weight [Ekbom et al., 1992; Michels et al., 1996; Sanderson et al., 1996; Stavola et al., 2000; Kaijser et al., 2001], but others have not been able to confirm this association [Le Marchand et al., 1988; Ekbom et al., 1997]. For birth length and placenta weight there have

been no clear findings, but preeclampsia in the mother, which is associated with reduced fetal growth, appears to reduce the risk of breast cancer in the daughters [Ekbom et al., 1992; Ekbom et al., 1997; Sanderson et al., 1998].

A small proportion of breast cancer cases, in particular cancers diagnosed at an early age, are attributable to hereditary predisposition to the disease, and two important genes have been identified (*BRCA1* and *BRCA2*). A family history of breast cancer in a first-degree relative has been associated with approximately a doubling of risk [Bain et al., 1980]. If both the mother and a sister have had breast cancer, the risk is even higher. These familial effects are enhanced if the relative had either early-onset cancer or bilateral disease.

The clinical behavior of breast cancer is characterized by a long natural history and by heterogeneity among patients in its clinical course. The prognosis of patients with breast cancer has been well documented in terms of size of the tumor and the presence and extent of involvement of regional lymph nodes. The most common sites of regional involvement of breast cancer are the axillary nodes, internal mammary nodes, and supraclavicular lymph node regions. Knowledge of the likelihood of involvement of these sites and their significance is important in the staging and planning of treatment. However, patients diagnosed with breast cancer are at risk for metastasis for extended time periods, and hence, the definition of cure in

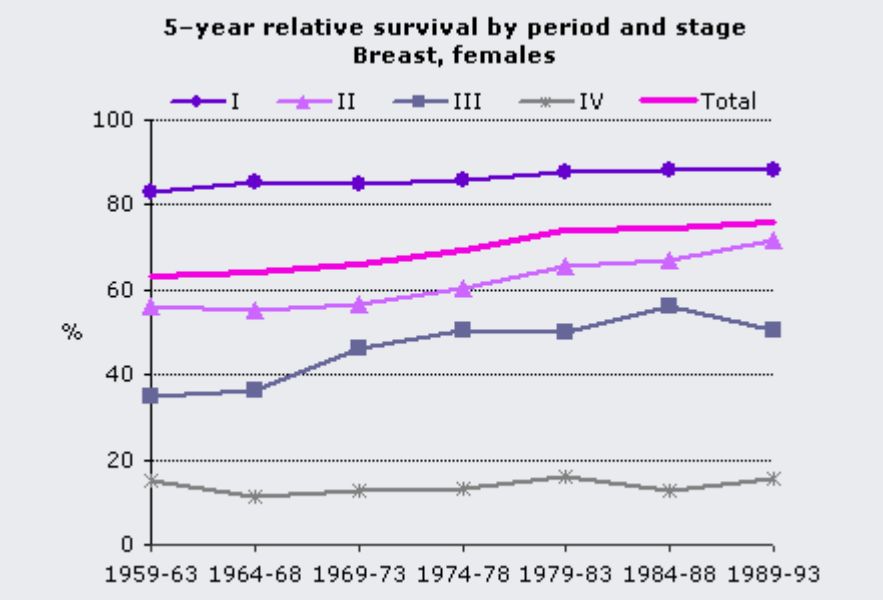

Figure 10: 5-year relative survival of breast cancer in Norway by period and stage [www.kreftregisteret.no]

the disease may be problematic. A personal cure for an individual refers to a patient living symptom-free from breast cancer and dying of other causes, while a group of treated patients may be considered statistically cured if their subsequent death rate from all causes is similar

to that of a normal population with the same age-distribution [Harris and Hellman, 1996]. It has been estimated that 80% of patients with tumor size 1 cm or smaller, and 70% of patients with tumor size between 1 and 2 cm, had personal cure [Rosen et al., 1989]. This means that many women treated for breast cancer will live out their normal life expectancy without further evidence of the disease. Survival curves for breast cancer patients in Norway show a 5-year relative survival for breast cancer of all stages combined of approximately 75% in the period 1989-1993 (Figure 10). Figure 10 also shows that the proportion of breast cancer patients who survive five years or more have increased with 10% over the past 30 years, mainly due to increased survival in women with stage II and stage III tumors.

2

Objectives

> Whoever whishes to investigate medicine properly should proceed thus in the first place to consider the seasons of the year, and what effect each of them produces. Then the winds, the hot and the cold, especially such as are common to all countries, and then such as are peculiar to each locality. One should consider most attentively the waters which the inhabitants use (…); and the ground (…); and the mode in which the inhabitants live, and what are their pursuits, whether they are fond of drinking and eating to excess, and given to indolence, or are fond of exercise and labor.
>
> *Hippocrates, fifth century B.C.*

The major objective of this thesis was to exploit data from a large cohort of Norwegian men and women to examine the influence of anthropometric, lifestyle, and demographic factors on the risk of cancer. Furthermore, we focused on the three most frequently diagnosed cancers in the Norwegian population, namely prostate cancer in men, breast cancer in women, and colorectal cancer in both sexes. Additionally, the incidence of pancreatic cancer is rising, and with a 5-year relative survival of 2% [Cancer Registry of Norway, 1998] it was the sixth leading cause of death from cancer in 1995 [Cancer Registry of Norway, 1999]. One of the initial goals in the Nord-Trøndelag Health Survey was to study the epidemiology of diabetes mellitus, and it has been suggested that pancreatic cancer is related to diabetes [Gordis and Gold, 1993]. Hence, we utilized available information to study possible risk factors for pancreatic cancer.

More specifically, we aimed at the following:

- To examine prospectively whether there is a positive association between prostate cancer risk and the anthropometric measurements height, weight, body mass index, and lean body mass, since this has been found in some, but not all, previous studies (Paper I).
- To prospectively investigate the association with different lifestyle and demographic variables previously suggested to be associated with the risk of prostate cancer, including cigarette smoking, alcohol consumption, physical activity, diabetes mellitus, marital status, educational attainment, and occupational socioeconomic status (Paper II).

- To prospectively explore to what extent different lifestyle factors are associated with the risk of pancreatic cancer in a large cohort of men and women, since epidemiologic knowledge of this inevitably fatal disease is sparse (Paper III).
- To prospectively examine the association between colorectal cancer risk and factors related to insulin resistance and hyperinsulinaemia (i.e. physical activity, diabetes mellitus, blood glucose, and BMI), since it has been suggested that insulin may promote the growth of colorectal tumors (Paper IV).
- To prospectively investigate whether the association between adult height and risk of breast cancer is modified by year of birth, since intrauterine life and prenatal conditions may influence both somatic growth and the future risk of breast cancer (Paper V).

3

Material and methods

> Some people hate the very name of statistics, but I find them full of beauty and interest. Whenever they are not brutalized but delicately handled by their higher methods, and are warily interpreted, their power of dealing with complicated phenomena is extraordinary. They are the only tools by which an opening can be cut through the formidable thicket of difficulties that bars the path of those who pursue the Science of man.
>
> *Sir Francis Galton, 1889*

3.1 The Nord-Trøndelag Health Survey (HUNT)

The county of Nord-Trøndelag is one of 19 Norwegian counties. Located in the central part of Norway (Figure 11), with a population of approximately 126,000, its geographical and demographic structures are fairly representative for the country as a whole. Between 1984 and 1986 the National Health Screening Service in Norway conducted the Nord-Trøndelag Health Survey (HUNT) – the largest medical survey ever performed in Norway.

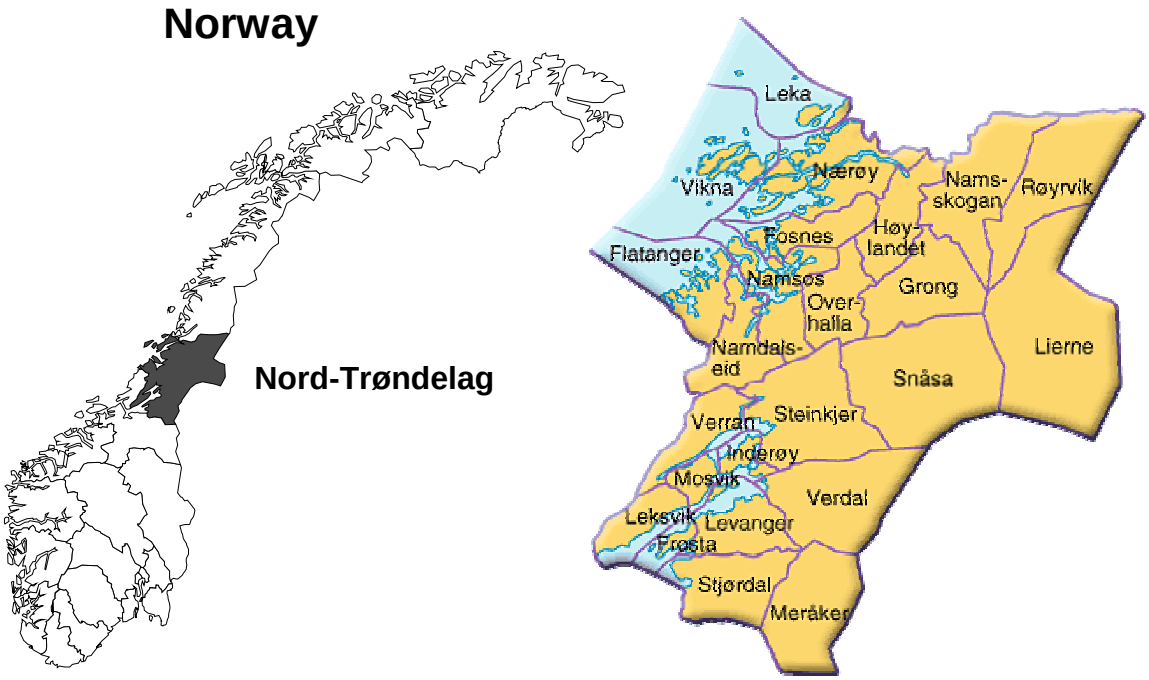

Figure 11: Study area – the county of Nord-Trøndelag and it's 24 municipalities [www.norge.no]

All residents in Nord-Trøndelag county aged 20 years or more were invited to participate, and among 85,100 eligible persons, 77,310 (90.8%) filled in the questionnaire that was mailed together with the invitation. The health examination included measurements of height, weight, blood pressure, pulse rate, and blood glucose. Additionally, a second questionnaire was handed out at the examination, together with a pre-stamped envelope, that the participants were asked to fill in and return from home. This second questionnaire contained queries on several medical and lifestyle factors, such as history of diabetes, smoking history, alcohol consumption, physical activity, educational attainment, and occupational category. A more comprehensive description of the participants, questionnaires, and screening procedures are previously given by Holmen and Midthjell [1990].

3.2 The Cancer Registry of Norway

Due to a circular from the Ministry of Health and Social Affairs 17 October 1951, the Cancer Registry has since 1953 kept a complete registry of all incident cases of cancer in Norway. Regulated by Norwegian law, medical practitioners are required to report cancer and all pre-cancerous lesions to the registry. Additionally, all pathological laboratories send copies of their laboratory reports to the Cancer Registry instead of filling in special forms. To further achieve a high degree of completeness and high data quality, the material of the Cancer Registry is matched against the Register of Deaths at Statistics Norway. Both Statistics Norway and the Cancer Registry send queries to hospitals, histopathological laboratories, and physicians in the case of incomplete reporting. As a consequence of this special cancer reporting system, most cases are reported repeatedly and from different sources. For all cases registered since 1953, 85% are histologically verified and less than 2% of the diagnoses are based on death certificate alone [Cancer Registry of Norway, 2000]. A completeness of nearly 100% has been shown for solid tumors [Lund, 1981].

The Cancer Registry database contained in 1997 information on 891,523 cancer cases registered from 1953. From 1984 to 1997, the annual number of new cases registered at the Cancer Registry has increased from 16,000 to nearly 21,000, with an age-adjusted male:female ratio in 1997 of 1.16. Prostate cancer is the most frequent cancer in men and breast cancer is most frequent in women. Combined, these sites accounted for 45% of all new cancers in Norway between 1993 and 1997 (Figure 12). Moreover, cancer of the colon and

rectum are frequent in both sexes, with 1,524 cases in men and 1,575 cases in women in 1997 [Cancer Registry of Norway, 2000].

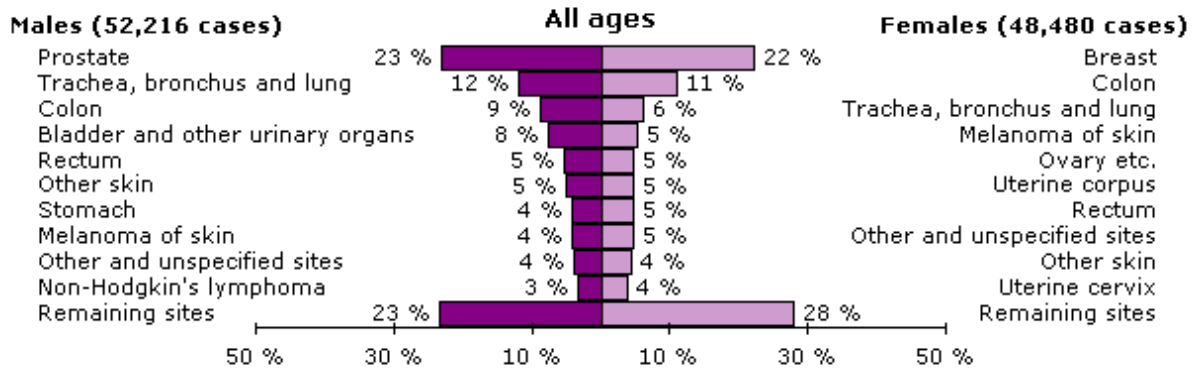

Figure 12: Cancer in Norway 1993–97. The most frequent types of cancer in males and females of all ages [www.kreftregisteret.no]

3.2.1 Follow-up

Every citizen in Norway is given a unique 11-digit identity number at the time of birth. This number enable linkage between different registers and data files on the same person. However, the use of the ID-number is strictly regulated through the Norwegian Data Inspectorate, which is an independent administrative body under the Norwegian Ministry of Justice set up to ensure enforcement of the Act relating to Personal Data Registers (Act of 9 June 1978). Being attached to each participant's record, we used the identity number to link information between the Nord-Trøndelag Health Survey database and the Cancer Registry, in order to ascertain all incident cases of cancer that occurred in the cohort during follow-up.

This linkage was performed in January 1998. Due to the punctilious cancer reporting system in Norway, there is a delay between the date of diagnosis and the date of registration in the Cancer Registry, and hence, the linkage provided complete information on all cancers in the cohort from 1953 through 1995. Hence, in our analysis presented in Paper II–V we used 1 January 1996 as cut-off for follow-up. However, in our analysis of anthropometric factors related to prostate cancer risk (Paper I) we utilized all incident cases of prostate cancer registered in the Cancer Registry; the latest registered person with prostate cancer was diagnosed in June 1997, and thus, we used 30 June 1997 as cut-off date.

After excluding 2,091 persons with prevalent cancer at study entry, the health survey cohort consisted of 75,219 persons aged 20 years or older who were eligible for follow-up. Each participant contributed person-years from the date of study entry (January 1984–April

1986) until the date of cancer diagnosis (at any site), death, emigration, or cut-off, whichever occurred first. Among 38,244 women and 36,975 men we observed a total of 751,922 person-years, and 2,298 female and 2,639 male cancer cases were registered altogether.

3.3 Study variables

Exposure data was collected from two sources; clinical data were obtained at the physical examination included in the screening program, and the self-administered questionnaires provided information on lifestyle and demographic characteristics.

3.3.1 Age

Age was defined as age at syntax date, which was the date for control of punched data, performed 7 to 21 days after the actual examination date. The participation rates were highest among the middle-aged people, and women younger than 65 years had a higher participation than men of the same age. In most age groups above 65 years, however, men participated more frequently than women [Holmen and Midthjell, 1990]. Since age is strongly associated with most cancers, it is an important variable to control for in analysis of potential risk factors. Depending on the number of cases with a specific cancer, we included age in the Cox regression model using 1, 2.5-, 5-, and 10-year categories.

3.3.2 Anthropometric variables

Standardized measurements of body height and weight were obtained from the health examination. Height was measured to the nearest centimeter, while weight was measured to the nearest half kilogram. Based on the values for height and weight, Quetelet's Index for body mass (BMI) was computed as weight in kilograms divided by the squared value of height in meters (kg/m^2). Lean body mass (LBM), which is an estimate of body components that are not adipose, was calculated as [2.447 – 0.09516 age (years) + 0.1074 height (cm) + 0.3362 weight (kg)] divided by 0.73 for males, and [–2.097 + 0.1069 height (cm) + 0.2466 weight (kg)] divided by 0.73 for females [Watson et al., 1980]. All anthropometric variables were analyzed in percentiles.

3.3.3 Lifestyle variables

Smoking

We classified smoking status in three categories, where individuals who had never smoked cigarettes daily were considered non-smokers, and those who reported previous or present daily smoking were classified as former and current smokers, respectively. Information on number of cigarettes smoked per day and duration of daily smoking were used to compute pack-years of smoking, and in the analyses of pancreatic cancer we used time since quitting smoking.

Alcohol

Information on alcohol consumption was collected as frequency of drinking during the past two weeks, and in the analysis of this variable we excluded teetotalers. Moreover, those who reported to be teetotalers were compared to drinking people, and those who reported periods of excessive drinking were compared to people without such periods.

Physical activity

In the health survey questionnaire on leisure-time physical activity, the participants were asked, “how often do you exercise?”, “how hard do you exercise?”, and “for how long do you carry on?”, with five, three, and four response choices, respectively. Regarding frequency of leisure-time physical activity, we considered those who exercised less than once a week as inactive, whereas individuals exercising 1–3 times per week and more than 3 times per week were classified as moderately active and highly active. In addition, we utilized the information on frequency, intensity, and duration to calculate a summary measure (index) of physical activity.

Occupational activity is an alternative marker to leisure-time physical activity, and might be more stable over time. In an attempt to assess the participants’ occupational physical activity level, we used information on how often they felt physically worn out after a day’s work.

3.3.4 Demographic variables

Marital status

Marital status was classified as married, unmarried, widow/widower, and divorced separated. Married women and men had the highest participation rate in all age groups, while those who were divorced or separated, especially young men, participated less frequently.

Educational attainment

In the analysis of prostate cancer, educational attainment was classified as primary and lower secondary school (0–9 years), upper secondary school (10–12 years), and college or university (>12 years). For pancreatic cancer, educational attainment was analyzed as a dichotomized variable with primary and lower secondary school (≤9 years) in one group, and upper secondary school, college or university in the other (>10 years).

Occupational socioeconomic status

We subjectively classified different occupational subgroups into the following categories: unemployed, unskilled manual workers, fishermen, and subordinate staff comprised the reference category of low socioeconomic status, while category two (i.e. occupations of higher socioeconomic status) included skilled manual workers, persons in professional or management positions, and self-employed individuals. The third category included subjects occupied in farming, agriculture, or forestry, which constitutes a major employment in this part of Norway.

3.3.5 Medical and physiological variables

History of diabetes mellitus (both insulin-dependent and non-insulin-dependent) was assessed from the self-administered baseline questionnaire. Blood glucose was measured in capillary blood in all participants ≥40 years of age. Levels of non-fasting blood glucose was dichotomized according to the cut point for a "positive screening" used in the health survey (≥ 8.0 mmol/L) [Holmen and Midthjell, 1990], which is in conformity with the WHO criteria of 1980 [WHO, 1980]. In the analysis of prostate cancer risk (Paper II) we also utilized information on cardiovascular fitness using pulse rate at the wrist and standardized blood pressure readings from the health examination. Both pulse rate and systolic blood pressure were analyzed in quartiles and as dichotomous variables.

3.4 Statistical analysis

We used the Cox proportional hazards model [Kleinbaum, 1995] to examine the association between the outcome of interest (risk of prostate cancer, pancreatic cancer, colorectal cancer, and breast cancer) and relevant exposure variables for which we had information, including anthropometric, lifestyle, and demographic factors. This statistical regression procedure is a popular and robust mathematical model often used to analyze data where survival time is

available, and where follow-up is censored (i.e. when individual time at risk of getting the disease can be computed). However, use of the Cox model requires that the hazard ratio is constant over time, or equivalently, that the hazard of one individual is proportional to the hazard of any other individual, where the proportionality constant is independent of time [Kleinbaum, 1995]. There are several approaches to assess this proportional hazards assumption of the Cox model [Kleinbaum, 1995; Hosmer and Lemeshow, 1999], but we have used a graphical procedure that involves comparing estimated log(-log) survival curves over different categories of variables being investigated, and where parallel curves indicate that the proportional hazards assumption is satisfied.

The most prominent advantage of regression modeling in epidemiologic studies is the opportunity to control for variables with a potentially confounding effect on the association of interest. Confounding is a distortion in the estimated effect of exposure brought about by the association of other factors with both the disease and the exposure [Greenland and Rothman, 1998]. Since the risk of almost every cancer strongly depends on age, we included age and the relevant exposure variable as independent variables in the regression model, and individual number of person-years as the dependent variable. This produced age-adjusted hazard ratios (incidence rate ratios) as estimates of the relative risk (RR) with 95% confidence interval (CI). When appropriate, a two-sided test for trend across exposure categories was calculated by treating the categories as ordinal variables in the proportional hazards model. In the studies of colorectal cancer and pancreatic cancer we conducted separate analyses for males and females.

Multivariable analyses (referred to as multivariate analyses in Paper I–V) were conducted to assess potential confounding by other factors for which we had information. Whether a variable qualified as a confounder was evaluated by the magnitude of discrepancy between the multivariate adjusted estimates and the age-adjusted estimates.

All statistical analyses were performed using the statistical software SPSS for Windows (*Release 8.0.0, Copyright © SPSS Inc., 1989 – 1997* for Paper I – IV and *Release 10.0.5, Copyright © SPSS Inc., 1989 – 1999* for Paper V).

4

Main results

> A *cause* is an act or event or a state of nature which initiates or permits, alone or in conjunction with other causes, a sequence of events resulting in an *effect*. A cause which inevitably produces the effect is *sufficient*. Most causes that are of interest in the health field are components of sufficient causes, but are not sufficient in themselves. If there exists a component cause which is a member of every sufficient cause, such a component is termed a *necessary* cause. Whereas many different component causes have been identified for several types of cancer, the hope exists for identification of a final common pathway representing a necessary cause for cancer of all types.
>
> *Kenneth J. Rothman, 1976*

Paper I: Anthropometry and prostate cancer risk: a prospective study of 22,248 Norwegian men

In this first paper we studied the association between body size and prostate cancer risk in a cohort of 22,248 men aged 40 years or more. During 12 years of follow-up (mean = 10.4 years), 642 men developed prostate cancer, and mean age at diagnosis was 75.2 years (range, 48–96 years).

Overall, we observed no significant trend for any of the study variables (height, weight, BMI, and LBM), although an excess risk of prostate cancer with increasing height was suggested by an age-adjusted relative risk of 1.2 (95% CI = 0.9–1.6) for the highest compared to the lowest quintile of men. When we analyzed height separately for localized and metastatic disease, we found practically no association between height and localized disease, but for metastatic disease there were positive but inconsistent associations with height (RR = 1.5; 95% CI = 0.9–2.6 comparing extreme quintiles). Mutual adjustments for height and BMI did not materially change the estimates of relative risk, and neither did adjustment for other potentially confounding factors, such as smoking, physical activity, educational attainment, and marital status.

Paper II: Socio-economic and lifestyle factors associated with the risk of prostate cancer

In the second prospective study of prostate cancer we utilized information on 22,895 men aged 40 years and more to explore the association with several lifestyle and

socioeconomic factors. During a mean follow-up of 9.3 years, 644 cases were registered with prostate cancer. Risk was elevated among men in occupations of high compared to low socioeconomic status (RR = 1.30; 95% CI = 1.05–1.61), and among men with high education compared to the least educated (RR = 1.56; 95% CI = 1.11–2.19). A relative risk of 1.56 (95% CI = 0.97–2.44) suggests a higher risk among divorced or separated men, compared with married men. We also found indications of a weak negative association with leisure-time physical activity (RR = 0.80; 95% CI = 0.62–1.03 for high versus low activity) that was stronger for metastatic prostate cancer (RR = 0.65; 95% CI = 0.40–1.06). There was a weak positive association with increasing number of cigarettes (*P* for trend = .046), while alcohol consumption was not related to the risk of prostate cancer. However, we found a slightly increased risk among teetotalers compared with men who reported not to be teetotalers (RR = 1.22; 95% CI = 0.96–1.55). Additionally, men with known diabetes mellitus had a relative risk of 1.31 (95% CI = 0.93–1.82) compared to men without the disease. Our findings were not materially changed after adjustment for potentially confounding variables.

To explore whether the results of the study could be biased due to differential testing with PSA between different categories of exposure, we used 1 January 1993 as cut-off date for follow-up. These analyses included 460 cases of prostate cancer diagnosed during a mean follow-up of 7.1 years, and mean age at diagnosis was 75.6 years. However, the estimates of relative risks were similar to those obtained with full follow-up.

Paper III: A prospective study of lifestyle factors and the risk of pancreatic cancer in Nord-Trøndelag, Norway

Epidemiologic knowledge of pancreatic cancer is meager, and the Nord-Trøndelag Health Survey provided the opportunity to explore the association with several lifestyle factors. In this study we included 31,000 men and 32,374 women aged 30 years or more, and during 12 years of follow-up (mean = 9.8), 166 incident cases of pancreatic cancer were registered (96 males and 70 females).

We found no significant association between history of diabetes and levels of blood glucose and risk of pancreatic cancer. Compared with never smokers, there was a two-fold higher risk among current smokers, and a dose-response association with number of cigarettes (*P* for trend = 0.02 for both men and women) and with number of pack-years (*P* for trend = 0.02 for men and 0.01 for women). Maybe most importantly, we found that cessation of smoking more than five years before study entry reduced the risk of pancreatic cancer to

nearly half the risk of current smokers, thus approaching the risk for never smokers. The estimated relative risks did not change appreciably after adjustment for alcohol consumption, physical activity, occupational physical activity, marital status, or occupational socioeconomic status.

Alcohol consumption was not significantly associated with risk of pancreatic cancer in these data. Similarly, we observed no significant association with leisure-time physical activity, but those who nearly always became physically worn out after a day's work had strongly elevated risk of pancreatic cancer compared with persons who reported never or infrequently to be physically worn out (RR = 2.9 (95% CI = 1.4–5.8) among men and 3.8 (95% CI = 1.6–9.2) among women). To further explore this finding, we excluded subjects who died, or were diagnosed with any cancer, within the first three years of follow-up, in order to reduce a preclinical effect of undiagnosed pancreatic cancer at baseline. In these analyses, the association was further strengthened among women (RR = 4.2; 95% CI = 1.4–12.7), but slightly reduced among men (RR = 2.2; 95% CI = 1.0–4.9).

We observed a higher risk of pancreatic cancer among divorced or separated men (RR = 3.1; 95% CI = 1.3–7.2) compared with married men. Also, men occupied in farming, agriculture or forestry (RR = 1.7; 95% CI = 0.9–3.1) and women in occupations of high socioeconomic status (RR = 2.5; 95% CI = 1.2–5.2) had a higher risk of pancreatic cancer compared with persons in occupations of low socioeconomic status.

Paper IV: Prospective study of colorectal cancer risk and physical activity, diabetes, blood glucose and BMI: exploring the hyperinsulinaemia hypothesis

The similarity of risk factors for colorectal cancer and diabetes mellitus has lead to the hypothesis that increased level of insulin may stimulate the growth of colorectal tumors. We prospectively examined the association between colorectal cancer risk and factors related to insulin resistance and hyperinsulinaemia in a cohort of 75,219 men and women aged 20 years and more. During 12 years of follow up (median = 10.8 years), 234 colon cancers and 128 rectal cancers were diagnosed in men, whereas 277 colon cancers and 91 rectal cancers developed in women.

In men, but not in women, we found a negative association with leisure-time physical activity (*P* for trend = .002), where the age-adjusted RR for the highest versus the lowest category of activity was 0.54 (95% CI = 0.37-0.79). No significant association with diabetes mellitus was found among men (RR = 0.66; 95% CI = 0.35–1.24), but women who reported

diabetes at baseline had 55% higher risk of colorectal cancer than women without diabetes (RR = 1.55; 95% CI = 1.04–2.31). Similarly, women with non-fasting blood glucose equal to or above 8.0 mmol/L had twice the risk of women with lower values (RR = 1.98; 95% CI = 1.31–2.98). Overall, we found no association between BMI and risk of colorectal cancer. We also compared age-adjusted and multivariable adjusted associations to assess potential confounding with any of the other main variables, and with marital status and educational attainment, but the results were not materially different.

Secondary analyses on 346 cases of metastatic colon cancer (162 males and 184 females) showed that the most physically active men had nearly 70% lower risk than the least active (RR = 0.33; 95% CI = 0.16–0.67). The increased risk in women associated with diabetes mellitus was not present for metastatic disease (RR = 1.12; 95% CI = 0.59–2.14), but the positive association with non-fasting blood glucose persisted (RR = 1.92; 95% CI = 1.06-3.47).

Paper V: Adult height and risk of breast cancer: a possible effect of early nutrition

The increased risk of breast cancer related to early reproductive development and tallness indicates that fetal and childhood nutrition can be important for its etiology. During World War II there was a marked reduction in average caloric intake in Norway, and a positive association between adult height and breast cancer risk might be stronger among women born during this period than among women born before or after the war. In this study, a total of 25,204 women born in 1925 or later were followed for a median of 11 years, and 215 cases of breast cancer were registered.

We found the strongest positive association between height and risk of breast cancer among the 3,792 women (43 cases) who where born during World War II. For this period, women in the highest tertile (>167 cm) had more than twice the risk of breast cancer compared with women in the lowest tertile (≤162 cm) (RR = 2.5; 95% CI = 1.2–5.5). Among women born before or after the war we found no clear association with height. Adjustment for BMI, smoking and physical activity did not change these results.

5

Discussion

> A causal hypothesis cannot be literally proven or disproven by science. Rather its credibility is repeatedly modified, up or down, as new evidence becomes available. Thus at any time and in the mind of each person, a causal hypothesis lies at a point on a spectrum of credibility.
>
> *Philip Cole, 1997*

In this thesis, my greatest effort has been to apply epidemiologically and statistically sound methods, trying to achieve accurate associations between the risk of some cancers and several environmental factors, or possible indicators of such factors. In brief, the main findings of this thesis were:

- Some evidence of a weak positive association between adult height and prostate cancer risk (Paper I).
- An increased risk of prostate cancer among divorced men, and among men with longest education and highest occupational socioeconomic status, and a reduced risk among the most physically active men (Paper II).
- A two-fold higher risk of pancreatic cancer among daily cigarette smokers compared with never smokers, a considerably reduced risk after five or more years of smoking cessation, and a strongly elevated risk among people who were most physically worn out after a day's work (Paper III).
- A substantially reduced risk of colorectal cancer with increased physical activity among men, and increased risk related to high blood glucose level and diabetes among women (Paper IV).
- A strong positive association between adult height and breast cancer risk among women born during the years of World War II, and no association with height among those who were born before or after the war (Paper V).

Although the results of an epidemiologic study may reflect the true effect of an exposure on the development of disease, it is also possible that the findings may have an alternative explanation [Hennekens and Buring, 1987]. One possibility is that the observed

association can be attributed to the play of chance, since random error may impair the precision of the estimated effect. A second explanation is that introduction of systematic error may distort the association between exposure and disease, either through biased selection of participants or through biased information obtained from these individuals, but also through confounding by other factors related both to the disease and to the exposure. However, judging whether the association is causal extends beyond these concepts of random and systematic error, and includes consideration of how the observed results relate to some general criteria of causality.

5.1 Methodological considerations

An overall goal of an epidemiologic study is accuracy in estimation. That is, to estimate the value of a certain parameter or exposure variable with as little error as possible [Rothman and Greenland, 1998]. As stated above, sources of error in estimation may be classified as either random or systematic, and the principles of study design emerge from consideration of approaches to reducing both types of error.

5.1.1 Precision (lack of random error)

In an epidemiologic study, random variation has many components, but a major contributor is the process of selecting the study subjects (i.e. sampling). One might expect that random error due to sampling is negligible in the Nord-Trøndelag Health Survey cohort, since almost 90% of the total adult population in the county participated. However, the statistical dictum that there is no sampling error if an entire population is studied does not apply to epidemiologic studies. Conceptually, the actual subjects are always considered a sample of a broader experience of interest [Rothman and Greenland, 1998].

Precision in measurement and estimation corresponds to the reduction of random error. The primary way to reduce random error, or increase precision, in an epidemiologic study is to enlarge the size of the study. Except for the stratified analyses of breast cancer associated with height in different birth cohorts, none of the analyses included in this thesis were based on fewer than 14,000 individuals, so the study size should in general be satisfactory. However, the concept of study efficiency may be of greater interest, since it deals with apportionment of subjects (or person-time units of observation) into different study groups. In our studies the statistical efficiency will depend upon the exposure variable studied, since some variables (e.g. anthropometry) with a continuos or ordinal origin were analyzed using equal categories (i.e. quintiles, quartiles, or tertiles), while other variables (e.g.

smoking history, marital status, and history of diabetes) with fixed categorization had to be analyzed with a small number of person-years and few cancer cases in some of the categories. Hence, the precision of the estimated association with some of these variables was reduced.

Sampling is only one source of error that contributes to unpredictable inaccuracies in epidemiologic studies. Other sources, such as the measurement of specific variables, also contribute to the overall inaccuracy. As a result, the usual statistical tools (i.e. test of statistical significance) that we use to quantify random variation provide at best minimum estimates of the actual statistical uncertainty in the data [Greenland, 1990]. The test of statistical significance involves a test statistic, such as the Pearson or Mantel-Haenszel χ^2 statistic and the Wald statistic, and the corresponding *P*-value for this statistic. A *P*-value is defined as the probability that an effect at least as extreme as that observed in a particular study could have occurred by chance alone, given that there is no true relationship between the exposure and the disease [Hennekens and Buring, 1987]. However, the *P*-value is a composite measure that reflects both the magnitude of the difference between the exposure groups and the sample size. Consequently, even a small difference may be statistically significant if the sample size is sufficiently large, and conversely, a larger effect may not achieve statistical significance if the sample size is insufficient. A more informative measure of precision is the confidence interval, which both provides information on statistical significance and gives an expression of the magnitude of the effect. In addition, the effect of sample size can be ascertained from the width of the confidence interval – the wider the interval, the greater the variability, and the smaller the sample size. In the presentation of our results we have based our judgement of statistical significance on the confidence interval, and only used the Wald statistic to evaluate possible linear trends over exposure categories. In accordance with Greenland [1990], we find it preferable to view the confidence limits as only a rough guide of the inherent uncertainty, since a 95% confidence level is an arbitrary chosen value without biological relevance.

5.1.2 Validity (lack of systematic error)

The validity of a study is usually separated into two components: the validity of the inferences as they pertain to the members of the source population (internal validity), and the validity of the inferences as they pertain to the people outside that population (external validity or generalization) [Rothman and Greenland, 1998]. Under such a scheme, internal validity is a

prerequisite for external validity, and will thus receive greatest attention in the following discussion.

The role of selection bias

Selection biases are distortions that result from procedures used to select subjects and from factors that influence study participation [Rothman and Greenland, 1998]. The common element of such biases is that the relation of the exposure to the disease is different between those who participate and those who are eligible for participation. The Nord-Trøndelag Health Survey cohort included almost 90% of those who were eligible for participation. This indicates that the study cohort is fairly representative for the total underlying population, and no serious bias in the selection of study participants is likely to be present. Nevertheless, the participation was highest among the middle-aged, among those who were married, and among people living in small municipalities. There is evidence suggesting that the non-participants had higher morbidity and mortality compared to the participants, but this affected, however, only 12% of the non-participants, and only elderly people [Holmen and Midthjell, 1990].

The role of information bias

Bias in evaluating an effect can occur from errors in obtaining the needed information. Information bias in a cohort study results from systematic differences in the way data on exposure are obtained. If data are inaccurate or incomplete, spurious associations may be introduced only if the inaccuracy or incompleteness affects the exposure categories to an unequal degree [Hennekens and Buring, 1987]. For discrete variables, measurement error is usually called classification error or misclassification. Classification error that depends on the values of other variables is referred to as differential misclassification, while classification error that does not depend on other variables is referred to as nondifferential misclassification [Rothman and Greenland, 1998]. Nondifferential or random misclassification will usually underestimate the effect (i.e. the direction of bias is towards the null value), since it increases the similarity between exposure groups. A more serious problem arises if the proportion of subjects misclassified differ between exposure groups. The bias caused by such differential misclassification can either exaggerate or underestimate the true effect of exposure on disease, depending on the particular situation. The prospective design of the studies included in this thesis will generally prevent bias due to misclassification, since information on exposure information was ascertained before the development of cancer. Nevertheless, preclinical effects of cancer may introduce bias to some of the variables studied, such as obesity (BMI)

and occupational physical activity (physically worn out after work). Potential misclassification due to preclinical effects was studied by excluding people with person-years below some specific value (e.g. those who where diagnosed with cancer or died within some specified time after study entry).

An inherent assumption of this type of study is that exposure stays constant over the observation period, and for certain variables (e.g. height, educational attainment, and occupational socioeconomic status) this is likely to be correct. However, the longer the follow-up, the higher the probability that the baseline information on some types of variables will change over time. In our studies this is especially pertinent to information regarding body weight, smoking habits, alcohol consumption, and physical activity. Nevertheless, most cancers, and certainly all cancers studied in this thesis may be initiated several years, or even decades prior to its clinically detectable stage. Thus, the importance of constant exposure during the period of follow-up may not be as important as the period prior to follow-up. Therefore, one might emphasize that the baseline information should reflect previous rather than future exposure status.

The Cancer Registry of Norway has a nearly complete registration of incident cancers [Lund, 1981], and hence, endpoints were ascertained with limited bias. Excluding subjects with previously diagnosed cancer at study entry would also reduce the potential for misclassification. Since the Cancer Registry is matched against the Registries of Deaths at Statistics Norway, we were able to censor persons who died or were diagnosed with other types of cancer during follow-up. Hence, loss to follow-up, which is regarded a major source of bias in the general prospective cohort design [Hennekens and Buring, 1987], is unlikely to play a role in our studies.

The role of confounding

Apart from low precision (i.e. chance findings) and various types of bias, the third alternative of explanation that must be considered is that an observed association (or lack of one), totally or in part, is due to a mixing of effects between the exposure, the disease, and some other factor(s). This mixing of effects is referred to as confounding, and the extraneous factors responsible for the difference in disease frequency between the exposed and unexposed are called confounders. Apart from being independent risk factors for disease in the absence of the exposure under study, a confounder should simultaneously be associated with the exposure. In addition, factors associated with these extraneous causal factors that can serve as surrogates for these factors are also commonly called confounders. The distortion of the

exposure/disease association introduced by a confounding factor can be large, and it can lead to overestimation or underestimation of an effect. Confounding can even change the apparent direction of an effect. However, a variable which exerts an intermediate effect between the exposure and the disease should not be regarded a confounding factor [Rothman and Greenland, 1998].

As previously stated, most cancers are strongly associated with increasing age and many exposure variables tend to be age-related. Hence, all our estimated associations were adjusted for confounding by age. Confounding by other variables for which we had measures was evaluated by the magnitude of change from the age-adjusted estimate, but none of these factors stood out as important confounders for any of the estimated associations. However, residual confounding cannot be ruled out. The ability to adjust for potential confounders depends on the quality of information obtained, and crude categorization of some variables (e.g. smoking history, physical activity, and educational attainment) and inability of the questionnaire to capture the true exposure (e.g. alcohol consumption, and leisure-time physical activity among women) may have caused residual confounding.

There may be other unmeasured factors that could explain our findings, but sparse etiologic knowledge of prostate cancer, pancreatic cancer, and colorectal cancer makes it difficult specify potentially confounding factors that should be considered. Although international variation and results from migration studies suggest that environmental factors are important in the etiology of these cancers, maybe especially prostate and colorectal cancer, no major causal factor has been identified. This means that confounding by any such unmeasured factor is unlikely to substantially distort the results. For breast cancer the situation is slightly different, since important risk factors have been identified. These factors include age at menarche, age at first full-term pregnancy, parity, and age at menopause [Kelsey et al., 1993]. These three factors are all potential confounders for the association between height and risk of breast cancer. The Nord-Trøndelag Health Survey did not provide information on any one of these factors, and that is a weakness of our study.

5.2 Appraisal of the main findings

5.2.1 Prostate cancer

Anthropometric measures, and especially adult height, may be useful in epidemiologic studies because they can reflect an influence of diet in the remote past (i.e. during childhood and

adolescence) that may be difficult to measure in any other way [Willett, 1998]. Some studies have shown a positive association between adult height and risk of prostate cancer [Andersson et al., 1997; Giovannucci et al., 1997; Hebert et al., 1997], although this is not a consistent finding [Albanes et al., 1988; Severson et al., 1988; La Vecchia et al., 1990; Andersson et al., 1996; Cerhan et al., 1997; Demark-Wahnefried et al., 1997]. In our study, we found a non-significant positive association between adult height and prostate cancer risk, but the magnitude of the association was similar to others [Andersson et al., 1997; Hebert et al., 1997].

A positive association between adult stature and risk of prostate cancer could be explained by endocrine mechanisms. Testosterone (T) and its high-affinity metabolite, dihydrotestosterone (DHT), are important hormones that influence mitotic activity of prostate cells. In addition, prostate epithelial cells have insulin-like growth factor I (IGF-I) receptors [Iwamura et al., 1993], and IGF-I stimulates cell proliferation [LeRoith et al., 1995], and increases the activity of the enzyme 5-α-reductase, which converts T to DHT [Horton et al., 1993]. At puberty, levels of IGF-I predict height velocity [Juul et al., 1994] and hence, men who attain greater height may be exposed to higher levels of IGF-I and androgens during adolescence. Recent epidemiologic studies indicate that IGF-I is an important factor in the development of prostate cancer [Mantzoros et al., 1997; Wolk et al., 1998; Chan et al., 1998; Stattin et al., 2000], and thus, it could be a mediator of a positive association between height and prostate cancer.

In our second paper on prostate cancer risk, we found that men with long education or who were employed in occupations of high socio-economic status had an elevated risk. This is in agreement with some studies [Rimpela and Pukkala, 1987; Yu et al., 1988; Williams et al., 1991; Harvei and Kravdal, 1997], but not with others [Talamini et al., 1986; Oishi et al., 1989; Severson et al., 1989; Fincham et al., 1990]. We also found that divorced or separated men might have a higher risk of prostate cancer than married men. Epidemiologic data on the association between marital status and prostate cancer are inconsistent [Newell et al., 1987; Yu et al., 1988; Severson et al., 1989; Hayes et al., 1992; La Vecchia et al., 1993; Harvei and Kravdal, 1997]. It is possible that the observed associations can be ascribed to differential dietary habits between the exposure groups, but also sexual factors could be important in prostate carcinogenesis [Rotkin, 1977; Ross et al., 1987; Oishi et al., 1990; La Vecchia et al., 1993]. Sexual activity may be associated with androgen levels, and men with high sexual activity may be at greater risk of being exposed to transmittable oncogenic agents. Although marital status is probably not a good indicator of sexual activity, the increased risk seen

among divorced and separated men in our study could be explained by such mechanisms. Moreover, the higher educated may have more sexual partners than those with less education [Binson et al., 1993].

We also found suggestive evidence of a negative association between physical exercise and risk of prostate cancer, and this association persisted in the analysis of metastatic disease. Physical activity may reduce levels of circulating testosterone [Aakvaag et al., 1978; Hackney et al., 1988], but previous findings have been inconsistent [Le Marchand et al., 1991; Lee et al., 1992; Thune and Lund, 1994; Hartman et al., 1998].

5.2.2 Pancreatic cancer

In agreement with previous reports from both cohort [Zheng et al., 1993; Fuchs et al., 1996; Harnack et al., 1997] and case control studies [Howe et al., 1991; Boyle et al., 1996; Whittemore et al., 1985; Bueno de Mesquita et al., 1991; Kalapothaki et al., 1993; Zatonski et al., 1993; Silverman et al., 1994; Ji et al., 1995; Muscat et al., 1997] we found a strong positive association between cigarette smoking and risk of pancreatic cancer. We also observed a significant dose-response relation with cigarettes per day and with pack-years of smoking that is in agreement with some studies [Whittemore et al., 1985; Howe et al., 1991; Zheng et al., 1993; Silverman et al., 1994; Boyle et al., 1996; Fuchs et al., 1996] but not with others [Bueno de Mesquita et al., 1991; Kalapothaki et al., 1993; Zatonski et al., 1993; Ji et al., 1995; Engeland et al., 1996; Harnack et al., 1997]. We also found that former smokers, who ceased smoking more than five years before study entry, had approximately the same risk as never smokers. Other studies have indicated that 10 to 15 years after quitting, former smokers have the same risk of pancreatic cancer as never smokers [Howe et al., 1991; Ji et al., 1995]. This may suggest that the latency period (i.e. the period between initiation and diagnosis) for this cancer is rather short, or alternatively that smoking exerts its effect as a promoter in late stages of pancreatic cancer. Mechanisms that could explain the association between smoking and pancreatic cancer are not clear, but may include tobacco-specific nitrosamines that have been shown to induce pancreatic tumors both in human [Hecht and Hoffmann, 1991] and in animal [Rivenson et al., 1988] studies. Moreover, autopsy studies have shown substantial pancreatic tissue damage among smokers compared with non-smokers [Auerbach and Garfinkel, 1986].

Although difficult to explain, our finding that persons who were physically worn out after a day's work had a three to four-fold higher risk of pancreatic cancer is intriguing.

Originally, we thought this information could mirror the experienced level of occupational physical activity, but given these results we can only speculate that persons who felt physically worn out after work may also tend to have some unmeasured factor that may influence pancreatic carcinogenesis? For example, occupational exposure to carcinogens is plausible [Ji et al., 1999], and the role of psychological factors cannot be ruled out [Garssen and Goodkin, 1999]. Furthermore, since being worn out could be a preclinical symptom of cancer, we excluded subjects who died, or were diagnosed with cancer, within the first three years of follow up, but this did not alter the results.

5.2.3 Colorectal cancer

Several cohort studies have shown that physical activity is negatively associated with colorectal cancer risk, and in accordance with our findings in men, a reduction of 40 to 50 percent has been reported [Wu et al., 1987; Lee et al., 1991; Giovannucci et al., 1995; Giovannucci et al., 1996; Thune and Lund, 1996; Martinez et al., 1997]. Two interpretations have been proposed for the reduced risk. First, physical activity stimulates colon peristalsis and decreases bowel transit time [Cordain et al., 1986], and this may reduce exposure to carcinogens. Second, physical activity may increase insulin sensitivity [Koivisto et al., 1986] and reduce plasma insulin [Regensteiner et al., 1991]. Insulin is a colon tumour promoter in rats [Tran et al., 1996], and *in vitro,* insulin is a mitogen for colon carcinoma cells [Koenuma et al., 1989].

Contrary to some other studies [Thune and Lund, 1996; Martinez et al., 1997], we found no significant association with physical activity among women. Misclassification of physical activity might contribute to the null finding in women, and little variation in physical activity could mask a difference in risk. Also, physically active women could be more health conscious and more likely to seek medical advice for early symptoms, which may lead to higher detection of early-stage cancer. Furthermore, physically active individuals may eat less saturated fat and more fibre than less active people. However, an inverse association with colorectal cancer risk has been shown, also after adjustment for dietary intake of saturated fat, red meat, and fibre [Whittemore et al., 1990; Giovannucci et al., 1995].

Previous studies have shown no consistent association between diabetes mellitus and risk of colorectal cancer [Ragozzino et al., 1982; O'Mara et al., 1985; La Vecchia et al., 1991; La Vecchia et al., 1997; Le Marchand et al., 1997], but recently, two prospective studies reported a positive association [Will et al., 1998; Hu et al., 1999]. In our study, there was also

a positive association with diabetes, but only among women. Several possibly causative mechanisms have been suggested; diabetes may slow down bowel transit [Iber et al., 1993]; production of bile acids that promote colon carcinogenesis may increase [Narisawa et al., 1974; Nakamura et al., 1993]; and high insulin levels may promote colon tumour growth [McKeown-Eyssen, 1994; Giovannucci, 1995]. Nonetheless, these factors cannot explain that a positive association with diabetes is present only among women. In this study, few men with diabetes developed colorectal cancer, and the statistical power to examine this question may be to low. Further, the positive association with diabetes in women may be a result of increased medical surveillance.

McKeown-Eyssen [1994] has suggested serum triglycerides and plasma glucose to be involved in colorectal carcinogenesis, possibly by increasing insulin secretion. In our study, we found a two-fold increased risk among women with a non-fasting blood glucose of 8.0 mmol/L or higher, which is in agreement with a recent study by Schoen et al. [1999]. In contrast to our results, they also found a similar association in men.

5.2.4 Breast cancer

In populations characterised by nutritional diversity, differences in adult height may, in addition to differences in genetic potential, reflect differences in childhood nutrition [Willett, 1998]. Adult stature has been positively associated with the risk of breast cancer in several studies [de Waard, 1975; Tretli, 1989; Vatten and Kvinnsland, 1990], and this may indicate that nutrition at a young age can be important for future breast cancer risk [MacMahon, 1975]. Additionally, recent epidemiologic evidence suggests an association between indicators of birth size and breast cancer risk, and some studies have reported a positive association with birth weight [Ekbom et al., 1992; Michels et al., 1996; Sanderson et al., 1996; Stavola et al., 2000; Kaijser et al., 2001]. Others, however, have not been able to confirm this finding [Le Marchand et al., 1988; Ekbom et al., 1997]. For birth length and placenta weight, there have been no clear findings, but preeclampsia in the mother, which is associated with reduced foetal growth, appears to reduce the risk of breast cancer in the daughters [Ekbom et al., 1992; Ekbom et al., 1997; Sanderson et al., 1998].

We found that the association between adult height and breast cancer risk was confined to women who were born during World War II. Women in the highest tertile of height had more than twice the risk of breast cancer compared with women in the lowest tertile, also after adjustment for differences in body mass index, smoking, and physical

activity. Among women born before or after the war we found no clear association with height. We had no information about age at menarche, age at first full-term pregnancy, and parity, and this may be a weakness of our study [Kelsey et al., 1993]. Moreover, by stratifying cases according to birth cohorts, the number of cases within each category of height was small, and this reduces the precision of the results. The cancer cases contributing to the effect of WWII in the present study were mainly pre-menopausal, and one could speculate that an association with height is more pronounced among pre-menopausal than post-menopausal women. Tretli, [1989] found, however, that the association between height and breast cancer did not substantially differ by age at diagnosis.

In Norway, there was an overall reduction in average caloric intake during World War II, from 3,475 kcal daily in 1939, to a minimum of 2,700 kcal in late 1944 and early 1945 [Galtung-Hansen, 1947; Strøm, 1948]. Therefore, we propose that the strong association with height among women born during WWII may reflect greater nutritional diversity during gestation among the mothers, and hence, that the nutritional conditions in intrauterine life may affect future risk of breast cancer.

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