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Cigarette smoking and pancreatic cancer risk in 83 500 Norwegian men and women.

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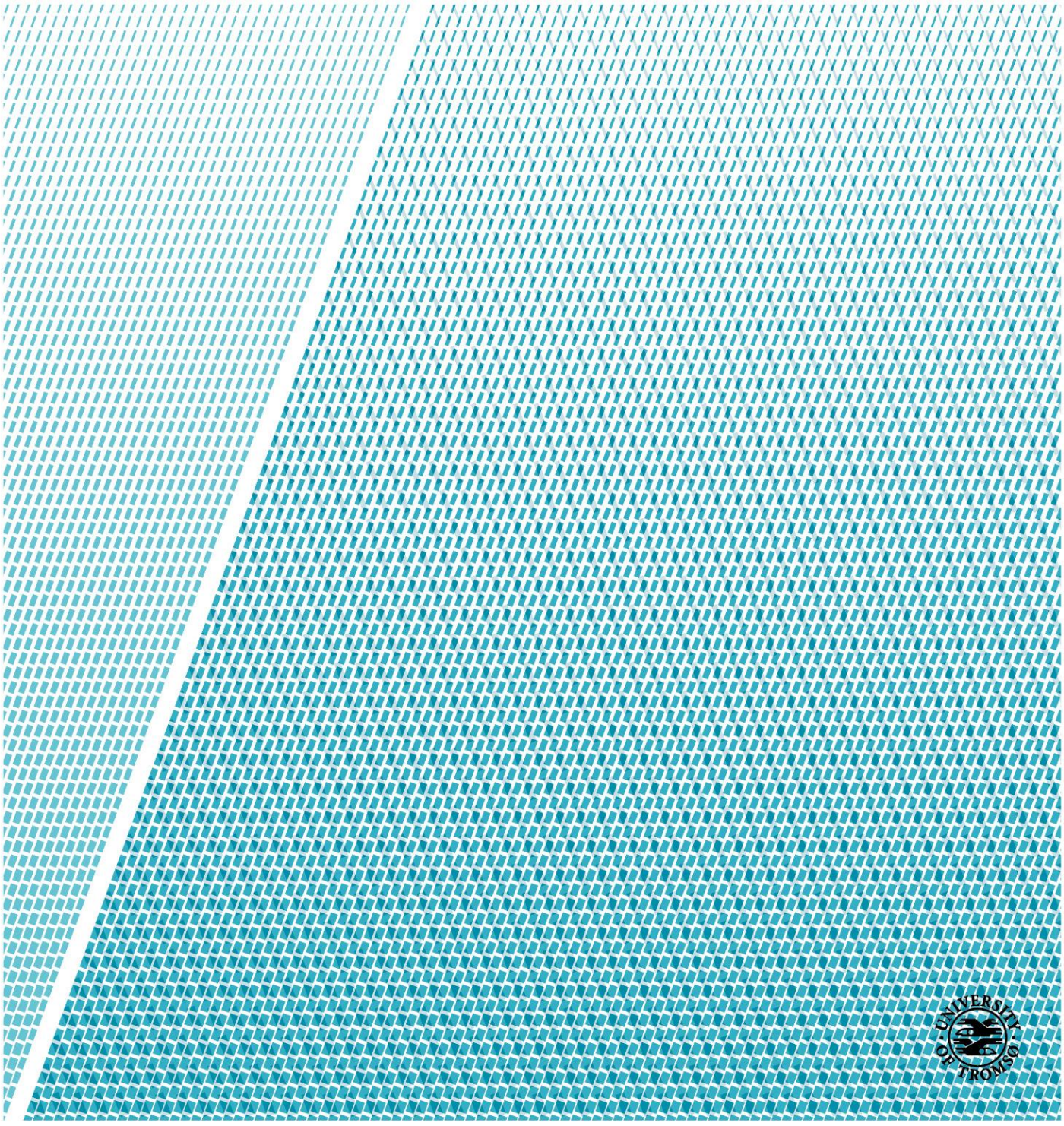

Preface and distribution of work

Writing this thesis has been a journey through new experiences, knowledge, challenges and personal development, and we have expanded our understanding and reflections on scientific writing and research. Except from doing some individual efforts in collecting the literature for this thesis at the beginning, all chapters, analysis and pages was written together on the same computer during continuous discussion and reflection among us, and each have participated the equal amount and effort in writing this thesis.

We like to thank our main supervisor professor Inger Torhild Gram for valuable feedback and her insight into the field of epidemiology, and for providing us with the opportunity to write this master's thesis. We would also like to thank our co-supervisor postdoctor Idlir Licaj for creating the statistical package needed to perform this thesis, and his help with our analysis.

In addition, we extend our gratitude to Tormod Brenn and Marko Lukic at the Institute for Community Medicine, for their participation in helping us recoding variables in SPSS. We are also thankful to the Norwegian Department of Public Health and CONOR for being able to use data from the Norwegian Counties Study in order to write our thesis.

"Individual commitment to a group effort – that is what makes a team work, a company work, a society work, a civilization work" – Vince Lombardi

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Abstract

Objective To investigate the association between cigarette smoking and the risk of developing pancreatic cancer and if there are any differences in risk between male- and female smokers. We also aimed to see if there is scientific consensus among recent expert reports (2013-2017) on smoking and pancreatic cancer.

Methods For our statistical analysis, we used data from 83 500 participants born between 1905 and 1968, recruited from the Norwegian Counties Study (NCS) during the survey periods of 1974-1988. The end of follow-up was Dec. 2013 and participants were followed through national registries in terms of cancer-diagnosis, death, emigration and other end-points. Cox proportional hazards model was used to obtain age-adjusted and multivariate hazard ratios with 95% confidence intervals for obtaining risk estimates for smoking and levels of smoking exposure. The multivariate analysis included the covariates; age, education level, body mass index and physical activity level.

Results In the age adjusted analysis, smoking was associated with a significant increased risk of pancreatic cancer for ever smokers compared with never smokers for both men (HR = 2.54, 95% CI = 1.92-3.34) and women (HR = 2.44, 95% CI = 1.68-3.54). In multivariate analysis, the overall smoking associated risk of pancreatic cancer compared with never smokers for both sexes were similar to that of the age adjusted analysis. For male smokers, the different measured smoking exposure variables (age at smoking-initiation, cigarettes per day, total years of smoking and pack years), total years of smoking had the strongest association for ever- compared with never smokers (HR = 2.82, 95% CI = 1.87-4.24). For female smokers,

early smoking initiation (≤ 19 years) had the strongest association (HR = 3.28, 95% CI = 2.22-4.82). Female smokers showed linear trends ($P_{trend} < 0.05$) across the different smoking exposure categories (age at smoking-initiation, cigarettes per day, total years of smoking and pack years). For male smokers, there was no observed linear trend for any of the corresponding exposure categories ($P_{trend} > 0.05$).

Conclusion In support of similar previous research, our findings conclude that there is a significant increased risk of pancreatic cancer associated with cigarette smoking. Furthermore, we find that female smokers have a dose-response relationship between smoking and pancreatic cancer risk, which was not evident for male smokers.

Key words *Pancreatic cancer, Cigarette smoking, Cohort study, Norwegian Counties Study.*

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Abbreviations

ACS – American Cancer Society

BMI – body mass index

CDC – Centre for Disease Control and Prevention

CI – confidence interval

ICD – International Classification of Disease

HR – hazard ratio

NCI – National Cancer Institute

NCS – Norwegian Counties Study

NDH – Norwegian Directory of Health/Helsedirektoratet

NET – neuroendocrine tumor

NIPH - Norwegian Institute of Public Health/Folkehelseinstituttet

RR – relative risk

SEER – Surveillance, Epidemiology and End Results

SGR – Surgeon General's Report

SPSS – Statistical Package for the Social Sciences

1. Introduction

Pancreatic cancer is considered one of the deadliest types of cancer as it often produces little or no symptoms in the early staged of the disease. It is usually discovered after it has metastasized to other organs, and there are often limited treatment options available. Given the poor prognosis of the disease, steps should be taken to prevent future cases of pancreatic cancer through identification and prevention the of risk factors associated with the disease.

There are certain risk factors that through research have been associated with the development of pancreatic cancer: Risk factors based on behaviour/lifestyle (risk factors that can be changed), risk factors that are based on hereditary factors, health situation (risk factors that cannot be changed), and risk factors that have inconclusive findings when it comes to the risk of developing pancreatic cancer. Behavioural risk factors such as smoking have previous been linked to approximately 25% of all pancreatic cancer cases (Wolfgang et al, 2013). We will examine this relationship further in this thesis. We will compare results from our analysis based on data from the Norwegian Counties Study (NCS) with published research that focuses on the association between smoking and pancreatic cancer published after inclusion ended (2012) for the Surgeon General's Report of 2014 – 50 years of progress. The Surgeon General's Report is one of the leading expert report on cancer and smoking as a risk. However, pancreatic cancer was not included in any large part. We will therefore examine recent cohort studies and reports on the effect of smoking on pancreatic cancer risk.

2. Objective of the thesis

This thesis aims to examine if cigarette smoking increases the risk of developing pancreatic cancer and if this association differs between male- and female smokers. To achieve this, we will examine relevant cohort studies regarding smoking and pancreatic cancer risk that has been published since 2013, and compare these findings to our own results from the statistical analysis based on the Norwegian Counties Study/Fylkesundersøkelsen for Finnmark, Sogn og Fjordane og Oppland.

2.1. Null hypothesis

- Null-hypothesis 1 ($1H_0$): There is no association between cigarette smoking and the risk of developing pancreatic cancer.
- Alternate-hypothesis 1 ($1Ha_0$): There is an association between cigarette smoking and the risk of developing pancreatic cancer.
- Null-hypothesis 2 ($2H_0$): There is no difference in the risk of developing pancreatic cancer between male- and female smokers.
- Alternate-hypothesis 2 ($2Ha_0$): There is a difference in risk of developing pancreatic cancer between male- and female smokers.

2.2. Research questions

In addition to the null hypothesis, we have developed the following research questions that we aim to answer with this thesis:

- Is there scientific consensus across the recent expert reports from 2013-2017 (after inclusion of the Surgeon General's Report) as to the adverse effects of smoking and pancreatic cancer?

- Do any of the possible confounders in the acquired dataset modify the exposure from smoking in terms of increased or decreased risk of developing pancreatic cancer?

3. Background and theory

3.1. Pancreatic cancer; incidence, risk factors, treatment and survival.

3.1.1. Introduction to the disease.

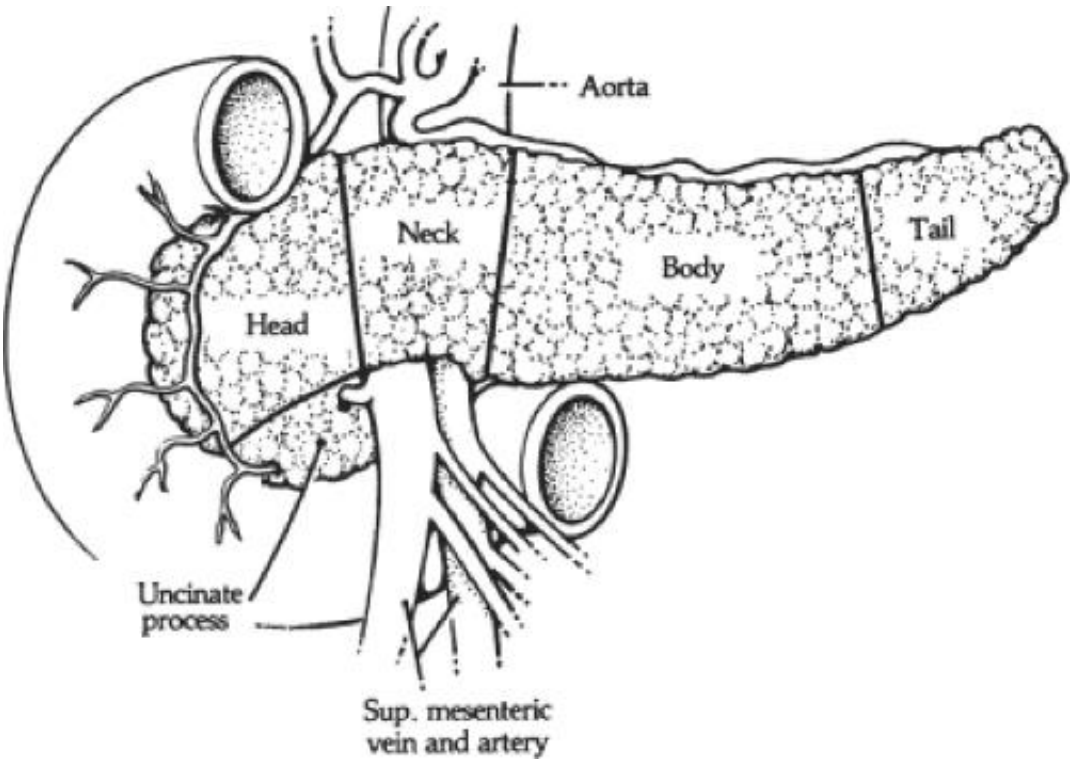
The pancreas is one of the largest digestive glands in our body, and is located posterior to the stomach in the upper left part of the abdomen and stretches from the curve of the duodenum and extends transversely across the retroperitoneum. Major blood vessels including the superior mesenteric vein and artery, the portal vein and the celiac axis surround the pancreas and provides the necessary blood supply (Rela & Reddy, 2016).

The two main functions of the pancreas are to help with digestion through the production of digestive enzymes, and the production of hormones that affect the metabolism but also the secretion of other hormones; insulin being one of the most common known. The digestive function of the pancreas is known as the “exocrine” function while the hormonal function is known as the “endocrine” function, of which the exocrine tissue mass is forming 98% of the pancreatic tissue and the endocrine pancreatic islets (or islets of Lagerhans), are embedded within (Rela & Reddy, 2016). The exocrine pancreatic glands produce enzymes such as amylase, that helps with the digestion of carbohydrates, lipase which contributes to the break-down of the fat-substances, and enzymes such as trypsin and chymotrypsin digest proteins.

These enzymes among others are released as part of the pancreatic juices through a series of canals or ducts that culminate in the main pancreatic duct (ductus pancreaticus) which joins the common bile duct (ductus choledocus) to form the ampulla of Vater (ampulla vaterii) located at the duodenum (Rela & Reddy, 2016).

The endocrine pancreatic islets consist of at least four different cell-types, which includes insulin-producing β-cells, glucagon-producing α-cells, somatostatin-producing δ-cells and pancreatic polypeptide-producing PP-cells. The total cell population is mainly comprised of β-cells (insulin producing) 60-80% and α-cells (glucagon-producing) 15-20%. (Campbell & Verbeke, 2013).

Figure 1: Anatomical illustration of pancreas location, blood supply and sections.



Source: Kooby et al (2016, Surgical anatomy of the pancreas.

Pancreatic cancer or carcinomas can be classified into two main categories depending in which cellular type the cancer originates, either exocrine or endocrine. The symptoms, prognosis, risk factor and causes for each type of pancreatic carcinoma will differ depending on what type of tumor is present. The National Cancer Institute (NCI) defines a tumor to be either benign or malign; in which benign tumors does not invade nearby cell tissue and rarely grows back after being surgically removed. Malignant tumors can invade nearby tissue and spread to other parts of the body, and may also reappear (recidivism) even after being surgically removed (NCI, 2015).

Because of the deep location of the pancreas, most tumors that develops in the pancreatic tissue will not be palpable and symptoms will in most cases first appear after the cancer have either grown large enough or started interfering with the surrounding organs; stomach, spleen, duodenum, liver or gallbladder which implies that the symptoms are rarely discovered before the cancer have reached a late stadium, affecting the prognosis (Casil, 2009).

3.1.1.1. Exocrine pancreatic cancers

Adenocarcinomas accounts for about 95% of all the exocrine pancreatic cancers (ACS, 2016) and is defined as a malignant tumor that originates in a glandular epithelium. “Adeno” meaning “pertaining to a gland” and “carcinoma” meaning cancer (Mandal, 2013). The most common types of pancreatic carcinomas originate from the ductular cells and is often referred to as ductal adenocarcinomas. They account for approximately 75-90% of all primary pancreatic adenocarcinomas (Lack, 2003).

Less common types of exocrine pancreatic cancers include squamous cell carcinomas, signet ring cell carcinomas, adenosquamous carcinoma and giant cell undifferentiated carcinomas and ampullary cancer (ACS, 2016). Ampullary cancer (carcinoma of the ampulla of Vater) are not technically defined as a type of pancreatic cancer, but they are treated very similarly, and also affect the bile ducts. They often produce symptoms at an early stage, which gives them a better prognosis than other pancreatic cancers (ACS, 2016).

3.1.1.2. Endocrine pancreatic cancers

Neuroendocrine tumors of the pancreas (NETs) or islet cell carcinomas accounts for the remaining 5% of pancreatic cancers. Approximately 75% of all neuroendocrine tumors are producing symptoms that can be related to the hormone peptides produced by the endocrine cells; either gastrin, insulin, glucagon, somatostatin, vasoactive intestinal peptide or pancreatic polypeptide (Beger, et al, 2015).

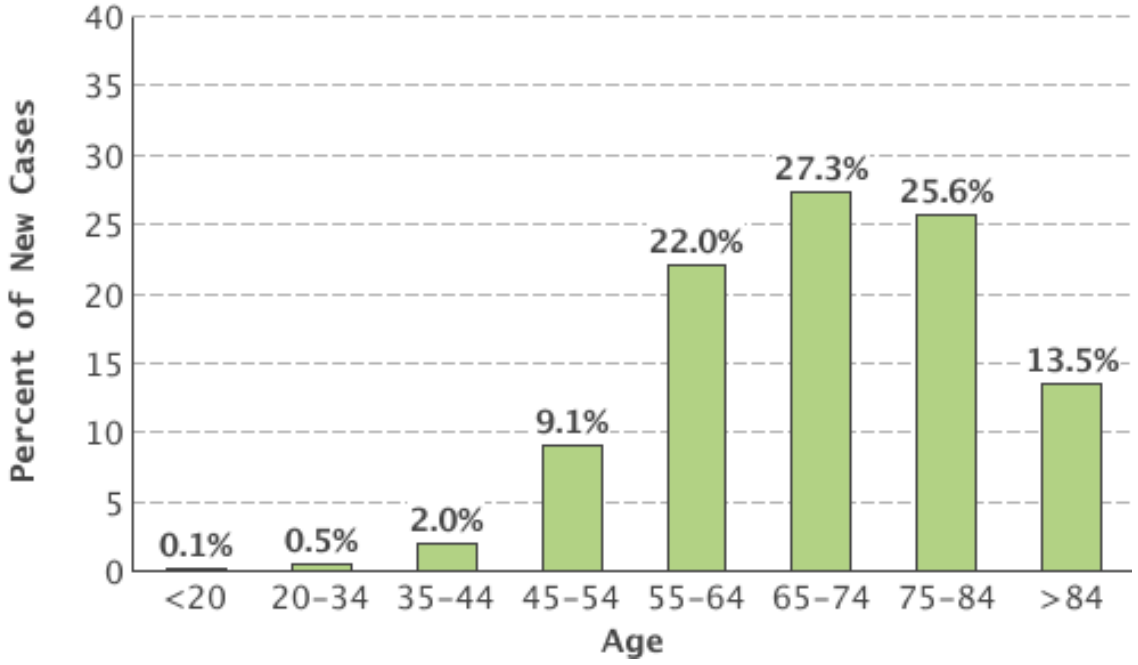
Approximately 50% of all gastrinomas are malignant, most glucagonomas, somatostatinomas, VIPomas (vasoactive intestinal peptide) and PPomas (pancreatic polypeptide) are malign and cancerous, while most insulinomas are benign. The most functioning NETs are either gastrinomas or insulinomas (ACS, 2016). The remaining 25% of NETs are non-functioning, meaning that they do not produce enough excess hormones to cause symptoms in the patient (Beger, et al, 2015).

3.1.2. Incidence of pancreatic cancer

The incidence of pancreatic cancer varies geographically with the highest incidence reported in GLOBOCAN 2012 being, Northern America (7.4 per 100.000) and Western Europe (7.3 per 100.000) and the lowest observed rate in Middle Africa and South-Central Asia (about 1 per 100.000). The highest rate of pancreatic cancer is seen in Czech Republic (9.7 per 100.000) and the lowest incidence is seen in Pakistan (0.5 per 100.000) (Ferlay, et al., 2014). This variation can be influenced by a difference in the diagnostic accuracy and reporting between countries (Ferlay, et al., 2013) as well as differences in exposure to different risk factors. There is also a gender-based variation in the incidence rate of pancreatic cancer, whereas men have a higher incidence (4.9 per 100.000) than woman (3.6 per 100.000) (Ferlay, et al., 2015), this is likely explained predominantly by differences in exposure to tobacco smoking (Ezzati, Henley, Lopez, & Thun, 2005; Giovino, et al., 2012).

The incidence rate of pancreatic cancer in western societies increases with age, regardless of gender, and is highest in individuals above 70 years of age, and more than 90% of all cases of pancreatic cancer is diagnosed in individuals above the age of 65, according to the American Cancer Society (ACS, 2016). The statistics from the Surveillance, Epidemiology and End Results (SEER) registries in the United States, shows that pancreatic cancer is predominantly a disease of the elderly (aged ≥ 65 years), although the risk increases significantly with age, pancreatic cancer can affect anyone at any age, as seen in figure 2.

Figure 2: Percentage of new cases of pancreatic cancer according to age for both sexes and all races.

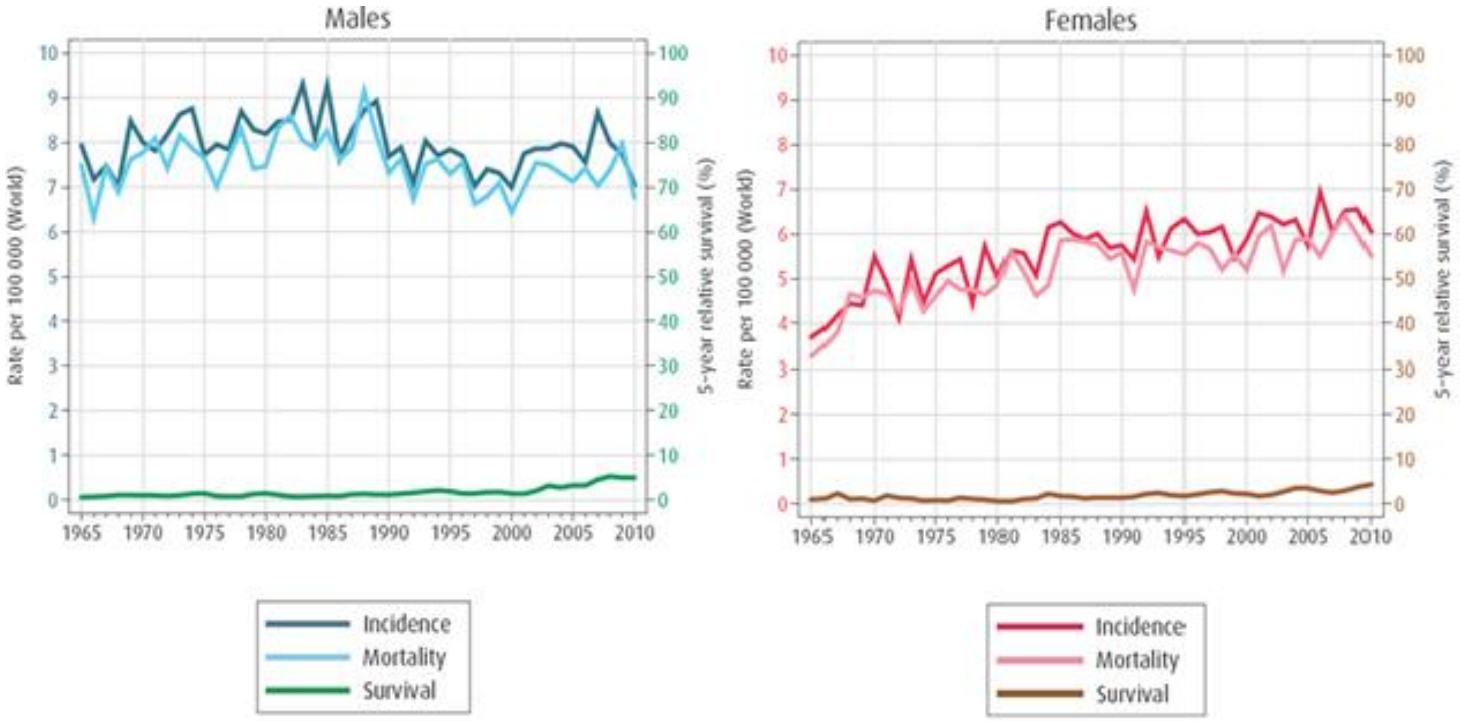


Source: National Cancer Institute, SEER-registries 18, 2009-2013, all races, both sexes.

3.1.2.1. Lifetime risk and Norwegian statistics

The lifetime risk of developing pancreatic cancer is about 1.5% regardless of gender and with an estimated 331.000 deaths per year in 2012 (Ferlay, et al., 2015) pancreatic cancer remains a fairly common malignant neoplasm, and is one of the leading causes of cancer mortality in the developed world. With a recorded 736 new cases in 2014 and incidence rates of 15.3 and 13.5 per 100.000 for men and women respectively, pancreatic cancer is a relatively rare cancer type in Norway. However, due to its poor prognosis of survival, it is ranked the fourth most deadly malignant neoplasm in Norway, accountable for about 713 deaths in 2014 (Cancer Registry in Norway, 2015; Larsen, Møller, Johannessen, Larønningen, 2015). These numbers are seen to be relatively stable for men, but somewhat rising for women the last 40 years (figure 3).

Figure 3: Pancreatic cancer statistics for Norway 1965-2012.



Source: Cancer Registry of Norway - Kreftregisteret (2015).

The estimated 5-year prevalence of people in the world living with pancreatic cancer is 4.1 per 100.000 (World Cancer Research Fund International, n.d), and the 5-year prevalence for Europe is 10.2 per 100.000 and 7.0 per 100.000 for Norway as off 2012 (World Health Organization, n.d).

3.1.3. Risk factors for the development of pancreatic cancer

According to the Dictionary of Epidemiology by M. Porta (2014), a risk factor is an aspect of personal behaviour or lifestyle, exposure through environment or a genetic characteristic that can be associated with health or health related condition(s), based on the scientific evidence. Risk factors can be classified as modifiable- non-modifiable- or unclear risk effects.

3.1.3.1. Modifiable risk factors

Modifiable risk factors are determinants that can be modified by intervention or behavioural/lifestyle choices, and thus reducing the probability for the disease (Burt, 2001).

3.1.3.1.1. Tobacco smoking

Tobacco smoking is the most important of all the modifiable risk factors for pancreatic cancer, and active smokers have been reported to having as much as 75% increased risk of pancreatic cancer compared with never smokers (Iodice, Gandini, Maisonneuve, & Lowenfels, 2008). Evidence from meta-analysis comprising of 30 retrospective, and 12 prospective studies (Zou, et al., 2014) indicates that cigarette smoking having a non-linear dose-response relationship between pancreatic cancer risk and duration of smoking,

cumulative amount of cigarettes, time since quitting and intensity, which increased up to a "moderate" consumption (25-30 cigarettes per day) then levelling off at higher intensities. The same association is also observed in form of risk reduction from smoking cessation. Iodice, Gandini, Maisonneuve, & Lowenfels (2008) reported that smoking cessation started to reduce the increased risk from smoking after a cessation period of ≥10 years, Schulte, et al. (2014) reported that the risk levels returned to baseline after approximatly 20 years of abstinense and that smoking intesity was of less importance than that of smoking duration or time since quitting.

Some studies have also found that there is a possible difference in the effect size of pancreatic cancer risk from smoking intensity between sexes whereas women have a higher, though non-significant effect size (Zou, et al., 2014; Nakamura, et al., 2011 & Duell, Holly, Bracci, Liu, Wiencke, & Kelsey, 2002).

3.1.3.1.2. Overweight and obesity

Being overweight or obese has been reported to increase the risk of pancreatic cancer and also the reduction of survival for patients with pancreatic cancer: Overweight measured in kg/m^2 (BMI) has been associated with an increased risk of pancreatic cancer, and results from meta-analysis shows that high BMI yields a multivariate relative risk of 1.55 (1.9-2.03 95% CI) for individuals with a high BMI (≥35 kg/m^2) compared with individuals with normal BMI (21-22.9 kg/m^2) (Genkinger, et al., 2011).

Genkinger and colleagues (2011) also showed a linear relationship between baseline BMI (21-22.9 kg/m^2) and pancreatic adenocarcinoma risk (multivariate relative risk = 1.14) for $5kg/m^2$ increment. Parkin, Boyd & Walker (2011) estimated that overweight and obesity was attributable for 12.2% of all pancreatic cancer incidence cases in the UK in 2010. Waist-to-hip measurement of abdominal obesity has also been linked to pancreatic cancer mortality, showing an increased relative risk (RR) of 1.07 (1.02-1.17 95% CI) per 10cm increment after adjustments for BMI (Genkinger, et al., 2015).

The underlying mechanisms which explain the association between obesity and pancreatic cancer are hypothesized to be linked to; hormonal and inflammatory effects of adipose tissue, i.e. obesity and high BMI has been associated to with increased insulin and C-peptide circulation, hyperglycaemia, insulin resistance and diabetes mellitus; increased exposure to carcinogens as a result of increased food consumption and; diminished physical activity (Bracci, 2012). Some studies have also reported an association with blood glucose levels prior to diagnosis and pancreatic cancer risk (Batty, Shipley, Marmot, & Smith, 2004; Jee, Ohrr, Sull, Yun, Ji, & Samet, 2005; Johansen, et al., 2010).

3.1.3.1.3. Exposure to certain chemicals

Exposure to certain types of chemical has also been thought to increase the risk of pancreatic cancer. In a clinic-based, case–control study Antwi, et al. (2015) found evidence from multivariate regression (controling for age, sex, smoking, diabetes, bmi and education status) that suggests that regular exposure to different chemicals might increase the risk of pancreatic cancer; pesticides (HR = 1.21, CI = 1.02-1.44), asbestos (HR = 1.34, CI = 1.23-1.92), benzene (HR = 1.70, CI = 1.23-2.35), and chlorinated hydrocarbons (HR = 1.63, CI = 1.32-2.02). These findings are consistent with a previous meta-analysis from 2001 on chemical exposure that suggest a weak association between Trichloroethylene, Poly-chlorinated biphenyls (PCB's), methylene chloride, and vinyl chloride and pancreatic cancer (Ojajärvi, et al., 2001).

3.1.3.2. Non-modifiable risk factors

Non-modifiable risk factors are the opposite of modifiable factors, these cannot be changed through intervention measures, and will remain a risk factor regardless of behavioural/lifestyle choices that are made.

3.1.3.2.1. Age

Age is considered one of the main risk factors for developing cancer as the incidence of most cancer-types increases with advancing age. The risk of developing cancer has been examined by White et al (2015), and shows a lifetime risk among U.S. citizens of 13,09% and 17,85% for developing cancer within 10years after being aged 60 and 70 years respectively. The risk of developing cancer for Norwegian aged 75 or younger, are 36,2% and 29,5% for men and women respectively (Cancer Registry of Norway, 2015). Although age cannot be held primary responsible for the development of cancer, it can modify other risk factors such as lifestyle and exposure to carcinogens, thus increasing the overall risk of cancer (White et al, 2015). For the Norwegian population, cancer is predominately present among those aged >50 years according to the Norwegian Cancer Report of 2015, with 91,5% and 85,7% for men and women respectively (Larsen, Møller, Johannessen, Larønningen, 2016).

3.1.3.2.2. Family history / hereditary factors

Several genetic syndromes have been linked to an increased risk of developing pancreatic cancer. Hereditary breast and ovarian cancer syndrome (HBOC), and particularly the BRCA2 mutations and Lynch syndrome have been linked to increased risk of pancreatic cancer (Risch, et al., 2006; Lynch, Voorhees, Lanspa, McGreevy, & Lynch, 1985). Peutz-

Jeghers syndrome has been seen as the genetic disposition with the highest increased lifetime risk for the development of pancreatic cancer (Giardiello, et al., 2000), but the syndrome is relatively rare, i.e. 1:8000 to 1:200 000 births (Lindor & Greene, 1998).

3.1.3.2.3. Pancreatitis

Patients with either chronic pancreatitis or those threated more than once for either acute or unspecified pancreatitis have a 2-fold excess risk of pancreatic cancer compared with those with only one discharge (Ekbom, et al., 1994). Pooled analysis from the International Pancreatic Cancer Case-control Consortium (PanC4) found that an estimated 1.34% of pancreatic cancers where attributable to chronic pancreatitis and that the risk for those diagnosed before the age of 65 had twice the risk of those diagnosed after the age of 65 (Duell, et al., 2012).

3.1.3.3. Unclear risk effects

Unclear risk effects are potential risk factors for the development of disease, however there is not enough scientific evidence to support the findings and claim that they increase the risk of disease.

3.1.3.3.1. Diabetes Mellitus

There seems to be a bidirectional relationship between diabetes mellitus and pancreatic cancer. Gupta, et al., (2006) found that for patients with new-onset diabetes mellitus, the incidence of pancreatic cancer was more than twice as high than for non-diabetics. However, only about 0.5% of patients with newly diagnosed diabetes developed pancreatic cancer

during a 6-year follow-up, so the absolute risk remains low. A multicenter case-control study from China reported that diabetics where more that twice as likely to develop pancreatic cancer (OR = 2.69, 95% CI = 1.51-4.77) than non-diabetics (Zheng, et al., 2016). Wang, Herrington, Larsson, & Permert (2003) on the other hand concluded in their review, that new-onset diabetes had the strongest association with pancreatic cancer and was actually largely responsible for the association with pancreatic cancer, and that this might be due to abnormal islet cell function.

Thus, there is no clear-cut answer to whether or not diabetes is a direct risk factor for pancreatic cancer since diabetes could be sequel to pancreatic cancer and there is no overwhelming body of evidence pointing in either direction in terms of causality.

3.1.3.3.2. Alcohol consumption

Evidence is inconsistent regarding alcohol and pancreatic cancer risk; this is largely due to the close association between alcohol and smoking which makes it problematic to implicate alcohol as an independent risk factor for pancreatic cancer. However, alcohol does affect the pathogenesis of pancreatitis indicating that it could promote other risk factors such as smoking (Yadav & Lowenfels, 2013). In a study of never smokers, Gapstur et al observed that a consumption of more than 3 drinks of liquor per day increased the risk of pancreatic cancer by 32%, whilst the consumption of beer and wine in the same amount did not yield the same increased risk (Gapstur, Jacobs, Deka, McCullough, Patel, & Thun, 2011).

3.1.3.3.3. Diet

Consumption of fat and animal fat in particular has been associated with an increased risk of pancreatic cancer regardless of smoking status (Zhang, Zhao, & Berkel, 2005). A high intake of the dietary mutagens: PhIP, BaP and MeIQx, has also been associated with a 2-fold risk increase of pancreatic cancer (Li, et al., 2007). Meta-analysis has shown that fruit and vegetable intake is associated with a reduction in risk of pancreatic cancer (Wu, Wu, Zheng, Xu, Ji, & Gong, 2016).

3.1.3.3.4. Physical activity

Physical activity has been suggested to reduce the risk of pancreatic cancer (Inoue et al., 2008; Jiao et al. 2009) but due to methodological limitations and inconsistency of the evidence this evidence is seen to be very limited (Kruk & Czerniak, 2013). Despite having been seen to have positive associations with obesity and elevated blood glucose, physical activity has not been consistently associated with pancreatic cancer risk (Michaud, 2017).

3.1.4. Treatment and survival

Treatment for pancreatic cancer depends on the tumor location and if the tumor is resectable. Medical consensus is that surgery should be the main form for treatment given a low-grade tumor and early stage, if the tumor is unresectable or there are other considerations there may be necessary to provide adjuvant chemotherapy to maximize treatment-effectiveness or to start neoadjuvant treatment before surgery is attempted (Dragovich, 2016). Depending on tumor location, the procedures may wary from cephalic pancreatoduodenectomy (Whipple procedure) and distal- or total pancreatectomy. Study-data from randomized controlled trials's have shown that more extensive resections is not associated with an increased survival, but instead increases the risk of postoperative complications and morbidity (Hidalgo, 2010).

For exocrine pancreatic cancers, surgical resection may not be curative but only palliative and life-prolonging. Should the patients be diagnosed with a locally or systematically advanced disease, then treatment-options is usually palliative care if form of surgery or chemotherapeutic medication. Chemo-radiation therapy may also prove useful as a part of the total treatment perspective, both in early stages as well as advanced stages of pancreatic cancer (Dragovich, 2016).

3.1.4.1. Stage and tumor grade – 5-year survival

In accordance to the World Health Organization's (WHO) classification and tumor grading, the stage of cancer is determined by several factors: if the cancer have metastasized to other organs, the size and location of the primary tumor and if there is involvement of the regional lymph nodes. Tumor grading is an indication of the growth-rate of the particular tumor. Tumors that have not deviated much in appearance from normal tissue cells tend to grow and develop slower than those who have clearly differentiated from a normal cellular appearance. With exception to a few different types of cancers, tumors are graded from 1-4 depending on how the abnormal the tumor-cells have become (Damjanov, Fang, 2013).

Because of the poor prognosis of pancreatic cancers, even early stage and low-grade tumors will have a mean survival of approximately two years depending on treatment, and patients diagnosed with advanced stages will on average only live for 4-10 months as shown in Table 1. The 5-year relative survival rates of pancreatic cancer were calculated to be 6,9% in 2010 in an epidemiological study by Sun et al, 2014. Data retrieved from the *Surveillance, Epidemiology and End Results* (SEER) registries in the United States of America, showed an increase in the relative 5-year survival from 3,1-6,9% over the decades from 1981-2010. 1-year survival also improved from 17-28,2% during the same time period, and the increased survival time could be a result of improved treatment and diagnostic techniques for pancreatic cancer patients over the last three decades (Sun et al, 2014). The Cancer in Norway (CIN) report of 2015 shows a 5-year relative survival for pancreatic cancer of 6,4% for men and 7,7% for women (Larsen, Møller, Johannessen, Larønningen et al, 2016).

Table 1: The World Health Organizations international grading of pancreatic tumors, different staging of pancreatic cancer and median survival in months dependent on tumor grade and metastasis.

Stage	***Tumor Grade***	***Distant Metastases***	***Median Survival***	***Characteristics***
IA	T1	M0	24.1 months	The tumor is limited to the pancreas and is ≤ 2cm in dimension.
IB	T2	M0	20. 6 months	The tumor is limited to the pancreas and is > 2cm in dimension.
IIA	T3	M0	15.4 months	The tumor have grown outside of the pancreas, but does not involve the celiac axis or the superior mesenteric artery.
IIB	T1, T2 or T3	M0	12.7 months	There is regional lymph-node-metastasis.
III	T4	M0	10.6 months	The tumor involves the celiac axis or the superior mesenteric artery. The tumor is not resectable.
IV	T1, T2, T3 or T4	M1	4.5 months	The tumor have spread to other organs causing distant metastasis.
T: Primary pancreatic tumor. M: Metastasis to other organs.				

Source: International Agency for Research on Cancer (IARC), World Health Organization international classification of tumors (2000).

3.2. Smoking: Global- and Norwegian prevalence.

3.2.1. Introduction to smoking as an exposure

Smoking continues to be one of the main causes of cancer world-wide. According to the World Health Organization (WHO) approximately six million people will annually die from smoking-related illnesses and diseases, of which approximately six hundred thousand of the total number of deaths will be from exposure to second-hand smoking. Despite an overall decreasing prevalence, there seems to be an increase in incidence in the African and the Eastern Mediterranean regions of the globe (WHO, 2016).

3.2.1.1. Global prevalence

The WHO's global report on trends in prevalence of tobacco smoking (2015), shows a large difference in prevalence among gender, due to large gender differences in low- and middle-income countries with men smoking almost five times more than women. Among high-income countries and much of the western part of Europe, there is little to no difference in the smoking-ratio between gender (Hitchman & Fong, 2010).

Research suggest several reasons for differences in smoking-ratio based on demography, but equal gender-rights and empowerment of women may be a reason for the similar smoking patterns in the western part of the world (Waldron, 1991). The WHO states that the regions of the world that still have gender inequalities in terms of civil rights such as certain parts of Africa, Asia, Western Pacific and the Eastern Mediterranean regions have lower prevalence of female smokers, while the Western societies that promotes gender equality have a much higher prevalence of female smokers (Hitchman & Fong, 2010)

The Surgeon General's Report of 2001 on Women and Smoking states that there was a higher prevalence of smoking among women with higher education (≥ 8 years of education) than among those with lower or none education in middle- to high-income countries (CDC, 2001). Numbers from the WHO's global report (2015) show that the highest prevalence of women that smoke are in Europe and the American continents, and lowest in Africa and South-East Asia. The highest prevalence of smoking among men are in the Western Pacific, Europe and Eastern Mediterranean regions as seen in Table 2.

Table 2: The prevalence of tobacco-smoking between gender for WHO regions.

Prevalence of smoking any tobacco product among any person aged >= 15 years of age in 2012 among WHO Regions.		
WHO Region	**Female**	**Male**
Africa	2,4	24,2
Americas	13,3	22,8
South-East Asia	2,6	32,1
Europe	19,3	39,0
Eastern Mediterranean	2,9	36,2
Western Pacific	3,4	48,5
Global	6,8	36,1

Source: World Health Organization's global report on tobacco (2015).

The WHO's global report (2015) further examines the trends and prevalence of smoking among the 194 member states, and have given estimates for the future prevalence for the period 2015-2025. This is part of WHO's target for combating non-communicable diseases (NCD) as a part of their global action plan, lists tobacco smoking as an individual target objective. The NCD-goal is to reduce the prevalence of tobacco smoking among adults aged > 15 years, by 30%. The report states that if there is a collectively reduction in smoking prevalence of 30% among all member states, the level of 22,1% in 2010 would be reduced to 15,4% by 2025. According to the WHO, this would imply a 14% overall relative reduction in smoking. Table 3 shows a global decrease in prevalence percentage for both genders over a 15-year period, with a 3,7% decrease for males and a 2,6% decrease for females, respectively (WHO, 2015).

Table 3: Overview of change in prevalence of current tobacco smoking among regions.

AFRO: African regions.

AMRO: American regions.

EMRO: Eastern Mediterranean Regions.

EURO: European Regions.

SEARO: South East Asian Regions.

WPRO: Western Pacific Regions.

Prevalence of current tobacco smoking (%) by region by sex, 2010 and 2025

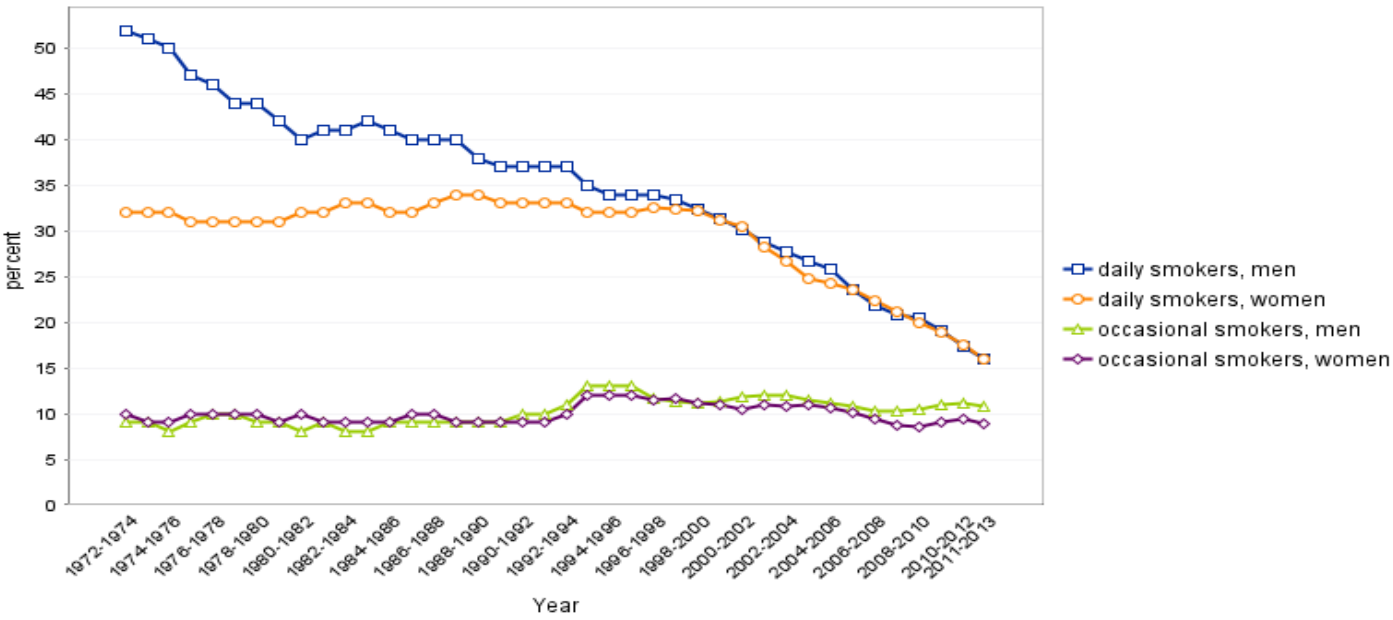
	2010			2025		
Region	male	female	both sexes	male	female	both sexes
AFRO	23.2	2.5	12.8	34.7	1.6	18.1
AMRO	24.1	14.2	19.0	16.3	8.6	12.3
EMRO	35.1	3.1	19.5	45.3	2.5	24.6
EURO	40.3	19.9	29.6	31.3	15.9	23.3
SEARO	33.1	2.9	18.2	27.5	1.2	14.5
WPRO	49.4	3.6	26.8	43.3	2.4	23.2
GLOBAL	**36.9**	**7.3**	**22.1**	**33.2**	**4.7**	**18.9**

Source: World Health Organization's global report on trends in prevalence of tobacco smoking (2015).

3.2.1.2. Prevalence in Norway.

The Norwegian Institute of Public Health (NIPH)/Folkehelseinstituttet has reported a continuous decrease in the prevalence of smoking among the adult population over the last decades and only 13% of the Norwegian population was reported to be a current smoker in 2014 (NIPH, 2015). This is a 14% decrease since the WHO's estimate of 27% current smokers within the Norwegian population from 2010 (WHO, 2015). There are currently only slight differences in male and female smoking prevalence in Norway, and the NIPH reports that the prevalence has been decreasing since 1973 for the male population and 2001 for the female population, as can be seen in figure 4. The prevalence of occasional smokers has been similar for both gender, and approximately steady around 10% since 1972.

Figure 4: Prevalence of smoking in adults (16-74 years) 1972-2013.



Source: Norwegian Institute of Public Health (NIPH), Folkehelseinstituttet (2015).

Numbers show that the main age-group of smokers in Norway are those between 45-64 years (21%), for those younger than 45 and older than 64 years there was only 12-14% daily smokers (NIPH, 2015). In the 2010 WHO-estimations, an average of 26,6% of all men and 25.2% of all women in Norway were current smokers. The WHO calculated that if tobacco control efforts in Norway continue in the current rate, these numbers will have fallen with more than 10% for both genders by 2025, as depicted in Table 4. This will have decreased the percentage of current smokers to approximately 13,7% and 13,6% for men and women respectively (WHO, 2015).

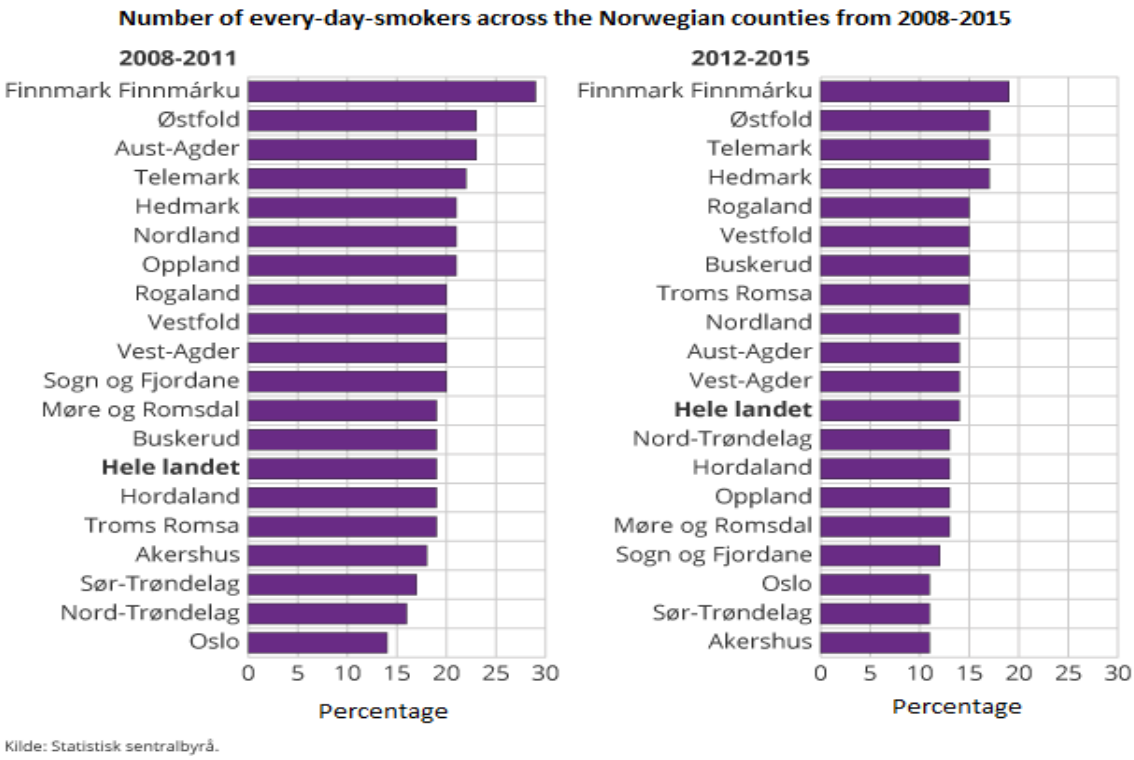
Table 4: Fitted age-specific rates of current tobacco smoking from 2010 to 2025 in Norway.

Age (years)	**2010**			**2025**		
	Men	**Women**	**Total**	**Men**	**Women**	**Total**
15-24	25.3	25.5	25.4	13.1	13.8	13.4
25-39	30.0	29.2	29.6	15.5	15.8	15.6
40-54	30.8	31.1	30.9	15.9	16.8	16.3
55-69	26.6	24.0	25.3	13.6	12.9	13.3
70+	20.6	16.5	18.2	10.6	9.0	9.7

Source: World Health Organization's global reports on trends in prevalence of tobacco smoking (2015).

Data from the Norwegian Bureau of Statistics/Statistisk Sentralbyrå (SSB) show that the number of smokers in Norway varies according to counties as shown in figure 4, where the numbers of every-day-smokers aged 16-74 years among all Norwegian counties are displayed in percentage. In the Norwegian counties study, which covers Finnmark, Sogn og Fjordane and Oppland, Finnmark had the highest number of smokers, with almost 20% of the inhabitants report to be smoking daily, which also is the highest nationally. Oppland have approximately 13% of daily-smokers while Sogn og Fjordane have 12% that reportedly are smoking every day (NIPH, 2015).

Figure 5: Number of every-day-smokers across the Norwegian counties from 2008-2015 measured in percentage.



Source: - Norwegian Bureau of Statistics, Norwegian Institute of Public Health - Statistisk Sentralbyrå (SSB), Folkehelseinstituttet (2015)

3.3. Pancreatic cancer and smoking: expert reports and recent cohort studies.

3.3.1. Introduction to the association between smoking and pancreatic cancer.

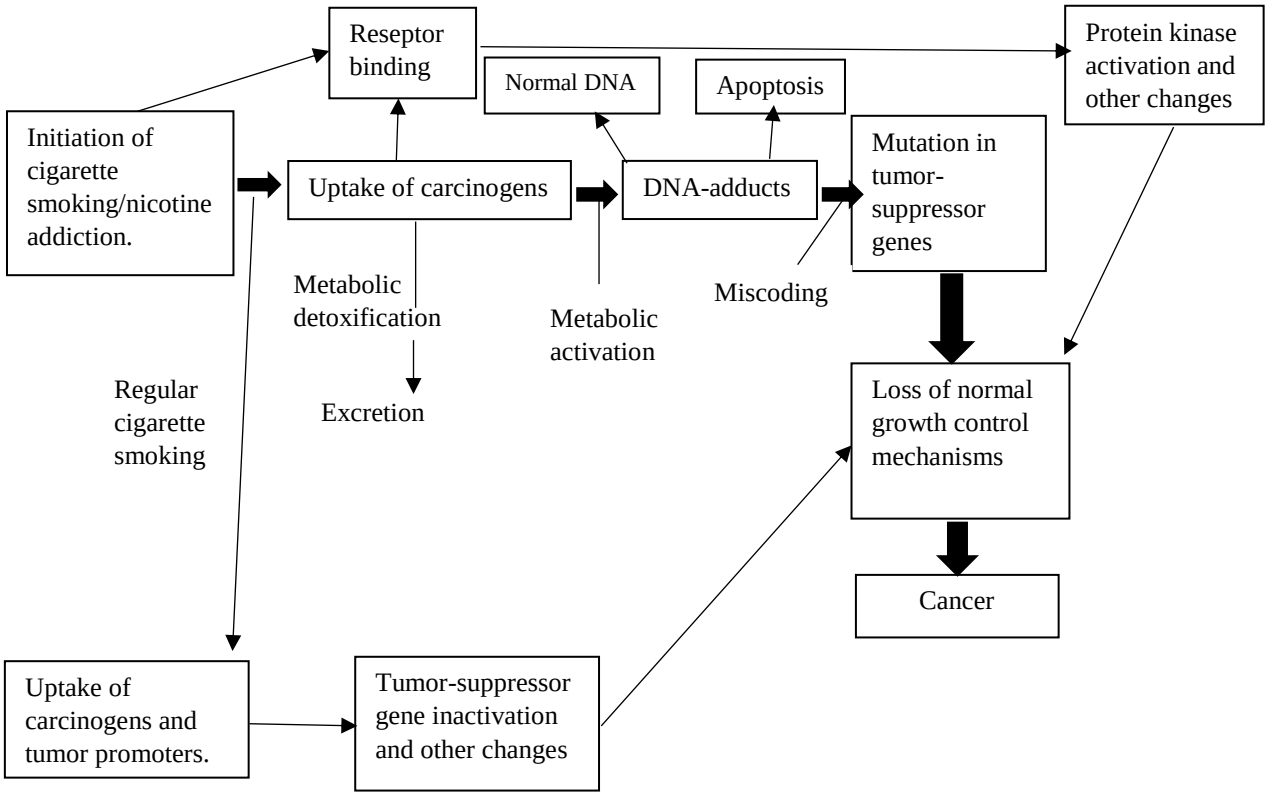
Over the 50 years since the Surgeon General's report of 1964, the Surgeon General's conclusions are that smoking is greatly involved with health. The reports have been moving from a few causal associations in 1964, to the inference of causal relationships between both active smoking and the exposure to second-hand smoke in the later reports. The 2004 and 2006 reports provided a comprehensive coverage of the adverse effects of both active smoking and second-hand smoke. The 2010 report addressed the underlying mechanisms for the causal relationships which are described in the earlier reports. The 2012 report focused on the effects of smoking on the health of children, adolescents, and young adults. The report highlighted the association between early life events and subsequent risk for disease. The 2014 review extended the list of diseases and other adverse health effects of smoking, reaffirming the adverse consequences of smoking, and noted that smoking affects nearly every organ in the human body.

3.3.2. The general carcinogenic effects of cigarette smoking.

The Surgeon General's Report (SGR) of 2014 explains the general mechanisms behind the exposure to the carcinogens in tobacco smoking and the causation of cancer. Tobacco smoke contains more than 7000 different chemicals, of which 69 are confirmed carcinogenic.

Nicotine is not considered a chemical carcinogenic, but it is the cause of tobacco addiction which in turn leads to prolonged exposure to the carcinogenic chemicals (CDC, 2014). These chemicals are foreign to the human body and in order to detoxify them, the body metabolises them to reactive intermediates which again may cause damage to DNA, leading to harmful mutations and cancer growth as illustrated in figure 6, retrieved from the SGR (CDC, 2014).

Figure 6: The pathway for causation of cancer by carcinogens in tobacco smoke.



Source: The Health Consequences of Smoking – 50 years of Progress. A Report of the Surgeon General (2014).

3.3.3. Overview of recent cohort studies (2013-2017)

In order to obtain relevant literature for the current study we conducted Boolean searches for studies involving the association between pancreatic cancer and smoking published in the period of 2013-2017. We conducted searched using search engines from PubMed, Cochrane Collaboration and Scopus. We used plain search terminology such as pancreatic cancer, cancer pancreas, pancreatic neoplasms, pancreatic adenocarcinoma and exocrine pancreatic tumors. We also used Boolean searches with MESH-terms, "pancreatic cancer OR pancreatic neoplasms OR cancer pancreas AND smoking". All searches were limited to articles and publications that were published in English. Individual searches were conducted by both authors in order to ensure best coverage during the literature search. Since the main interest of the study is smoking as a risk factor and not the disease itself we then limited ourselves to cohort studies and meta-analysis done with cohort data on the association between smoking and pancreatic cancer.

A study from the UK with 7119 pancreatic cancer cases (Hippisley-Cox & Coupland, 2015) found that male -and female smokers had similar risk increases for all three levels of cigarette consumption, light (1-9 per day) moderate (10-19 per day) and heavy (20+) compared to never smokers. Heavy smoking had a significant 2-fold risk increase for both male –and female smokers. They also reported a slight significant 9% increased risk for male former smokers while female former smokers had a non-significant increase of (3%) compared with corresponding never smokers.

Another study from Sweden (163 pancreatic cancer cases) (Andersson, Wennersten, Borgquist & Jirström, 2015) reported that regular smoking significantly increased pancreatic

cancer risk for both men (3-fold increased risk) and women (2-fold increased risk) compared to never smokers. The impact of occasional smoking was reported as a significant risk factor only for female smokers, with a 3-fold risk increase compared to never smokers. Exposure to passive smoke over a long period (<20 years) also yielded a significant risk increase for pancreatic cancer for women, who had a 2-fold risk of that of non-exposed.

A Japanese study (611 pancreatic cancer cases) examining the association between active and passive smoking and the risk of death from pancreatic cancer in Japan (Lin et al., 2013) . They found a significant 70% increased risk of pancreatic cancer for current smokers compared to never smokers. Unlike that of Andersson, Wennersten, Borgquist & Jirström, (2015), they found no significant associations between passive smoke exposure and increased pancreatic cancer risk.

In a Swiss study (127 pancreatic cancer cases) on the association between overweight, smoking and pancreatic cancer (Meyer et al., 2015) reported an almost 2-fold increased risk of pancreatic cancer for high smoking exposure (≥20 cigarettes per day). The study also reported that of all deaths, deaths due to pancreatic prostate cancer 29% were attributable to ever smoking and overweight combined, respectively.

In a meta-analysis of 19 population-based prospective cohort studies from European countries and the USA by Ordóñez-Mena and colleagues (2016) found that current smokers had a significant 90% increased risk of pancreatic cancer than that of never smokers. They also found that a longer time passed since smoking cessation was significantly associated with a decrease in total lung and pancreatic cancer incidence and mortality. After 10 years

since smoking cessation, former smokers would have almost 30% less risk than current smokers and after 20 years since smoking cessation the risk would be more than halved compared with current smokers

Ordóñez-Mena et al (2016) found in their meta-analysis that the duration of smoking cessation was associated with a decreased risk of pancreatic cancer. After 10 years since smoking cessation, former smokers would have almost 30% less risk than current smokers and after 20 years since smoking cessation the risk would be more than halved compared with current smokers.

Lin et al (2013) examined the association between active or passive smoking and the risk of death from pancreatic cancer in Japan, finding a significant 70% increased risk of death from pancreatic cancer for smokers compared with that of never smokers but no significant associations between environmental tobacco smoke in public spaces and increased pancreatic cancer risk.

Table 5: Expert reports on the association of pancreatic cancer and smoking post 2013.

Study type	Average years follow-up, N[a], baseline age.	Smoking status	No. of cases	Multivariate HR[b]-ratio (95% CI)	N PC[c] confirmed	Adjustment/Matched for/ Other information
Cohort study	N: 28094	Never smoker	10599	1.0 (reference)	43	Adjusted for age and sex in the multivariate model.
Andersson, Wennersten, Borgquist, Jirstrom.	Baseline mean: 58,1	Occasional smoker	1250	2.74 (1.40-5.34)	11	
		Former smoker	9456	1.43 (0.94-2.16)	49	
Bio of Sex. diff. 2016 (EPIC)		Current smoker	6614	2.86 (1.92-4.27)	60	
Cohort study	Follow-up time: 15 years.	*Risk factor by gender*				The pancreatic cancer model included age (1 Fractional Polynomial (FP) term for women and men. BMI (linear for women, 2 FP for men). Townsend Deprivation Index (linear and positive for women only).
Hippisley-Cox, Coupland	N: 4,96 mill. in open cohort.	**Men**				
BMJ Open 2015.		Never smoker	1081822	1.0 (reference)		
	N: 7119 pancreatic cancer cases only.	Ex-smoker	448480	1.09 (1.00-1.18)		
		Light smoker (1-9 cig/day)	351559	1.56 (1.41-1.73)		
		Moderate smoker (10-19 cig/day)	167089	1.96 (1.70-2.27)		
	Baseline-mean: Men 44,3. Women 44,9.	Heavy smoker (≥20 cig/day)	139985	1.94 (1.68-2.24)		
		Women				
		Never smokers	143346	1.0 (reference)		
		Ex-smoker	392870	1.03 (0.94-1.13)		
		Light smoker (1-9 cig/day)	284482	1.77 (1.59-1.97)		
		Moderate smoker (10-19 cig/day)	152115	1.89 (1.65-2.17)		
		Heavy smoker (≥20 cig/day)	86114	2.02 (1.71-2.39)		

[a] N:Number of study participants. [b] HR: Hazard Ratio with a 95% Confidence Interval.
[c] PC: Number of pancreatic cancer cases confirmed

Study type	Average years follow-up, N[a], baseline age.	Smoking status	No. of cases	Multivariate HR[b]-ratio (95% CI)	N PC[c] confirmed	Adjustment/Matched for
Cohort study Meyer et al. *Cancer Epi. Biomarkers and Prevention. 2015*	Follow-up: 18,9 and 31,9. N: 35703	Never smoker	16756	1.0 (reference)	56 (5,7%)	Adjusted for years of education, nationality, marital status, level of physical activity, alcohol consumption and healthy diet in the multivariate model.
		Former (ever smoked > 6months)	6426	1.46 (0.89-2.46)	28 (5,7%)	
		Current light (< 20 cig/day)	7320	1.46 (0.89-2.39)	26 (5,6%)	
		Current heavy (≥ 20 cig/day)	5171	1.84 (1.01-3.37)	17 (3,9%)	
Cohort Study Lin et al. *Pancreatology 2013*	N: 110 585 Follow-up for mortality from baseline (1988-1990) trough 2009.	Smoker Never smoker		RR: 1.70 95% CI (1.33-2.19) For women exposed to environmental tobacco smoke RR: 1.20 95% CI (0.87-1.67) but stat. insignificant.	611	Adjusted for potential confounders. Data showed 70% increased risk of death from pancreatic cancer in association to cigarette smoking.
Meta-analysis based on Cohort studies. Ordonez-Mena et al. *BMC Med. 2016.*	Follow-up: 12 years. N: 897021	Never smoker	321984	1.0 (reference)	921	Adjusted for age (continuous, years), sex, education level (primary or less, more than primary but less than university/college and university or college). Vigorously physical activity (yes/no), history of diabetes mellitus (yes/no), BMI (continuous, kg/m^2) and daily alcohol intake (continuous, grams/day). In MORGAM Finland and Sweden Cohorts, physical activity was not available and therefore not adjusted for.
		Former smoker	351311	1.13 (0.95-1.35)	1216	
		Current smoker	128615	1.90 (1.48-2.43)	635	
		Years since smoking cessation. *(Reference: Current smoker)*				
		< 9 years	19049	0.83 (0.62-1.11)	74	
		10-19 years	18511	0.71 (0.52-0.96)	62	
		≥ 20 years.	24651	0.47 (0.31-0.70)	65	

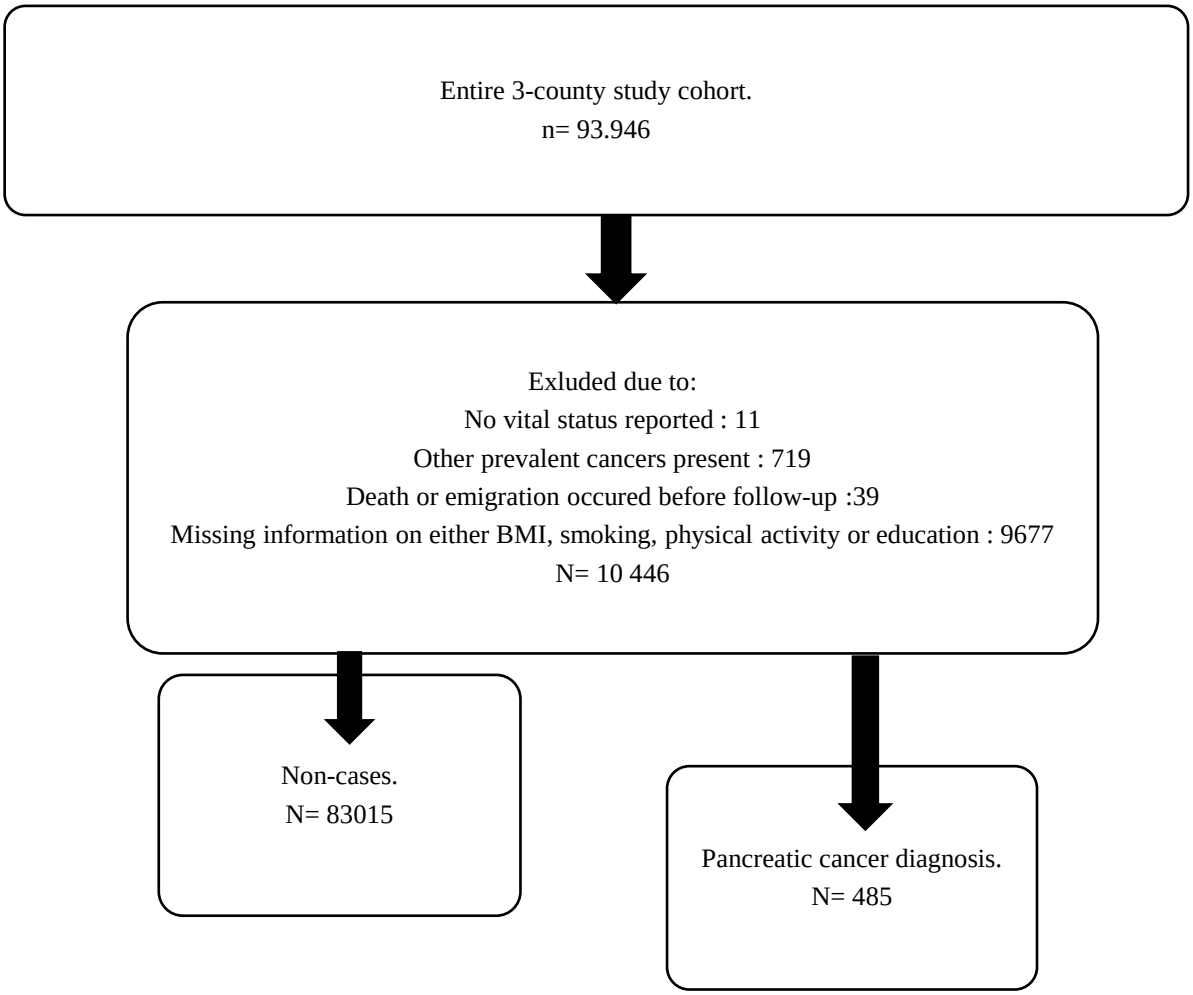
[a] N:Number of study participants. [b] HR: Hazard Ratio with a 95% Confidence Interval.
[c] PC: Number of pancreatic cancer cases confirmed

4. Materials and Methods.

4.1. Study population

The study population used for this Master thesis is comprised of Norwegian men and women that were born between 1905 and 1968, which were recruited for a prospective cohort study that was divided into three study periods. A total of 93 946 participants was included in the cohort. For this thesis, the following exclusion criteria was applied: any participant that had missing information on vital status (n = 11), had other prevalent cancers present (n =719), death or emigration before follow-up (n = 39) of which 27 participants had died and 12 emigrated, smoking status (n = 4354), body mass index (n = 3641), level of physical activity (n = 30) and educational level (n = 1652) was excluded from this dataset. This left 83 500 Norwegian participants (41 587 women and 41 913 men) that was eligible to use in this cohort. Among these participants there was a total of 485 cases in which a participant was diagnosed with pancreatic cancer, and the remaining 83 015 participants was regarded as non-cases, which the flowchart in figure 7 illustrates.

Figure 7: Flowchart of exclusion criteria used to select the study participants.

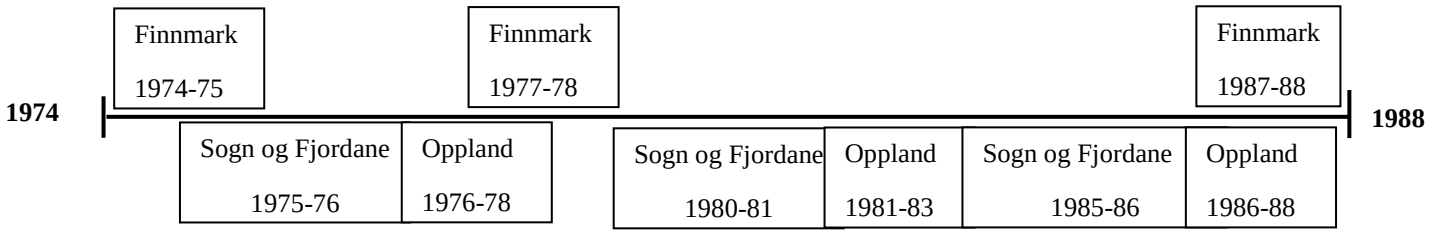


4.1.1. The Norwegian counties study

The Norwegian counties study (NCS) was a Cohort study conducted from 1974 to 1988 in the counties of Finnmark, Sogn og Fjordane and Oppland and was developed because of the Oslo-survey in 1972 which revealed cardiovascular risk factors among males aged 20-49 years. The Norwegian Counties Study aimed to reduce to mortality from cardiovascular diseases through documentation of potential risk factors and intervention (NIPH, 2015).

The study was divided into 3 screening periods; 1974-1978, 1977-1983 and 1985-1988. Attendance for the study was 88% for the 1st and 2nd period, and 84% for the 3rd (Stocks et al, 2010; Tverdal et al, 1989; Tverdal & Bjartveit, 2006). During the first screening period, men and women born between 1925-1927 and 1939-1941 was invited to participate. The study later invited everyone born in these time-periods (aged 35-49 years) to participate, as well as a selection of men and women aged 20-34 years (10% of the general population). Previous participants were also invited to the following two screening periods which also included new participants. The response rate for each of the counties first study period was: 82,4%, 90,1% and 89,8% for Finnmark, Sogn og Fjordane and Oppland counties, respectively, minimizing the risk of non-response bias. The screening was conducted in Sogn og Fjordane during the periods 1975-1976, 1980-1981 and 1985-1986, in Oppland during 1976-1978, 1981-1983 and 1986-1988, and in Finnmark during 1974-1975, 1977-1978 and 1987-1988 (NIPH, 2015), as shown in figure 8.

Figure 8: Timeline of the Norwegian Counties Study's three survey periods, for Finnmark, Sogn og Fjordane and Oppland counties.



Source: Norwegian Institute of Public Health (NIPH) - Folkehelseinstituttet (2015) –The Norwegian Counties Study.

4.1.2 Exposure information

The questionnaire used for the counties study regarding was comprised of 8 main question categories labelled A-G, with sub-questions in the first two surveys (Appendix 1). One questionnaire was used for Finnmark county and a separate was used for Oppland- and Sogn og Fjordane. The questions included own medical history and medication, symptoms, exercise, smoking, education/employment status, hereditary factors and questions linked directly to cardiovascular hereditary factors. Smoking status had questions that asked about smoking habits in terms of daily smoking, former smoking or never smoking.

Participants were also asked to answer number of cigarettes smoked per day, total smoking duration and packs per week. For former smokers, the questions revolved around time since smoking cessation and previous smoking habits. Participants who reported being either current or former smokers were asked also to report their smoking initiation age, for how long they had been smoking and total number of cigarettes smoked per day.

Physical activity was categorized into four groups based on what level of activity they reported at enrolment to the study. Sedentary (reading, watching television or other sedentary activities), Light (walking or bicycling more than 4 hours a week), Moderate (light sports or heavy gardening) and Heavy (hard exercise, competitive sports regularly). We collapsed the light and moderate level and created a three categoric variable comprising of sedentary, moderate and heavy levels of activity.

BMI was divided into four categories (underweight, normal weight, overweight and obese) where normal weight and underweight was collapsed into one variable, due to few participants reporting to be underweight. Level of education was categorized into three categories; Low (less than 10years of education), Moderate (10-12 years of education) and High (equal to or more than 13 years of education). The selected variables are described with score range and response options, as shown in Table 6.

Table 6: Description of variables showing score range and response options for all levels of the selected variables.

Variable name	Range	Level 1	Level 2	Level 3	Level 4
Smoking status	1 – 3	Never smoker	Former smoker	Current smoker	
Age at smoking initiation	1 – 3	≤ 19 years of age	20-24 years of age	≥ 25 years of age	
Number of cigarettes smoked per day	1 – 3	≤ 5 cig/day	6-15 cig/day	≥ 16 cig/day	
Total years of smoking	1 – 3	1-10 years' duration	11-20 years' duration	≥ 21 years' duration	
Physical activity	1 – 4	Sedentary	Light	Moderate	Heavy
Body mass index	1 – 4	15 - 18,49	18,5 – 24,49	24,5 – 29,99	+ 30
Years of education	1 – 3	< 10 years	10-12 years	≥ 13 years	

4.1.3 Follow-up and Endpoints

The Norwegian Counties Study followed the participants using personal identification number to locate them through the Norwegian Central Population Register (Folkeregisteret), the Norwegian Cancer Registry (Kreftregisteret) and the Norwegian Cause of Death registry (Dødsregisteret), in order to obtain accurate information about cancer cases, diagnosis, emigration or time of death (Bjerkaas, 2014).

Stage of pancreatic cancer at the time of diagnosis or any treatment the participant was undergoing during the study time was not considered. The endpoint was defined as either being diagnosed with cancer, death or emigration. For all other participants, the end of follow-up was set at 31st December 2013. The outcome of interest was the diagnosis of pancreatic cancer among the study participants.

Pancreatic cancer was defined by the Norwegian Directory of Health's (NDH) ICD-10 classification in terms of tumor in the pancreatic head segment (caput pancreatic), body segment (corpus pancreatis) and tail segment (cauda pancreatis), the exocrine ducts of the pancreas, overlapping tumor growth in pancreatic tissue and unspecified pancreatic tumor/cancer (NDH, 2015). This study does not differentiate between exocrine- and neuroendocrine tumors (NETs) when it comes to determining the outcome of pancreatic cancer being present or not present, but any pancreatic cancer type listed above is considered an outcome event.

Table 7: ICD-codes used for the determination of pancreatic cancer among the study population.

ICD- Classification	Type of malignant tumor in the pancreas
C250	Malignant tumor in the head-segment of the pancreas
C251	Malignant tumor in the body-segment of the pancreas
C252	Malignant tumor in the tail-segment of the pancreas
C253	Malignant tumor in the pancreatic exocrine ducts
C257	Malignant tumor in other specific parts of the pancreas
C258	Overlapping malignant tumors in the pancreas
C259	Malignant tumor in the pancreas, unspecified

Source: Norwegian Directory of Health (NDH) - Helsedirektoratet (2015): ICD-10 classification

4.2. Statistical analysis

Cox proportional hazards model was used with total follow-up time as the underlying time scale to estimate age-adjusted- and multivariate hazard ratios with a 95% confidence intervals (CI) for the association between smoking status (never, former, current), and pancreatic cancer. Separate age-adjusted and multivariate analysis, adjusted for; age at enrolment, education level, body mass index and physical activity level, were also conducted investigating if there was a dose-response relationship between smoking and pancreatic cancer risk, comparing never smokers to different levels of exposure; age of smoking initiation (≤19, 20-24, ≥25), number of cigarettes per day (≤5, 6-15, ≥16), duration of smoking in years (1-10, 11-20, ≥21), and number of pack years, calculated as a dose of 20 cigarettes each day, multiplied by the number of years smoking (0-5, 6-15, ≥16).

Entry time was defined as the age at enrolment and the exit time was whichever occurred fist; age at exit, the date of incident cancer diagnosis, emigration, death or the end of follow-up (31 December 2013). Independent *t*-tests were implicated to investigate intergroup variance for groups; pancreatic cancer cases and non-cases, and smokers and never smokers for all covariates (age at enrolment, education level, body mass index, physical activity level and smoking status), for the follow-up time, a Mann-Whitney 2-sample test was used. All analyses where conducted separately by gender.

Tests for linear trend were conducted for all levels of smoking exposure including the reference category. Linear trends were obtained by using both categorical and scale variables using never smoker as a reference for all groups. All analyses were conducted with the use of SPSS version 24 (IBM)

4.2.1. Confounders

The possible confounders that were included in the final models were age at enrolment (continuous), due to the established increased risk of cancer by advancing age (White et al, 2015), years of education (categorical: <10, 10-12, ≥13) as greater education can be associated with both never and former smoking (Chapman, Fiscella Duberstein, Kawachi, 2009), body mass index (categorical: normal, overweight, obese) was included due to associations with increased pancreatic cancer risk (Genkinger et al, 2011; Genkinger et al, 2015). and level of physical activity (categorical: sedentary, moderate, heavy) which has been suggested to reduce the risk of pancreatic cancer (Inoue et al, 2008; Jiao et al, 2009).

5. Results

During the Counties-Study's 39-year follow-up period, 485 incidence cases of pancreatic cancer where recorded. The overall incidence among men and woman was 256.5 per 100.000 and 259.7 per 100.000 respectively. Among the study population (N= 83500) 64.2% reported being either current or former smokers (74% of all men and 54.2% of all women).

Table 8 presents the selected descriptive characteristics from the Norwegian Counties Study. The majority of the study population (64%) reported being either active or former smokers. On average the smoker included in the study started smoking at the age of 21 and had an average consumption of 12 cigarettes per day within a 17 year (median) smoking period (10 pack years mean). The participants that reported being a current smoker accounted for 45,7% of the total study population (39,7% of all women, 51,1% of all men) and former smokers accounted for 18,7% (14,6% of all women and 22,9% of all men), the remaining 35,8% reported being never smokers (45,8% of all women and 26% of all men).

Table 8: Descriptive characteristics from the Norwegian Counties Study, among 83,500 Norwegian men and women at enrolment (1974-2013).

Descriptive characteristics	**N = 83500**
Study period	1974-1987
Age , $\bar{X}$ mean, SD	39 ± 7
Year of birth, median (range)	1939 (1905-1968)
Year at pancreatic cancer diagnosis, $\bar{X}$ mean, SD	67 ± 9
Follow-up years, median	32
Years of education, mean level	10-12 years
Body mass index , $\bar{X}$ mean (kg/m^2)	24
Level of physical activity, mean level	Light [a]
Smoking status (%) [b]	
Never smokers	36
Ever smokers	64
Ever smokers	
Age at start smoking, mean age	21
Total years of smoking, median	17
Number of cigarettes smoked per day, $\bar{X}$ mean	12
Number of pack-years, median	10

[a] *Light activity level is defined as "walking, bicycling and other activities at least 4 hours per week".* [b] *Ever smokers include former and current smokers.*

Table 9 presents the selected characteristics by smoking status at enrolment with corresponding p-values from independent t-tests. Smokers were overly represented in the male population with as many as 74% reporting either being active or former smokers. Male smokers were generally less educated, but generally more active than those that reported never smoking. For female smokers, the distribution between smokers and never smokers were more even 54% and 46% respectively. Female smokers were generally leaner, but unlike male smokers they had similar physical activity level and education levels as their never smoking counterparts.

From the result of independent t-test, we found that there was a statistically significant difference in the variances between ever and never smokers in all groups of covariates for both male and female participants at the critical significance level of 0.05 as shown in Table 9.

Table 9: Selected characteristics of the study population at enrolment in the Norwegian Counties Study (N = 83500) by smoking status.

	Ever smoker	**Never smoker**	**p[a]**
Men N = 41 913 (%)	31 015 (58)	10 898 (36)	
Follow-up time, median (IQR)[b]	30 (26-37)	33 (27-37)	< 0.001
Age at enrolment (mean year)	40	38	< 0.001
Age at diagnosis (mean year)	66	65	
Years of education (%)			< 0.001
< 10 years	43	27	
10-12 years	46	50	
≥ 13 years	11	23	
Body mass index (kg/m^2) (%)			0.008
WHO group 1-2	54	55	
WHO group 3	40	39	
WHO group 4	6	6	
Physical activity[c] (%)			< 0.001
Sedentary	20	14	
Moderate	52	47	
Heavy	28	39	
Women (N = 41 587)	22 555 (54)	19 032 (46)	
Follow-up time, median (IQR)[b]	32 (27-37)	36 (27-37)	< 0.001
Age at enrolment (mean year)	39	40	< 0.001
Age at diagnosis (mean year)	67	69	
Years of education (%)			< 0.001
< 10 years	45	37	
10-12 years	46	48	
≥ 13 years	9	15	
Body mass index (kg/m^2) (%)			< 0.001
WHO group 1-2	71	62	
WHO group 3	22	28	
WHO group 4	7	10	
Physical activity[c] (%)			< 0.001
Sedentary	23	19	
Moderate	67	69	
Heavy	10	12	

[a] The p-value are from t-test or χ^2 test for difference between the participants with and without pancreatic cancer. [b] The p-value are from Mann-Whitney 2-sample test/Wilcoxon test. [c] The levels of physical activity is defined as; Sedentary (reading, watch television, other sedentary activity), Moderate (walking, bicycling and other activity > 4 hours per week), Heavy (light sports, heavy gardening etc. and hard exercise, competitive sports regularly).

Table 10 displays the selected characteristics by pancreatic cancer status. Participants with pancreatic cancer were predominantly smokers (86% men 66% women). Female never smokers comprised 34% of all female pancreatic cancer cases, while male never smokers only comprised 14% of the male pancreatic cancer cases. Male and female cases did however not differ much in terms of age, BMI, education and physical activity and both male and female cases received their diagnosis at similar ages (mean 66 and 67 years respectively).

From the result of independent t-test, we find that for pancreatic cancer cases and non-cases there is no statistically significant difference in the variances between cases and non-cases in any group of covariates BMI, education or physical activity for male smokers, nor any statistically significant differences in covariates education or physical activity for female smokers at the critical significance level of 0.05.

Table 10: Selected characteristics of the study population at enrolment in the Norwegian Counties Study (N = 83500) for the participants with and without pancreatic cancer, sorted by sex.

	Participants with pancreatic cancer	**Participants without pancreatic cancer**	**p[a]**
Men (N = 41 913)	241	41642	
Follow-up time, median (IQR)[b]	25 (18-30)	31 (26-37)	< 0.001
Age at enrolment (mean year)	39	41	< 0.001
Age at diagnosis (mean year)	66		
Years of education (%)			0.327
< 10 years	42	39	
10-12 years	42	47	
≥ 13 years	16	14	
Body mass index (kg/m^2) (%)			0.671
WHO group 1-2	53	55	
WHO group 3	42	39	
WHO group 4	5	6	
Physical activity[c] (%)			0.136
Sedentary	21	18	
Moderate	52	51	
Heavy	27	31	
Smoking status at enrolment			< 0.001
Never smoker	14	26	
Ever smoker	86	74	
Women (N = 41587)	244	41343	
Follow-up time, median (IQR)	26.5 (20-33)	33 (27-37)	< 0.001
Age at enrolment (mean year)	42	39	< 0.001
Age at diagnosis (mean year)	67		
Years of education (%)			0.056
< 10 years	54	41	
10-12 years	39	47	
≥ 13 years	7	12	
Body mass index (kg/m^2) (%)			0.010
WHO group 1-2	61	66	
WHO group 3	28	25	
WHO group 4	11	9	
Physical activity (%)			0.861
Sedentary	21	21	
Moderate	68	68	
Heavy	11	11	
Smoking status at enrolment			< 0.001
Never smoker	34	46	
Ever smoker	66	54	

[a] The p-value are from t-test or χ^2 test for difference between the participants with and without pancreatic cancer. [b] The p-value are from Mann-Whitney 2-sample test/Wilcoxon test. [c] The levels of physical activity is defined as; Sedentary (reading, watch television, other sedentary activity), Moderate (walking, bicycling and other activity > 4 hours per week), Heavy (light sports, heavy gardening etc. and hard exercise, competitive sports regularly).

Table 11 presents the age adjusted and multivariate hazard ratio (HR) estimates with 95% confidence intervals (CIs) for pancreatic cancer by smoking status and exposure variables (age at smoking initiation, number of cigarettes per day, total years of smoking and pack-years) for men and women respectively.

In the age adjusted analysis, smoking was associated with a significantly greater risk of pancreatic cancer compared with never smokers for both men (HR = 2.54, 95% CI = 1.92-3.34) and women (HR = 2.44, 95% CI = 1.68-3.54). Compared with never smokers, men that reported having been smokers previously, but had quit smoking (no exact quitting date) had a 62% (HR = 1.62, 95% CI = 1.05-2.49) increased risk while women in the same group showed only a non-significant 15% risk increase (HR = 1.15, 95% CI = 0.73-1.80) compared with never smokers.

For both male –and female smokers the age and multivariate hazard ratios were similar. Both male -and female ever smokers had significant increased risk of pancreatic cancer compared with never smokers in all exposure categories with the exception of those smoking less than 5 cigarettes per day.

In the multivariate analysis, we found a close to 3-fold increase in risk of pancreatic cancer when comparing male smokers in the highest exposure category for all exposure variables with never smokers. While female smokers had just above 3-fold increase in risk of pancreatic cancer compared with never smokers. Compared with never smokers, male smokers had similar associations for those who reported age start smoking ≤ 19 years (HR =

2.81, 95% CI = 1.87-4.20), more than 21 years of smoking (HR = 2.82, 95% CI = 1.87-4.24) and more than 16 pack years (HR = 2.80, 95% CI = 1.84-4.24).

Compared with never smokers, female smokers also showed similar association between exposure and risk of pancreatic cancer. Age at start smoking ≤19 years of age (HR = 3.28, 95% CI = 2.22-4.82), more than 16 pack-years (HR = 3.23, 95% CI = 2.02-5.14), number of cigarettes per day (HR = 3.14, 95% CI = 1.90-5.19) and ≥21 total years of smoking (HR = 3.08, 95% CI = 2.12-4.45).

The tests for linear trend across the different exposure categories for age at initiation, number of cigarettes per day, smoking duration, and pack-years also shown in Table 11 show that all reported trends where statistically significant ($P_{trend} < 0.05$) for female participants. For male participants, there was no observed linear trend for any of the exposure categories ($P_{trend} > 0.05$ for all categories).

Table 11: Age adjusted and multivariate hazard ratios (HRs) and 95% confidence intervals (CIs) for pancreatic cancer cases [a] by sex, including selected covariates, tested for linear trends.

Smoking exposure	**Men**			**Women**		
	Cases[b] (%)	**HR 95% CI age adjusted**	**HR 95% CI multivariate**	**Cases[b] (%)**	**HR 95% CI age adjusted**	**HR 95% CI multivariate**
Never smoker	34 (14)	Ref.	Ref.	82 (33)	Ref.	Ref.
Former smoker	54 (22)	1.62 (1.05-2.49)	1.66 (1.07-2.54)	25 (10)	1.15 (0.73-1.80)	1.16 (0.74-1.81)
Current smoker	153 (63)	2.54 (1.92-3.34)	2.61 (1.78-3.80)	137 (56)	2.44 (1.68-3.54)	2.50 (1.89-3.31)
Ever smoker [d]	207 (86)	2.16 (1.50-3.10)	2.24 (1.55-3.23)	162 (66)	2.14 (1.63-2.79)	2.10 (1.60-2.75)
Age start smoking						
≥25 years	17 (7)	2.08 (1.16-3.74)	2.17 (1.20-3.90)	38 (16)	1.73 (1.17-2.54)	1.69 (1.14-2.49)
20-24	43 (18)	2.28 (1.45-3.58)	2.42 1.53-3.81)	53 (22)	3.01 (2.12-4.26)	2.99 (2.10-4.26)
≤ 19 years	93 (39)	2.62 (1.76-3.87)	2.81 (1.87-4.20)	46 (19)	3.40 (2.32-4.96)	3.28 (2.22-4.82)
			P_{trend}: 0.428			P_{trend}: 0.003
Cigarettes/day						
≤ 5 cig/day	11 (5)	1.25 (0.63-2.47)	1.29 (0.63-2.47)	21 (9)	1.12 (0.69-1.80)	1.11 (0.68-179)
6-15 cig/day	134 (56)	2.23 (1.53-3.25)	2.33 (1.58-3.40)	121 (50)	2.39 (1.90-5.18)	2.36 (1.76-3.13)
≥ 16 cig/day	53 (22)	2.31 (1.50-3.55)	2.39 (1.54-3.68)	19 (8)	3.14 (1.06-1.10)	3.14 (1.90-5.19)
			P_{trend}: 0.325			P_{trend}: < 0.001
Total years of smoking[c]						
1-10 years	32 (13)	1.80 (1.10-2.93)	1.83 (1.12-2.99)	36 (15)	1.41 (0.94-2.09)	1.40 (0.93-2.08)
11-20 years	75 (31)	1.92 (1.28-2.88)	2.01 (1.33-3.02)	80 (33)	2.20 (1.61-3.00)	2.18 (1.59-2.98)
≥ 21 years	100 (42)	2.64 (1.76-3.95)	2.82 (1.87-4.24)	46 (19)	3.11 (2.15-4.48)	3.08 (2.12-4.45)
			P_{trend}: 0.101			P_{trend}: < 0.001
Pack-years[e]						
0-5 years	40 (17)	2.10 (1.32-3.31)	2.15 (1.35-3.40)	44 (18)	1.29 (0.89-1.87)	1.28 (0.88-1.85)
6-15 years	85 (35)	1.89 (1.26-2.80)	1.96 (1.31-2.93)	94 (39)	2.69 (1.99-3.61)	2.66 (1.96-3.59)
≥ 16 years	73 (30)	2.68 (1.77-4.09)	2.80 (1.84-4.24)	23 (9)	3.23 (2.02-5.13)	3.23 (2.02-5.14)
			P_{trend}: 0.070			P_{trend}: < 0.001

[a] For pancreatic cancer cases (n = 83 500 with 485 cases). [b] Cases of pancreatic cancer for multivariate analysis. [c] Total number of years smoking. [d] Ever smoker defined as former and current smokers combined. [e] One pack having 20 cigarettes: number of cigarettes smoked daily multiplied with the number of years smoking.

Multivariate analysis adjusted for; age at enrolment, education, body mass index and level of physical activity.

6. Discussion

There are not many studies that examine the differences between male and female smokers in relation to pancreatic cancer risk. Our study is one of few studies done on the association between smoking and pancreatic cancer risk in Norway and to our knowledge the first to find a linear dose-response relationship between exposure level and pancreatic cancer risk for female smokers. Our study shows that both male and female smokers have an increased risk of pancreatic cancer compared with never-smokers. The risk was of the same magnitude and had overlapping confidence intervals. The risk of pancreatic cancer was greater for current smokers than for former smokers for both males and females. Furthermore, our study shows that female smokers have a dose-response relationship between the different measures of smoking exposure and increased risk of pancreatic cancer, which was not evident for male smokers. In our multivariate analysis, the overall smoking associated risk of pancreatic cancer compared with never smokers for both sexes were similar to that of the age adjusted analysis, indicating only a minor modification from the addition of covariates; education level, body mass index and physical activity level to the model.

Our results are consistent with previous findings that there is an increased pancreatic cancer risk for smokers compared with never smokers. (Bosetti et al, 2012; Schulte et al, 2014; Lynch et al, 2009). Previous studies have also found a dose-response relationship between the association between different levels of smoking exposures and pancreatic cancer risk (Zou et al, 2014; Iodice et al; Hippisley-Cox & Coupland, 2015; Meyer et al, 2015). More support for the results is found in the carcinogenic effects of smoking (CDC, 2014). Our study found a non-linear dose-response relationship between smoking and

pancreatic cancer risk for male smokers, consistent with the findings from earlier meta-analysis (Zou et al,. 2014). However, opposite that of Zou et al (2014) our study found that there is a linear dose-response relationship between smoking and PC risk for female smokers for initiation age, intensity, duration and cumulative amount (pack-years).

6.1. Gender differences in smoking related pancreatic cancer

We found that women have a dose-response related risk for pancreatic cancer across all exposure covariates (age at initiation, cigarettes/day, total years of smoking and packyears). Although the incidence rate for pancreatic cancer in Norway is evenly distributed between men and women, and the increased pancreatic cancer risk is similar for both male and female smokers, only female smokers showed a dose-response relationship

In the heaviest exposure categories, female smokers showed a three-fold increase in risk from early initiation (≤ 19 years old), high consumption (≥16 cigarettes per day), and long smoking duration (≥21 years) compared with never smokers. We found that in the heaviest categories, the risk of pancreatic cancer was 3-folded among women and nearly 3-folded for men.

The differences in exposure based risk between male and female smokers might be explained by interactions of genes and smoking (Duell et al, 2002) or an increased susceptibility to tobacco carcinogens in women, as has been suggested to be the case for lung cancer (International Early Lung Cancer Action Program Investigators, 2006; Papadopoulos et al., 2014).

6.2. Strengths and limitations to the study

6.2.1. Strengths

The strengths of the study are that it is a large prospective cohort containing a large proportion of both male and female smokers from geographically separated populations in Norway. The cohort's long follow-up period gives more stable risk estimates, smoking history was accessed at enrolment, minimizing the risk of recall bias.

The Norwegian Counties study shows a total mortality within the study population (the counties of Oppland, Sogn- og Fjordane and Finnmark) that is similar for that of the total national mortality (Vollset, Selmer, Tverdal, & Gjessing, 2006). Therefore, we assume that the current study holds good external validity for the whole of the Norwegian population. It must also be considered a strength of the study, that the cohort has as many as 485 incidence-cases of pancreatic cancer. This number is relatively high considering the Surgeon General (2014) only presented two cohort studies, one including 355 (Dandona et al, 2011) and the other 126 incidence-cases (Jamal et al, 2010).

6.2.2. Limitations

The study has several limitations. The current study has no information on alcohol consumption, which might modify the sex-differences in that Norwegian men have higher alcohol consumption than Norwegian women (Strand & Steiro, 2003), as alcohol may increase the risk of pancreatic cancer (Gapstur, Jacobs, Deka, McCullough, Patel, & Thun, 2011).

Information concerning occasional smoking, second-hand smoke, diabetes mellitus history as well as any history of hereditary cancer is also missing and can therefore not be adjusted for. Lack of information regarding occasional smoking and second-hand smoke exposure could lead to biased results since 10% of Norwegians are occasional smokers (Lund & Lindback, 2007). These individuals are likely to be included in the reference group.

Risk estimates on smoking might also be tainted, i.e. current and former smokers might be misleading since participants reporting being current smokers at enrolment might stop smoking during the follow-up period, and former smokers might start smoking again. This will influence the risk estimates in that the true estimates for a pure current smoker group would lie somewhat higher and pure former smoker group would lie somewhat lower than our estimates.

6.2.3. Internal validity

Internal validity is defined as the extent to which a causal conclusion based on the study is warranted. Internal validity depends on both systematic and random error i.e. confounding and bias, thus the internal validity is thus determined by the degree to which the study minimizes bias. Internal validity is evaluated by whether the observed changes in the outcome measure, in this case pancreatic cancer risk can be attributed to the main exposure, and not to other factors. The representativeness of the study population or lack thereof is one of the largest factors concerning internal validity.

6.2.4. External validity

External validity refers to the validity of generalized inference i.e. to what extent the results can be generalized to other populations then the sample used in the study (Bonita, Beaglehole, & Kjellstrom, 2006). Due to the fact that our data is collected in Norway, although representative for a random sample of the Norwegian population, it can be difficult to generalize our study results to a wider European population (NIPH, 2015). We assume that our results can be generalized to the Western Causation population as done in previous studies (Parajuli, 2014). At the time of data-collection (Norwegian Counties Study), the Norwegian prevalence was somewhat higher, as the prevalence for males peaked (65%) in the late 1950's, while women peaked (37%) in the 1970's (Norway's Public Reports, 2000).

6.2.5. Random error

Random error might occur because the estimates we produce are based on samples, and these samples may not accurately reflect the population at large. Random error might therefore lead to non-reproducibility of the study results, weakening the association between the exposure and the outcome. Thus, a larger sample size gives increased precision to a study. Our study was of a large prospective cohort containing a large proportion of both male and female smokers from a geographically separated population in Norway, minimalizing the sampling error and thus increasing the precision (Bonita, Beaglehole, & Kjellstrom, 2006).

Random error issues are also addressed in terms of the statistical procedures used in our study. Our hypothesis was tested at the 5% level and 95% confidence intervals are calculated for all the analysis.

6.2.6. Systematic error

Systematic error or "Bias" is used to describe a deviation of the result that on a systematic level differentiates from the truth. This can be further defined as an error that affects the design, method of collection, interpretation, analysis, publication or review that leads to a result that is untrue (Porta, 2014). The measurements involving body mass index (BMI) might be flawed i.e. measurements conducted at different times and places open for information measurement error. This might be due to differences in equipment used for the measurements, or human error e.g. reading or reporting the wrong measurements for height or weight etc. For all questionnaire based surveys we will not know whether participants under- or over reports certain aspects of their lifestyle related activities e.g. physical activity or smoking amount. This possible under- or over reporting might than lead to misclassification.

Non-response bias occurs when the response of the participants varies from the potential response of those who did not participate in the study. This might lead to under- or overreporting. The reason for under- or over reporting might also be due to recall bias i.e. participants might not fully remember, or forget some of the information regarding smoking exposure or age at initiation etc. (Finchman, 2008). We have no reason to assume that this will differ according to our reported cases and non-cases, as the Norwegian Counties Study was designed to examine risk factors for cardiovascular disease and not pancreatic cancer.

Selection bias occurs when there is a systematic difference between the characteristics of the people selected for a study and the characteristics of the people who are not. Selection bias usually occurs if there is an aspect of self-selection involved, i.e. the participants are allowed to choose the study they want to join. If subjects are allowed the choice, certain personality traits seem to encourage study participation. Thus, any result might be due at least in part by the differences in characteristics between participants and non-participants (Katz, Elmore, Wild, & Lucan, 2013).

6.3. Implications for Public Health

The prevention of pancreatic cancer should be considered a public health issue, given the poor prognosis of the disease and limited treatment options. Most of the patients diagnosed with this disease will not benefit effectively from surgery or chemotherapy. This is reflected in the poor 5-years survival rates. Prevention should be considered equally or more important than the treatment. The efforts of prevention may prove to be far costlier than the treatment-options, but could decrease the current incidence-rates. Our study found that

smoking was the most significant risk factor for the development of pancreatic cancer given the available exposure variables in our study.

The prevention of exposure from tobacco smoking should be a key factor in the prevention of this cancer type, as approximately 20-30% of all pancreatic cancer cases can be contributed to smoking (Tranah, Holly, Wang, Bracci, 2011). Working towards the World Health Organization's NCD-goal of 2025 should be prioritized in order to achieve a 30% decrease in prevalence among smokers, and reduce future cases of pancreatic cancer and other smoking-related diseases.

Tobacco-control and preventive measures should further be enforced in society, as smoking is one of the most significant modifiable risk factor for many diseases. Smoking cessation should be encouraged and further restrictions to public smoking should be applied in order to prevent harm.

6.4. Suggestions for further research

Our findings suggest that the carcinogenic effects of smoking may be more hazardous for women in terms of pancreatic cancer risk, which highlights the importance of taking potential sex differences into consideration in further studies and prevention efforts. Our study does not include alcohol consumption, a factor that could influence the effect of smoking on pancreatic cancer risk.

We lacked detailed information on smoking cessation but found that current smokers had higher risk estimates than former smokers, though estimates for female former smokers were non-significant compared with none smokers. Further research on the effects of smoking cessation between genders might therefore be warranted in larger cohorts with higher number of pancreatic cancer cases.

7. Conclusion

The main aim of this thesis was to examine the association between smoking and the risk of pancreatic cancer. Our study found in accordance to similar previous research that there is a significant increased risk of pancreatic cancer associated with smoking. We also found that female smokers have a statistical significant dose-response relationship between smoking and pancreatic cancer risk, which was not present for male smokers. The dose-response relationships for female smokers were revealed for all the exposure variables (age at smoking initiation, number of cigarettes per day, total years of smoking and pack-years) examined in our analysis. We found similar results for both the age-adjusted and multivariate analysis, indicating no modification by the covariates (education level, body mass index and physical activity level) on the effect of smoking on pancreatic cancer risk.

All cohort-studies published between January 2013 to February 2017 on the association between smoking and pancreatic cancer risk, are in consensus with our study that there is a causal relationship between smoking and the risk of pancreatic cancer. This is also in accordance to previous research on the subject.

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9. Appendices

Appendix 1:

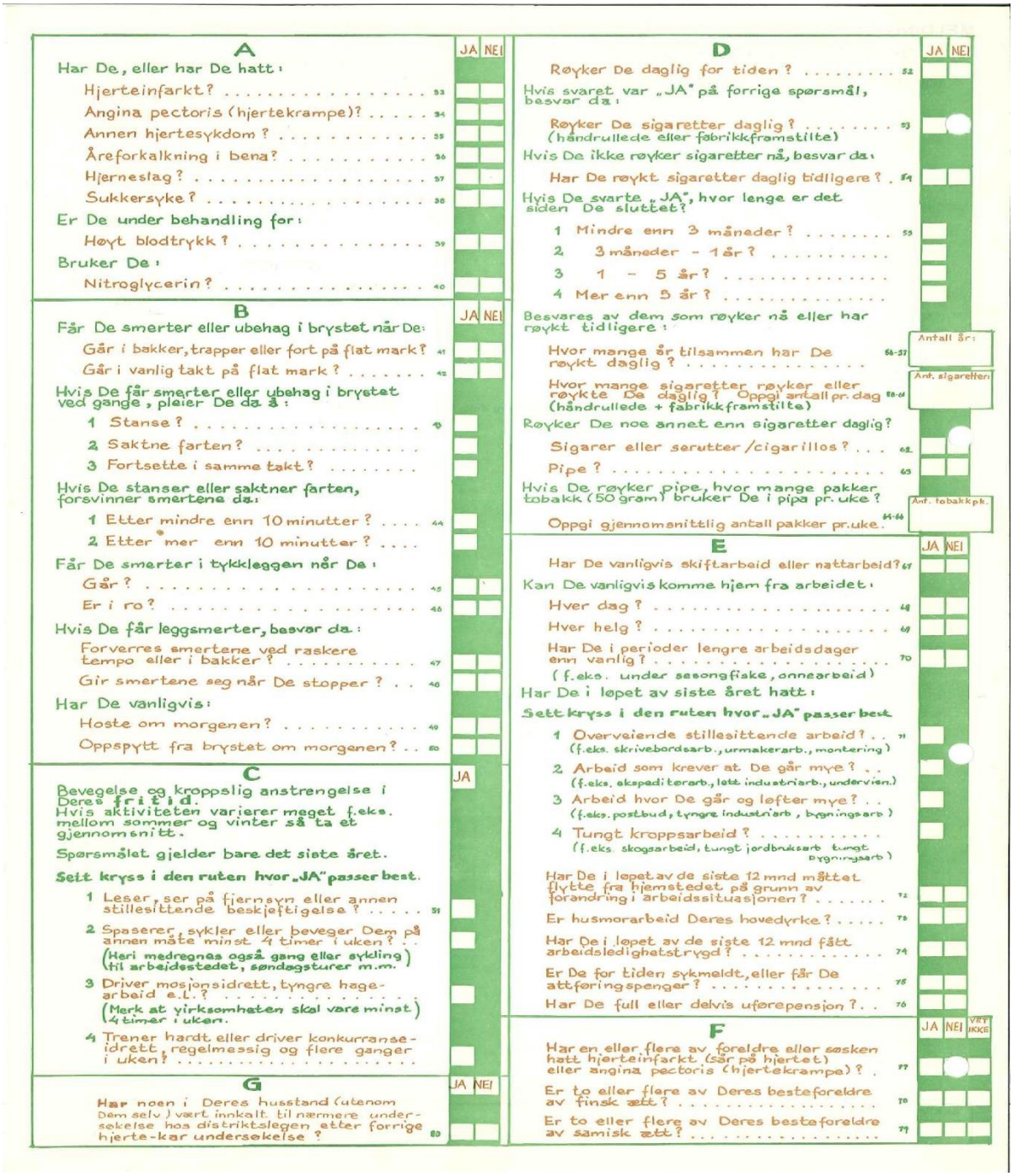
- *Questionaire used in the Norwegian Counties Study: Finnmark County. Round 1 and 2 in Norwegian.*

- *Questionaire used in the Norwegian Counties Study: Sogn og Fjordane and Oppland Counties. Round 1 and 2 in Norwegian.*

Appendix 2:

- *Final report from the Norwegian Counties Study: report from each county in each survey (1974-78, 1977-83 and 1985-88), Finnmark, Sogn og Fjordane and Oppland counties.*

Appendix 1. *Questionaire used in the Norwegian Counties Study: Finnmark County. Round 1 and 2 in Norwegian.*



A

Har De, eller har De hatt:

	JA	NEI
Hjerteinfarkt? 33		
Angina pectoris (hjertekrampe)? 34		
Annen hjertesykdom? 35		
Åreforkalkning i bena? 36		
Hjerneslag? 37		
Sukkersyke? 38		
Er De under behandling for:		
Høyt blodtrykk? 39		
Bruker De:		
Nitroglycerin? 40		

B

	JA	NEI
Får De smerter eller ubehag i brystet når De:		
Går i bakker, trapper eller fort på flat mark? 41		
Går i vanlig takt på flat mark? 42		
Hvis De får smerter eller ubehag i brystet ved gange, pleier De da å:		
1 Stanse? 43		
2 Saktne farten?		
3 Fortsette i samme takt?		
Hvis De stanser eller saktner farten, forsvinner smertene da:		
1 Etter mindre enn 10 minutter? 44		
2 Etter mer enn 10 minutter?		
Får De smerter i tykkleggen når De:		
Går? 45		
Er i ro? 46		
Hvis De får leggsmerter, besvar da:		
Forverres smertene ved raskere tempo eller i bakker? 47		
Gir smertene seg når De stopper? 48		
Har De vanligvis:		
Hoste om morgenen? 49		
Oppspytt fra brystet om morgenen? 50		

C

Bevegelse og kroppslig anstrengelse i Deres **fritid**.
Hvis aktiviteten varierer meget f.eks. mellom sommer og vinter så ta et gjennomsnitt.
Spørsmålet gjelder bare det siste året.
Sett kryss i den ruten hvor „JA" passer best.

	JA
1 Leser, ser på fjernsyn eller annen stillesittende beskjeftigelse? 51	
2 Spaserer, sykler eller beveger Dem på annen måte minst 4 timer i uken? (Heri medregnes også gang eller sykling til arbeidsstedet, søndagsturer m.m.)	
3 Driver mosjonsidrett, tyngre hagearbeid e.l.? (Merk at yirksomheten skal være minst 4 timer i uken.	
4 Trener hardt eller driver konkurranseidrett, regelmessig og flere ganger i uken?	

G

	JA	NEI
Har noen i Deres husstand (utenom Dem selv) vært innkalt til nærmere undersøkelse hos distriktslegen etter forrige hjerte-kar undersøkelse? 80		

D

	JA	NEI
Røyker De daglig for tiden? 52		
Hvis svaret var „JA" på forrige spørsmål, besvar da:		
Røyker De sigaretter daglig? 53 (håndrullede eller fabrikkframstilte)		
Hvis De ikke røyker sigaretter nå, besvar da:		
Har De røykt sigaretter daglig tidligere? 54		
Hvis De svarte „JA", hvor lenge er det siden De sluttet?		
1 Mindre enn 3 måneder? 55		
2 3 måneder - 1 år?		
3 1 - 5 år?		
4 Mer enn 5 år?		
Besvares av dem som røyker nå eller har røykt tidligere:		
Hvor mange år tilsammen har De røykt daglig? 56-57 — Antall år:		
Hvor mange sigaretter røyker eller røykte De daglig? Oppgi antall pr. dag 58-61 (håndrullede + fabrikkframstilte) — Ant. sigaretter:		
Røyker De noe annet enn sigaretter daglig?		
Sigarer eller serutter/cigarillos? 62		
Pipe? 63		
Hvis De røyker pipe, hvor mange pakker tobakk (50 gram) bruker De i pipa pr. uke?		
Oppgi gjennomsnittlig antall pakker pr. uke. 64-66 — Ant. tobakkpk:		

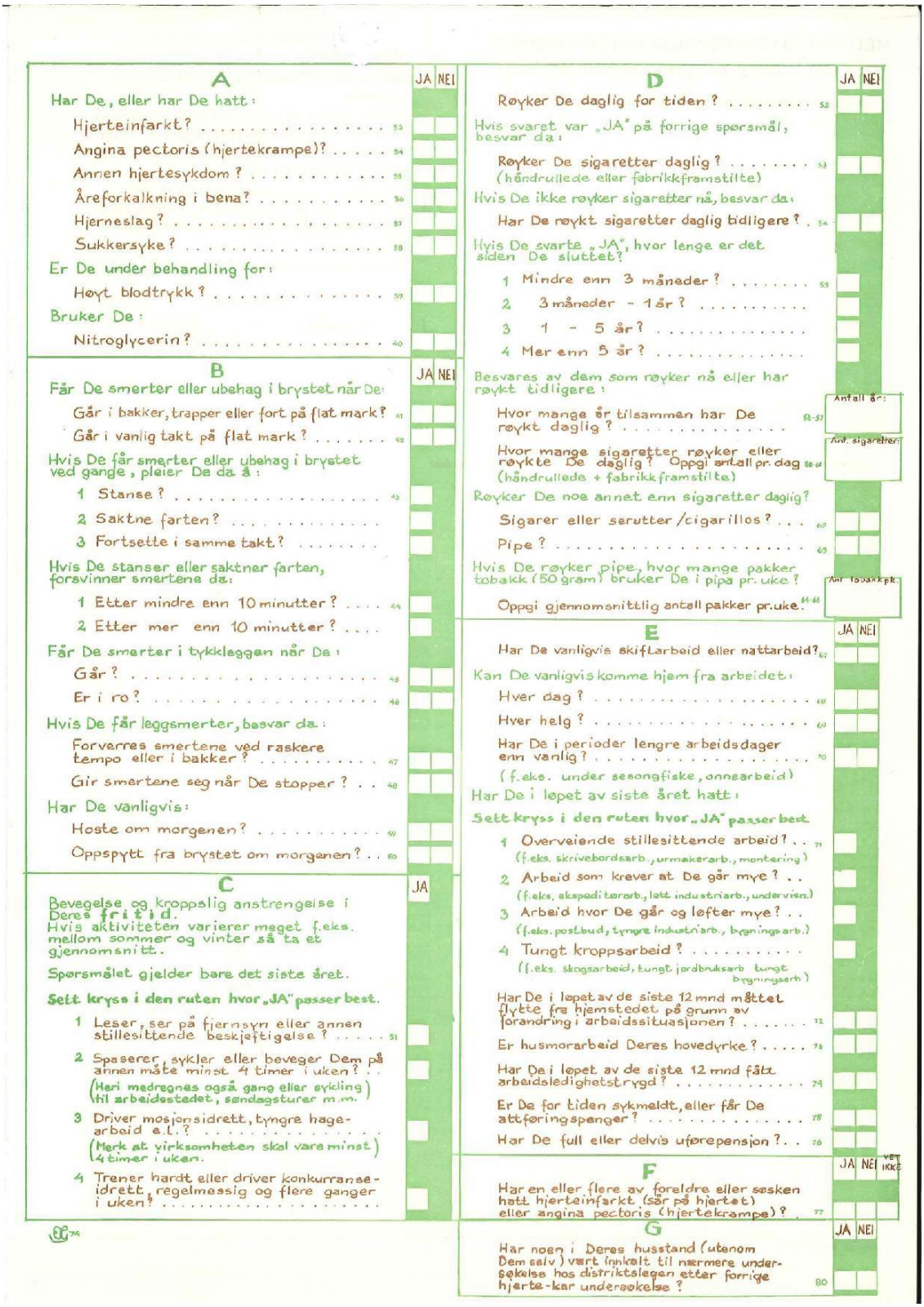
E

	JA	NEI
Har De vanligvis skiftarbeid eller nattarbeid? 67		
Kan De vanligvis komme hjem fra arbeidet:		
Hver dag? 68		
Hver helg? 69		
Har De i perioder lengre arbeidsdager enn vanlig? 70 (f.eks. under sesongfiske, onnearbeid)		
Har De i løpet av siste året hatt:		
Sett kryss i den ruten hvor „JA" passer best.		
1 Overveiende stillesittende arbeid? 71 (f.eks. skrivebordsarb., urmakerarb., montering)		
2 Arbeid som krever at De går mye? (f.eks. ekspeditørarb., lett industriarb., undervisn.)		
3 Arbeid hvor De går og løfter mye? (f.eks. postbud, tyngre industriarb, bygningsarb)		
4 Tungt kroppsarbeid? (f.eks. skogsarbeid, tungt jordbruksarb tungt bygningsarb)		
Har De i løpet av de siste 12 mnd måttet flytte fra hjemstedet på grunn av forandring i arbeidssituasjonen? 72		
Er husmorarbeid Deres hovedyrke? 73		
Har De i løpet av de siste 12 mnd fått arbeidsledighetstrygd? 74		
Er De for tiden sykmeldt, eller får De attføringspenger? 75		
Har De full eller delvis uførepensjon? 76		

F

	JA	NEI	VET IKKE
Har en eller flere av foreldre eller søsken hatt hjerteinfarkt (sår på hjertet) eller angina pectoris (hjertekrampe)? 77			
Er to eller flere av Deres besteforeldre av finsk ætt? 78			
Er to eller flere av Deres besteforeldre av samisk ætt? 79			

Questionnaire used in the Norwegian Counties Study: Sogn og Fjordane and Oppland Counties. Round 1 and 2 in Norwegian.



A

Har De, eller har De hatt: — JA NEI

- Hjerteinfarkt? 33
- Angina pectoris (hjertekrampe)? 34
- Annen hjertesykdom? 35
- Åreforkalkning i bena? 36
- Hjerneslag? 37
- Sukkersyke? 38

Er De under behandling for:

- Høyt blodtrykk? 39

Bruker De:

- Nitroglycerin? 40

B

Får De smerter eller ubehag i brystet når De: — JA NEI

- Går i bakker, trapper eller fort på flat mark? 41
- Går i vanlig takt på flat mark? 42

Hvis De får smerter eller ubehag i brystet ved gange, pleier De da å:

- 1 Stanse? 43
- 2 Saktne farten?
- 3 Fortsette i samme takt?

Hvis De stanser eller saktner farten, forsvinner smertene da:

- 1 Etter mindre enn 10 minutter? 44
- 2 Etter mer enn 10 minutter?

Får De smerter i tykkleggen når De:

- Går? 45
- Er i ro? 46

Hvis De får leggsmerter, besvar da:

- Forverres smertene ved raskere tempo eller i bakker? 47
- Gir smertene seg når De stopper? 48

Har De vanligvis:

- Hoste om morgenen? 49
- Oppspytt fra brystet om morgenen? 50

C

Bevegelse og kroppslig anstrengelse i Deres **fritid**. Hvis aktiviteten varierer meget f.eks. mellom sommer og vinter så ta et gjennomsnitt. — JA

Spørsmålet gjelder bare det siste året.

Sett kryss i den ruten hvor „JA" passer best.

1. Leser, ser på fjernsyn eller annen stillesittende beskjeftigelse? 51
2. Spaserer, sykler eller beveger Dem på annen måte minst 4 timer i uken? (Heri medregnes også gang eller sykling til arbeidsstedet, søndagsturer m.m.)
3. Driver mosjonsidrett, tyngre hagearbeid e.l.? (Merk at virksomheten skal være minst 4 timer i uken.)
4. Trener hardt eller driver konkurranseidrett, regelmessig og flere ganger i uken?

D

Røyker De daglig for tiden? 52 — JA NEI

Hvis svaret var „JA" på forrige spørsmål, besvar da:

- Røyker De sigaretter daglig? 53 (håndrullede eller fabrikkframstilte)

Hvis De ikke røyker sigaretter nå, besvar da:

- Har De røykt sigaretter daglig tidligere? 54

Hvis De svarte „JA", hvor lenge er det siden De sluttet?

- 1 Mindre enn 3 måneder? 55
- 2 3 måneder - 1 år?
- 3 1 - 5 år?
- 4 Mer enn 5 år?

Besvares av dem som røyker nå eller har røykt tidligere:

- Hvor mange år tilsammen har De røykt daglig? 56-57 — Antall år:
- Hvor mange sigaretter røyker eller røykte De daglig? Oppgi antall pr. dag 58-59 (håndrullede + fabrikkframstilte) — Ant. sigaretter:

Røyker De noe annet enn sigaretter daglig?

- Sigarer eller serutter/cigarillos? 62
- Pipe? 63

Hvis De røyker pipe, hvor mange pakker tobakk (50 gram) bruker De i pipa pr. uke? — Ant. tobakkpk.

- Oppgi gjennomsnittlig antall pakker pr. uke. 64-66

E

Har De vanligvis skiftarbeid eller nattarbeid? 67 — JA NEI

Kan De vanligvis komme hjem fra arbeidet:

- Hver dag? 68
- Hver helg? 69
- Har De i perioder lengre arbeidsdager enn vanlig? 70 (f.eks. under sesongfiske, onnearbeid)

Har De i løpet av siste året hatt:

Sett kryss i den ruten hvor „JA" passer best.

1. Overveiende stillesittende arbeid? 71 (f.eks. skrivebordsarb., urmakerarb., montering)
2. Arbeid som krever at De går mye? (f.eks. ekspeditørarb., lett industriarb., undervisn.)
3. Arbeid hvor De går og løfter mye? (f.eks. postbud, tyngre industriarb., bygningsarb.)
4. Tungt kroppsarbeid? (f.eks. skogsarbeid, tungt jordbruksarb. tungt bygningsarb.)

Har De i løpet av de siste 12 mnd måttet flytte fra hjemstedet på grunn av forandring i arbeidssituasjonen? 72

Er husmorarbeid Deres hovedyrke? 73

Har De i løpet av de siste 12 mnd følt arbeidsledighetstrygd? 74

Er De for tiden sykmeldt, eller får De attføringspenger? 75

Har De full eller delvis uførepensjon? 76

F

Har en eller flere av foreldre eller søsken hatt hjerteinfarkt (sår på hjertet) eller angina pectoris (hjertekrampe)? 77 — JA NEI vet ikke

G

Har noen i Deres husstand (utenom Dem selv) vært innkalt til nærmere undersøkelse hos distriktslegen etter forrige hjerte-kar undersøkelse? 80 — JA NEI

Appendix 2. *Final report from the Norwegian Counties Study: report from each county in each survey (1974-78, 1977-83 and 1985-88), Finnmark, Sogn og Fjordane and Oppland counties.*

The cardiovascular surveys in Finnmark, Sogn og Fjordane and Oppland 1974-78, 1977-83 and 1985-88. Sources: Final reports from each survey in each county

County	Period	Age groups invited	Number invited	Number attending	% attendance, fully invited ages
Finnmark	1974-75	All residents in age 35-49 by Dec 1974 (born 25-39). Age 20-34: 10% random samples	17401	14340	82.4 Men: 78.8, women: 86.2
	1977-78	All residents born 1925-42, samples in younger ages from 20 years.	20647	17145	83.0 Men: 79.2 women: 87.3
	1987-88	All residents in age 40-62 by Dec 1987 (born 1925-47) + those aged 30-39 and invited in 1977-78 + 10 % of non-invited in age 20-39. All residents 18 years or older in Bugøynes.	22994	17852	77.6 Men: 73.4, women: 82.6
Sogn og Fjordane	1975-76	All residents in age 35-49 by Dec 1975 (born 1926-40) + 10 % random sample in age 20-39.	16603	14966	90.1 Men: 87.4, women:93.1
	1980-81	All residents born 1926-40 + samples in younger ages from 17 years.	19506	17473	89.6 Men: 86.8, women:92.6
	1985-86	All residents in age 40-54 by Dec 31 1985 (born 1931-45) + those younger than 40 years and invited in 1980-81 + 5-% sample of those in age 20-39 not invited in 1980-81 +10 % sample of invited in 1980-81 in age 55-59. A few older subjects in a hypertension register.	21423	18669	87.1 Men: 83.9, women: 90.7
Oppland	1976-78	All in age 35-49 by Dec 1976 (born 1927-41) +10- % random sample in age 20-39.	31620	28399	89.8 Men: 87.8, women: 91.8
	1981-83	All residents born 1927-41 + samples in younger ages from 20 years.	31581	28437	90.0 Men: 88.1, women: 91.9
	1986-88	All residents aged 40-54 on Dec 1986 (born 1932-46) + all residents below 40 years and a 10 % sample in age 55-59 if invited in 1981-83 + 5-% of not invited in 1981-83 in age 20-39. A few older subjects in a hypertension register.	37270	32124	86.2 Men: 83.5, women: 88.9

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