UiT The Arctic University of Norway

Faculty of Health and Sciences

The association between smoking and the risk of pancreatic cancer - The Norwegian women and cancer (NOWAC) study

Muneeba Anwar

Master's thesis in Public Health: HEL-3950. May, 2021

Department of Community medicine, UiT – The Arctic University of Norway

Main supervisor: Inger Torhild Gram (Professor - M.D, Ph.D)
Co-supervisor: Tonje Braaten (Associate Professor – Department of Community Medicine)

Preface

It has been a remarkable journey studying at UiT – The Arctic University of Norway. The collaboration with international students with diverse academic backgrounds allowed me to gain invaluable experience and knowledge. I spent my last two years working as a medical content and research writer. However, I felt the need to polish and enhance my professional skills where the teachers at UiT helped me greatly.

Working and researching on cancer is something I have always been interested in, and my main supervisor professor Inger Torhild Gram was my inspiration for this. Both her and my co-supervisor Tonje Braaten kept motivating me and provided useful insights to complete my master's thesis.

I would also like to thank my parents, my husband and my entire family for their continuous support throughout the time I've been working on my thesis. Without their support, it wouldn't have been possible for me to push myself and go that extra mile to complete my thesis.

One who treads a path in search of knowledge has his path to Paradise made easy by Allah Almighty.

- Prophet Muhammad (Riyadh us-Saleheen:245)

Abstract

Aims

To examine the strength of association between cigarette smoking and the risk of pancreatic cancer in a cohort of Norwegian women.

Methods

A total of 149,243 women from Norwegian Women and Cancer Study were included in the statistical analysis. The participants were followed using the Cancer Registry of Norway and Norwegian Central Population Register till they were diagnosed with cancer, died or emigrated. The end of follow-up period was December, 2019. Age-adjusted and Multivariate adjusted Hazard Ratios with 95% CIs were obtained to examine the association between cigarette smoking and the risk of pancreatic cancer. Age at enrollment, education, BMI and physical activity were included as covariates in the final multivariate analysis.

Results

In age-adjusted and multivariate adjusted analysis, hazard ratios for pancreatic cancer in former smokers and current smokers were found to be higher than the reference category. Ever smokers had an overall 66% statistically significant increased risk of pancreatic cancer (HR = 1.66; CI = 1.34-2.06) as compared to never smokers. Former smokers had an overall 10% non-significant (HR = 1.10; 95% CI = 0.85-1.42), and current smokers had an overall 2-fold (HR = 2.39; 95% CI = 1.90-3.02) significant increased risk of pancreatic cancer, compared with never smokers. Higher age at the time of smoking initiation (>25 years), higher number of cigarettes smoked per day (>15) and higher number of total years of smoking (>30 years) were associated with 72% (HR = 1.72; CI = 1.11-2.67), 77% (HR = 1.77; CI = 1.26-2.48) and 89% (HR = 1.89; CI = 1.44-2.48) statistically significant increased risk of pancreatic cancer as compared to never smokers.

Conclusion

The findings of this thesis are in accordance with the previously published studies showing that ever smokers are at an increased risk of developing pancreatic cancer as compared to never-smokers. We also observed a dose-response relationship between the exposure and the outcome. Therefore, our findings are in support of a causal association between cigarette smoking and risk of pancreatic cancer.

Keywords

Cigarette smoking, pancreatic cancer, cox proportional, cohort, NOWAC study

Table of Contents

List of Tables

List of Figures

Abbreviations

ACS – American Cancer Society

BMI – Body mass index

CDC – Centre for Disease Control and Prevention

CI – Confidence interval

GLOBOCAN – Global Cancer Incidence, Mortality, and Prevalence

HDI – Human developmental Index

IARC - International Agency for Research on Cancer

ICD – International Classification of Disease

IPMN - Intraductal Papillary Mucinous Neoplasm

HR – Hazard Ratio

MCN – Mucinous Cystic Neoplasm

NCI – National Cancer Institute

NET – Neuroendocrine Tumor

NOWAC – Norwegian Women and Cancer Study

PanIN – Pancreatic Intraepithelial Neoplasia

PanC4 – The Pancreatic Cancer Case-Control Consortium

PanNET – Pancreatic Neuroendocrine Tumors

PDAC – Pancreatic Ductal Adenocarcinoma

SPSS – Statistical Package for the Social Sciences

Chapter 1: Introduction

Consistent results of positive association between cigarette smoking and pancreatic cancer have resulted in acclamation of cigarette smoking as one of the most important modifiable risk factors for pancreatic cancer. However, the relationship is dose-response dependent. This means that the association was greater for increasing dose, intensity, and duration of smoking. (1-4)

IARC has referred to smoking as a definite causal factor for pancreatic cancer. However, they have also found that the risk of developing pancreatic cancer due to smoking increases with the duration of smoking (in years) and the number of cigarettes smoked per day. (5, 6) Similar consistent results were obtained from a pooled analysis of 30 cohorts(7), a meta-analysis(8) and two population based studies(9, 10).

From the findings of innumerable researches, the International Agency for Research on Cancer and other organizations working on pancreatic cancer, we can establish the modifiable and non-modifiable risk factors of pancreatic cancer. (11) Smoking(5), obesity, alcohol consumption(1), and lifestyle/dietary habits(12) are modifiable risk factors whereas family history, age, gender, ethnicity, and environment, etc. are non-modifiable.(13) (11) To control the new incidence rates and high mortality rates worldwide and in Europe, it is very important to understand the etiology of the disease and modify the factors causally associated with pancreatic cancer.

Pancreatic cancer contributes significantly to the burden of death caused by all-type cancers. Although the prevalence of pancreatic cancer is not very high the mortality rates due to pancreatic cancer are very high. (14)

The incidence and mortality rates are particularly very high in Europe and North America. The highest incidence rates and mortality rates are in Western Europe (8.3%, 7.6%), North America (7.6%, 6.5%), Central and Eastern Europe (7.5%,7.3%), Northern Europe

(7.3%,6.5%) and Southern Europe (7.2%,6.4%). In Norway, pancreatic cancer is 11th most common cancer type with 783 (2.3%) new cases and 900 deaths (7.6%) in 2018. (14, 15)

According to the estimates from GLOBOCON 2018, pancreatic cancer is 12th most common cancer globally with 458918 new cases and 432242 deaths in 2018, which equals to 4.5% of deaths caused by all-type cancers. (15) Despite the advancements in screening techniques better understanding of the disease and its prognosis, and pancreatic cancer being very uncommon, the mortality rates are still very high.

Poor prognosis, inability to detect cancer in its early stages, and lack of adequate screening tools have made it more difficult to control this burden. (16, 17) Pancreatic cancer also has one of the lowest 5-year survival rates as compared to other cancersi.e., 9% (9.23% in Norway). (15)

The rich countries of the world from Europe and the United States observed a steep increase in smoking in the early 20th century. Almost all the countries shared a similar trajectory till most of the latter half, however, in the ending quarter of the 20th century they observed a decline in cigarette smoking. Today, low and middle-income countries are following the same trajectory of smoking and cigarette consumption. (18) High life expectancies owing to better health care services and aging population, cigarette smoking, and alcohol consumption contributed a lot to cancer cases in Europe however, this trend might shift towards low and middle-income countries in the future. Previous studies have shown a significant dose response relationship between cigarette smoking and the cases of breast cancer, epithelial ovarian cancer, colorectal cancer and pancreatic cancer. (19-22)

Researchers have found that the risk of pancreatic cancer development is higher in smokers as compared to non- smokers. Furthermore, the risk of developing pancreatic cancer was found to be 2 times higher in ever smokers as compared to non-smokers. (13, 23, 24) In 2011, a study conducted in the UK showed that cigarette consumption was linked to 26% and 31%

increased risk of pancreatic cancer in men and women. (25)

It is important to understand the role of smoking and cigarette consumption in the development of pancreatic cancer; therefore, we are focused on estimating the strength of association between smoking and pancreatic cancer by estimating HRs using cox proportional hazard model.

Chapter 2: Research question and Aims

2.1 Research question

What is the strength of association between cigarette smoking and the risk of pancreatic cancer in a cohort of Norwegian women?

2.2 Aims

The aim of my thesis is to use the Norwegian Women and Cancer Study (NOWAC) data to examine the association between different measures of smoking and risk of pancreatic cancer.

Chapter 3: Background and Theory

3.1 Pancreatic cancer – Development, Types, Incidence, Risk factors and Survival rates

3.1.1 Anatomy and histology of pancreas

Pancreas is a unique organ due to its dual functionality i.e., it works both as an endocrine and an exocrine organ. Located in the retroperitoneal cavity of the upper abdomen, the head of the pancreas leans on the duodenum and the tail touches the spleen. (26)

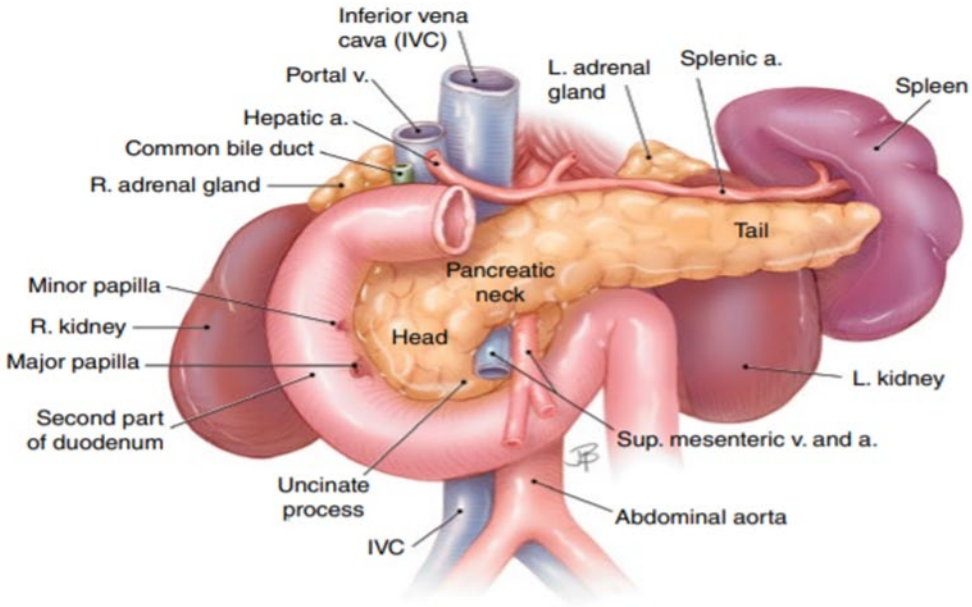

Figure 1 - The two dimensional representation of pancreas in relation to the surrounding organs and circulatory vessels. (26)

Microscopic imaging of pancreas shows the presence of two parenchymal cells. The lighter stained parenchymal cells represent endocrine tissues or Islets of Langerhans and the darker stained parenchymal cells represent exocrine tissues or acini. Acini or acinar cells are responsible for the production of digestive enzymes, which are transported to the duodenum via ductal cells. The Islets of Langerhans are further divided into α-cells (15-20%), β-cells (65-80%), gamma cells (3-5%), δ -cells (3-10%), and ε-cells (<1%). Different cells of Islets of Langerhans produce different hormones, α-cells produce glucagon, β-cells produce insulin and

amylin, δ-cells produce somatostatin, gamma cells produce Pancreatic Polypeptide (PP) and ε-cells produce ghrelin. (26)

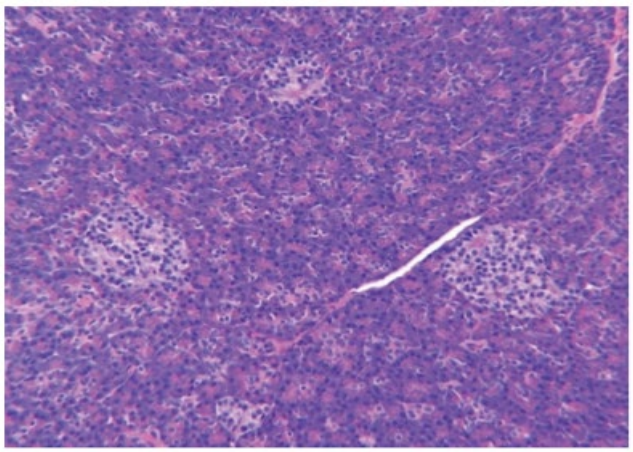

Figure 2 - Image shows four Islet cells surrounded by Acinar cells. Islet cells are brightly stained (H & E staining) as compared to surrounding Acinar cells. (26, 27)

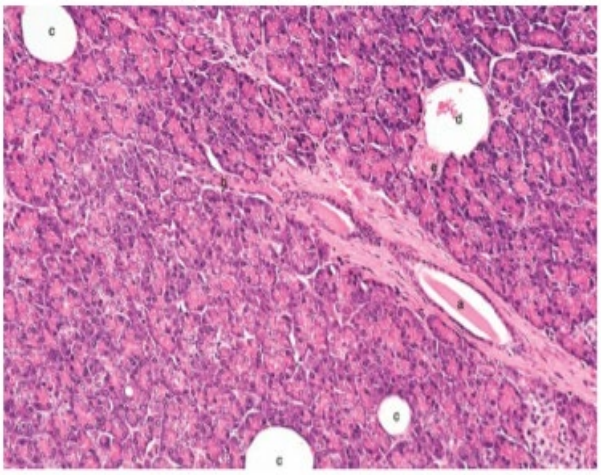

Figure 3 - Image shows acinar cells and acinar tubules and a small Islet in the lower right corner of the image. (26, 27)

3.1.2 Development and disease progression of pancreatic cancer

PDAC occurs because of stepwise mutations in the normal mucosa. The normal mucosa of the ductal epithelium turns into pre-malignant lesion, a precursor to further invasive malignant tumor. Furthermore, accumulation of genetic mutations contributes significantly to the progression and development of pancreatic cancer. The three very well studied premalignant

precursor lesions of PDAC are referred to as Pancreatic Intraepithelial Neoplasia (PanIN), Intraductal Papillary Mucinous Neoplasms (IPMN), and finally Mucinous Cystic Neoplasm (MCN).(28)

PanIN is established and very well-characterized lesion occurring in smaller ducts of the pancreas. It was found that presence of PanINs might result in the development of pancreatic adenocarcinoma in men (1.5%) and women (1.3%) over the course of life. (29)IPMN is less established and occurs in the main pancreatic duct. (16, 30, 31)

The genetic mutation involves inactivation of tumor suppressor genes known as CDKNA2, TP53, and DPC4 along with the expression or activation of oncogene called KRAS2.(32, 33)

3.1.3 Types of pancreatic cancers and ICD codes

The diagnosis of pancreatic cancer is made by taking the multifactorial approach. The type and location of the cells from which the tumor originates, size of the tumor and symptoms such as abdominal pain, back pain and unexplained weight loss are the indicators of type of tumor. Based on the cells the tumor arises from, pancreatic cancers are generally categorized into exocrine and neuroendocrine tumors.

The Pancreatic Ductal Adenocarcinoma or PDAC is the most common type of pancreatic cancer constituting about 90% of all cases of pancreatic cancer. Due to this, PDAC is often generally referred to as pancreatic cancer. PDAC arise from exocrine part of the pancreas. Other type of pancreatic cancers also referred to as Pancreatic Neuroendocrine Tumors or PanNETs arise from endocrine part of the pancreas and are rare, constituting about 1-5% of the total cases of pancreas.(34) Poor prognosis, gradually developing non-specific symptoms such as weight loss, jaundice, back or abdominal pain and fatigue, lack of advanced screening techniques and lack of specific tools to diagnose PDACs in their early stages contributes to high mortality rates of pancreatic cancer. (2, 35)

According to International Classification of Diseases codes, 10th revision, Clinical Modification, ICD-10-CM, pancreatic cancers or malignant neoplasms of pancreas are coded as C25 with child codes for 8 different types of malignant neoplasms of pancreatic cancers given below.

Table 1 - International Classification of Diseases – 10th Revision- Clinical Modification, ICD-10-CM codes for neoplasms of pancreatic cancer.(36)

C25. Malignant neoplasms of pancreas	
C25.0	Head of pancreas
C25.1	Body of pancreas
C25.2	Tail of pancreas
C25.3	Pancreatic duct
C25.4	Endocrine pancreas
C25.7	Other parts of pancreas
C25.8	Overlapping sites of pancreas
C25.9	Unspecified ones

3.1.4 Incidence and mortality rates of pancreatic cancer – Global and Norwegian statistics

Globally in the year 2018, pancreatic cancer was the 12th most leading cause of morbidity and accounted for 458,918 new cases of pancreatic cancer. Mortality due to pancreatic cancer was as high as 4.5% making it the 7th most common cause of death with a staggering high number of deaths (432,242) worldwide.

The incidence and mortality rates of pancreatic cancer are relatively a little higher in men than women. The incidence of pancreatic cancer in males is 243,033 (age standardized risk of 5.5%)

whereas in females the estimated new number of cases of pancreatic cancer is 215,885 (age standardized risk of 4.0%). However, poor survival rate and high mortality rate in men (226,910 deaths or 5.1% ASR) and women (205,332 deaths or 3.8% ASR) contributes significantly to the global burden of disease due to pancreatic cancer.(15)

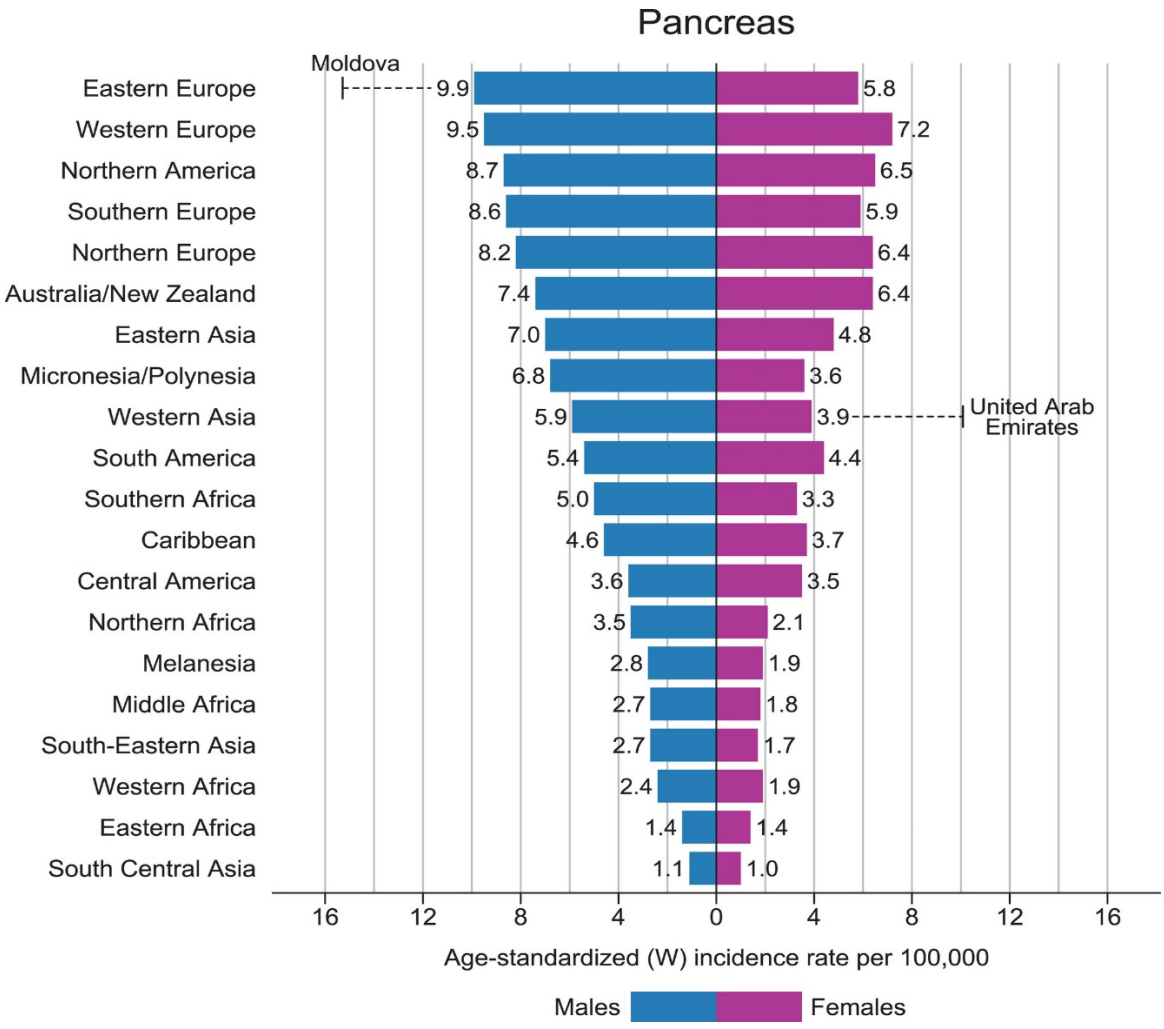

Figure 4 - Bar chart showing region specific incidence rates of pancreatic cancer worldwide by sex. The incidence rates are Age standardized for both men and women. (15)

The figure 4 represents the incidence rate of pancreatic cancer per 100,000 population in descending order for men and in no specific order for women. The incidence was seen to be higher in the regions where most of the high Human Development Index (HDI) countries are situated. On the other hand, currently developing or underdeveloped regions of the world have

relatively lower burden of pancreatic cancer incidences. However, females in all the regions of the world have comparatively lower incidences of pancreatic cancer.

According to the estimated data published by International Agency for Research on Cancer in 2020, North America has the highest rate of pancreatic cancer incidence i.e., 8.0 (Age Standardized Rate per 100,000 world population) followed by Europe (7.8 ASR), Oceania (6.6 ASR), Latin America and Carribean (4.5), Asia (4.0) and Africa (2.3) for both sexes and all ages. On the other hand, Europe ranks higher than North America for the incidence of pancreatic cancer among males.

Table 2 - Table showing estimated Incidence and Mortality rates for pancreatic cancer in 2020 in different continents of the world, both sexes, all ages. Source. IARC, Global Cancer Observatory. Accessed from https://gco.iarc.fr/ on 17th May, 2021.

Continents	Number (Incidence)	ASR per 100,000	Number (Mortality)	ASR per 100,000
Asia	233,701	4.0	224,034	3.8
Europe (Norway)	140,116 (924)	7.8 (7.5)	132,134 (868)	7.2 (6.9)
North America	62,643	8.0	53,277	6.5
Latin America and Caribbean	37,352	4.5	36,030	4.3
Africa	17,070	2.3	16,549	2.3
Oceania	4,891	6.6	3,979	5.2

Pancreatic cancer is relatively rare in Norway; however, mortality rates are adding to the already high burden of disease. According to the statistics obtained from Cancer Registry of Norway (2019), Norwegian females suffered from 388 cases of pancreatic cancer as compared

to men who suffered from 496 cases of pancreatic cancer. The incidence was significantly higher in the older age groups particularly 70-79 for both men (193) and women (137).(37)

The high rate of cancer mortality due to pancreatic cancer can be attributed to its poor survival rate, low response rate to the chemotherapy and radiotherapy, unfavorable anatomical position to perform a tissue biopsy, rapid and aggressive pathological course and low success rates when it comes to the treatment. (3)

3.1.5 Risk factors leading to pancreatic cancer

3.1.5.1 Tobacco smoking

Cigarette smoking is an established risk factor for pancreatic cancer. Numerous single studies and combined studies (meta-analysis, large cohorts, etc.) have provided sufficient evidence to consider the strong direct association between cigarette smoking and the risk of pancreatic cancer. Moreover, these studies also concluded that there is a strong dose-response relationship between the two. (4, 38-40)

A meta-analysis based on 82 studies was conducted in 2008. It involved 42 case control, 5 nested case control and 35 cohort studies published between 1950 and 2007. The aim of the analysis was to estimate the strength of association between cigarette smoking and risk of pancreatic cancer. It was concluded that the risk of pancreatic cancer was 75% higher in smokers as compared to non-smokers. The risk continued to be higher up to 10 years of cessation of smoking. However, this direct relationship was found to be dose-response in relationship i.e., greater the number and duration of cigarettes smoked, higher will be the risk of pancreatic cancer. (41)

Similar results were observed in another study where data pooled from 8 cohorts included in international Pancreatic Cancer Cohort consortium (1481 cases and 1539 control) was analyzed. The primary aim of this pooled analysis was to estimate the effects of intensity,

duration, dose and cessation of smoking with respect to increased risk of pancreatic cancer. The results were consistent with the meta-analysis(39) published earlier i.e.; smokers were 80% more likely to develop pancreatic cancer than non-smokers. Risk of developing pancreatic cancer diminishes after 10-15 years of smoking with a strong dose-response relationship between the two.(40) Another study analyzed 12 case-controls studies included in Pancreatic cancer Case-Control Consortium (PanC4). The results were consistent with other studies and showed that smokers were at two-fold higher risk of developing pancreatic cancer as compared to non-smokers. Moreover, the risk of cigarette smoking and pancreatic cancer was dose-response based.(4)

Furthermore, cigarette smoking was also found to be associated with poor survival rates in pancreatic cancer. A prospective cohort study consisting of concluded that current cigarette smoking reduces 5-year survival rate and increases the risk of death by 40%.(42) Similar results were reported in an Italian study(24) and a Korean study(43) i.e., 42% and 20% increased risk of death in current smokers.

3.1.5.2 BMI and physical activity

Cancer is a multifactorial disease with numerous clinical and genetic risk factors. Among the clinical risk factors of certain cancers such as endometrial cancer and breast cancer, obesity might play a significant role. Clinical findings suggest that high BMI and obesity has a significant role to play in the pathogenesis of pancreatic cancer and poor survival rates. (44-48)

A meta-analysis consisting of 9504 cases from 23 studies on BMI and risk of pancreatic cancer found that high BMI, higher waist circumference and increase in waist-to-hip ratio were associated with increase in the risk of pancreatic cancer by 10%, 11% and 19% respectively. (47)

Another meta-analysis consisting of 6391 cases from 14 studies published between 1966 and 2003 estimated the strength of association between obesity and risk of pancreatic cancer. The results showed that there is a weak association between the two but with the possibility of being a confounder. (49)

A case-control study consisting of 841 cases conducted between 2004 and 2008 studied the relationship between the risk of pancreatic cancer and obesity. The results were consistent with other studies. Individuals with BMI in overweight range (25-29.9) or obese range (greater than 30) were at an increased risk of developing pancreatic cancer. Similarly, the age of onset was also reduced for these people by 2 to 6 years. Lastly, being overweight or obese between the ages of 30 and 79 years showed poor survival rates. (45)

The evidence suggestive of any kind of relationship between physical activity and risk of pancreatic cancer is very limited. (50) Findings from some of the published studies are inconsistent and cannot be used to draw a conclusion. (51) However, lower physical activity is often associated with high abdominal fats, high sexual hormones, decline in immune function and inflammation which might contribute to the pathology of pancreatic and other cancers. (52)

3.1.5.3 Alcohol consumption

The association between alcohol consumption and the risk of pancreatic cancer is not very well understood. Findings from some studies suggest no relationship between the two (53, 54), some studies concluded that there's a weak association between the two(55), while only a few studies and meta-analysis (56)suggest that there is some association of clinical significance between alcohol consumption and pancreatic cancer.

A case-control study conducted in Italy consisting of 652 cases, concluded that there was a significantly increased risk (4.3 folds) of pancreatic cancer within heavy drinkers (greater than

21 drinks/week). (57) Similarly, a pooled analysis conducted on 5585 cases from 10 studies concluded that heavy drinking habits (greater than 9 drinks/ day) were associated with increased risk of pancreatic cancer. (58) A metanalysis consisting of 2524 cases of pancreatic cancer showed that there is a 5% increase in the risk of pancreatic cancer with the consumption of 50grams of alcohol per day and the risk might increase to 18% with the consumption of 100 grams/day. However, since the number of heavy drinkers were small, the results were statistically significant.(56) In another pooled analysis of 14 studies, an increase of 22% was estimated in the risk of pancreatic cancer associated with the consumption of 30 gram or more/day of alcohol. (55) all these studies are suggestive of a significant dose-relationship between the two, however, more in-depth evidence is needed to confirm it.

An important factor to consider is that heavy alcohol drinking is often associated with tobacco smoking(59) and higher incidences of pancreatitis(60, 61), established risk factors for pancreatic cancer. These risk factors might modify the effects of alcohol consumption on the risk of pancreatic cancer. Therefore, the strength of association of association between the two is not very well understood till date.

3.1.5.4 Diabetes

The International Diabetes Federation (IDF) reported that the cases of diabetes increased from 285 million in 2009 to 425 million in 2017. Being one of the top 10 causes of deaths worldwide, diabetes was responsible for 4 million deaths globally in the year 2017. (62) Diabetes plays an important in the development of certain diseases such as nerve damage, stroke, kidney diseases, heart diseases, certain cancers and hypertension.(62)

The relationship between diabetes type 2 and pancreatic risk is multidimensional complex. Researchers have found an association between long standing diabetes type 2 and pancreatic

cancer. (63, 64) However, pancreatic ductal adenocarcinoma (PDAC) was also found to be a risk factor for diabetes. (65)

Studies have found that in 85% of the diabetic patients, diabetes was diagnosed either 2 years prior to the diagnosis of pancreatic cancer or during their cancer treatments. This type of diabetes is often referred to as New Onset Diabetes or NOD. Two meta-analysis consisting of all the major studies estimated the association between diabetes and risk of pancreatic cancer. Findings were consistent and suggestive of clinically significant association between the two. (64, 66) In another pooled analysis, consisting of 2192 cases from 3 large studies, presence of diabetes was associated with an increase in the risk of pancreatic cancer by 1.8 folds. (67) However, further studies are needed to better understand the direction of relationship between the two. So far, from what we know already, diabetes is modifiable and many cases of pancreatic cancer can be prevented by changing our diets and lifestyle.

3.1.5.5 Dietary factors

Researchers have found that only 5-10% cases of pancreatic cancer are hereditary and the remaining 90-95% of the cases are attributable to environmental risk factors. Furthermore, among these environmental risk factors, poor dietary patterns might contribute to 50% of the cases of pancreatic cancer.(68-70)

Among different dietary patterns, fruits, vegetables and whole grains were found to have inverse association with the risk of pancreatic cancer.(71-73) Food rich in fats and high fructose contents were found to have positive association. (74)Furthermore, increased consumption of red, ultra-processed meats(75, 76) and heavy alcohol consumption(1) were also linked positively with the risk of pancreatic cancer. On the other hand, dairy products (77) and total carbohydrate intake (74)was shown to have no association.

3.1.5.6 Age

Aging is an inevitable natural process that occurs with time and results in loss of organ function gradually. Aging has a significant role to play in the pathogenesis of cancer and other diseases owing to the fact that aging results in decline in cell and organ function. Furthermore, ever increasing life expectancies are also contributing to the worst effects of aging and cancer. (78)However, one thing that makes aging and cancer comparable is the fact that both are caused by the gradual and time-dependent accumulation of cell and cellular function damage.

Moreover, aging and cancer both can be characterized by genomic instabilities, epigenetic alterations, problems with nutrient sensing in the cells and also telomere attrition. (79) Recently, a study was conducted to estimate the association between aging or age acceleration and risk of cancer. It was found that epigenetic aging might increase the risk of cancer by 4-9%, similarly, the risk of death by cancer was also increased by 2-6% for each 5 years of age acceleration.(80)

3.1.5.7 Pancreatitis

Pancreatitis, inflammation of the pancreas, is considered to be an established risk factor for pancreatic cancer. Recently, multiple studies have provided consistent results of positive association between the two. (81, 82) A cohort consisting of 1656 patients were enrolled in a study to estimate the association between pancreatitis and risk of pancreatic cancer. It was estimated that the risk increases significantly in pancreatitis patients as compared to patients with no pancreatitis.(83) In another study, the presence of chronic pancreatitis was associated with 8-fold increase in the risk of pancreatic cancer after 5-years of diagnosis. (84) Although, an association between the two is very well-established, however, the direction of association might not be fully explored.

3.1.5.8 Hereditary factors

Only 5-10% of pancreatic cancer cases are estimated to have a hereditary cause behind them. To elaborate further, familial cancer syndromes like Peutz-Jeghers, Hereditary Breast Ovarian Cancer (HBOC), and Lynch syndromes have a significant positive association with the risk of pancreatic cancer. Peutz-Jeghers syndrome, caused by mutations in tumor suppressor genes known as STK11or LKB1 results in a 35% increased risk of pancreatic cancer. (85)Lynch syndrome increases the risk by 8.6 times as compared to people with no history of Lynch syndrome.(86) Similarly, HBOC caused by mutations in BRCA1 and BRCA2, increases the risk of pancreatic cancer markedly. (87) Similarly, mutations in CDKN2A, ATM, MLH1, MSH2,and MSH6 germlines have also been associated with an increased risk of pancreatic cancer.(85, 88)

3.1.6 Five-year survival rate of pancreatic cancer

The ability to survive past 5 years after the initial diagnosis or the start of the treatment in diseases like cancer is referred to as 5-year survival rate. 5-year survival rate in cancer infers that the diagnostic tools and techniques and treatment strategies are improving or mortality trends are falling. The 5-year survival rate in pancreatic cancer ranges between 2-9%. However, for advanced and metastasized tumors of stage III and IV the survival rates falls down between 1-3%. (89, 90)

The 5-year survival rate in pancreatic cancer depends on multiple factors such as gender and age of the patient, quality of treatment and follow ups, lifestyle, diet, co-morbidities, and most importantly the stage of tumor. However, the onset of symptoms of pancreatic cancer is often very late and unspecific in nature. Clinical presentations, stage and location of the tumor are decisive factors in whether or not the patient can undergo surgical removal of the tumor tissues.(91) It is estimated that only 10% of the patients can undergo surgery at the time of

diagnosis, 30% of the patients have locally advanced stage tumors and cannot undergo surgical resection, and 60% of the patients present with advanced metastatic pancreatic cancers.(92, 93) 5-year survival rate after successful surgical removal is usually 27%, for locally advanced disease survival is estimated to be 6-11 months and for metastatic disease, the survival is even lower i.e., 2-6 months(16)

3.2 Cigarette smoking and the risk of pancreatic cancer

3.2.1 Trends in cigarette smoking – Globally and in Norway

Tobacco smoking is one of the leading factors that result in higher mortality rates due to diseases like lung cancer, pancreatic cancer, heart diseases and respiratory diseases as well. To put this into perspective, it is estimated that 100 million people died due to tobacco smoking alone in the 21st Century and this number might increase to 1 billion deaths in the 22nd century. In the year 2017 alone, 8 million people (every 1 in 6 people) died prematurely due to smoking, 7 million people (1 in every 7 people) died due to active smoking and 1.2 million people died due to passive or second-hand smoke.

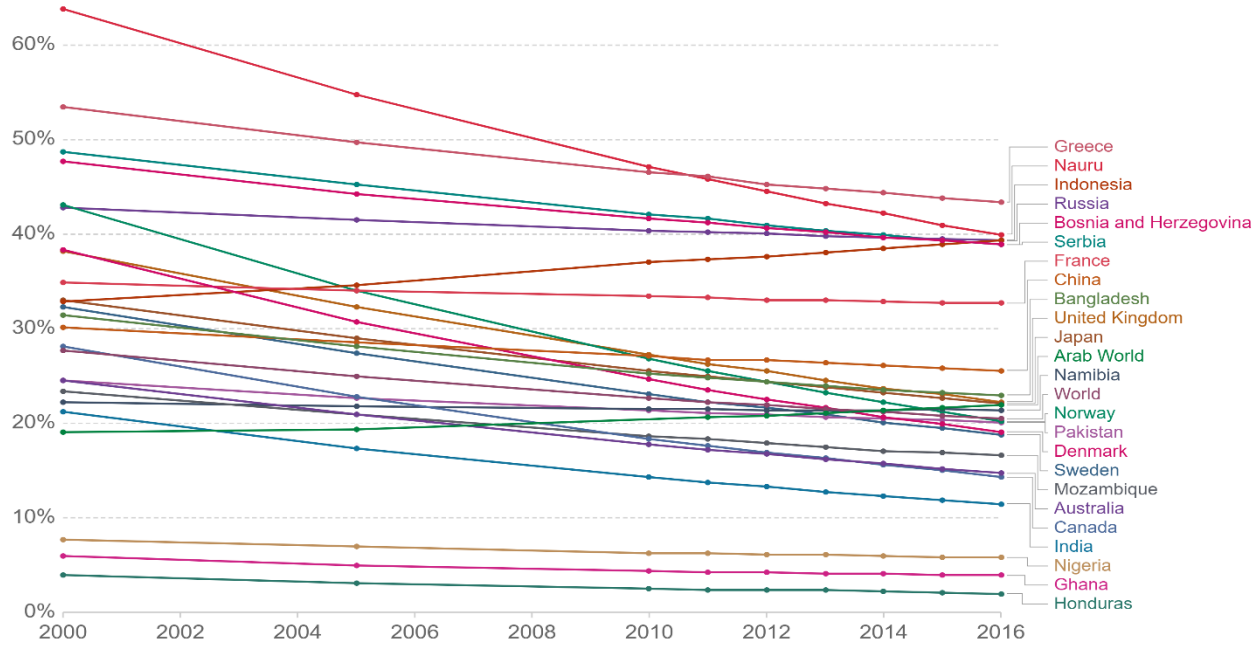

Figure 5 - Prevalence of smoking in adults aged 15 or older from the year 2000-2016 in different countries of the world. Source: Our World in Data. Accessed from: https://ourworldindata.org/smoking. Accessed on 19th May, 2021.

The overall prevalence of smoking in the world was estimated to be 20.48%. Highest prevalence of smokers was found in Pacific islands (Nauru 40%, Kiribati 47%, and Timor 43%). Two countries from the Balkans region (Greece 43% and Montenegro 46%) along with Indonesia, Russia, Bosnia, Serbia and Chile top the list of countries with highest prevalence of smokers. Some lower income countries like Ghana, Nigeria, Ethiopia and Honduras contribute very little to the overall prevalence of smokers in the world. However, countries like Norway (22.2%), Denmark (19.10%), Sweden (18.80%) and Pakistan (20.10%) also has a relatively higher prevalence of smokers.

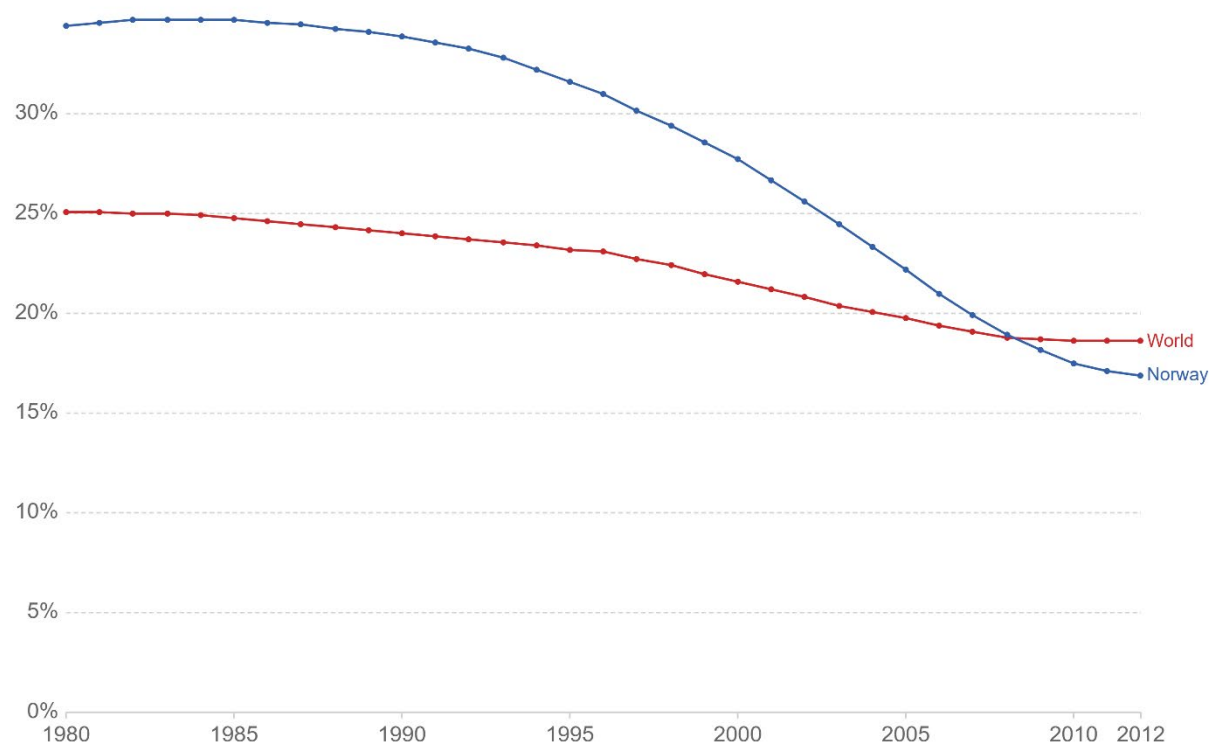

Figure 6 - Prevalence of daily smokers, both sexes, all ages in Norway and worldwide from the year 1980 to 2012. Source: Institute for Health Metrics and Evaluation (IHME). Accessed from: http://ghdx.healthdata.org/record/ihme-data/global-smoking-prevalence-and-cigarette-consumption-1980-2012.

In the late 20th century, almost all the rich countries of the world had relatively higher prevalence of daily smokers. The prevalence of daily smokers in Norway was as high as 34.40% in Norway relative to the global prevalence of 25.10%. However, the number of daily smokers started dropping gradually and in the year 2016, the estimated prevalence of daily smokers in Norway dropped down to 16.90% relative to the global prevalence of 18.60%. (94)

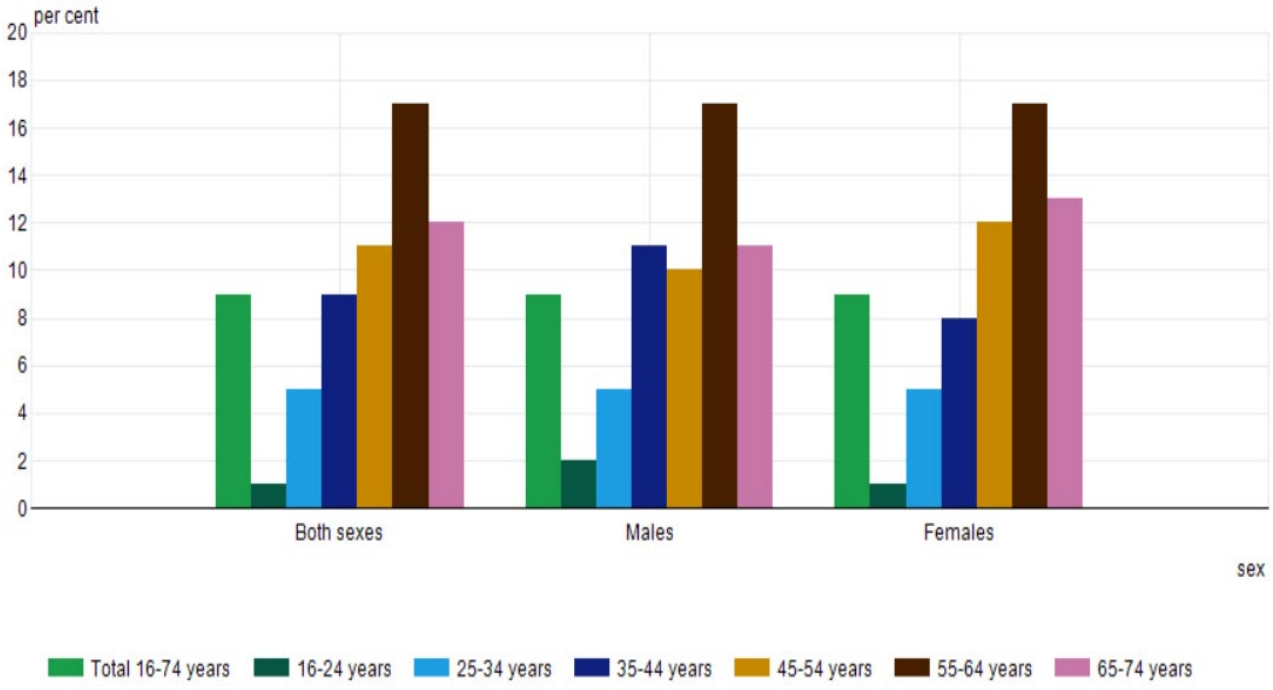

Figure 7 - Bar chart showing percentage of daily smokers in Norway for the year 2020 distributed by different age groups. Source: IHME and Statistics Norway. Accessed from: https://www.ssb.no/en/statbank/table/05307/. Accessed on: 19th May. 2021.

In the year 2020, it was estimated that the total percentage of daily smokers in Norway for both sexes remained almost the same. The highest percentage of daily smokers was in the age group of 55-64 years for both males and females and lowest prevalence was estimated for the age group of 16-24 years for both. Males have a relatively higher prevalence of daily smokers for the age group of 35-44years as compared to females. On the other hand, for the age groups of 45-54 years and 65-74 years, females have comparatively higher prevalence of daily smokers than men.

3.2.2 How cigarette smoking might increase the risk of pancreatic cancer – physiological and pathological perspective?

Innumerable studies have found a positive and dose-dependent association between smoking and the risk of pancreatic cancer. However, the pathogenesis of pancreatic cancer due to cigarette smoking is yet to be understood and studied in depth. (95)

Out of 7000 compounds present in tobacco smoke, 60 are known to be carcinogenic in nature. (96)Most of the carcinogenic compounds come from the metabolism of nicotine and are known as nitrosamines such as NNAL, NNK, and NNN. (97) Nicotine and some of its metabolites are absorbed from lung into the bloodstream. Researchers have found 7 folds higher quantities of nicotine and its metabolite to be present in pancreatic juices of smokers as compared to non-smokers. (98) Nicotine and NNK are known to cause the mutation of TTN gene, it also activates the COX2 pathway via β- adrenergic receptors leading to increase in the growth of pancreatic cancer cells. (99, 100)

Some studies conducted on animal models suggest that prolonged exposure to tobacco smoke might result in inflammation and fibrosis in pancreas.(101) Inflammation and fibrosis are prerequisites of pancreatitis, a known clinical risk factor for pancreatic cancer. (102) In another study, treatment with NNK resulted in increased infiltration of immune cells (macrophages) into the neoplastic lesions. The infiltration was primarily accelerated by the presence of inflammatory mediators (MIP-1α, IL-1β, and TGF-β)(101, 103)

3.2.3 How strong is the evidence for the association of cigarette smoking and pancreatic cancer?

Cigarette smoking is an important modifiable risk factor of pancreatic cancer. The results from literature published till date are consistent and support the fact that cigarette smoking have a strong association with an increased risk of pancreatic cancer. Moreover, the relationship between the two is dose-response based. The risk of developing pancreatic cancer increases with the numbers of cigarette smoked, duration of smoking and intensity of smoking. However, the risk of pancreatic cancer was seen to diminish after 10-15 years of smoking cessation with similar risks for never smokers and >20 years of smoking cessation. (4, 39, 40, 42, 104)

Another analysis based on 30 cohorts consisting of 420,310 individual Asian participants and

99,333 participants from Australia and New Zealand found similar results. (7)Evidence from a meta-analysis consisting of 42 observational studies(8), and two Japanese studies is again consistent with the findings of the previously published literature(9, 10).

Limited number of researches also studied the effect of current cigarette smoking at the time of diagnosis on 5-year survival rates. The results showed that the risk of death was higher in current smokers. However, further research and more detailed analysis are still needed to solidify the findings of these researches. (24, 42, 43)

To conclude, the evidence suggesting that there is dose-response relationship between cigarette smoking and the risk of pancreatic cancer is ‘strong’ and modifiable. A large number of deaths due to pancreatic cancer are often attributable to tobacco smoking and contributes to the global burden of disease.

Chapter 4: Material and methods

4.1 Study design

The NOWAC study, started enrollment in 1991. It is a representative national cohort with a prospective design.(105) We used data collected in the NOWAC study to examine the association between smoking and pancreatic cancer.

4.2 NOWAC study

The population-based national cohort study was initiated with a primary aim of investigating the association between breast cancer and oral contraceptive use. To briefly summarize, random sample of women was selected through the National Population Register of Norway using an 11-digit personal number which is assigned to every citizen of Norway. These women were then invited to respond to a questionnaire and via three recruitment phases (1991, 1996, and 2003), more than 172,000 women participated in the study. The total response rate from the women was 52.7%

The questionnaires elicited information on the use of oral contraceptives, hormone therapies, reproductive history, smoking habits, dietary habits, drinking, physical activity, socioeconomic status, etc.

NOWAC study was approved by the Norwegian Data Inspectorate and Regional Committee for Medical Research Ethics.(105)

4.3 Study population

Women who responded to the first, second and third recruitment mailings (1991,1996, and 2003) were included. The total number of included women was 172,472. We excluded the number of women with prevalent cancer cases (2794). We also excluded women who died (2) or emigrated (4) before the start of follow-up. Furthermore, we also excluded women who had

missing information on important variables such as smoking status (2294), weight and height (3886), alcohol drinking (7260), and education (6989) were also excluded. No prevalent pancreatic cancer cases were observed before the start of the follow-up, therefore, altogether our final cohort sample had 149,243 women left.

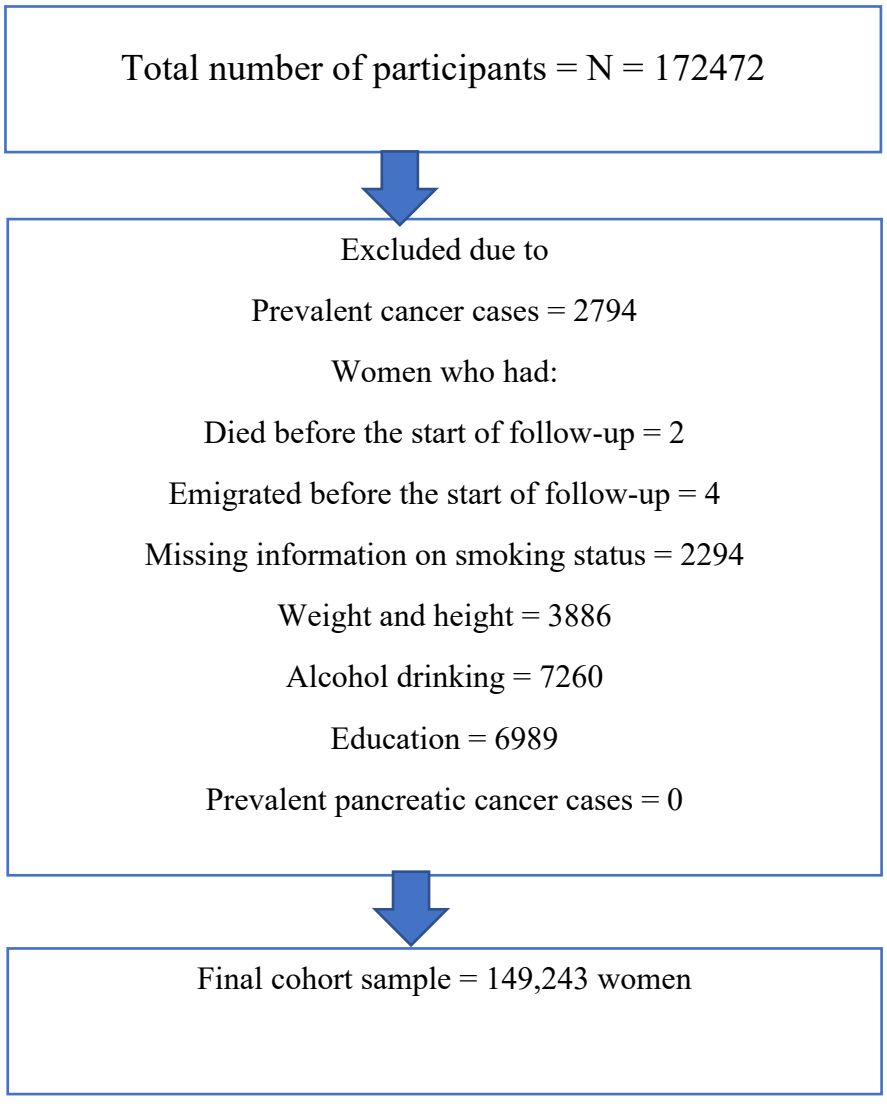

Figure 8 - Flowchart representing the exclusion criteria for the selection of final cohort sample.

4.4 Collection of data for exposure variables and outcome variable

Women who responded to questionnaires reported about ever smoking, average cigarettes smoked per day, and whether they currently smoke daily. Using this reported information, we calculated pack-years of smoking. (Described in detail in section 4.5.3. Different measures of smoking variable).

The Cancer Registry of Norway and Norwegian Central Population Register was used to estimate the outcome i.e., pancreatic cancer and events such as death or emigration. The unique 11-digit identification number was used to identify all cancer cases and the women who died or emigrated before or during the follow-up. The individual follow-up time was calculated for each participant from the start of the follow-up to the time when cancer, death or emigration occurred. The outcome i.e., pancreatic cancer was identified from the Cancer Registry of Norway by its unique International classification of Diseases (ICD) code 10th Revision CM. The code for malignant pancreatic cancer neoplasms was C25. (Table 1)

4.5 Statistical analysis

The IBM SPSS Statistics Version 26 was used to run all the statistical analyses.

4.5.1 Descriptive statistical analysis of selected characteristics

In order to estimate the distribution of selected characteristics of the participants among different statuses of smoking (never, former and current), we calculated the numbers (percentages) or the means (standard deviations) for each variable and the results were tabulated in the table 3 below.

4.5.2 Cox Proportional Hazard Model

A Cox proportional Hazard analysis was run in order to examine the strength of association between different measures of our exposure variable, smoking, and the risk of pancreatic cancer. With total number of follow-up years used as an underlying time scale and pancreatic

cancer (=1) used as a status, both Age-adjusted and Multivariate Adjusted Hazard Ratios were estimated using 95% Confidence Interval (CI).

4.5.3 Different measures of exposure variable smoking

At the time of enrollment, women reported whether they ever smoked, average number of cigarettes smoked daily, and whether they smoke currently. Using this information, we calculated, age at which they initiated smoking, total years smoked, pack-years of smoking. We calculated pack-years of smoking as the number of daily cigarettes smoked on average divided by 20, multiplied by the total years of smoking. All of these exposures were divided into categories: for age at smoking initiation (<15 years, 15-19 years, 20-24 years, and >25 years), total years smoked (0-10 years, 11-20 years, 21-30 years, >30 years), and number of pack-years of smoking (≤5, 6-10, 11-15, >15). Never smokers were used as the reference category throughout the study.

4.5.4 Covariates

The multivariable analysis included covariates which could potentially confound the association because they changed the HRs by 5% between cigarette smoking and risk of pancreatic cancer. The different variables included in the final multivariate model were; (1) Years of education (<10, 10-12, 13-16, and ≥17) because increasing years of education were also found to have inverse effect on the exposure variable smoking even after the adjustment with different socio-economic and geographical variables. (106), (2) Body Mass Index (<20, 20-24.9, 25-29.9, and ≥30) because higher BMI levels were found to be associated with increased risk of development of pancreatic cancer. Higher BMIs, waist-to-hip ratios and waist circumference were also found to play a significant role in the pathogenesis of pancreatic cancer. (44, 47, 48), (3) physical activity (sedentary, light, moderate and heavy) and (4) age at enrollment (continuous) because time dependent and gradual decline in cell function,

accumulation of the cell damage over the years during aging or age acceleration might also contribute to increased risk of developing certain cancers.(79, 80). (Table 3)

Chapter 5: Results

Out of 149,243 women, 34.3% (51233) reported to be never, 34.8% (51933) former, and 30.9% (46077) current smokers. The mean age of never smokers was 49.7 (±s.d = 8.6), for former smokers 49.8 (±s.d = 8.1) and for current smokers 47.2 (±s.d = 8.2). (Table 3).

Table 3 shows that the proportion of pancreatic cancer cases were higher in current smokers as compared to never smokers. Similarly, higher education i.e., greater than 13 years of education was also less common in current smokers. Table 4 also represents the fact that number of alcohol drinkers was higher in current smokers with average consumption of 4.45grams of alcohol/day.

Table 3 - Selected characteristics of the women by smoking status at enrollment, Norwegian Women and Cancer Study (NOWAC), 1991-2019, (N=149,243)

Characteristics	**Never smokers**		**Former smoker**		**Current smokers**	
	N (%)	Mean (s.d.)	N (%)	Mean (s.d.)	N (%)	Mean (s.d.)
Women	51233(34.3)		51933(34.8)		46077(30.9)	
Age at enrollment		49.7(8.6)		49.8(8.1)		47.2(8.2)
Person years	1,042,734(34.8)		996,665(33.3)		957,843(31.9)	
Follow-up years		20.4(6.4)		19.2(6.5)		20.8(6.7)
Pancreatic cancer cases	134(0.26)		135(0.25)		243(0.53)	
Age at diagnosis		67.6(8.9)		64.7(7.8)		64.0(8.2)
Higher education ≥13 years	26,426(51.6)		23,700(45.6)		14,421(31.3)	
Non-drinkers	9525(18.6)		2828(5.5)		2288(4.9)	
Alcohol consumption		2.7(4.3)		4.47(5.9)		4.45(7.2)
BMI		24.4(3.9)		24.6(3.9)		23.6(3.8)
Physical activity score		5.7(1.8)		5.8(1.9)		5.6(1.9)

Table 4 represents the selected characteristics of the total participants (149,243) based on their pancreatic cancer status. The results show that percentage of ever smokers (73.8%) was higher in the participants diagnosed with pancreatic cancer as compared to never smokers (26%). The mean age of the participants at the time of cancer diagnosis was 65.1 years. Similarly, participants with less than 10 years of education had a higher percentage (49.8%) of pancreatic cancer cases as compared to those who had 13-16 years of education (21%) and greater than 17 years of education (8.9%). Independent samples t-test showed that there were no clinically significant differences between the BMIs (p-value 0.908) and physical activity (p-value 0.284). Scores of the participants in two groups.

Table 4 - Selected characteristics of the participants at enrolment in the NOWAC study participants (149,243) by pancreatic cancer status

Characteristics	Pancreatic cancer diagnosed	Pancreatic cancer not diagnosed	p-values[a]
Women(N)	512	148731	
Age at enrollment-Mean(s.d.)	51.2(8.82)	48.9(8.4)	<0.001
Follow-up years-Mean(s.d.)	13.9(7.0)	20.1(6.5)	<0.001
Age at diagnosis-Mean(s.d.)	65.1(8.4)	-	
Smoking status (%)			<0.001
Never	26	34.3	
Ever	73.8	65.6	
Years of education (%)			<0.01
<10	49.8	34.8	
10-12	20.3	22	
13-16	21	28	
≥17	8.9	15	
BMI-Mean(s.d.)	24.6(3.9)	24.2(3.9)	0.908
Physical activity score	5.55	5.71	0.284
a – p-values were estimates using independent samples t-test			

Table 5 shows that for both age-adjusted and multivariate adjusted analysis, hazard ratios for pancreatic cancer in former smokers and current smokers were found to be higher than the reference category. Former smokers had an overall 10% (HR = 1.10; 95% CI = 0.85-1.42) statistically non-significant increased risk of pancreatic cancer, however, current smokers had an overall 2-fold (HR = 2.39; 95% CI = 1.90-3.02) significant increased risk of pancreatic cancer, compared with never smokers. Similarly, ever smokers had an overall 66% significantly increased risk of pancreatic cancer (HR= 1.66; CI = 1.34-2.06) as compared to never smokers.

Table 5 also shows that higher age at the time of smoking initiation (>25 years) was associated with 72% increased risk of pancreatic cancer i.e. (HR = 1.72; CI = 1.11-2.67). as compared to the reference. Moreover, increasing number of cigarettes smoked per day were also associated with statistically significant increasing risk of pancreatic cancer. An average 6-10 cigarettes smoked per day were associated with 59% increased risk of pancreatic cancer i.e (HR = 1.59; CI = 1.22-2.08). An average of 11-15 cigarettes smoked per day were associated with 61% increased risk of pancreatic cancer i.e. (HR = 1.61; CI = 1.22-2.12). Similarly, more than 15 cigarettes smoked per day were associated with 77% increased risk of pancreatic cancer i.e. (HR = 1.77; CI = 1.26-2.48). All these results were statistically significant.

Similarly, increasing number of years of smoking were also associated with increasing risk of pancreatic cancer, strengthening the hypothesis of dose-response relationship between smoking as an exposure and pancreatic cancer as an outcome. Smoking between 21 to 30 years and more than 30 years significantly increases the risk of pancreatic cancer by 92% (HR = 1.92; CI = 1.46-2.54) and 89% (HR = 1.89; CI = 1.44-2.48), respectively. This association is suggestive of dose-response relationship between the exposure and the outcome.

Table 5 - Age-adjusted- and Multivariate-a adjusted Hazard Ratio (HR) estimates for pancreatic cancer with 95% confidence intervals (CIs) for different measures of smoking exposures, Norwegian Women and Cancer Study, 1991–2019

Smoking exposures	Cases (%)	HR 95% CI (age adjusted)	HR 95% CI – multivariate adjusted) [a]
Smoking status			
Never smokers[b]	134(26.1)	1.0 (Ref)	1.0 (Ref)
Former smokers	135(26.3)	1.13(0.89-1.44)	1.10(0.85-1.42)
Current smokers	243(47.4)	2.44(1.97-3.02)	2.39(1.90-3.02)
Ever Smokers	378(73.8)	1.71(1.41-2.09)	1.66(1.34-2.06)
Age for smoking initiation			
Never smokers[b]	134(26.1)	1.0 (Ref)	1.0 (Ref)
15-19 years	191(510)	1.28(1.03-1.59)	1.39(1.11-1.76)
20-24 years	105(28.1)	1.81(1.40-2.34)	1.93(1.47-2.53)
>25 years	32(8.6)	1.68(1.14-2.47)	1.72(1.11-2.67)
		p-trend[d] - <0.001	p-trend[d] - <0.001
Cigarettes per day			
Never smokers[b]	134(26.1)	1.0 (Ref)	1.0 (Ref)
6-10	90(29.3)	1.46(1.14-1.87)	1.59(1.22-2.08)
11-15	49(15.9)	1.44(1.11-1.87)	1.61(1.22-2.12)
>15	55(17.9)	1.65(1.19-2.28)	1.77(1.26-2.48)
		p-trend[d] - 0.005	p-trend[d] – 0.001
Pack years of smoking[c]			
Never smokers[b]	134(26.1)	1.0 (Ref)	1.0 (Ref)
6-10	56(18.2)	1.55(1.15-2.09)	1.55(1.12-2.15)
11-15	24(7.8)	1.60(1.20-2.14)	1.86(1.37-2.52)
>15	73(23.7)	1.66(1.29-2.14)	1.87(1.43-2.43)
		p-trend[d] - <0.001	p-trend[d] - <0.001
Years for smoking			
Never smokers[b]	134(26.1)	1.0 (Ref)	1.0 (Ref)
11-20	75(20.3)	1.25(0.93-1.61)	1.23(0.89-1.68)
21-30	100(28.1)	1.69(1.30-2.19)	1.92(1.46-2.54)
>30	110(29.8)	1.65(1.28-2.14)	1.89(1.44-2.48)
		p-trend[d] - <0.001	p-trend[d] - <0.001
a – adjusted for age at enrollment, education, BMI and physical activity			
b – never smokers was used as the reference group			
c – number of cigarettes smoked per day divided by 20, multiplied by total years smoked			
d- Never smokers included in the model			

Chapter 6: Discussion

6.1. Cigarette smoking is associated with an increased risk of pancreatic cancer

To the best of our knowledge, this study is one of very few studies that estimated the strength of association between cigarette smoking and the risk of pancreatic cancer in Norwegian women using nationally representative prospective cohort data (NOWAC). (22)

The findings of this study nullify the hypothesis of no association between the exposure (i.e., cigarette smoking) and outcome (i.e., pancreatic cancer). The results show ever smokers had an overall 66% statistically significant increased risk of pancreatic cancer (HR = 1.66; CI = 1.34-2.06) as compared to the never smokers. Furthermore, there is a 10% and 2-fold increase risk of pancreatic cancer in former and current smokers as compared to never smokers, respectively. However, the association between former smokers and never smokers was not statistically significant.

Furthermore, a dose-response relationship was also observed with increasing number of cigarettes smoked per day (>15) and higher number of total smoking years (21-30) and (>30). The risk of pancreatic cancer was 77% in women who smoked more than 15 cigarettes per day. Similarly, the risk was estimated to be 92% and 89% in women who have been smoking for 21-30 years and more than 30 years, respectively. (4, 39, 40) These findings are consistent with previously published literature. (38, 42).

When performing the multivariate analysis, the HRs for different smoking measures and exposure were similar in both, age-adjusted and multivariate-adjusted groups. This is suggestive of the fact that the covariates we included in our analysis have very little effect on the association between cigarette smoking and pancreatic cancer.

6.2. Strengths and limitations

The study under discussion was clearly focused to identify the strength of the association between cigarette smoking and the risk of pancreatic cancer cases using Cox proportional Hazards Model and 95% CI. The main exposure i.e., smoking will be subdivided into categories to estimate the risk of pancreatic cancer (outcome) associated with different levels and status of smoking. The outcome i.e., incident pancreatic cancer is confirmed from the National Cancer Registry so it's well-diagnosed.

The strength of this study is based on following factors: National Prospective Cohort i.e., NOWAC study is representative of Norwegian population, therefore, women participating in the NOWAC study gave a clear estimation of association between smoking and pancreatic cancer cases in Norwegian women. Moreover, given the fact that the sample size was large (N=149243), the follow-up time was also large, and confounders (age, BMI, etc.) were adjusted for, the results obtained from this study can also be applied to the general population. This is another possible strength of this study.

Another factor that might limit the findings of this study is that the number of pancreatic cancers was small in the data set i.e., 512. Smoking is self-reported and might be under or overreported purposefully or by mistake. This might lead to recall bias and misclassification. This is also one of the limitations of the study.

6.3. Implications for Public Health

Pancreatic cancer will continue to add to the global burden of disease due to its poor prognosis and poor 5-year survival rates. Failure to diagnose pancreatic cancer in its early stages, its aggressive nature and lack of responsiveness to the treatment options available makes it a serious threat for public health.

Under these circumstances, where treatment results and survival rate are not very promising, we need to focus on the preventive measures. According to this study, higher dose (>15 cigarettes per day) and more smoking years (>30) of cigarette smoking are associated with higher risks of pancreatic cancer. Therefore, joint efforts focused at reducing the dose and duration of cigarette smoking needs to be implemented.

Chapter 7: Conclusion

The major aim of this thesis was to estimate the strength of association between different measures of cigarette smoking and the risk of pancreatic cancer. The findings of this thesis are in accordance with the previously published studies, showing that ever smokers (former and current) had a statistically significant increased risk of pancreatic cancer (66%) as compared to the never smokers.

Moreover, we observed a dose-response relationship between the exposure and the outcome. Our findings suggest that, higher dose and higher duration of cigarette smoking is associated with increased risk of pancreatic cancer. Our findings are consistent with previously published literature and therefore, in support of a causal association between cigarette smoking and the risk of pancreatic cancer.

Chapter 8: References

1. Wang Y-T, Gou Y-W, Jin W-W, Xiao M, Fang H-YJBc. Association between alcohol intake and the risk of pancreatic cancer: a dose–response meta-analysis of cohort studies. 2016;16(1):1-11.
2. Hidalgo M, Cascinu S, Kleeff J, Labianca R, Löhr JM, Neoptolemos J, et al. Addressing the challenges of pancreatic cancer: Future directions for improving outcomes. Pancreatology. 2015;15(1):8-18.
3. Poruk KE, Firpo MA, Adler DG, Mulvihill SJ. Screening for pancreatic cancer: why, how, and who? Ann Surg. 2013;257(1):17-26.
4. Bosetti C, Lucenteforte E, Silverman DT, Petersen G, Bracci PM, Ji BT, et al. Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4). Annals of Oncology. 2012;23(7):1880-8.
5. Ezzati M, Henley SJ, Lopez AD, Thun MJJIjoc. Role of smoking in global and regional cancer epidemiology: current patterns and data needs. 2005;116(6):963-71.
6. Smoke T, Smoking IJI, Lyon. IARC monographs on the evaluation of carcinogenic risks to humans. 2004:1-1452.
7. Ansary-Moghaddam A, Huxley R, Barzi F, Lawes C, Ohkubo T, Fang X, et al. The Effect of Modifiable Risk Factors on Pancreatic Cancer Mortality in Populations of the Asia-Pacific Region. 2006;15(12):2435-40.
8. Zou L, Zhong R, Shen N, Chen W, Zhu B, Ke J, et al. Non-linear dose–response relationship between cigarette smoking and pancreatic cancer risk: Evidence from a meta-analysis of 42 observational studies. European Journal of Cancer. 2014;50(1):193-203.
9. Matsuo K, Ito H, Wakai K, Nagata C, Mizoue T, Tanaka K, et al. Cigarette smoking and pancreas cancer risk: an evaluation based on a systematic review of epidemiologic evidence in the Japanese population. Japanese journal of clinical oncology. 2011;41(11):1292-302.
10. Katanoda K, Marugame T, Saika K, Satoh H, Tajima K, Suzuki T, et al. Population attributable fraction of mortality associated with tobacco smoking in Japan: a pooled analysis of three large-scale cohort studies. Journal of epidemiology. 2008;18(6):251-64.
11. Midha S, Chawla S, Garg PKJCl. Modifiable and non-modifiable risk factors for pancreatic cancer: A review. 2016;381(1):269-77.
12. Michaud DS, Skinner HG, Wu K, Hu F, Giovannucci E, Willett WC, et al. Dietary patterns and pancreatic cancer risk in men and women. 2005;97(7):518-24.
13. Mizuno S, Nakai Y, Isayama H, Kawahata S, Saito T, Takagi K, et al. Smoking, family history of cancer, and diabetes mellitus are associated with the age of onset of pancreatic cancer in Japanese patients. 2014;43(7):1014-7.
14. Carrato A, Falcone A, Ducreux M, Valle JW, Parnaby A, Djazouli K, et al. A systematic review of the burden of pancreatic cancer in Europe: real-world impact on survival, quality of life and costs. 2015;46(3):201-11.
15. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal AJCacjfc. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. 2018;68(6):394-424.
16. McGuigan A, Kelly P, Turkington RC, Jones C, Coleman HG, McCain RSJWjog. Pancreatic cancer: A review of clinical diagnosis, epidemiology, treatment and outcomes. 2018;24(43):4846.
17. Rawla PJWjoo. Epidemiology of prostate cancer. 2019;10(2):63.
18. Roser HRaM. smoking. 2013.
19. Gram IT, Little MA, Lund E, Braaten TJBjoc. The fraction of breast cancer attributable to smoking: the Norwegian women and cancer study 1991–2012. 2016;115(5):616-23.
20. Gram IT, Braaten T, Adami HO, Lund E, Weiderpass EJIjoc. Cigarette smoking and risk of borderline and invasive epithelial ovarian cancer. 2008;122(3):647-52.
21. Gram IT, Braaten T, Lund E, Le Marchand L, Weiderpass EJCC, Control. Cigarette smoking and risk of colorectal cancer among Norwegian women. 2009;20(6):895-903.

22. Sivertsen MN, Båtstad HS. Cigarette smoking and pancreatic cancer risk in 83 500 Norwegian men and women: UiT Norges arktiske universitet; 2017.
23. Kuzmickiene I, Everatt R, Virviciute D, Tamosiunas A, Radisauskas R, Reklaitiene R, et al. Smoking and other risk factors for pancreatic cancer: a cohort study in men in Lithuania. 2013;37(2):133-9.
24. Pelucchi C, Galeone C, Polesel J, Manzari M, Zucchetto A, Talamini R, et al. Smoking and body mass index and survival in pancreatic cancer patients. 2014;43(1):47-52.
25. Parkin DM, Boyd L, Walker LJBjoc. 16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. 2011;105(2):S77-S81.
26. Longnecker DS, Gorelick F, Thompson EDJTpaitobs, medicine,, surgery. Anatomy, histology, and fine structure of the pancreas. 2018:10-23.
27. Hruban R, Pitman M, Klimstra DJFs, Fascicle. Tumors of the pancreas: AFIP atlas of tumor pathology. 2007;6:191-218.
28. Esposito I, Konukiewitz B, Schlitter AM, Klöppel G. Pathology of pancreatic ductal adenocarcinoma: facts, challenges and future developments. World J Gastroenterol. 2014;20(38):13833-41.
29. Peters MLB, Eckel A, Mueller PP, Tramontano AC, Weaver DT, Lietz A, et al. Progression to pancreatic ductal adenocarcinoma from pancreatic intraepithelial neoplasia: Results of a simulation model. Pancreatology. 2018;18(8):928-34.
30. Hidalgo M. Pancreatic Cancer. 2010;362(17):1605-17.
31. Lensing RJ, Bipat S. Incidences of Pancreatic Malignancy and Mortality in Patients With Untreated Branch-Duct Intraductal Papillary Mucinous Neoplasms Undergoing Surveillance: A Systematic Review. Pancreas. 2017;46(9):1098-110.
32. Vogelstein B, Kinzler KWJNm. Cancer genes and the pathways they control. 2004;10(8):789-99.
33. Feldmann G, Beaty R, Hruban RH, Maitra AJJoh-b-ps. Molecular genetics of pancreatic intraepithelial neoplasia. 2007;14(3):224-32.
34. Jun SY, Hong SM. Nonductal Pancreatic Cancers. Surgical pathology clinics. 2016;9(4):581-93.
35. Rawla P, Sunkara T, Gaduputi V. Epidemiology of Pancreatic Cancer: Global Trends, Etiology and Risk Factors. World J Oncol. 2019;10(1):10-27.
36. Hwang Y-J, Park SM, Ahn S, Lee J-C, Park YS, Kim N. Accuracy of an administrative database for pancreatic cancer by international classification of disease 10(th) codes: A retrospective large-cohort study. World J Gastroenterol. 2019;25(37):5619-29.
37. Kreftregisteret.no. Pancreatic Cancer in Norway https://www.kreftregisteret.no/en/2019 [Available from: https://sb.kreftregisteret.no/insidens/?lang=en.
38. Vrieling A, Bueno-de-Mesquita HB, Boshuizen HC, Michaud DS, Severinsen MT, Overvad K, et al. Cigarette smoking, environmental tobacco smoke exposure and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition. 2010;126(10):2394-403.
39. Iodice S, Gandini S, Maisonneuve P, Lowenfels AB. Tobacco and the risk of pancreatic cancer: a review and meta-analysis. Langenbeck's Archives of Surgery. 2008;393(4):535-45.
40. Lynch SM, Vrieling A, Lubin JH, Kraft P, Mendelsohn JB, Hartge P, et al. Cigarette Smoking and Pancreatic Cancer: A Pooled Analysis From the Pancreatic Cancer Cohort Consortium. American Journal of Epidemiology. 2009;170(4):403-13.
41. Iodice S, Gandini S, Maisonneuve P, Lowenfels ABJLsaos. Tobacco and the risk of pancreatic cancer: a review and meta-analysis. 2008;393(4):535-45.
42. Yuan C, Morales-Oyarvide V, Babic A, Clish CB, Kraft P, Bao Y, et al. Cigarette Smoking and Pancreatic Cancer Survival. 2017;35(16):1822-8.
43. Park SML, Min Kyung, Shin SAY, Young Ho %J Journal of clinical Oncology. Impact of prediagnosis smoking, alcohol, obesity, and insulin resistance on survival in male cancer patients: National Health Insurance Corporation Study. 2006;24(31):5017-24.

44. Davoodi SH, Malek-Shahabi T, Malekshahi-Moghadam A, Shahbazi R, Esmaeili S. Obesity as an important risk factor for certain types of cancer. Iranian journal of cancer prevention. 2013;6(4):186-94.
45. Li D, Morris JS, Liu J, Hassan MM, Day RS, Bondy ML, et al. Body mass index and risk, age of onset, and survival in patients with pancreatic cancer. Jama. 2009;301(24):2553-62.
46. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. The New England journal of medicine. 2003;348(17):1625-38.
47. Aune D, Greenwood DC, Chan DS, Vieira R, Vieira AR, Navarro Rosenblatt DA, et al. Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis of prospective studies. Annals of oncology : official journal of the European Society for Medical Oncology. 2012;23(4):843-52.
48. Xu M, Jung X, Hines OJ, Eibl G, Chen Y. Obesity and Pancreatic Cancer: Overview of Epidemiology and Potential Prevention by Weight Loss. Pancreas. 2018;47(2):158-62.
49. Berrington de Gonzalez A, Sweetland S, Spencer E. A meta-analysis of obesity and the risk of pancreatic cancer. British journal of cancer. 2003;89(3):519-23.
50. Inoue M, Yamamoto S, Kurahashi N, Iwasaki M, Sasazuki S, Tsugane S. Daily total physical activity level and total cancer risk in men and women: results from a large-scale population-based cohort study in Japan. Am J Epidemiol. 2008;168(4):391-403.
51. Kruk J, Czerniak UJAPJoCP. Physical activity and its relation to cancer risk: updating the evidence. 2013;14(7):3993-4003.
52. Friedenreich CM, Neilson HK, Farris MS, Courneya KS. Physical Activity and Cancer Outcomes: A Precision Medicine Approach. 2016;22(19):4766-75.
53. Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Bouvard V, et al. Carcinogenicity of alcoholic beverages. 2007;8(4):292-3.
54. Fund WCR, Research AIfC. Food, nutrition, physical activity, and the prevention of cancer: a global perspective: Amer Inst for Cancer Research; 2007.
55. Genkinger JM, Spiegelman D, Anderson KE, Bergkvist L, Bernstein L, Van Den Brandt PA, et al. Alcohol intake and pancreatic cancer risk: a pooled analysis of fourteen cohort studies. 2009;18(3):765-76.
56. Bagnardi V, Blangiardo M, La Vecchia C, Corrao GJBjoc. A meta-analysis of alcohol drinking and cancer risk. 2001;85(11):1700-5.
57. Talamini R, Polesel J, Gallus S, Dal Maso L, Zucchetto A, Negri E, et al. Tobacco smoking, alcohol consumption and pancreatic cancer risk: A case-control study in Italy. European Journal of Cancer. 2010;46(2):370-6.
58. Lucenteforte E, La Vecchia C, Silverman D, Petersen GM, Bracci PM, Ji BT, et al. Alcohol consumption and pancreatic cancer: a pooled analysis in the International Pancreatic Cancer Case–Control Consortium (PanC4). Annals of Oncology. 2012;23(2):374-82.
59. Lowenfels AB, Maisonneuve PJBp, gastroenterology rC. Epidemiology and risk factors for pancreatic cancer. 2006;20(2):197-209.
60. Spanier BM, Dijkgraaf MG, Bruno MJJBp, gastroenterology rC. Epidemiology, aetiology and outcome of acute and chronic pancreatitis: An update. 2008;22(1):45-63.
61. Witt H, Apte MV, Keim V, Wilson JSJG. Chronic pancreatitis: challenges and advances in pathogenesis, genetics, diagnosis, and therapy. 2007;132(4):1557-73.
62. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas. 2019;157:107843.
63. Eibl G, Cruz-Monserrate Z, Korc M, Petrov MS, Goodarzi MO, Fisher WE, et al. Diabetes Mellitus and Obesity as Risk Factors for Pancreatic Cancer. Journal of the Academy of Nutrition and Dietetics. 2018;118(4):555-67.

64. Everhart J, Wright DJJ. Diabetes mellitus as a risk factor for pancreatic cancer: a meta-analysis. 1995;273(20):1605-9.
65. Andersen DK, Korc M, Petersen GM, Eibl G, Li D, Rickels MR, et al. Diabetes, Pancreatogenic Diabetes, and Pancreatic Cancer. 2017;66(5):1103-10.
66. Huxley R, Ansary-Moghaddam A, De González AB, Barzi F, Woodward MJBjoc. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. 2005;92(11):2076-83.
67. Li D, Tang H, Hassan MM, Holly EA, Bracci PM, Silverman DT. Diabetes and risk of pancreatic cancer: a pooled analysis of three large case-control studies. Cancer causes & control : CCC. 2011;22(2):189-97.
68. Anand P, Kunnumakara AB, Sundaram C, Harikumar KB, Tharakan ST, Lai OS, et al. Cancer is a preventable disease that requires major lifestyle changes. 2008;25(9):2097-116.
69. Salem AA, Mackenzie GG. Pancreatic cancer: A critical review of dietary risk. Nutrition Research. 2018;52:1-13.
70. Willett WCJTo. Diet and cancer. 2000;5(5):393-404.
71. Wu Q-J, Wu L, Zheng L-Q, Xu X, Ji C, Gong T-TJEJoCP. Consumption of fruit and vegetables reduces risk of pancreatic cancer: evidence from epidemiological studies. 2016;25(3):196-205.
72. Li L-y, Luo Y, Lu M-d, Xu X-w, Lin H-d, Zheng Z-qJWjoso. Cruciferous vegetable consumption and the risk of pancreatic cancer: a meta-analysis. 2015;13(1):1-8.
73. Lei Q, Zheng H, Bi J, Wang X, Jiang T, Gao X, et al. Whole grain intake reduces pancreatic cancer risk: a meta-analysis of observational studies. 2016;95(9).
74. Aune D, Chan D, Vieira A, Rosenblatt DN, Vieira R, Greenwood D, et al. Dietary fructose, carbohydrates, glycemic indices and pancreatic cancer risk: a systematic review and meta-analysis of cohort studies. 2012;23(10):2536-46.
75. Zhao Z, Yin Z, Pu Z, Zhao QJCG, Hepatology. Association between consumption of red and processed meat and pancreatic cancer risk: a systematic review and meta-analysis. 2017;15(4):486-93. e10.
76. Larsson S, Wolk AJBjoc. Red and processed meat consumption and risk of pancreatic cancer: meta-analysis of prospective studies. 2012;106(3):603-7.
77. Genkinger JM, Wang M, Li R, Albanes D, Anderson K, Bernstein L, et al. Dairy products and pancreatic cancer risk: a pooled analysis of 14 cohort studies. 2014;25(6):1106-15.
78. Siegel RL, Miller KD, Jemal AJCacjfc. Cancer statistics, 2015. 2015;65(1):5-29.
79. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer GJC. The hallmarks of aging. 2013;153(6):1194-217.
80. Dugué P-A, Bassett JK, Joo JE, Jung C-H, Ming Wong E, Moreno-Betancur M, et al. DNA methylation-based biological aging and cancer risk and survival: Pooled analysis of seven prospective studies. 2018;142(8):1611-9.
81. Sadr-Azodi O, Oskarsson V, Discacciati A, Videhult P, Askling J, Ekbom A. Pancreatic Cancer Following Acute Pancreatitis: A Population-based Matched Cohort Study. 2018;113(11):1711-9.
82. Kirkegård J, Cronin-Fenton D, Heide-Jørgensen U, Mortensen FV. Acute Pancreatitis and Pancreatic Cancer Risk: A Nationwide Matched-Cohort Study in Denmark. Gastroenterology. 2018;154(6):1729-36.
83. Hao L, Zeng X-P, Xin L, Wang D, Pan J, Bi Y-W, et al. Incidence of and risk factors for pancreatic cancer in chronic pancreatitis: A cohort of 1656 patients. Digestive and Liver Disease. 2017;49(11):1249-56.
84. Kirkegård J, Mortensen FV, Cronin-Fenton D. Chronic Pancreatitis and Pancreatic Cancer Risk: A Systematic Review and Meta-analysis. 2017;112(9):1366-72.
85. Benzel J, Fendrich VJOr, treatment. Familial pancreatic cancer. 2018;41(10):611-8.
86. Kastrinos F, Mukherjee B, Tayob N, Wang F, Sparr J, Raymond VM, et al. Risk of pancreatic cancer in families with Lynch syndrome. 2009;302(16):1790-5.
87. Brose MS, Rebbeck TR, Calzone KA, Stopfer JE, Nathanson KL, Weber BLJJotNCI. Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. 2002;94(18):1365-72.

88. Vasen H, Gruis N, Frants R, van Der Velden P, Hille E, Bergman WJIjoc. Risk of developing pancreatic cancer in families with familial atypical multiple mole melanoma associated with a specific 19 deletion of p16 (p16-Leiden). 2000;87(6):809-11.
89. Ilic M, Ilic IJWjog. Epidemiology of pancreatic cancer. 2016;22(44):9694.
90. Luo J, Xiao L, Wu C, Zheng Y, Zhao NJPo. The incidence and survival rate of population-based pancreatic cancer patients: Shanghai Cancer Registry 2004–2009. 2013;8(10):e76052.
91. Vincent A, Herman J, Schulick R, Hruban RH, Goggins MJTl. Pancreatic cancer. 2011;378(9791):607-20.
92. Gillen S, Schuster T, Zum Büschenfelde CM, Friess H, Kleeff JJPm. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. 2010;7(4):e1000267.
93. Strobel O, Neoptolemos J, Jäger D, Büchler MW. Optimizing the outcomes of pancreatic cancer surgery. Nature Reviews Clinical Oncology. 2019;16(1):11-26.
94. Ng M, Freeman MK, Fleming TD, Robinson M, Dwyer-Lindgren L, Thomson B, et al. Smoking prevalence and cigarette consumption in 187 countries, 1980-2012. 2014;311(2):183-92.
95. Pandol SJ, Apte MV, Wilson JS, Gukovskaya AS, Edderkaoui M. The burning question: why is smoking a risk factor for pancreatic cancer? Pancreatology : official journal of the International Association of Pancreatology (IAP) [et al]. 2012;12(4):344-9.
96. Control CfD, Prevention. How tobacco smoke causes disease: The biology and behavioral basis for smoking-attributable disease: A report of the surgeon general. 2010.
97. Hoffmann D, Hoffmann I, El-Bayoumy K. The less harmful cigarette: a controversial issue. a tribute to Ernst L. Wynder. Chemical research in toxicology. 2001;14(7):767-90.
98. Chowdhury P, Doi R, Chang LW, Rayford PL. Tissue distribution of [3H]-nicotine in rats. Biomedical and environmental sciences : BES. 1993;6(1):59-64.
99. Blackford A, Parmigiani G, Kensler TW, Wolfgang C, Jones S, Zhang X, et al. Genetic mutations associated with cigarette smoking in pancreatic cancer. Cancer research. 2009;69(8):3681-8.
100. Weddle DL, Tithoff P, Williams M, Schuller HM. Beta-adrenergic growth regulation of human cancer cell lines derived from pancreatic ductal carcinomas. Carcinogenesis. 2001;22(3):473-9.
101. Wittel UA, Pandey KK, Andrianifahanana M, Johansson SL, Cullen DM, Akhter MP, et al. Chronic pancreatic inflammation induced by environmental tobacco smoke inhalation in rats. The American journal of gastroenterology. 2006;101(1):148-59.
102. Alexandre M, Pandol SJ, Gorelick FS, Thrower EC. The emerging role of smoking in the development of pancreatitis. Pancreatology. 2011;11(5):469-74.
103. Edderkaoui M, Park C, Lee I, Nitsche C, Gerloff A, Grippo P, et al., editors. Novel model of pancreatic neoplastic lesions induced by smoking compound NNK. Pancreas; 2011: LIPPINCOTT WILLIAMS & WILKINS 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA.
104. Vrieling A, Bueno-de-Mesquita HB, Boshuizen HC, Michaud DS, Severinsen MT, Overvad K, et al. Cigarette smoking, environmental tobacco smoke exposure and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition. 2010;126(10):2394-403.
105. Lund E, Dumeaux V, Braaten T, Hjartåker A, Engeset D, Skeie G, et al. Cohort Profile: The Norwegian Women and Cancer Study—NOWAC—Kvinner og kreft. International Journal of Epidemiology. 2007;37(1):36-41.
106. Zhu BP, Giovino GA, Mowery PD, Eriksen MP. The relationship between cigarette smoking and education revisited: implications for categorizing persons' educational status. Am J Public Health. 1996;86(11):1582-9.