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Smoking and incidence and mortality of colorectal cancer

Ranjan Parajuli

A dissertation for the degree of Philosophiae Doctor-2014

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NORWEGIAN **CANCER** SOCIETY

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Summary

Smoking is one of the most important causes of cancer and premature death worldwide. Two different reports, the most recent monograph published by International Agency for Research on Cancer (IARC) in 2012 and the Unites States Surgeon General's report of 2014, concluded that smoking is risk factor for both colon and rectal cancer. In addition to being one of the most common cancers in Norway, mortality from colorectal cancer (CRC) is also high. The main aim of this thesis was to examine the association between smoking and CRC incidence and mortality overall and by gender. We examined the association between smoking and colon cancer by location and gender (Paper I), rectal cancer by gender (Paper II) and CRC mortality by subsite and gender (Paper III).

The cohort included 652,792 Norwegians (49% men) recruited from four Norwegian health screening surveys. These surveys were conducted between 1972 and 2003: the Oslo study I (1972-1973), the Norwegian counties study (1974-1988), the 40 years cohort (1985-1999) and the Cohort of Norway (CONOR, 1994-2003). The participation rate for the different surveys varied from 56-88%.

Women ever smokers had a 19% and men ever smokers had 8% increased risk of colon cancer. Furthermore, women ever smokers had an increased risk of proximal colon cancer compared to men ever smokers (Paper I). Ever smokers had an increased risk of rectal cancer at around 25% and the risk increased was similar for men and women (Paper II). Men and women ever smokers had a similar increased risk of CRC mortality of about 20%. The risk of rectal and proximal colon cancer mortality was most pronounced among men and women smokers, respectively (Paper III).

In conclusion, smoking increased the risk of colon cancer, especially proximal colon cancer among women. Furthermore, smoking increased the risk of rectal cancer, with a similar risk

being observed among women as in men ever smokers. Smoking is associated with increased CRC mortality among both men and women. The risk of rectal and proximal cancer mortality was most pronounced among men and women smokers, respectively.

List of papers

This thesis is based on the three papers listed below:

Paper I

Parajuli R, Bjerkaas E, Tverdal A, Selmer R, Le Marchand L, Weiderpass E, Gram IT. **The increased risk of colon cancer due to cigarette smoking may be greater in women than men.** *Cancer Epidemiol Biomarkers Prev.2013; 22(5), 862-71. PubMED:PMID 23632818)*

Paper II

Parajuli R, Bjerkaas E, Tverdal A, Le Marchand L, Weiderpass E, Gram IT. **Smoking increases rectal cancer risk to the same extent in women as in men: Results from a Norwegian cohort study.** *BMC Cancer (submitted)*

Paper III

Parajuli R, Bjerkaas E, Tverdal A, Le Marchand L, Weiderpass E, Gram IT. **Cigarette smoking and colorectal cancer mortality among 602,242 Norwegian males and females.** *Clinical Epidemiology, Dovepress (Online)*

List of figures and tables

Abbreviations

ASR	Age standardized rates
BMI	Body mass index
CI	Confidence interval
CONOR	Cohort of Norway
CRC	Colorectal cancer
DNA	Deoxyribonucleic acid
EPIC	European Prospective Investigation into Cancer and Nutrition
FAP	Familial adenomatous polyposis
HNPCC	Hereditary non polyposis colorectal cancer
HR	Hazard ratio
HRT	Hormonal replacement therapy
IARC	International Agency for Research on Cancer
IBD	Inflammatory bowel disease
PAH	Polycyclic Aromatic Hydrocarbons
REK	Regional komité for medisinsk og helsefaglig forskningsetikk (Regional Committee for Medical Research Ethics)
WHO	World Health Organization

1 Introduction

This thesis describes the association between cigarette smoking and colorectal cancer (CRC) incidence and mortality overall and by subsite among Norwegian men and women who participated in four different Norwegian health surveys.

1.1 Definition and epidemiology of colorectal cancer

In 2012, there were around 14 million new cancer cases (all types combined), 8 million cancer deaths and around 32 million people were living with cancer worldwide. Fifty-seven percent (8 million) of these new cancer cases and 65% (5.3 million) of cancer deaths occurred in low and medium income countries (1).

CRC is one of the major causes of morbidity and mortality around the world (2). CRC is confined to the main parts of large intestine, the colon and rectum. Adenocarcinoma is the predominant histological subtype and begins as adenomatous polyps before reaching the malignant stage. The progression from adenomatous polyps to carcinoma occurs with potential damage to DNA. Other histological subtypes of CRC include carcinoid tumors, gastrointestinal, stromal tumors, lymphomas and sarcomas. More than 95% CRC are sporadic, originating in individual without significant genetic or hereditary risk factor (3). If the diagnosis is made early, CRC is highly treatable. CRC is known as disease of western world as it is more prevalent in high-income countries.

Globally, CRC is the third most common cancer in men and the second most common cancer in women representing about 9% and 10% of all incident cancer respectively (2). CRC incidence rates worldwide have changed with time, but usually men have higher rates compared to women (2). There is a wide variation in CRC incidence across the world population but the patterns of variation in men and women are similar. The CRC incidence rates vary tenfold, with the highest estimates in Australia and New Zealand (age-standardized

incidence rate, ASR 44.8 and 32.2 per 100,000 in men and women, respectively) and the lowest in Western Africa (4.5 and 3.8 per 100,000 in men and women, respectively) (1). There is also a geographical difference in the global occurrence of CRC. High-income countries usually have higher incidence rates and accounts for almost 55% of all incident cases CRC worldwide (4).

CRC incidence rates are decreasing in the United States, whereas in Northern and Western Europe CRC incidence rates are stabilizing. However, high income countries like Japan, Singapore, and some Eastern European countries are showing a substantial increase in CRC incidence (5;6).

CRC accounts for 8% of all cancers deaths, which makes it the fourth most common cause of death from cancer worldwide (7). It has been reported that about 12% of CRC deaths are attributed to smoking (6;8). CRC mortality rates are lower in women than men except in the Caribbean region (7). Worldwide, CRC mortality rates vary less than CRC incidence rates (six fold in men, and four fold in women). The highest mortality rates are observed in Central and Eastern Europe (20.3 and 11.7 per 100.000 among men and women, respectively) and lowest in western Africa (3.5 and 3.0 per 100,000 among men and women, respectively) (1). In the United States, it is the third most common cause of cancer death although the overall mortality rates have decreased by 2.8% and 2.6% per year in men and women, respectively since 1998 (9). CRC is the second most common cause of cancer deaths in Europe (1). Latest CRC incidence and mortality rates worldwide are shown in figure 1.

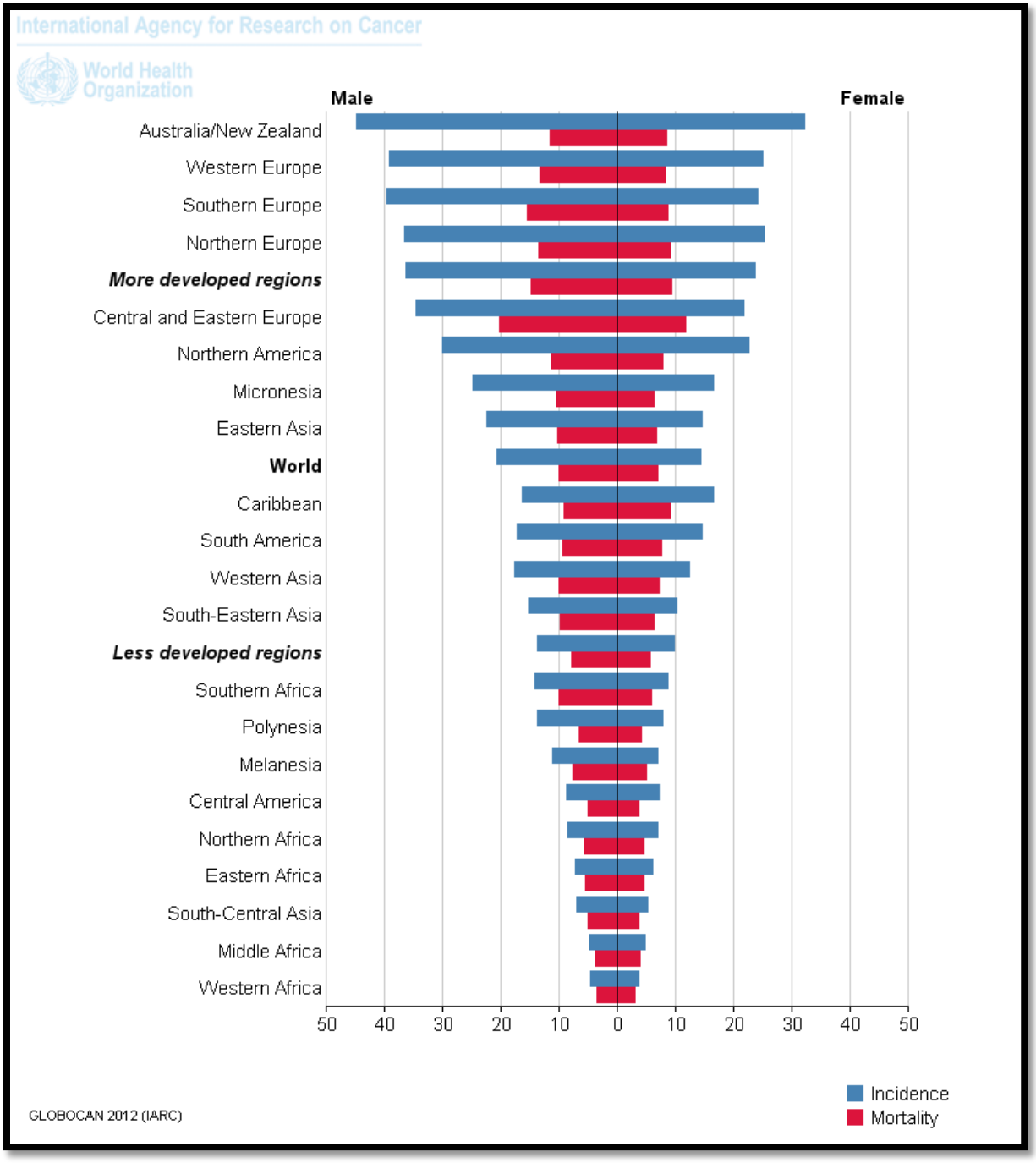

Figure 1: Worldwide estimated age standardized rates of CRC incidence and mortality rates per 100,000 by gender. (Globocan 2012, IARC)

1.2 Incidence of colorectal cancer in Nordic countries

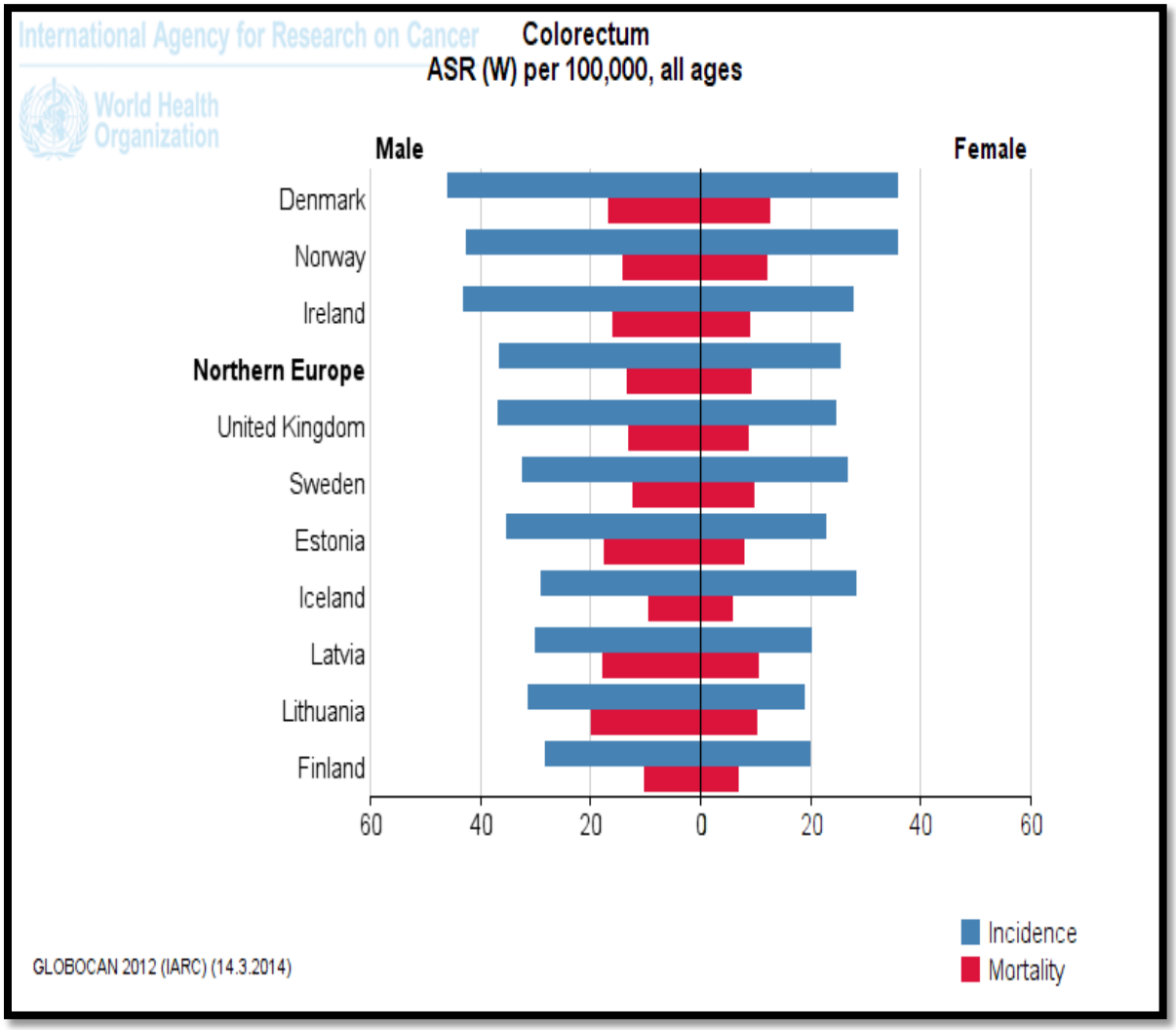

Figure 2: Estimated age standardized CRC incidence and mortality rates per 100,000 in Northern Europe by gender (Globocan 2012, IARC)

Figure 2 illustrates the present CRC incidence and mortality rates in Northern Europe among men and women.

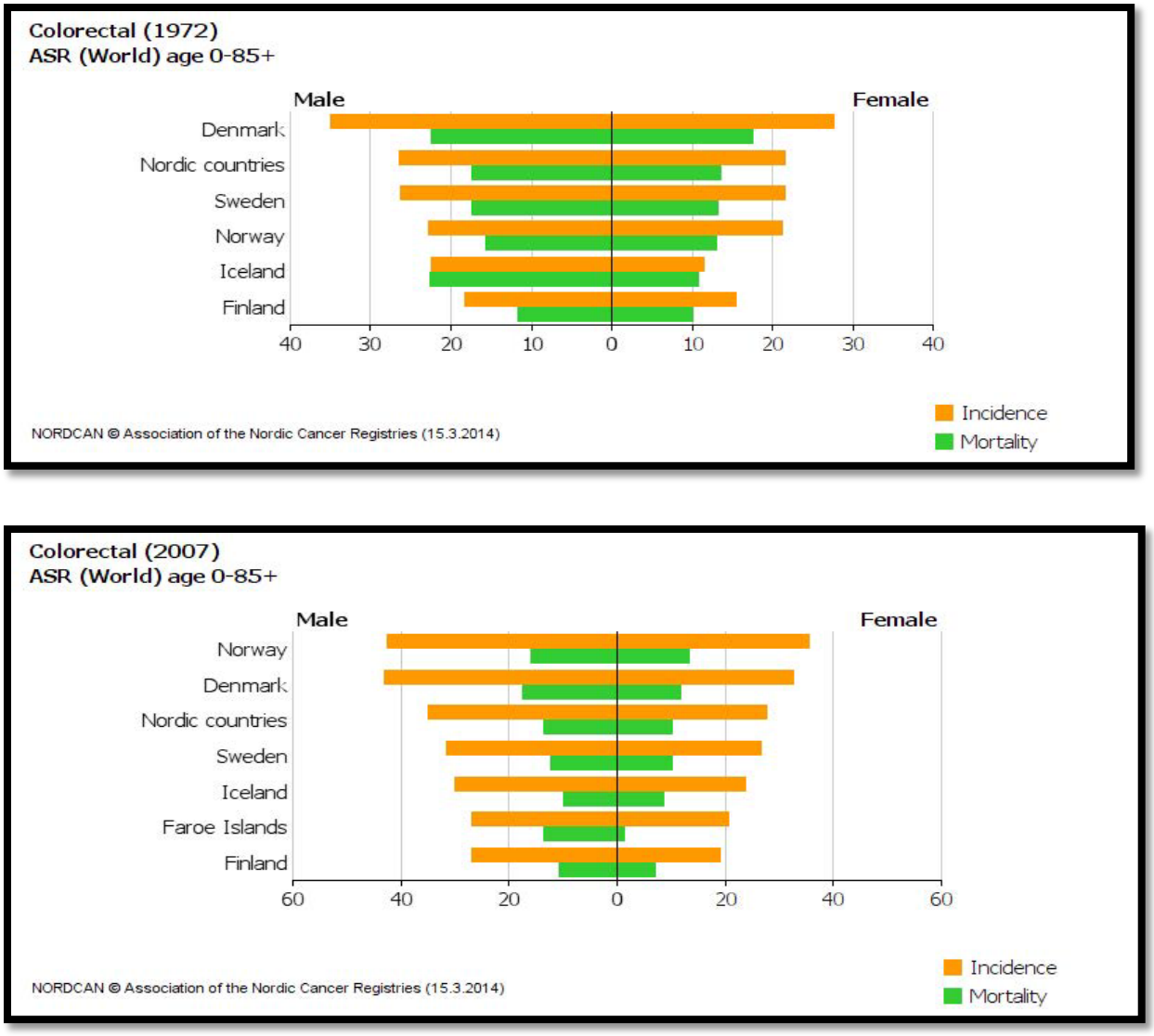

Figure 3: Age standardized rate of CRC incidence and mortality rates per 100,000 in the Nordic countries 1972 and 2007 (NORDCAN)

Figure 3 shows the incidence and mortality rates in the Nordic countries during 1972 and 2007 that is the beginning and end of our study period, respectively. Denmark had the highest incidence rate back in 1972 both among men and women. By 2007, Norway and Denmark were observing almost similar CRC incidence rates. Norwegian women had slightly higher incidence rate compared to Danish women. However, regarding mortality rates, Icelandic men had the highest rates followed by Danish men during 1972 whereas by 2007 highest rates were observed in Denmark and Norway. Danish men had highest CRC mortality rate whereas the rates were highest among Norwegian women in 2007.

1.2 Colorectal cancer in Norway

Over the last half century, Norway has experienced one of the most rapid and steady rises in CRC incidence. In the late 1950s, the age standardized incidence rate for colon cancer was 10 per 100,000 for both men and women. The incidence rate of rectal cancer in the same period was approximately around 7 and 4 for per 100,000 for men and women, respectively. By the beginning of 1970s, the incidence rate of colon cancer was around 14 for both men and women; the incidence rate of rectal cancer was 11 and 8 per 100,000 for men and women, respectively. Current incidence rates of both colon and rectal cancer are more than double what they were 50 years ago for both men and women. The present age standardized five year incidence rate of CRC for year 2007-2011 is 43 for and 35 per 100,000 for men and women respectively. Among men, the incidence rate of colon and rectal cancer is 26 and 17 per 100,000 respectively. Similarly, for women, the incidence of colon and rectal cancer is 24 and 11 per 100,000 respectively (10). The corresponding figures for CRC incidence rate and by subsite in Norway by gender from 1972-2011 are presented in the figure below (Figure 4, 5, and 6).

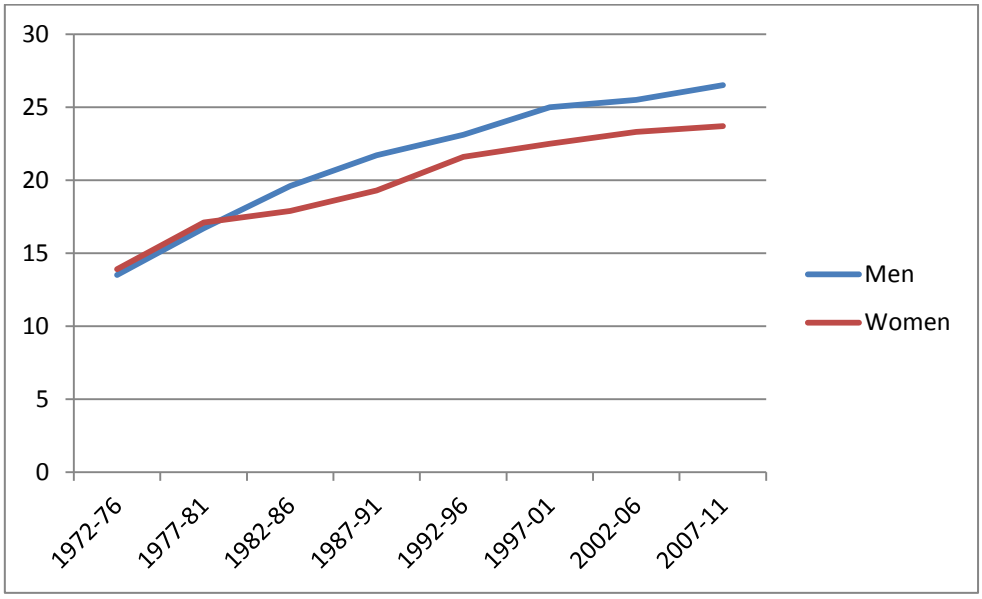

Figure 4: Age standardized incidence rate of colon cancer by gender in Norway (1972-2011) (Norwegian Cancer Registry, 2013)

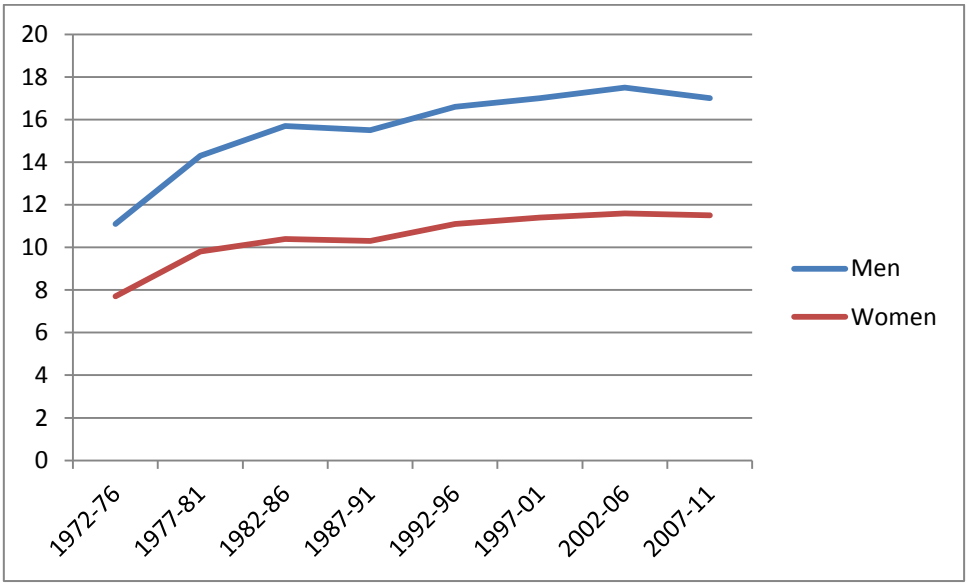

Figure 5: Age standardized incidence rate of rectal cancer by gender in Norway (1972-2011) (Norwegian Cancer Registry, 2013)

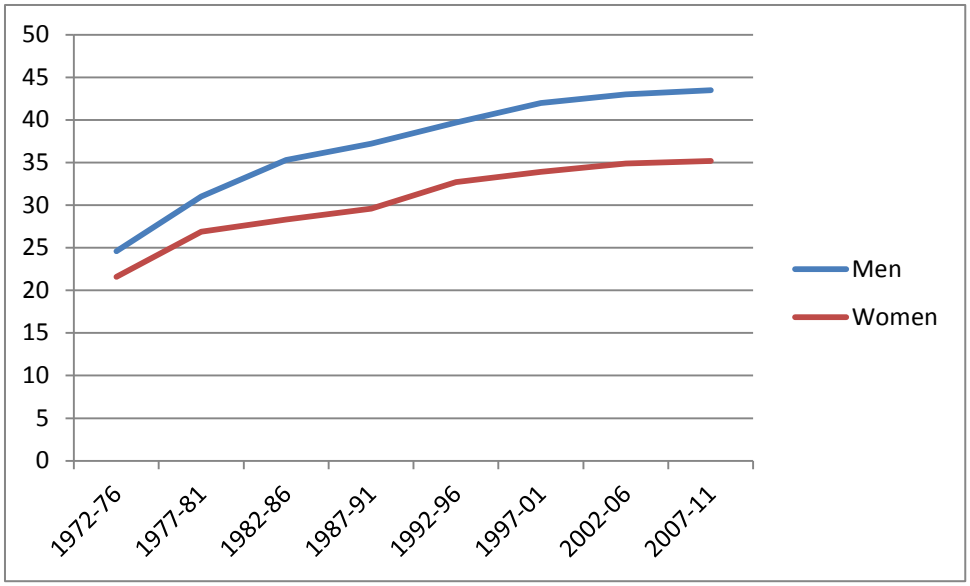

Figure 6: Age standardized incidence rate of CRC by gender in Norway (1972-2011) (Source: Norwegian Cancer Registry, 2013)

The colon cancer incidence rates among men and women are almost similar but men have higher incidence of rectal cancer than women. The gender difference in CRC incidence is due to men having more rectal but not colon cancer than women.

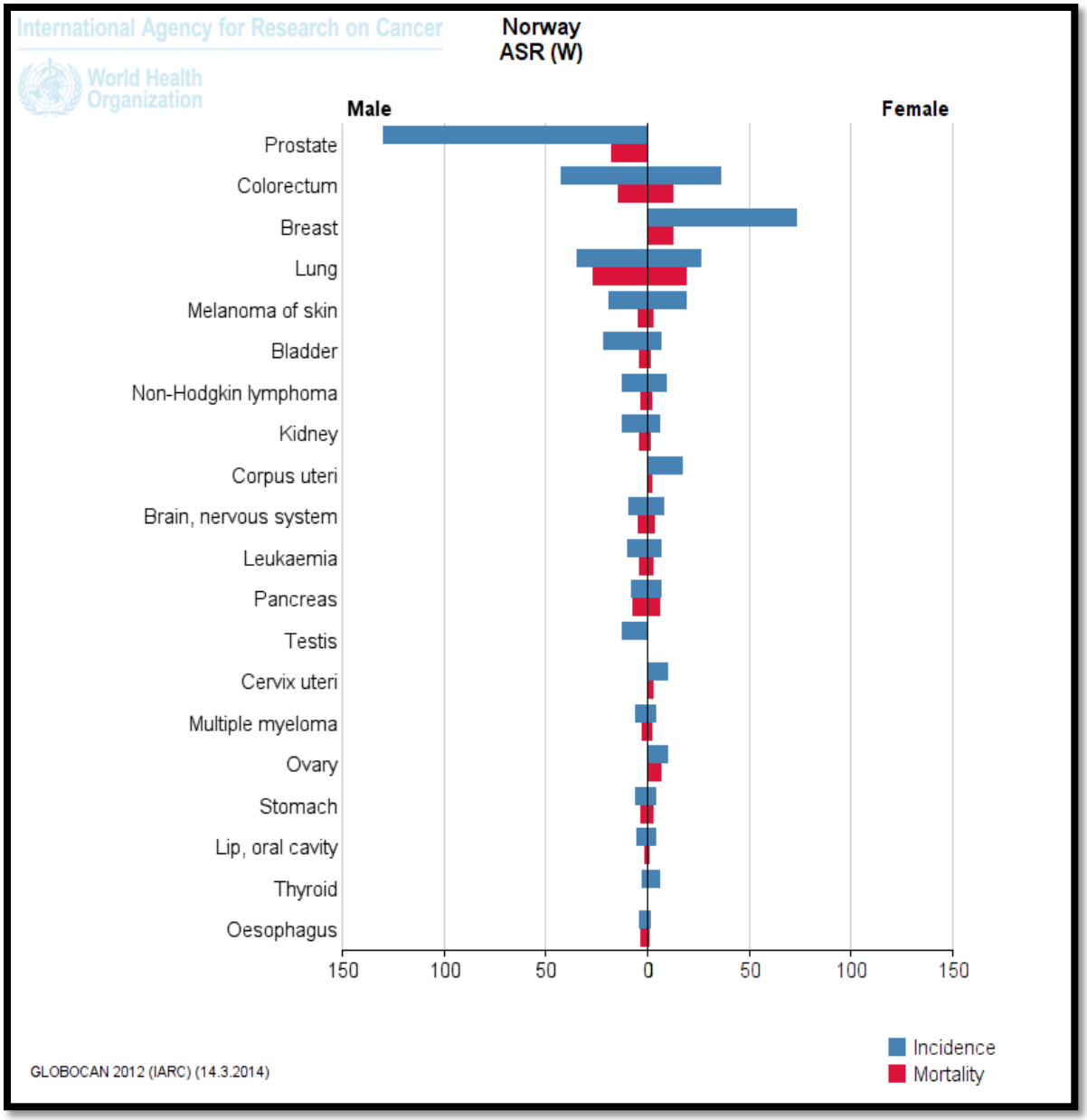

Figure 7: Estimates of age standardized incidence and mortality rate per 100,000 for different cancer sites in Norway by gender (Globocan 2012)

Figure 7 shows the ASR for different cancer in Norwegian by gender in 2012. In 2002, women in Norway had the highest CRC incidence rate in Europe and second highest incidence rate worldwide, only surpassed by women in New Zealand (11). In addition to being one of the most common cancers among Norwegian, CRC is also a cancer type with a high mortality. The latest report showed that in Norway, the CRC mortality rate is ranked

second after lung cancer among women and third after lung and prostate cancer among men (10).

1.3 Prevalence of smoking

1.3.1 Global prevalence

There are an estimated 1.3 billion smokers worldwide and that number is expected to increase to 1.6 billion by 2025 (12;13). Seventy-three percent of smokers are from low and medium income countries. Smoking is one of the major leading preventable causes of death in the world (13-15) and attributed to approximately 6 million premature deaths each year globally. If prevention measures are not implemented soon, the deaths toll could reach approximately 8 million by 2030. Recent report on tobacco from World Health Organization (WHO) reported that in the 20th century almost 100 million deaths have been caused by tobacco smoking and if this trend continues further, one billion smoking related deaths will occur in the 21st century (13).

A four stage model for describing the effects of smoking on mortality was purposed by Lopez and colleagues almost 2 decades ago (16). Women in high-income countries lagged behind men by 20-30 years in relation to smoking and its attributed mortality. This model was further reviewed in 2012 and the predictions matched recent trends in smoking and smoking related mortality (Figure 8). The authors concluded that the model reflected the situation of many high income countries reasonably well with a few exceptions in low and medium income countries (17).

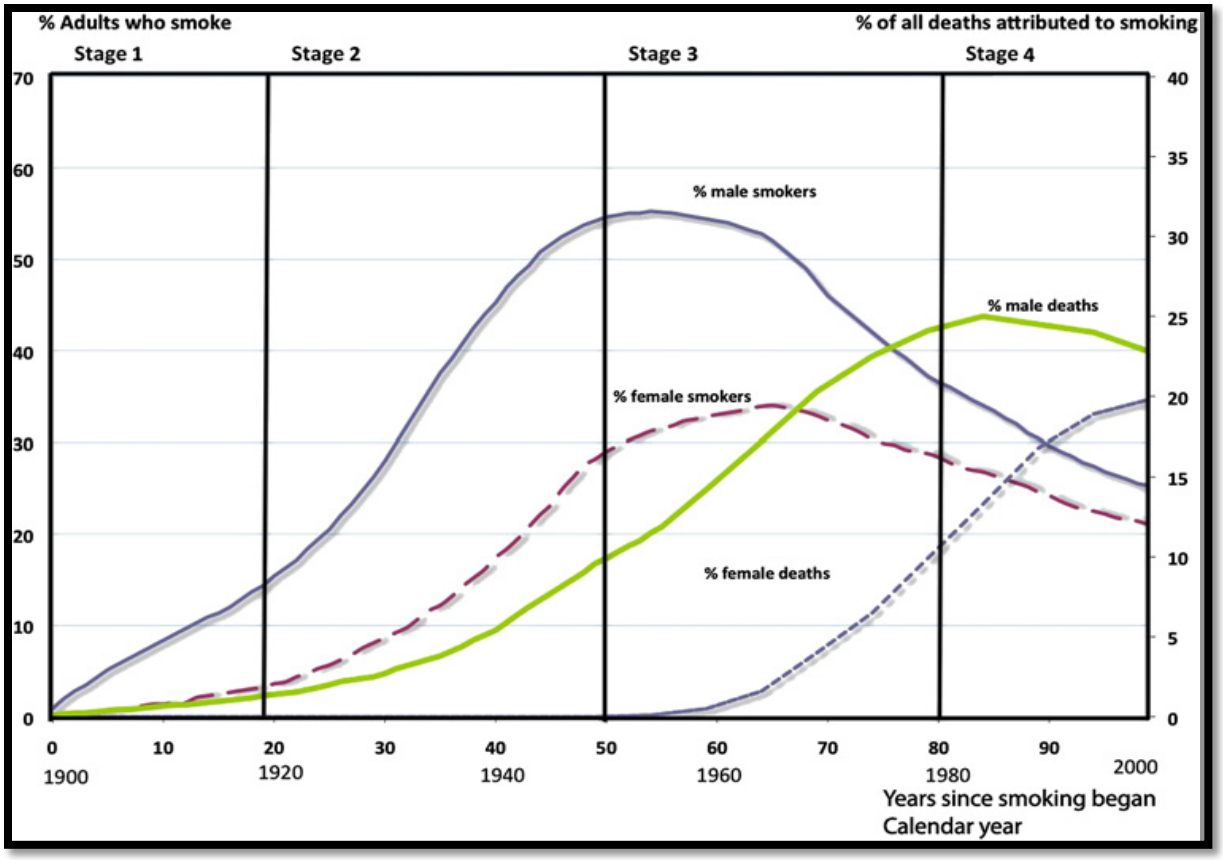

Figure 8: A descriptive model of cigarette epidemic in developed countries (Lopez et al. 1994)
Stages of the cigarette epidemic on entering its second century (Thune et al 2012):
(Reprinted with permission from BMJ publisher group)

1.3.2 Prevalence of smoking in the Nordic countries

In 1920, Denmark had the highest prevalence of smoking in the Nordic countries. A report from 2006 showed the highest prevalence in Denmark and Norway (25 and 24, respectively), and the lowest prevalence in Sweden and Iceland (18). Direct comparisons of the smoking prevalence in Nordic countries are somewhat difficult as the data on smoking habits are collected in different age groups. However, in all of the Nordic countries a decreasing trend in the prevalence of smoking was associated with an increased level of education (19).

1.3.3 Prevalence of smoking in Norway

The trend of smoking prevalence for men current smokers has been different from that of women in Norway. The prevalence of smoking among men peaked at 65 % in the late 1950's; and then decreased to 50% in 1975 and 33% in 1999. This decrease continued through 2007, when the prevalence of smoking among men was 50% lower than that in the 1970s. This is quite different from the corresponding figures of smoking prevalence among women. In 1954, the prevalence of smoking among women which was 23% in 1954, peaked at 37% in 1970 and then stabilized to 32% for the rest of the century. After 2002, a decline in the prevalence of smoking was seen among women and by 2007 which is the end of our follow-up period; the prevalence was similar in both men and women (18;20;21). By the year 2013, 15% Norwegian men and women were current smokers (22). This smoking pattern is in accordance with the tobacco epidemic stages model suggested by Lopez et al. almost 20 years ago (16) which suggested that the smoking-attributed mortality for women, will in the same way as the smoking prevalence, lagged behind that of men and both will peak at a lower level than that of men. The difference in smoking habits is one of the main explanations for social inequalities in health in Norway. Recently, it has been reported that Norway is one of the four countries along with Canada, Iceland and Mexico that are successful in achieving reductions of smoking prevalence in both men and women by more than 50% (23). Figure 9 shows the prevalence of current smokers by gender in Norway between years 1973-2013.

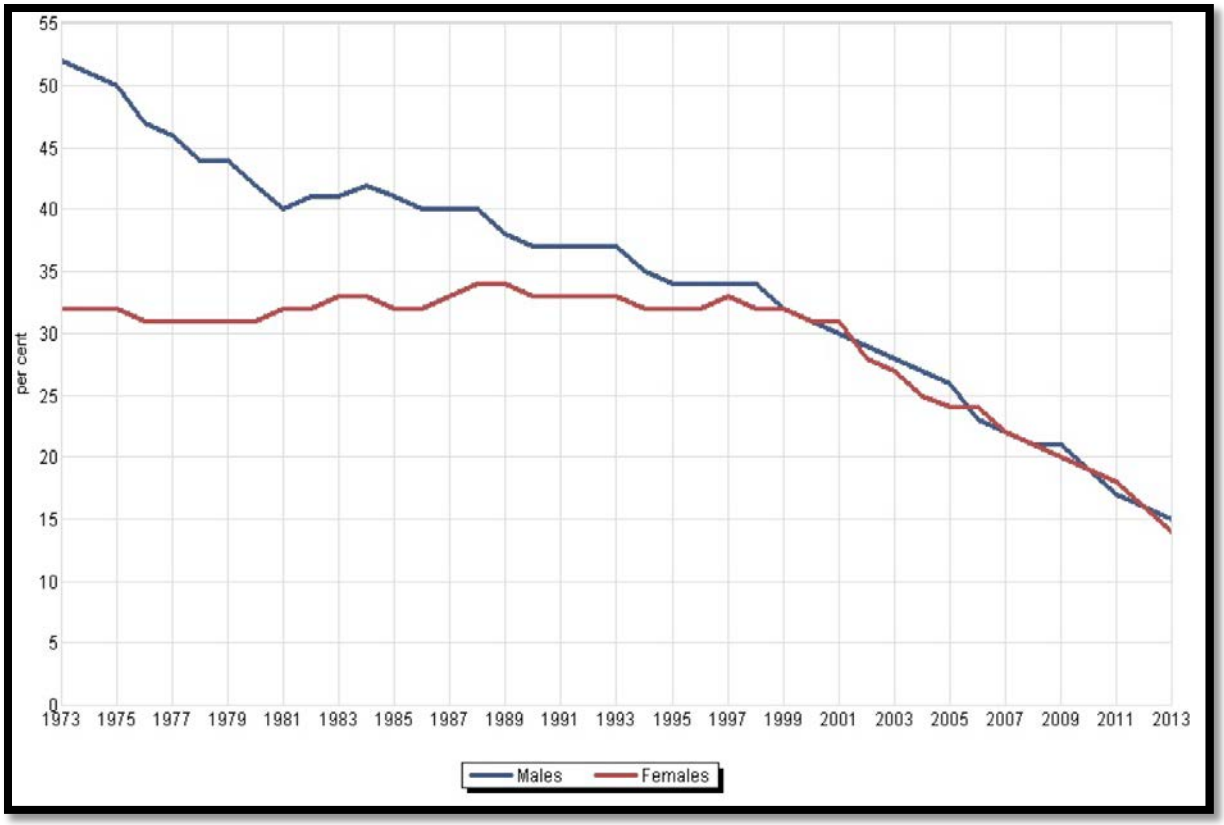

Figure 9: Men and women current smokers aged 16-74 years old since 1973-2009
Source: Statistics Norway

1.4 Assessment of risk factors for colorectal cancer

1.4.1 Non-modifiable risk factors

Age

Increased life span is one of the contributors for increasing number of cancer cases and CRC is no exception (24). CRC is common in older age groups: people aged 50 years and older accounting for more than 90% of cases and CRC incidence is low among people aged less than 50 years (25). However, recent trends show that CRC incidence is also increasing among those under 50 years of age (26;27).

Gender

As previously mentioned, CRC incidence and mortality rates are generally higher among men than women (6) and this difference may reach 35-40% higher in men compared to women(9). Differences by gender in CRC incidence are more obvious for rectal cancer which has a higher incidence among men. The reason for this difference is difficult to explain but may be partly due to exposures to different risk factors and hormones (28).

Geographical variations and race

CRC prevalence varies according to geographical locations and race. The number of CRC cases is declining in the United States, and stabilizing in most of Northern and Western Europe (25;29). Although, rates are low in Asia and Africa, CRC incidence is increasing in countries like Japan, Singapore and most Eastern European countries.

Adenomatous polyps

Adenomatous polyps are recognized precursor lesions of CRC and are common after 50 years of age. They represent almost two-thirds of colorectal adenomas and have a high potential to progress to malignancy. The majority of CRC develop from adenomatous polyps through a

series of genetic changes (30) but only around 10% of adenomatous polyps develop into cancer (31). An association between cigarette smoking and adenomatous polyps has been reported recently and it was suggested that smoking could play an important role in both the formation and aggressiveness of adenomatous polyps (32;33).

Inflammatory bowel diseases

Inflammatory bowel diseases (IBD) such as ulcerating colitis and Crohn's disease might predispose to CRC development though these diseases account for very few cases of CRC in the general population and only around 15% of all CRC deaths occur among individuals with IBD (34;35). Factors such as early age at IBD diagnosis, longer duration of symptoms and severity of dysplasia and inflammation increase the risk of CRC.

Family and personal history of colorectal cancer or adenomatous polyps

A family history of CRC is a well-established risk factor (28) and is associated with an increased risk of the CRC (36). Individuals with a family history of CRC and colorectal adenomas mainly adenomatous polyps have higher risk of CRC (37). The risk of CRC is increases when a first degree relative has one or more colorectal adenomas mainly adenomatous polyps (38) and the risk is doubled when a first degree relative is affected with CRC. Similarly, individuals with multiple relatives affected with CRC who were diagnosed at a young age have a risk of CRC that is three to six times than that of general population (39). Almost 20% of all CRC cases have a close relative who have been diagnosed with the same cancer (40). Person who had CRC are more likely to develop it again in other areas of colon and rectum. This can occur even when the first cancer is removed completely. The risk further increases if the first cancer is diagnosed at 60 years of age or younger (9). Furthermore, person with previous adenomatous polyps are in increased risk of CRC and this is more probable if the polyps were multiple and were of large sizes (41).

Genetic risk factor

The risk of CRC associated with hereditary conditions is about 5 to 10% (42). The two types of hereditary conditions are familial adenomatous polyps (FAP) and lynch syndrome, which is also known as hereditary non-polyposis colorectal cancer (HNPCC). The genes that mutate and lead to carcinogenesis have been identified in both of these conditions. MLH1 and MLH2 are responsible for mutations in individuals with HNPCC (43) whereas APC genes are responsible for mutation in FAP (44). HNPCC is the most common of these genetic syndromes and accounts almost 2- 4% of CRC (45), whereas AFP accounts for less than 1% (46).

1.4.2 Modifiable risk factors

Physical activity and obesity

The association between a high level of physical activity and decrease colon and rectal risk of cancer has been reported previously in a recent meta-analysis which included 52 cohort and case control studies (47). The study reported around a 20-30% decreased risk of colon cancer among physically active individuals compared with less active ones. Similarly, another meta-analysis concluded that physical activity is associated with reduced risk of both proximal and colon cancer which did not differ by location (48). Lack of physical activity can also lead to obesity, another major risk factor for CRC (49), but a high level of physical activity can lower the risk of CRC even without the significant weight loss (50). Nevertheless, many studies have supported the notion that obesity leads to the development of CRC, and have reported that obesity as an independent risk factor (51-56).

Diet

Diet is a major modifiable risk factor for CRC. It has been reported that changes in dietary patterns can reduce the CRC burden by 70% (49;57). Diets that are high in fat and high meat consumption have been implicated in the development of CRC (49;58;59). Diets consisting of large amounts of red meat and highly refined carbohydrates increase the risk of CRC as do diets low in vegetables and fruits (50;60-62).

Alcohol consumption

The IARC has concluded that alcohol consumption is a potential risk factor for CRC (33). Indeed, alcohol consumption is one of the most important modifiable risk factors for all human cancers (63). Heavy alcohol consumption is linked to an increased CRC and could even give rise to CRC at younger age (8;64). Metabolic product of alcohol such as acetaldehyde is considered to be carcinogenic (65). Alcohol can also work as a solvent which could allow other carcinogenic molecules into the colon and rectum mucosa (66). Similarly, an individual with high alcohol consumption and a diet low in essential nutrients is more vulnerable to the carcinogenic effects of alcohol. Several meta-analysis and pooled studies carried out in different parts of the world reported an increased risk of CRC with high regular alcohol consumption (67-75).

Medications, supplements and hormonal replacement therapy

There is growing evidence that COX inhibitors such as aspirin, calcium supplements and hormonal replacement therapy (HRT) may have preventive effects towards the CRC (9;76;77) Calcium supplements have been shown to reduce the risk of recurrent polyps (78). The long-term use of aspirin has been shown to have preventive effects on CRC (77;79) but it is not prescribed routinely for this purpose because of its side effects which includes gastrointestinal bleeding (9). Although, HRT has shown protective effects against CRC, it can increase the

risk for breast and other cancers, and therefore is not presently used for CRC prevention (76;77;79;80).

1.5 Smoking and colorectal cancer

Smoking is a major contributing factor to human carcinogenesis and is one of the most important modifiable risk factors for cancer and premature death worldwide (24). The main hazards of smoking are related to exposures such as age at smoking initiation, numbers of cigarettes smoked per day, smoking inhalation or type of cigarettes such as either tar and nicotine, or content or filter type (81). Cigarette smoke contains more than 7000 chemical compounds majority of which are carcinogens such as polycyclic aromatic hydrocarbons (PAH) and nitrosamines in addition to other promoters. These mixtures contribute to complete carcinogenesis in the mucosa of the colon and rectum (82). The carcinogenic effects of smoking could be initiated through multiple pathways such as DNA binding and mutations, oxidative stress, epigenetic changes, or inflammation (14). Figure 10 shows the pathway for causation of cancer via the carcinogenic effects of smoking. In the most recent monograph published in 2012 (33), and the report from the Unites States Surgeon General (15), the conclusion was that there is a casual association between smoking and CRC. The association between smoking and CRC risk has been shown to be dose-related (83-85). A longer exposure to or duration of smoking (35-40 years) has been shown to be associated with increased risk of CRC (86;87). The association between smoking and colorectal adenomas which are precursor lesions for most CRC was confirmed in a recent meta-analysis (32).

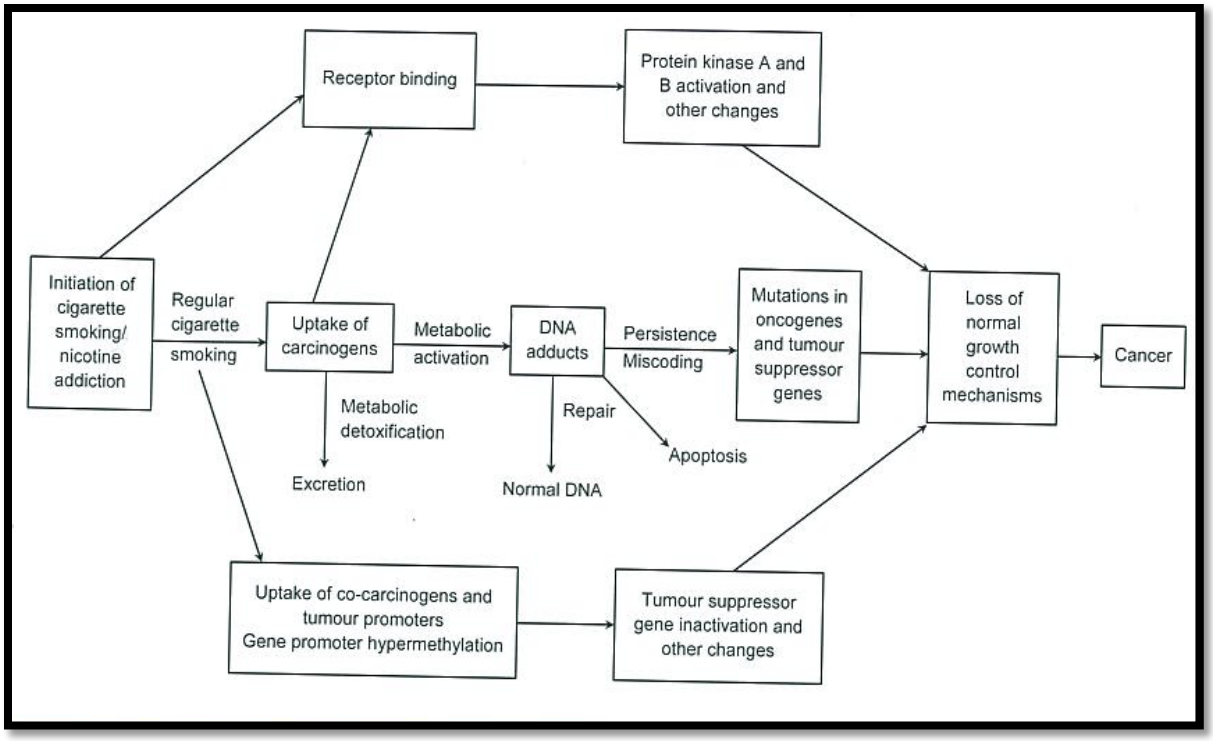

Figure 10: Pathway for causation of cancer by carcinogens in tobacco smoke
(Reprinted from the United States Department of Health and Human Services (2004). *The Health consequences of Smoking: A Report of the Surgeon General*. Atlanta, GA: The United States Department of Health and Human Services, Center for Disease Control and Prevention, National Center for Chronic Disease)

2 Aims of the thesis

The main aim of this thesis was to examine the association between smoking and CRC incidence and mortality overall and by subsites and gender.

The specific objectives were:

1. To investigate the association between smoking and the risk of colon cancer overall, and by localization and gender.

2. To investigate the association between smoking and the risk of rectal cancer by gender.

3. To examine the association between smoking and CRC mortality overall, by subsites and gender.

4. To examine the association between different smoking exposures i.e., age at smoking initiation, numbers of cigarettes smoked per day, smoking duration and number of pack-years smoked and colon and rectal cancer by gender.

5. To examine the association between different smoking exposures i.e., age at smoking initiation, numbers of cigarettes smoked per day, smoking duration and number of pack-years smoked CRC mortality by gender.

3 Materials and Methods

3.1 Study population

The cohort included 652,792 Norwegians (49% men) born between 1897 and 1975, recruited from several Norwegian health screening surveys initiated by the National Health Screening Service (now included in the Norwegian Institute of Public Health). These surveys were conducted between 1972 and 2003 and are as follows: the Oslo study I (1972-1973), the Norwegian counties study (1974-1988), the 40 years cohort (1985-1999) and the Cohort of Norway (CONOR, 1994-2003).

In all surveys included, information was gathered through questionnaires and a short health examination. The design and protocol of these surveys were very similar, but there were some modifications during different time periods, mainly in the questionnaires regarding questions on smoking, alcohol consumption, physical activity and other lifestyle factors. In most surveys, the attendees were given another supplementary questionnaire which they completed at home and mailed back in a pre-addressed stamped envelope. The participation rates for the different surveys varied from 56-88%. A flow chart with a detailed description of study participants has been provided below (Figure 11).

The Oslo study I

This survey was conducted in 1972-1973 among men living in the municipality of Oslo. Men aged 40-49 years in Oslo and a random sample of 7% of the general male population aged 20-39 years were invited to participate in screening for tuberculosis and cardiovascular disease. About 30,000 men were invited and almost 18,000 attended the screening (i.e., a participation rate of approximately 60%). The participants answered one-page questionnaire which focused on symptoms of cardiovascular disease and diabetes, smoking habits and physical activity. This was one of the first large epidemiological studies of that period and became a model for

establishing other population based health studies in Norway later on. Height, weight and blood pressure were measured during screening using a standard procedure (88-91).

The Norwegian counties study

These surveys included participants of cardiovascular disease screening in three Norwegian counties (Finnmark, Sogn og Fjordane and Oppland) during three different time periods: 1974-1978, 1977-1983 and 1985-1988. All residents aged 35-49 years as well as random sample of 10% of the general population aged 20-34 years were invited to a first screening. A second and third screening was carried out, and included a combination of previous cohort as well as new ones. Similar protocols and questionnaires were applied for these surveys. The attendance rates were 88%, 88% and 84% at the three screening rounds, respectively (91-93).

The 40 years cohort

These surveys included about 420,000 Norwegian men and women, and were carried out in all of the 19 counties of Norway in 1985-1999 for cardiovascular disease screening. Men and women aged 40-42 years were the largest invited population. Individuals aged 65-67 years were also invited to the first round of surveys in some of the counties (Nord-Trøndelag, Møre and Romsdal and Hordaland). The participation rate was 69% (94;95). Of all the surveys included in this thesis, the 40 years cohort had the largest number of participants.

The Cohort of Norway

CONOR is a very large collaborative project including regional data from 10 epidemiological studies conducted in 1994-2003 which have been merged into a national database (please refer to Table 1 for details of surveys included in CONOR). Standardized protocols, procedures and questionnaires were used together with a short health examination. The questions used in CONOR have been validated previously. The response rate varies across the surveys. The average response rate for the 10 different surveys in the CONOR study was

56%. Altogether, around 309,000 individuals were invited of which about 181,000 accepted to participate and provided consent (91;96;97).

Table 1: List of different surveys included in the study

Name of Survey	**Year Conducted**	**Populations from**	**Surveys**
The Oslo study I	1972	Oslo (only men)	1
The Norwegian counties study	1974-88	Oppland, Sogn og Fjordane, Finnmark	9
40 years cohort	1985-99	All Norwegian counties included	19
CONOR			
Tromsø Health Study IV	1994-95	Tromsø	1
The second Nord-Trøndelag Health study (HUNT 2)	1995-1997	Nord-Trøndelag	1
Hordaland Health Study(HUSK)	1997-99	Hordaland	1
Oslo study II	2000	Oslo	1
HUBRO(The Oslo Health Study)	2000-2001	Oslo	1
Oppland and Hedmark Health Study (OPPHED)	2000-1	Oppland and Hedmark	1
Tromsø Health Study V	2001	Tromsø	1
I-HUBRO(The Oslo Immigrant Health Study)	2002	Oslo	1
Troms and Finnmark Health Study (TROFINN)	2002	Troms and Finnmark	1
MoRo II(The second part of the Romsås in Motion Study	2003	Romsås	1
Total			**39**

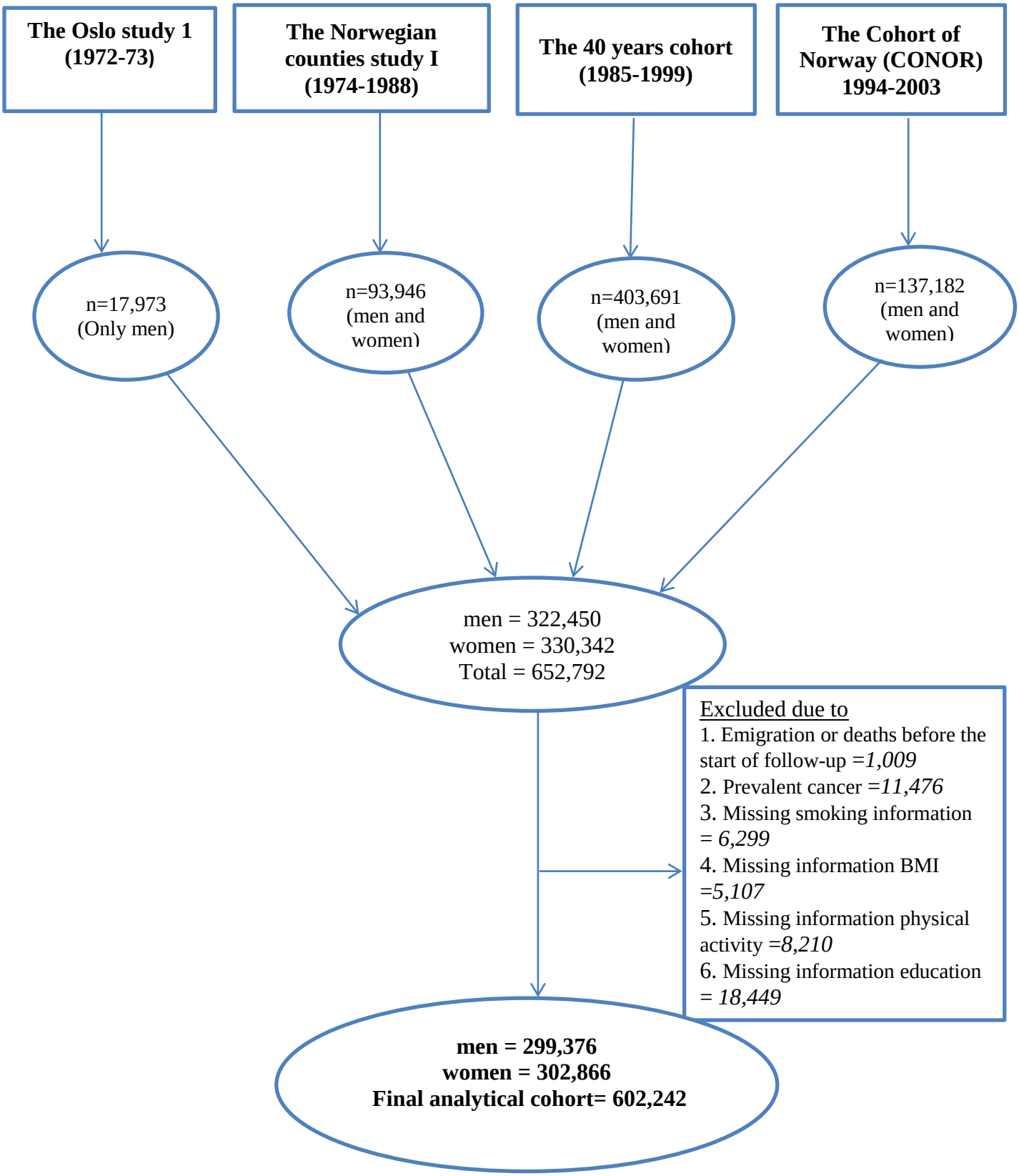

Figure 11: Detailed flowchart of participants from the different surveys

3.1 Pooling Datasets

After obtaining specified variables from each survey's primary data using the unique key identifier for each participant, we created a standardized data base for the pooled analyses. There were total 833,871 registered observations including 181,079 doubles or more. For participants who took part in more than one survey, only the earliest survey was included. Variables common to all surveys were transformed to the same format. The variables in the CONOR study were adequately structured and this was taken as a reference for standardizing the questionnaires. All surveys had a baseline questionnaire, which included detailed assessments of smoking habits, physical activity, and other lifestyle factors. At the screening facility height and weight were measured in a standardized way by a trained person, which allowed us to calculate body mass index (BMI, kg/m^2). Question on smoking habits were similar but not identical across all surveys. The questions asked about current and former daily smoking habits, smoking duration, average number of cigarettes smoked per day and in few surveys former smokers were asked about time since cigarette quitting. Only the CONOR study asked about age at smoking initiation. In the other surveys, this variable was estimated for both current (age at enrolment minus duration of smoking in years) and former (age at enrolment minus years since quitting and duration of smoking) smokers. We also found common formats for other variables such as menopause, menarche, HRT and alcohol consumption which were available only in the latest surveys such as 40 years III and IV and CONOR. Due to large missing in these variables which reached more than 50%, we were not able to use them in our main analysis. Detailed information on how the files were merged into single database is included in the appendix section (Appendix 3).

3.3 Exposure information

Participants who smoked daily were categorized as current smokers, and those who answered that they had smoked previously but not currently or if they answered the year since quitting smoking were categorized as former smokers. Current and former smokers were then combined into a single category called ever smokers. In Paper I, we further categorized ever smokers according to: age at smoking initiation (≤16, 17-19, 20-24, ≥25), numbers of cigarettes smoked per day (1-9, 10-19, ≥20), smoking duration in years (1-19, 20-29, 30-39, ≥40) and number of pack-years smoked (i.e., number of cigarettes smoked per day, divided by 20, multiplied by the duration of smoking in years) (0-9, 10-19, ≥20) . In Paper II and III, we categorized ever smokers by different measures of smoking exposure: age at smoking initiation (≤19, 20-24, ≥25), numbers of cigarettes smoked per day (1-9, 10-19, ≥20), smoking duration in years (1-19, 20-29, ≥30) and number of pack-years smoked (0-9, 10-19, ≥20). In all three papers, participants who were neither current nor former smokers were classified as never smokers. Participants were categorized into three groups based on their level of physical activity at enrolment: sedentary (reading, watching television, sedentary activity, or walking, bicycling <4 hours per week), moderate (walking, bicycling, and/or similar activities ≥4 hours per week), and heavy (light sports or heavy gardening ≥4 hours per week, heavy exercise or daily competitive sports). The most recent information regarding duration of education was obtained from Statistics Norway and was used to assign subjects to one of three categories of duration of education (<10, 10-12, ≥13 years).

3.4 Follow-up and endpoints

The study population comprised individuals who participated in of one of the four health surveys included in our thesis. We excluded participants who had emigrated or died before the start of follow-up n = 1,009 (50% women) and those with prevalent cancer n = 11,476 (62% women). We also excluded participants with missing information on either smoking exposure n = 6,299 (45% women) or on any of the co-variates [BMI, physical activity, education n = 31,766 (50% women)]. Altogether 50,550 (48% women) participants were excluded leaving 602,242 subjects (51% women) in the analytical cohort for all papers.

We followed all participants aged 19–67 years at enrolment through a linkage to the Cancer Registry of Norway and the Central Population Register, utilizing the unique 11-digit personal identification number to identify all cancer cases, emigrations and deaths. The participants were linked to the Cancer Registry of Norway, the Norwegian Cause of Death Registry and the Central Population Register. The national registries have accurate and detail information regarding cancer incidence and mortality (98). The national registries are both accurate and virtually complete (98;99). The start of follow-up was set at 1 January of the year after the baseline questionnaire was completed. In Paper I, person-years were calculated from the start of follow-up to the date of colon cancer diagnosis, the date of any incident cancer diagnosis (except skin basal cell carcinoma), emigration, death, or the end of follow-up, i.e., December 31, 2007, whichever occurred first. In Paper II, person-years was calculated from the start of follow-up to the date of rectal cancer diagnosis, the date of any incident cancer diagnosis (except skin basal cell carcinoma), emigration, death, or the end of follow-up, i.e. December 31, 2007, whichever occurred first. In paper III, follow-up ended at the time of death from primary CRC cancer, death from any other cancer (except basal cell carcinoma of the skin), emigration, death from other causes, or the end of follow up (December 31, 2007), whichever occurred first.

Colon and rectal cancer were classified according to the Seventh Revision of the International Statistical Classification of Diseases (ICD-7) (codes 153 and 154 respectively), and colon cancer was further categorized according to tumor location, i.e., proximal (codes 153.0/153.1) and distal (codes 153.2/153.3). Tumors that were overlapping (code 153.4), were specified as appendix (code 153.6), or were unspecified (code 153.9) were classified as "others" and were included in the analyses for the whole colon only. CRC mortality was classified according to ICD-9 and ICD-10.

3.5 Statistical analyses

We performed all analyses separately by gender. We used the t-test and χ^2 test for investigating differences in the distribution of selected characteristics between cases and non-cases and between ever and never smokers. The Cox proportional hazards model was used with age as the underlying time scale to estimate multivariate-adjusted hazard ratios (HR) with 95% confidence intervals (CIs) for the associations between different measures of smoking exposure age at smoking initiation, numbers of cigarettes smoked per day, smoking duration in years and number of pack-years smoked and colon cancer overall, and according to tumor location (Paper I), rectal cancer (Paper II) and CRC mortality (Paper III) with never smokers as the reference group. In Paper I, entry time was defined as age at enrolment and exit time was age at diagnosis of colon cancer, the date of any incident cancer diagnosis (except basal cell carcinoma), emigration, death, or the end of follow-up (31 December, 2007), whichever occurred first.

In Paper II, entry time was defined as age at enrolment and exit time was age at diagnosis of rectal cancer, the date of any incident cancer diagnosis (except basal cell carcinoma), emigration, death, or the end of follow-up (31 December, 2007), whichever occurred first.

In Paper III, entry time was defined as age at enrolment and exit time was age at death, emigration, or end of follow-up (31 December, 2007), whichever occurred first.

The possible confounders included in the final models in Paper I, II and III, selected a priori, were age at enrolment (continuous), level of physical activity (sedentary, moderate and heavy), BMI (continuous), all at enrolment and duration of education in years (<10, 10-12, ≥13). Tests for linear trends were obtained by creating an ordinal exposure variable with equally spaced scores and including it in the models with never smokers as the reference group. Test of heterogeneity by gender and its effect on the association between smoking and the risk of colon cancer overall, and by location, rectal cancer and CRC mortality were tested using Wald χ^2 statistics in Paper I, II and III, respectively. Two-sided p-values <0.05 were considered statistically significant. All analyses were conducted using STATA version 12.0 (Stata Corp., College Station, TX, USA).

In all the papers, the same methods of statistical analysis were used; only the outcome variable differed. Outcome for Paper I was colon cancer, Paper II was rectal cancer and Paper III was CRC mortality.

In all the papers, we re-analyzed the data excluding the 8,151 (99% men) participants who reported smoking only cigars or pipes. We had information on alcohol consumption for 37% (n = 221,748) of the participants. We did sensitivity analyses by gender for the main outcomes based on this population (49% men) with and without adjustment for alcohol consumption in all papers.

3.6 Ethical aspects

Oral or written informed consent was obtained from participants in the different surveys. Surveys carried out in 1995 and after had written consent. We also obtained approval from the respective steering committees to all the health surveys included. We obtained approvals from

the National Data Inspection Board, the Regional Committee for Medical Research Ethics (REK), the Norwegian Directorate of Health, Norwegian Tax Administration and Norwegian Public Health Institute. The data was handled in accordance with the permissions taken from the above mentioned governmental bodies.

4 Results – summary of papers

4.1 Paper I

The increased risk of colon cancer due to cigarette smoking may be greater in women than men.

In Paper I, we investigated the association between smoking and colon cancer overall, by location and gender. The study followed 602,242 Norwegian men and women and 3,998 colon cancer cases (46% of cases in women). Women ever smokers had a 19% (HR = 1.19, 95% CI = 1.09-1.32) and men ever smokers had 8% (HR = 1.08, 95% CI = 0.97-1.19) increased risk of colon cancer compared with gender specific never smokers. For all four dose-response variables examined, women ever smokers in the most exposed category of age at smoking initiation, (HR = 1.48, 95% CI = 1.21-1.81), number of cigarettes smoked per day (HR = 1.28, 95% CI = 1.06-1.55), smoking duration (HR = 1.47, 95% CI = 1.11-1.95), and pack-years smoked (HR = 1.33, 95% CI = 1.11-1.57) had a significantly increased risk of more than 20% for colon cancer overall and of more than 40% for proximal colon cancer compared with never smokers. Women ever smokers had a higher risk of proximal colon cancer compared to men ever smokers (Wald χ^2, p = 0.02).

Sensitivity analyses were carried out for participants with information on alcohol consumption which mainly included participants enrolled after 1995 (37% of total analytical cohort, n = 221,748). The corresponding risk estimates for women ever smokers were 16% (HR = 1.16, 95% CI = 0.86-1.74), 27% (HR = 1.27%, 95% CI = 0.82-1.51) and 11% (HR= 1.11, 95% CI = 0.78-1.59) for colon, proximal colon and distal colon cancer, respectively. However, among men ever smokers risk estimates were (HR = 0.99, 95% CI = 0.78-1.25), (HR = 0.97, 95% CI = 0.75-1.64), (HR = 0.82, 95% CI = 0.68-1.15) for colon, proximal colon

and distal colon cancer, respectively. Risk estimates with and without alcohol adjustment did not differ significantly.

The conclusion was that women smokers may be more susceptible to colon cancer and especially to proximal colon cancer than men smokers.

4.2 Paper II

Smoking increases rectal cancer risk to the same extent in women as in men: Results from a Norwegian cohort study.

In Paper II, we examined the association between smoking and rectal cancer incidence by gender among 602,242 Norwegian men and women. During a mean follow-up of 14 years, 2,176 cases (61% cases in men) were diagnosed with invasive rectal cancer. Both men and women ever smokers had a significantly increased risk of rectal cancer of more than 25% for men (HR = 1.27, 95% CI = 1.11-1.45) and women (HR = 1.28, 95% CI = 1.11-1.48) compared with gender specific never smokers. Men smoking ≥20 pack-years had an increased risk of rectal cancer of 35% (HR = 1.35, 95% CI = 1.14-1.58), whereas women showed an increased risk of 47% (HR = 1.47, 95% CI = 1.13-1.91) compared with gender specific never smokers. For both men and women, we observed significant dose-response associations with rectal cancer risk when looking at age at smoking initiation, number of cigarettes smoked per day, smoking duration and number of pack-years smoked and using never smokers as the reference group (p-trend<0.05). The test for heterogeneity by gender was not significant between smoking status and the risk of rectal cancer (Wald χ^2, p value; current smokers = 0.85; former smokers = 0.87 and ever smokers = 1.00).

In the sensitivity analyses for participants, mainly enrolled after 1995, with information on alcohol consumption, the risk estimate of rectal cancer incidence was 13% (HR = 1.13, 95%

CI = 0.83-1.55) with alcohol adjustment and 12% (HR = 1.12, 95% CI = 0.82-1.54) without alcohol adjustment among men ever compared with men never smokers. The risk estimate was 37% (HR = 1.37, 95% CI = 0.99-1.92) with alcohol adjustment and 39% (HR = 1.39, 95% CI = 1.00-1.94) without alcohol adjustment among women ever compared with women never smokers.

In conclusion, increased risk of rectal cancer due to smoking is similar in women as in men.

4.3 Paper III

Cigarette smoking and colorectal cancer mortality among 602,242 Norwegian men and women.

In Paper III, we examined the association between different measures of smoking exposure and CRC mortality overall and by subsites among 602,242 Norwegian men and women and 2,333 CRC deaths (60% in men). There were 1,607 (57% in men) colon cancer and 726 (67% in men) rectal cancer deaths. Women ever smokers had a 22% (HR = 1.22, 95% CI = 1.06-1.40) increased risk CRC mortality compared with women never smokers. Men ever smokers had a CRC mortality risk of 23% (HR = 1.23, 95% CI = 1.08-1.40) when compared with men never smokers. Women ever smokers had an almost 50% (HR = 1.49, 95% CI = 1.20-1.87) increased risk of mortality from proximal colon cancer compared with women never smokers.

A test for heterogeneity by gender showed an increased risk of mortality from proximal colon cancer among women, which was statistically significant for ever smokers and former smokers (Wald χ^2 = 0.02 and 0.04, respectively). It was also significant for former smokers and the risk of rectal cancer showing increased risk among men (Wald χ^2 = 0.02).

In the sensitivity analyses among participants with information on alcohol consumption (37% of total analytical cohort), the risk estimates of CRC mortality was (HR = 0.84, 95% CI =

0.60–1.18) and (HR = 1.25, 95% CI = 0.89–1.74) among men and women ever smokers respectively. Risk estimates with and without alcohol adjustment did not differ significantly.

In conclusion, smoking is associated with increased CRC mortality both among men and women. The risk of rectal and proximal colon cancer mortality was more pronounced among men and women smokers, respectively.

5 Discussion

5.1 Methodological issues

A detailed discussion of the findings is presented separately in each paper. In the following chapter, discussions of those aspects which are applicable to this thesis in general are presented. Epidemiological studies primarily provide important information regarding the general population. The main purpose of such studies is to generalize the results to another target population and to establish the association between a risk factor and an outcome. In this regard, validity of the study is a very important issue. The validity of an epidemiological study can be divided into two groups: internal validity and external validity.

5.1.1 Internal Validity

Internal validity is defined as the true measure of the variable obtained for the study subjects and refers to the logical conclusions drawn from them. It deals mostly with the accuracy of observed results of the study. Internal validity is evaluated by determining whether the observed changes or outcomes can be attributed to the main exposure and not to other causes. Several factors can influence the validity of observed association between an exposure and an outcome (100;101). A major threat to internal validity could be lack of representativeness of the study population. The two major errors that can occur in epidemiological studies are random and systematic errors. Internal validity depends both on random error as well as systematic errors such as bias and confounding (100;101). Figure 12 shows the diagrammatic view of error and its classification which are often encountered in a large epidemiological study.

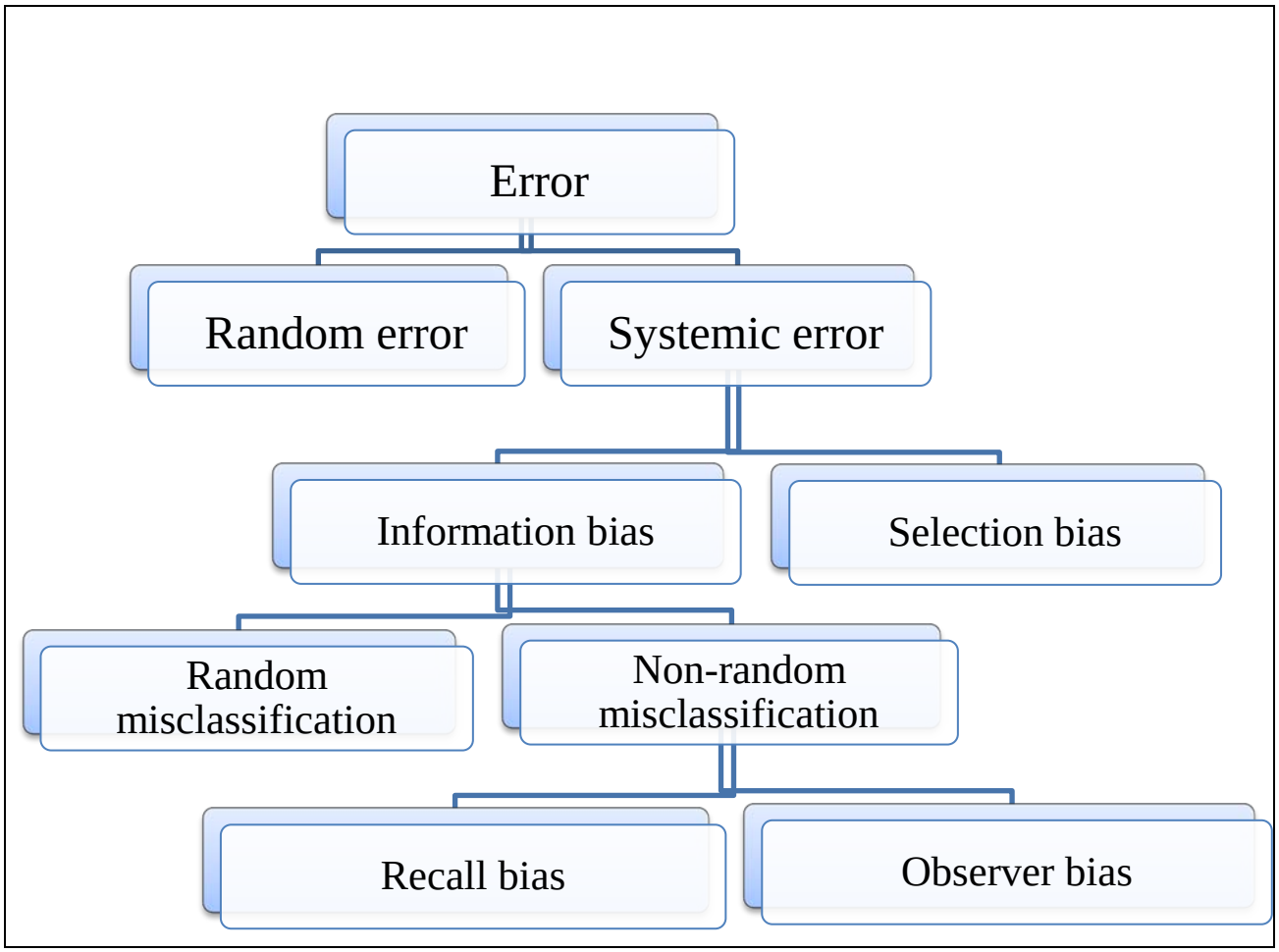

Figure 12: A systematic approach to bias
(Source: Appraising the evidence: what is selection bias? Henderson M et al: Reprinted with permission)

Random error can arises due to sampling variability and can be addressed by appropriate statistical hypothesis testing. Random error may lead to non-reproducibility of study results which in turn could weaken or restrict the association between an exposure and an outcome (100). A large sample size gives more precision to a study. In our study, the large sample size minimized the sampling error and thus increased the precision (100). We have also addressed the issue of random error by applying the appropriate statistical procedures. Our hypothesis was tested at the 5% alpha level and 95% confidence intervals were calculated. The null hypothesis was rejected at a less than 5% level. Another error encountered in epidemiological studies is systematic error. Epidemiological studies with a minimal systematic error have a high accuracy. These errors are independent of the size of the study and statistical significance

does not suggest the absence of any bias (102;103). We consider the discussion of selection and measurement bias relevant in relation to our study.

Selection bias (Paper I-III)

Selection bias in cohort studies results from the process of selecting study participants and can arise due to systematic differences in selection criteria (100). The possibility of this bias arises when a study sample is not representative of the source population (104). However, it is also true that selection bias is less probable in cohort studies than other epidemiological studies as the outcome is not known at the time of enrolment (105). In our study, we had no possibility to control for differences between responders and non-responders as there was no information available for the non-responders.

In all of the surveys included in our study, age was a major criterion for enrolling participants. Most of the men and women enrolled were between 40-45 years of age and a large group of participants were included from the 40 years cohort. The detail description of the study participants categorized by age group during the time of enrolment in different surveys is shown in table 2. The overall participation rate ranged from 56-88%. The attendance rate in CONOR was 56% (range 30-76%) whereas in the Oslo study I, it was approximately 60%. The participation rate for the Norwegian counties study remained between 78-90%. In 40 years cohort, the overall response rate was 69% but during 1994-99, the participation rate went down to 62%.

Table 2: Age at enrolment of participants included in different health surveys

Age at enrolment	Oslo study I	Norwegian counties study	40 years cohort	CONOR study	Total (%)
16-30	869	9,778	740	9,492	20,879 (3.5)
31-39	689	20,216	652	23,873	45,430 (7.5)
40-44	4,782	29,282	364,285	25,583	423,932(70.4)
45-50	9,506	23,458	5,281	16,675	54,920 (9.1)
≥50	1,100	752	13,809	41,420	57,081 (9.5)
Total	**16,946(3)**	**83,486(14)**	**384,767(64)**	**117,043(19)**	**602,242**

Non-response bias is always a major issue in large longitudinal epidemiological studies like ours and declining participation rate is one of the major problems. However, low participation rates do not always indicate a high level of bias. Indeed, there has been very little evidence of substantial bias as a result of non-response and non-response introduces less influence on exposure-disease associations (106-108). Furthermore, we had a similar proportion of men and women participants in our study. A total of 50,550 participants excluded, 48% of which were women due to missing covariates. Thus, our study had a same proportion of men and women excluded due to the missing data. Those excluded group were similar to the analytical cohort in regards to their level of education and physical activity. Incidence rates for colon and rectal cancer among excluded group were also similar to the analytical cohort**.** Furthermore, smoking prevalence among participants from different health surveys in our cohort was comparable to the Norwegian general population during the same period (Fig 13 and 14).

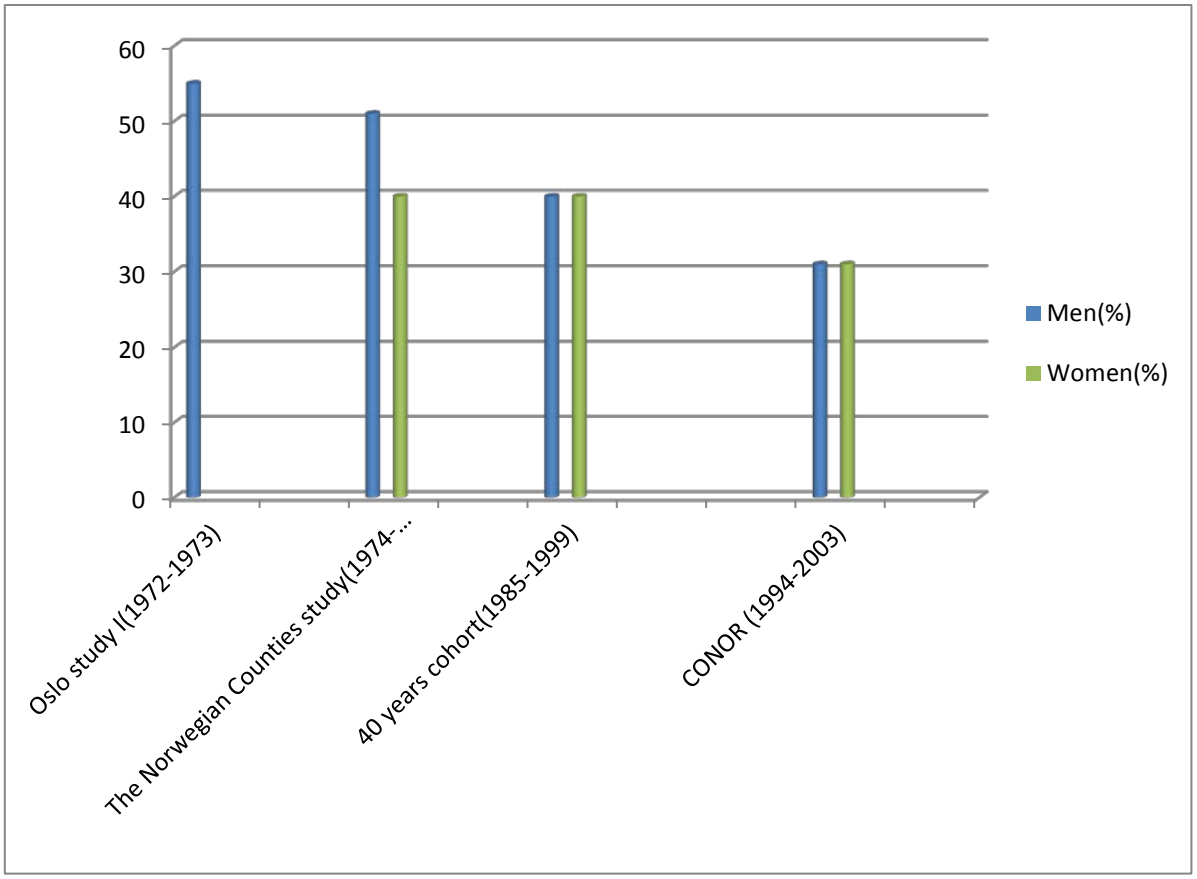

Figure 13: The prevalence of current smokers included in surveys by gender

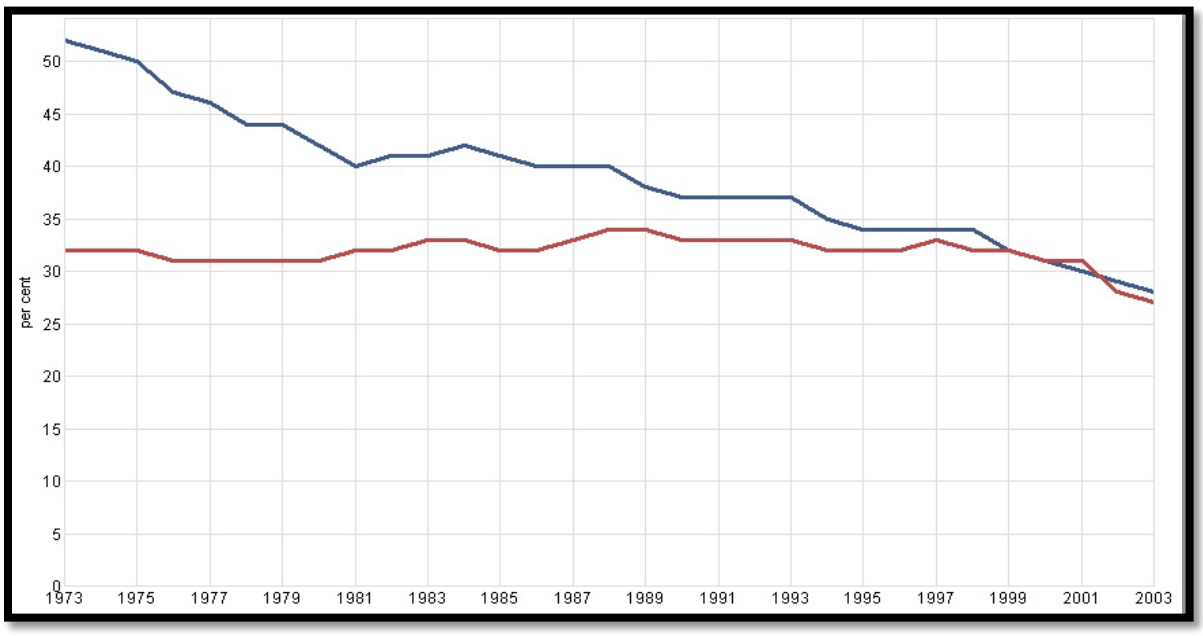

Figure 14: The prevalence of current smokers aged 16-74 years from 1973-2003 in Norway by gender

Information bias (Paper I-III)

Information bias is also known as observation, classification or measurement bias and arises from incorrect determination of an exposure, an outcome, or both (109). Measurements bias occurs when exposures and outcome variables are incorrectly measured (100). In the different surveys included in our study, height and weight were measured according to the standard procedure to minimize the measurement errors. There were some differences in the measurement of exposures variable but we minimized these differences by finding a common format during the merging of the datasets. Smoking history was obtained at study enrolment, and so was not subject to recall bias. Furthermore, smoking habits change; current smokers could have stopped smoking whereas never smokers may have started smoking. Our analysis was based on ever and never smokers, thus only the status of never smokers could have changed during follow-up. In addition to this, very few Norwegians start to smoke after the age of 30, and the mean age at enrolment for our study is more than 40 years, thus minimizing this type of bias. We assume that the possibility of information bias in our study is limited.

Confounding and statistical analyses (Paper I-III)

Confounder is defined as a variable which is associated with main exposure variable but at the same time an independent risk factor for the dependent variable (100;101). As a confounding variable is associated with the exposure and also with outcome but does not stand in the intermediate pathway in the chain of causation between an exposure and an outcome (109), it leads to the mixing or blurring of effects. This is one of the major challenges of an observational study as it can either attenuate or inflate an association between an exposure and an outcome. In a way, confounder is similar to bias but it can be controlled by stratification and adjustment in multivariate models. The magnitude of confounding can be evaluated by comparing crude and adjusted effect measure. Age and gender are almost always potential confounders (100;101). Our analyses were stratified by gender and hazard ratios

(HRs) and 95% CI were estimated by fitting Cox proportional hazard models where age was the primary time variable. In Papers I, II and III, age, BMI, physical activity at enrolment and duration of education were the confounders based on a priori, and were controlled for when estimating the association between smoking and colon and rectal cancer incidence and CRC mortality. The other important covariates that are established risk factors for CRC, such as alcohol consumption, HRT, diet such as red meat and COX inhibitors such as aspirin could not be adjusted for in the main analyses. Information on alcohol consumption was missing on more than 60% of the total participants whereas information on HRT was missing in more than 70% of total women. It has been reported that women could have protective hormonal effects until menopause from HRT which delay or protect them from development of CRC (76). The use of HRT declined after there was growing evidence that it could be risk factor for breast cancer and other cardiovascular disease (110). Similarly, we lacked information on molecular data and CRC screening, as it was not common in Norway when the surveys included in our study were conducted. In addition to this, the information on staging of CRC was also not available. Cigar and pipe smoking may have less potential to be confounders and this could be the reason our sensitivity analyses excluding those smoking only cigar and pipe did not materially change the estimates (33). We also performed the sensitivity analyses among participants who had information on alcohol consumption, with and without alcohol adjustment. Only 37% of the total cohort (48% men) had information on alcohol consumption. Our sensitivity analyses including only those with information on alcohol consumption, risk estimates increased among women and but decreased among men ever smokers for rectal cancer incidence as well as for CRC mortality compared to risk estimates for the main cohort. For colon cancer, the estimates were more or less similar for women but decreased among men compared to risk estimates for the main cohort. However, the results did not change materially with and without alcohol adjustment in this sub cohort either among

men or women indicating that the lack of alcohol intake in the main cohort might not be a major limitation. However, the interpretation of our sensitivity analyses should be done with caution as they included fewer cases, younger participants with less follow-up time than in the main cohort. We should be very cautious to interpret the results of our sensitivity analyses as we lost a large number of cases and follow up time period (>75%). The studies such as Oslo study I, the Norwegian counties study and earlier rounds of 40 years cohort did not have the information on alcohol consumption. It is also true that the alcohol consumption is higher among men than women in Norway (111). Thus, the lack of adjustments of alcohol consumption in our main cohort analyses is likely to have inflated the estimates among men more than women and thus attenuated the gender difference.

The statistical approach to use Cox proportional hazards analysis with age as primary time variable to examine the association between smoking and CRC incidence and mortality was considered appropriate to answer the research questions in Papers I, II and III. Modelling the events using a proportional hazards model with age as the time scale has been recommended as an appropriate method in large health surveys with disease or death as outcome. Furthermore, it has been suggested that using age as a primary time variable is more meaningful and less restrictive than using time on study as the time scale (112).

5.1.2 External validity

External validity is the probability of generalizing the study results to a wider population. This can be also referred as the possibility, or the degree to which the results of the study is applicable to different population in other places and at different time periods (100;101;113). Internal validity is always a pre-requisite for external validity. Although, we had some issues with internal validity, we are convinced that it did not distort our results. Our study includes

very large participants from all over Norway. The separate health surveys included in our study have well-validated datasets. In general, it is difficult to generalize the study results to a wider population but we assume our study conclusion could be generalized to the Caucasian and Western population.

5.2 Discussion of the main results

The main findings are discussed in the respective papers (Papers I-III) in detail. Despite some methodological limitations in the three papers, they have contributed to further support the fact that smoking increases CRC incidence and mortality among both men and women. The discussion below is focused on the main messages of the three papers regarding the association between smoking and CRC.

5.2.1 Gender differences in smoking related colon cancer

The findings from Paper I is in agreement with IARC and United States Surgeon General's recent conclusion that cigarette smoking is associated with colon cancer (15;33). Incidence rates are more important and reliable indicator of trends in disease occurrence than mortality rates as incidence is not influenced by changes in treatment and survival (6). The main difference in CRC in general observed by gender is due to the higher incidence of rectal cancer in men than women. There is not much difference in incidence rates of colon cancer between men and women in Norway.

There are gender reported differences in incidence of colon cancer by location (i.e. proximal vs. distal colon cancer). Some studies have concluded in general that the risk of distal colon cancer is lower among women than in men (114-116). Previous knowledge regarding smoking and colon cancer incidence in general varies by gender. Some studies reported that

the association between smoking and colon cancer may be stronger in men as compared to women (75;117;118). However, these reports could be attributed to the low prevalence of ever smoking women. On the other hand, the results of the studies among women only (119-122) reported findings which were more or less comparable to men for both colon as well as rectal cancer. A recent study from Europe which included men and women from ten European countries reported the risk estimates by subsites and indicated that the ever smokers have an increased risk of colon cancer, which was especially pronounced in the proximal than in the distal colon (123). However, this study did not report the risk estimates by gender. Another study of Norwegian women reported an increased risk of proximal than distal colon cancer among women ever smokers (119). A study among postmenopausal women in the United States aged 55-69 years at baseline also reported an increased risk of proximal than distal colon cancer (120). Furthermore, smoking has been shown to be associated with a higher incidence proximal colon cancer among Caucasian women in the United States as compared with distal colon cancer (124). A study from Japan which was conducted both among men and women and included around 400 colon cancer, reported the risk estimates by gender and the findings were insignificant increase risk of colon cancer among both men and women ever smokers (125). Increased risk of proximal colon cancer among women smokers has been reported to be related with epigenetic changes which are induced by tobacco related carcinogens (120). It has also been suggested that gender-related differences in hormonal factors (126) or susceptibility to tobacco related carcinogens (127) could have influenced the observed different associations for proximal and distal colon cancer by gender (120) which might explain the reason for increased risk of proximal colon cancer among women smokers compared to men smokers. There are not many prospective cohort studies examining the association between smoking and colon cancer by location and gender in detail. Our study is among the very few studies with a very large numbers of incidence cases as well as a large

proportions of ever and never smokers that examined the association between smoking and colon cancer incidence by location and gender. The findings from our study suggested that women smokers maybe more prone to colon cancer especially for proximal colon cancer than men smokers. Our findings could be a strong warning for the women smokers who could be more vulnerable to smoking related colon cancer than men. This may have important clinical and research implications if further confirmed by other large population based epidemiological studies.

5.2.2 Smoking related risk of rectal cancer among women is same as in men

The epidemiologic evidence supports that it takes decades before the increased risk of rectal cancer appears and that smoking plays an important role in early carcinogenesis both among men and women (15;86;87). The incidence rate of rectal cancer is higher among Norwegian men compared to Norwegian women and as mentioned earlier this is the main reason for gender difference in CRC incidence rate in general. The difference in rectal cancer incidence rate was almost 1.5 fold higher among Norwegian men in the beginning of our study period and the situation remained similar until the end of our study period. In the latest report from Norwegian Cancer Registry, this difference is also valid for the present time period (10). Risk patterns were shown to be generally consistent for colon and rectal cancer (73;75). However, some studies reported a stronger dose response association between smoking and rectal rather than colon cancer (8;118;121;122;128). Recent meta-analyses also concluded that the ever smokers are in increased risk of rectal cancer (70;83-85), however these studies did not present the risk estimates by gender. Our findings are in accordance with findings of these meta-analyses regarding higher risk estimates for rectal than colon cancer. In a study done among women in the United States, an increased risk of rectal cancer but not colon cancer was observed among ever smokers (121). Another study done among Norwegian women

reported the higher risk for colon than rectal cancer among smokers (119). Furthermore, two recent studies, one from 10 European countries including almost half a million men and women and 950 rectal cancer cases (123) and another from Asia including 329 rectal cancer cases (64) are the largest cohort study done before ours examining the association between smoking and rectal cancer. The study from 10 European countries found a non-significant increase in rectal cancer; however the later study found a significant increased risk of rectal cancer among ever smokers. These studies did not report the risk estimates by gender. A few studies from Japan examined the association between smoking and rectal cancer, however they included 200 or less cases (73;74). Furthermore, these studies showed an insignificant increased risk of rectal cancer among men and women ever smokers. Our study is one of the few to examine the association between smoking and rectal cancer by gender in detail. Our findings indicated that there is a significant increased risk for rectal cancer among men and women ever smokers. Furthermore, the findings also concluded that the risk was similar for women as in men. This could be a very important finding as the impact of cigarette smoking could be reflected in future rectal cancer incidence among women as the smoking epidemic among women began later than men, and as for colon cancer, rectal cancer also has a long latent period.

5.2.3 Smoking increases the risk of CRC Mortality

In Paper III, we found increased risk of CRC mortality both among men and women ever smokers. We concluded that the risk of rectal cancer mortality was higher among men smokers and risk of proximal colon cancer mortality was higher among women smokers. Similarly, the increased mortality risk by subsites was slightly more pronounced among current smokers compared with the former smokers both among men and women. The higher risk of rectal cancer mortality among men ever smokers and increased proximal colon cancer mortality risk among women ever smokers could be a mere reflection of the colon and rectal

cancer incidence in our cohort. As mentioned earlier, smoking is one of the major preventable causes of death worldwide. Mortality from different diseases has been decreased in last decades due to early diagnosis and treatment; however current smokers have an increased risk of mortality compared to never smokers. Recently, two meta-analyses also reported that the risk of CRC mortality was higher among current than former smokers (83;84). Long term smoking is associated with an increased risk of CRC mortality both among men and women (15). Furthermore, increased mortality among current smokers could be due to possible differences in health behaviours. A recent report from the United States Surgeon General concluded that there is a sufficient evidence to infer a causal relationship between cigarette smoking and increased all-cause and cancer-specific mortality (15). Quitting smoking can decrease the mortality burden and CRC patients should be encouraged to quit smoking as smoking can lead to poorer response to cancer treatment (129). Furthermore, the relationship between smoking and mortality is stronger than before and recommendations encouraging smokers to quit is very important.

6 Conclusions

The main aim of this thesis was to examine the association between smoking and CRC incidence and mortality overall and by subsites and gender.

The conclusions to be drawn from the studies are:

1. Smoking increased the risk of colon cancer among both men and women. The increased risk of colon cancer especially proximal colon cancer due, to smoking may be greater in women than men.

2. Smoking increased the risk of rectal cancer among both men and women. The risk was similar for women as for men.

3. Smoking increased the risk of CRC mortality among both men and women. The risk of rectal and proximal colon cancer mortality was most pronounced among men and women ever smokers, respectively.

4. The observed smoking related increased risk in colon and rectal cancer was dependent on different smoking exposures such as age at smoking initiation, number of cigarettes smoked per day, duration of smoking and pack years smoked both among men and women.

5. The observed smoking related increased risk in CRC mortality was dependent on different smoking exposures such as age at smoking initiation, number of cigarettes smoked per day, duration of smoking and pack years smoked both among men and women.

7 Implications for public health practice and further perspectives

CRC is one of the major public health problems in Norway. Our findings are consistent with the latest report from the IARC (1) and the United States Surgeon General (15) regarding the association between smoking and CRC. Smoking is possibly the most important modifiable risk factor of CRC. Detailed knowledge about the adverse harmful effects of smoking is important for general public health and future strategy planning. Additional strict rules against tobacco companies and tobacco sales should be implemented. The general population should be made aware of the possible harmful effects of smoking on the risk of CRC and younger age groups should be given special attention regarding smoking cessation and encouraged not to start smoking. Since women may be more vulnerable to the carcinogenic effects of smoking in relation to CRC, women-oriented awareness of harmful effects of smoking should be initiated. Current smokers should be encouraged to quit since the comorbid situation is increased among current smokers. More emphasis should be placed on taxes and price policies in the control of tobacco use to improve public health. Furthermore, CRC screening programme could be very helpful for early diagnosis and treatment.

As there is a long latent period between smoking and risk of CRC, an investigation with a longer follow up period could reveal more exact risk estimates. Future studies should focus on the replication of the present findings and it will be very important to conduct these studies with detailed information on most available covariates in relation to smoking and CRC.

8 Erratum

In Paper I:

For the excluded men and women, the overall incidence of colon cancer was 53 and 59 per 100, 000 person-years, respectively.

The overall incidence of colon cancer among men and women was 49 and 44 per 100, 000 person-years, respectively.

Above presented overall incidence rates were for CRC and not only for colon cancer.

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PAPER I

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