The role of cardiorespiratory fitness, leisure-time physical activity and inflammatory biomarkers in lung cancer risk, and cancer death is limited. Among men, this follow-up study suggests that high levels of cardiorespiratory fitness reduces the risk for lung cancer and cancer death. Whereas, high levels of C-reactive protein and leukocyte count increase lung cancer risk and cancer death. Furthermore, poor cardiorespiratory fitness combined with high C-reactive protein had a four-fold increased risk for lung cancer.
Cardiorespiratory fitness, physical activity and inflammation in cancer risk

A prospective cohort study in men
PERFENIA PAUL PLETNIKOFF

Cardiorespiratory fitness, physical activity and inflammation in cancer risk
A prospective cohort study in men

To be presented, by permission of the Faculty of Health Sciences, University of Eastern Finland, for public examination in auditorium TTA, Tietoteknia building of the University of Eastern Finland, Kuopio, on Friday, December 15th 2017, at 12 noon

Publications of the University of Eastern Finland
Dissertations in Health Sciences
Number 443

Institute of Public Health and Clinical Nutrition, Faculty of Health Sciences, University of Eastern Finland, Kuopio
Kuopio
2017
Author’s address: Faculty of Health Sciences, School of Medicine and Institute of Public Health and Clinical Nutrition
University of Eastern Finland
KUOPIO
FINLAND

Supervisors: Professor Tomi-Pekka Tuomainen, M.D., Ph.D.
Institute of Public Health and Clinical Nutrition
University of Eastern Finland
KUOPIO
FINLAND

Docent Sudhir Kurl, M.D., Ph.D.
Institute of Public Health and Clinical Nutrition
University of Eastern Finland
KUOPIO
FINLAND

Reviewers: Professor Shulin Cheng, Ph.D.
Department of Health Sciences
University of Jyväskylä
JYVÄSKYLÄ
FINLAND

Docent Katja Borodulin, Ph.D.
Health Monitoring Unit
National Institute for Health and Welfare
HELSINKI
FINLAND

Opponent: Professor Pekka Jousilahti, M.D., Ph.D.
Health Monitoring Unit
National Institute for Health and Welfare
HELSINKI
FINLAND
ABSTRACT
Presently, knowledge on the role of cardiorespiratory fitness (CRF) and leisure-time physical activity (LTPA) in the prevention of lung cancer is scarce. In addition, only a few studies have assessed the joint impact of inflammatory markers and CRF with lung cancer risk or cancer death. Therefore, population studies that combine all the three, CRF, LTPA and inflammation in predicting long-term associations with cancer mortality and morbidity are warranted.

The aim for this thesis was to study the associations between CRF (as measured with maximal oxygen uptake capacity, VO\textsuperscript{2max}), LTPA, leukocyte count and C-reactive protein (CRP) on cancer outcomes in a longitudinal setting. Specifically, the objectives of this thesis include 1) to investigate the prognostic value of CRF and LTPA with lung cancer risk, 2) to examine the joint impact of the CRF and CRP with the risk of lung cancer, and 3) to explore the joint impact of inflammatory markers and CRF with cancer mortality.

Study population formed of the participants of the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD), a prospective general male population follow-up study in Eastern Finland that recruited a randomly selected sample of 2682 men, aged 42 to 60 at the baseline examinations, from the town of Kuopio and the surrounding communities. Baseline examinations took place in 1984 to 1989.

In the study I, in multivariable adjusted Cox regression models, men in the lowest quartile in VO\textsubscript{2max} had nearly a three-fold risk for lung cancer, as compared with men in the highest quartile (HR 2.88, 95% CI 1.14 to 7.22, \(P=0.02\)). In a similar model, LTPA was not statistically significant predictor of lung cancer. In the study II, in multivariable adjusted Cox regression models, men in the joint lower VO\textsubscript{2max} half and higher CRP half, had over four-fold risk for lung cancer, as compared with men in the joint higher VO\textsubscript{2max} half and lower CRP half (HR 4.19, 95% CI 1.66 to 10.57, \(P<0.01\)). In the study III, in multivariable adjusted Cox regression models, men in the lowest VO\textsubscript{2max} quartile had a two-fold risk for cancer death, as compared with men in the highest quartile (HR 2.01, 95% CI 1.33 to 3.44, \(P<0.01\)). Furthermore, men in the joint lower VO\textsubscript{2max} half and higher leukocyte count half had a 85% increased risk for cancer death, as compared with men in the joint higher VO\textsubscript{2max} half and lower leukocyte count half (HR 1.85, 95% CI 1.30 to 2.63, \(P<0.01\)). When CRP was used
instead of leukocyte count, the similar comparison did not reach statistical significance ($P=0.14$).

In conclusion, the results from the thesis studies I to III show that CRF is a strong predictor of lung cancer, that middle-aged men with both high levels of CRF and low levels of CRP are at a low risk for development of lung cancer, and that men with both high levels of CRF and low leukocyte count have a reduced risk for cancer mortality.

National Library of Medicine Classification: QT 250, QT 256, QY 402, WH 400, WF 658, WA 900
Medical Subject Headings: Leisure activities; physical fitness; leukocyte count; C-reactive protein; Neoplasms; Mortality; Risk; Men
Pletnikoff, Perfenia Paul
Kardiorespiratorinen suorituskyky, fyysinen aktiivisuus, tulehdustekijät ja syöpäriski. Miesväestön seurantatutkimus
Itä-Suomen yliopisto, terveyttieden tiedekunta
Publications of the University of Eastern Finland. Dissertations in Health Sciences 443. 2017. 64 p.

TIIVISTELMÄ

Tämän väitöskirjatutkimuksen tarkoituksena on tarkastella CRF:n, vapaa-ajan kuntosyövän (LTPA), veren valkosolujen ja veriseerumin C-reaktiivisen proteiinin (CRP) pitoisuuden yhteyttä keuhkosyövän ja syöpäkuoleman riskiin. Tarkemmin, tarkoitus on tutkia 1) maksimaalisen hapenottokyvyn (VO$_{2\max}$), joka on erinomainen CRF mittari, ja LTPA:n yhteyttä keuhkosyövän riskiin, 2) VO$_{2\max}$:n ja CRP:n yhteyttä keuhkosyövän riskiin, ja 3) veren valkosolu- ja veriseerumin CRP-pitoisuuden ja VO$_{2\max}$:n yhteyttä syöpäkuoleman riskiin.

Tutkimusväestönä oli Kuopio Ischaemic Heart Disease Risk Factor Study –tutkimuksen (KIHD) osallistujat. KIHD on etenevä väestötutkimus, johon värvättiin vuosina 1984-9 satunnaisotannalla 2682 keski-ikäistä miestä Kuopiosta ja kehyskunnista.

Osatyössä I havaittiin että miehillä, jotka kuuluivat VO$_{2\max}$:n alimpaan neljännekseen, oli monimuuttujamallin mukaan (Cox:n suhteellisten vaarojen malli) lähes kolminkertainen riski sairastua keuhkosyöpään tutkimuksen aikana verrattuna miehiin, jotka kuuluivat VO$_{2\max}$:n ylimpään neljännekseen (HR 2,88, 95% LV 1,14-7,22, $P=0,02$). Osatyössä II havaittiin että miehillä, jotka kuuluivat samanaikaisesti sekä CRF:n alimpaan että CRP:n ylimpään puolikkaaseen, oli yli nelinkertainen riski sairastua tutkimuksen aikana keuhkosyöpään, verrattuna miehiin, jotka kuuluivat VO$_{2\max}$:n ylimpään neljännekseen (HR 4,19, 95% LV 1,66-10,57, $P<0,01$). Osatyössä III havaittiin että miehillä, jotka kuuluivat VO$_{2\max}$:n alimpaan neljännekseen oli noin kaksinkertainen riski kuolla syöpään tutkimuksen aikana verrattuna miehiin, jotka kuuluivat VO$_{2\max}$:n ylimpään neljännekseen (HR 2,01, 95% LV 1,33-3,44, $P<0,01$). Osatyössä III havaittiin myös että miehillä, jotka kuuluivat samanaikaisesti sekä VO$_{2\max}$:n alimpaan että veren valkosolupitoisuuden ylimpään puolikkaaseen oli 85% lisääntynyt riski kuolla syöpään tutkimuksen aikana, verrattuna miehiin, jotka kuuluivat samanaikaisesti sekä
VO_2\text{max}:n ylempään että veren valkosolupitoisuuden alempaan puolikkaaseen (HR 1,85, 95% LV 1,30-2,63, \( P<0,01 \)), kun taas vastaavassa mallissa, jos veren valkosolupitoisuuden sijaan käytettiin veriseerumin CRP-pitoisuutta, yhteys ei ollut tilastollisesti merkitsevä. Yhteenvetona voi todeta että tämä väitöskirjatutkimus osoitti että matala CRF on keuhkosyövän riskitekijä, että keski-ikäisten miesten yhtäaikainen korkea CRF ja matala CRP on keuhkosyövän suojatekijä, ja että miehillä, joilla on yhtäaikaisesti sekä hyvä CRF että matala veren valkosolupitoisuus, on alentunut syöpäkuoleman riski.

Luokitus: QT 250, QT 256, QY 402, WH 400, WF 658, WA 900
Yleinen suomalainen asiasanasto: Vapaa-ajan liikunta, fyysinen aktiivisuus, valkosolumäärä, C-reaktiivinen proteiini, kasvaimet, kuolleisuus, riski, miehet
Acknowledgements

This Ph.D. work was conducted at the Institute of Public Health and Clinical Nutrition, School of Medicine, Faculty of Health Sciences, Kuopio campus, University of Eastern Finland, and Kuopio Research Institute of Exercise Medicine, Kuopio, Finland.

I would like to thank my principal supervisor, Professor Tomi-Pekka Tuomainen M.D., Ph.D, for his continuous support in my efforts as a Ph.D. student. With his guidance, it was possible to overcome the challenges related to research and doctoral education. Professor Tuomainen's knowledge in the field of epidemiology and public health was essential for developing the skills necessary for this Ph.D.

During this doctoral program, I was fortunate to work with Docent, Sudhir Kurl M.D., Ph.D. Dr. Kurl's expertise in the field of epidemiology and research was an integral piece of this doctoral thesis. His invaluable experience was a strong asset to my research goals, and I am grateful for his guidance and support during this process.

I would like to recognize Professor Jussi Kauhanen, M.D., Ph.D., for his support during this period. His support was an essential for the progress and completion in the Doctoral Program in Public Health.

I wish to acknowledge the support and advice from Docent Jari A. Laukkanen M.D., Ph.D. I am thankful for his vast knowledge in research and epidemiology.

I also would like to thank Mr. Kimmo Ronkainen, MSc, for his assistance with statistical analysis, knowledge and advice.

Lastly, I would like to thank my family for their continuous and everlasting support.

Paul Pletnikoff
LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications:


The publications were adapted with the permission of the copyright owners.
# Contents

1 INTRODUCTION ........................................................................................................................1
2 REVIEW OF THE LITERATURE ..................................................................................................2
   2.1 Cancer ................................................................................................................................2
      2.1.1 Cancer Etiology ..........................................................................................................2
      2.1.2 Lung Cancer .............................................................................................................4
      2.1.2.1 Epidemiology of lung cancer ..............................................................................4
      2.1.2.2 Types of lung cancer ............................................................................................5
   2.2 Cancer and risk factors ....................................................................................................8
      2.2.1 Risk factors for cancer ............................................................................................8
      2.2.2 Smoking & never smokers ......................................................................................8
      2.2.3 Alcohol ....................................................................................................................8
      2.2.4 Diet ...........................................................................................................................9
      2.2.5 Physical activity .......................................................................................................9
      2.2.6 Obesity ...................................................................................................................10
      2.2.7 Infections and Inflammation ..................................................................................10
      2.2.8 Environment ..........................................................................................................11
      2.2.9 Family history ........................................................................................................11
   2.3 Cohort studies exploring the role of physical activity, cardiorespiratory fitness and inflammation with lung cancer risk and cancer death ..................................................................................14
      2.3.1 Cardiorespiratory fitness and lung cancer ...............................................................14
      2.3.2 Physical activity and lung cancer ..............................................................................14
      2.3.3 Inflammation and lung cancer ................................................................................15
      2.3.4 Physical activity, inflammation and lung cancer ....................................................15
      2.3.5 Cardiorespiratory fitness and cancer mortality .......................................................16
      2.3.6 Physical activity, cardiorespiratory fitness with cancer risk and mortality ..............17
      2.3.7 Inflammation and cancer mortality .........................................................................17
      2.3.8 Other studies ...........................................................................................................18
      2.3.9 Summary ................................................................................................................19
   2.4 Measurements of physical activity and cardiovascular fitness .....................................22
      2.4.1 Assessment of leisure-time physical activity .........................................................23
      2.4.2 Assessment of direct and indirect cardiorespiratory fitness ..................................23
      2.4.3 Determinants of cardiorespiratory fitness ...............................................................24
   2.5 Measurement of inflammatory biomarkers ..................................................................23
      2.5.1 Assessment of inflammatory biomarkers ..............................................................23
      2.5.2 Determinants of inflammatory biomarkers ............................................................24
   2.6 The role of physical activity, cardiorespiratory fitness and inflammatory biomarkers measurements in risk prediction ..........................................................24
      2.6.1 The role of cardiorespiratory fitness in risk prediction .......................................24
2.6.2 The role of leisure-time physical activity in risk prediction..........26
2.6.3 The role of inflammatory biomarkers in risk prediction............26
2.6.4 The joint effect of inflammatory biomarkers and cardiorespiratory fitness in risk prediction.................................27
2.7 Summary of review of literature..................................................27

3 AIMS OF THE STUDY....................................................................................28

4 METHODS....................................................................................................29
4.1 Study Population....................................................................................29
4.2 Assessment of cardiorespiratory fitness..............................................32
4.3 Assessment of leisure-time physical activity.....................................32
4.4 Biochemical analyses............................................................................32
4.5 Obesity..................................................................................................33
4.6 Smoking and alcohol consumption.....................................................33
4.7 Education..............................................................................................33
4.8 Fruits and vegetables...........................................................................33
4.9 Blood pressure........................................................................................33
4.10 Baseline diseases................................................................................34
4.11 Collection and classification of follow-up events............................34
4.12 Statistical methods..............................................................................34
4.13 Study I..................................................................................................34
4.14 Study II...............................................................................................35
4.15 Study III.............................................................................................35

5 RESULTS......................................................................................................36
5.1 Study 1: LTPA, CRF and lung cancer risk..........................................36
  5.1.1 Leisure-time physical activity and lung cancer risk.......................36
  5.1.2 Cardiorespiratory fitness and lung cancer risk..............................36
5.2 Study 2: CRF, CRP and lung cancer risk..........................................37
  5.2.1 Cardiorespiratory fitness and lung cancer risk..............................37
  5.2.2 C-reactive protein and lung cancer risk........................................37
  5.2.3 C-reactive protein, cardiorespiratory fitness and lung cancer risk....38
5.3 Study 3: Inflammatory markers, CRF and cancer mortality.............39
  5.3.1 Cardiorespiratory fitness and cancer mortality..............................39
  5.3.2 C-reactive protein and cancer mortality.........................................40
  5.3.3 C-reactive protein, cardiorespiratory fitness and cancer mortality...40
  5.3.4 Leukocyte count and cancer mortality............................................41
  5.3.5 Leukocyte count, cardiorespiratory fitness and cancer mortality......41
  5.3.6 Summary of main findings.............................................................42

6 DISCUSSION..................................................................................................45
6.1 Leisure-time physical activity, cardiorespiratory fitness and lung cancer risk........45
6.2 C-reactive protein, cardiorespiratory fitness and lung cancer risk........46
6.3 Inflammatory biomarkers, cardiorespiratory fitness, and the risk of cancer mortality.................................................................47
6.4 Strengths and limitations of this study.................................................48
Abbreviations

BMI  Body mass index
EE   Energy expenditure
COPD Chronic obstructive pulmonary disease
CRF  Cardiorespiratory fitness
hs-CRP High-sensitivity C-reactive protein
DNA  Deoxyribonucleic acid
GI   Gastrointestinal
HIV  Human immunodeficiency virus
HPV  Human papillomavirus
HR   Hazard ratio
ICD  International Classification of Diseases
ICD-O International Classification of Diseases for Oncology
KIHD Kuopio Ischaemic Heart Disease Risk Factor Study
LTPA Leisure-time physical activity
MET  Metabolic equivalent
OR   Odds ratio
RR   Relative risk
SD   Standard deviation
TB   Tuberculosis
WBC  White blood-cell count
VO₂max Maximal oxygen uptake
1 Introduction

Cancer is the leading cause of death in developed nations, and second within developing nations (Jemal et al. 2011). The probability of being diagnosed with cancer over a lifetime for men is (42%) and slightly lower for women (38%) (Siegal et al. 2016). Globally, lung cancer is the leading cause of cancer mortality (World Health Organization 2015). As the leading cause of cancer death among men (Ahmad & Gadgeel 2016), improving the current knowledge to reduce lung cancer risk is essential.

The current epidemiological evidence suggests that physical activity has positive effects in non-communicable disease prevention. Physical activity may improve the quality of life and reduce the risk of premature mortality and disease. However, 1 in 4 deaths in the US are due to cancer (Siegel et al. 2014). This trend may continue, due to increasing age and unfavorable lifestyles choices which include smoking, poor diet and physical inactivity (Jemal et al. 2011). Therefore, major lifestyle changes may be necessary to reduce behavioral and environmental risk factors (Anand et al. 2008). Chronic inflammation has been shown to be a risk factor for several types of cancers. Inflammation has been linked to cancer at all stages of development: initiation, promotion, progression, and metastasis (Dubinett 2015). Inflammation has also been suggested to be the seventh hallmark of cancer, as an “enabling characteristic” (Allin et al. 2016).

To prevent cancer morbidity and mortality, reducing sedentary time through bouts of moderate and vigorous physical activities has shown beneficial results for reducing cancer risks. The physiological benefits of physical activity may include; improved cardiovascular, respiratory, musculoskeletal, endocrine functions, (US Dept 1996) and have anti-inflammatory effects (Wärnberg et al. 2010). The cumulative effect of physical activity (frequency, intensity, time, and type) can contribute to increasing an individual’s cardiorespiratory fitness (CRF). The physiological effects of high CRF may provide long-term health benefits, which includes reducing cancer risk. At present, little is known about the joint impact of inflammatory markers and CRF with cancer. To strengthen the current knowledge, further investigation into the independent and joint effects of inflammatory biomarkers and CRF with cancer outcomes may demonstrate the benefits of high CRF in cancer prevention.

The main objective for this doctoral thesis was to explore the independent predictive value of CRF, leisure-time physical activity (LTPA) and inflammatory markers with lung cancer risk and cancer death. Furthermore, to investigate the joint impact of CRF and inflammatory biomarkers with cancer outcomes. The aims for this doctoral thesis included; to compare CRF and LTPA in predicting lung cancer risk, and elucidate their prognostic value; to examine the independent and joint impact of CRF and C-reactive protein (hs-CRP) with the risk of lung cancer; and to examine the independent and joint impact of inflammatory markers (leukocyte count, hs-CRP) and CRF with cancer mortality.
2 Review of the literature

2.1 CANCER

Cancer is a word that comes from Greek *karkinos* (carcinoma), which directly translates into crab. “Cancer”, refers to over 100 different cancerous diseases which can harm many different cell types in the body (Thune 2010). These large number of diseases are characterized as cells that develop abnormally and divide uncontrollably, and may invade nearby tissues (National Cancer Institute 2015). This collection of closely related diseases, consist of cellular divisions which no longer respond to signals for controlling cellular growth. During normal cellular division, genes help control cell division by signaling damaged cells that should undergo apoptosis. There is a balance between cell proliferation and suppression. However, cancerous cells have genetic mutations with inadequate control of cell proliferation. In general, the primary cause of cancer is from damage to the genetic apparatus of the cells (Bukhtoyarov & Samarin 2015). Cancers are capable of infiltrating and destroying normal body tissues. Cancer may spread throughout the body, and the prognosis and treatments for cancer may vary depending on the underlying cancer site. An effective way to reduce cancer is through primary prevention, since, a third of cancers are preventable (Vineis & Wild 2014).

2.1.1 Cancer Etiology

Today, current research has identified several environmental, behavioral, and hereditary factors for cancer. Common causes of cancer may originate from multiple factors. Environmental factors may include long-term exposure to sunlight or secondhand smoke. Behavioral factors may include smoking cigarettes, alcohol consumption, poor dietary choices, and physical inactivity. Genetic factors may contribute to an increased risk for cancer among individuals with family history of cancer. Furthermore, chemical (asbestos, benzpyrene) biological, (viruses, fungi, bacteria) and physical factors (Bukhtoyarov & Samarin 2015) may contribute to the initiation of cancer and carcinogenesis.
Figure 1. Estimated numbers (thousands) of new cancer cases (incidence) and deaths (mortality) in more developed and less developed regions of the world of (a) men (b) women in 2012, modified from Ferlay et al. (2015)
2.1.2 Lung Cancer

2.1.2.1 Epidemiology of lung cancer

Globally, lung cancer is the leading cause of cancer death in men, and the second leading cause of death among women (Jemal et al. 2011). Currently, the 5-year survival rate for lung cancer is about 18% (Seigal et al. 2016). Several risk factors for lung cancer exist, such as age and sex (Figure 2), environmental exposures, and lifestyle factors that include smoking, diet and physical activity (Alberg et al. 2013). Lung cancer risk is influenced by environmental and lifestyle factors, which may be preventable.

The etiology of lung cancer consists of an interrelationship between exposure to agents and an individual’s susceptibility to these agents (Alberg et al. 2013). The primary cause of lung cancer is from cigarette smoking, which contributes to eighty to ninety percent of all lung cancer cases (Ahmad & Gadgeel 2016). Cigarette smoking is associated with all histological types of lung cancer, although, the strength of the association may depend on the histologic type (Khuder 2001). After smoking initiation, the onset of lung cancer may take decades to develop and is therefore, more commonly observed in the elderly (Ahmad & Gadgeel 2016). Some other causes of lung cancer may include exposure to outdoor air pollution, diesel engine exhaust, radon and asbestos (Stewart & Wild 2014). Lung carcinogenesis originates in the lung and may spread throughout the body. Lung cancer is diagnosed into two main types, recognized as non-small cell and small cell lung cancer. The third type, is lung carcinoid tumors.

Globally, there are variations in lung cancer incidence and mortality (Figure 1, Figure 3). For example, lung cancer among men is approximately 50% higher (44.7 cases per 100,000) in developed regions as compared to less developed regions (30.0 cases per 100,000) (Ahmad & Gadgeel 2016). In Finland, lung cancer incidence among men is about 28.1 cases per 100,000, and 13.3 cases per 100,000 among women (Finnish Cancer Registry 2016). In general, the highest rates have been observed in high-income countries such as, North America, Europe and Oceania (Ahmad & Gadgeel 2016).
Figure 2. Lung cancer incidence and mortality rates by sex and age in the United States, 2006-2010. Rates are per 100,000 and age-adjusted to the 2000 U.S. standard population modified from Ahmad & Gadgeel (2016)

2.1.2.2 Types of lung cancer
Up to 85% of lung cancers are classified as non-small cell lung cancers. The three main forms include adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Other forms of non-small cell lung cancer are less common. The most common is adenocarcinoma, which originates in the cells that produce mucus. This lung cancer includes approximately 40% of the cases, and it is the most common lung cancer among non-smokers. This lung cancer type has a slower progression than other lung cancers. The second type is squamous cell carcinoma, which consists of about 30% of cases, and originates in the inner airways of the lungs. The third type of lung cancer is large cell
carcinoma, which consists of about 10 to 15% of lung cancers and can grow and spread more rapidly than other lung cancers (WebMD 2017a,c).

An estimated 15% of lung cancers are small cell lung cancers. The origin is commonly located in the bronchi, and the disease may spread throughout the body in early stages. Heavy smokers and the elderly form nearly 90% of the patients (WebMD 2017b). A third type of lung cancer is less common, and makes up about 5% of cases. Carcinoid tumors are a type of neuroendocrine tumor, which include four subtypes, small cell lung cancer, large cell neuroendocrine carcinoma, and atypical and typical carcinoid tumor (WebMD 2017c). In general, the development of lung cancer may begin from harmful exposure to carcinogens. This exposure may initiate mutations and promote tumors, and the cell outgrowth may contain such mutations (Minna 1993). In a multi-step process, the genetic and epigenetic alterations resulting DNA damage can transform normal epithelial cells of the lung into lung cancer (Larsen & Minna 2011).
Figure 3. The global incidence and mortality for lung cancer by sex and region, 2012. The rates age-adjusted to the 1960 world standard population and per 100,000, modified from Ahmad (2016)
2.2 CANCER AND RISK FACTORS

2.2.1 Risk factors for cancer
Behavioral and environmental factors play a pivotal role in cancer prevention. Behavioral factors which include; smoking, poor diet, alcohol consumption and physical inactivity may increase cancer risk. Exposure from environmental factors, such as, radiation from sunlight or radon may increase the risk (Anand et al. 2008). The risk of cancer may rely on several interacting factors; genetics, age, physical health, diet, obesity, and environmental exposure (Cancer & Env 2015) (Table 1).

2.2.2 Smoking
Smoking may contribute to the development of 14 different cancers (Anand et al. 2008). Cigarette smoke has adverse effects on human health (Stämpfli & Anderson 2009). Epidemiological evidence shows that active or passive cigarette smoking causes lung cancer, and is responsible for worldwide cancer related deaths (Stämpfli & Anderson 2009). Smoking cigarettes causes oxidative stress, which initiates lung inflammation and cell death (Friedrich 2010). At the same time, heavy smoking can eventually reduce maximal exercise capacity, (Tzani et al. 2008) whereas; maximal exercise capacity reduces cancer mortality risk (Sawada et al. 2003). In lung cancer, smoking is responsible for an estimated 90% of cases among high-income countries (Stewart & Wild 2014). Current evidence suggests that lung cancer development from smoking tobacco products may be related to oxidative stress and inflammation (Dubinett 2015).

Globally, up to 25% of lung cancer cases among men and women are not a result of smoking (Sun et al. 2007). Only a few studies have investigated the associations between never smokers and cancer other than the lung, for example, as oral and pharyngeal (Fioretti et al. 1999). Environmental exposure to secondhand smoke, radon, indoor air pollution, occupational agents, previous viral or lung disease, and ionizing radiation may increase lung cancer risk (Samet et al. 2009) (Table 2).

2.2.3 Alcohol
The association between alcohol consumption and cancer has been observed for about a century. Alcohol consumption may be responsible for nearly 68% of the aerodigestive tract cancers, which includes the oral cavity, pharynx, hypopharynx, larynx, and esophagus (Anand et al. 2008). Heavy alcohol consumption, of more than 4 drinks per day, is a strong risk factor for several cancer sites, such as, oral, pharyngeal, esophageal, and laryngeal (Pelucchi et al. 2011). In a meta-analysis of alcohol consumption and cancer, Bagnardi et al. suggest that the synergy between alcohol and tobacco can multiply the cancer risk of the digestive and respiratory tract (Bagnardi et al. 2001). Alcohol may contribute to carcinogenesis through ethanol. Ethanol is a co-carcinogen, when metabolized, free radicals
and acetaldehyde develop and the presence of free radicals may contribute to alcohol-associated carcinogenesis (Anand et al. 2008).

2.2.4 Diet
Dietary factors may contribute to cancer prevention and risk. However, the results have been inconsistent. In a review between diet and cancer, the investigators suggest that obesity and alcohol consumption are associated with cancer. Meat and fat do not seem to increase the risk. Populations with adequate nutritional resources, acquire little benefit by increasing their consumption of fruits, vegetables, tea or coffee (Wicki & Hagmann 2011). In a review of the Mediterranean diet in cancer prevention, Kontou et al. concluded that consumption of diets similar to the Mediterranean diet may provide a protective association from overall cancer incidence and mortality; however, there is no clear evidence that suggests a strong association between several cancer types and specific diets (Kontou et al. 2011). In the Mediterranean diet, carotenoids such as lycopene can be found, and lycopene may have an anticancer effect through several proposed mechanisms. Furthermore, carotenoids may have anti-inflammatory and anticarcinogenic activity (Anand et al. 2008). In lung cancer, fruit and vegetable consumption has been shown to share an inverse association. Especially with fruit intake, which shares a stronger association with lung cancer than vegetable intake (Linseisen et al. 2007).

2.2.5 Physical activity
Globally, physical inactivity is the fourth leading cause of death (Kohl III et al. 2012). Physical activity is defined as behaviors which result in any movement contributing to total energy expenditure (Caspersen et al. 1985). Physical activity is a modifiable behavior, which may require major lifestyle changes (Anand et al. 2008). Lifestyle behaviors which include a sufficient volume of physical activity, may reduce cancer risk. Epidemiological studies suggest that physical activity may reduce the risk of different types of cancer and displays an inverse association with the risk (Na & Oliynyk 2011, Kruk 2007). The effects of physical activity on carcinogenesis are partly due to, physical activity behaviors, age, and gender (McTiernan 2008). Physical inactivity has been associated with an increased risk of breast, colon, prostate, pancreatic cancers and melanoma (Anand et al. 2008). Current evidence suggests that adults should engage in at least 150 minutes of moderate intensity, or 75 minutes of vigorous activity per week to have health benefits, which include a reduced cancer risk. However, 300 minutes of moderate intensity activity or 150 minutes of vigorous activity may provide additional protection from cancer (Kushi et al. 2012).

The direct biological mechanisms for reducing lung cancer risk through physical activity remains unclear. However, the benefits of physical activity on inflammation and the immune system may reduce lung cancer risk. Physical activity reduces inflammation (Zhong et al. 2016), which has been shown to have a role in cancer promotion (Allin et al. 2016). Furthermore, physical activity enhances immune function, which reduces cancer by
improving natural killer cells. These cells are able to attack cancers and are effective in tumor suppression (Zhong et al. 2016).

2.2.6 Obesity
Up to 20% of all cancers are contributed to weight, mainly weight gain and obesity. In the past quarter-century, obesity accounts for approximately 14% of cancer deaths in men and 20% for women (Wolin et al. 2010). Cancer and obesity have common features, which include; insulin like growth factor, insulin, leptin, sex steroids (steroid hormones), insulin resistance and inflammation (Anand et al. 2008). There is evidence suggesting that an increase of BMI by 5 kg/m² increases risk of colon, thyroid, kidney, and esophageal among men and endometrium, gallbladder and renal cancers among women (Wolin et al. 2010). Obesity is associated with several cancers through various mechanisms. To prevent cancer, maintaining a healthy body weight over the course of a lifetime with physical activity, and appropriate energy intake (diet of plant-based foods, limit red meat, avoid processed meat and salty food) reduces cancer risk (Vucenik & Stains 2012). Furthermore, among obese people who lose weight, there is evidence that they experience a reduction in cancer incidence and mortality (Basen-Engquist & Chang 2011).

2.2.7 Infections and inflammation
Nearly 20% of cancers are a result of infections, autoimmune disease or irritant exposure (vapors, fumes, gases) (CruSZ & Balkwill 2015). Globally, an estimated 17% of neoplasms are associated with infections (Anand et al. 2008). Viruses, bacteria, and parasites have been identified as risk factors for several cancer sites. For example, human papillomavirus (HPV) is one of the most frequent oncogenic DNA viruses, among developed countries (Anand et al. 2008). In a review on lung cancer, an increased risk was observed with several diseases that increased lung inflammation. These diseases include, chronic obstructive pulmonary disease (COPD), emphysema, tuberculosis (TB), and pneumonia (Brenner et al. 2011). Chronic airway inflammation may promote the conditions necessary for lung cancer. As observed among smokers, chronic lung inflammation may result into cancer progression and metastasis (Dubinett 2015).

Strong evidence suggests that chronic inflammation is estimated to be associated with up to 25% of all cancers (Dubinett 2015). Inflammation as an acute process, which can substantially increase circulating levels of inflammation in a response of the immune system to damaging stimuli from trauma or infection. However, a chronic inflammatory state may lead to negative health consequences (Beavers et al. 2010). Inflammation has been hypothesized to be a risk factor for several cancers (Erlinger et al. 2004). It has been suggested that inflammation may represent a seventh hallmark of cancer, recognized as an “enabling characteristic”, in addition to the six hallmarks of cancer from Hanahan and Weinberg (Allin et al. 2016). The six hallmarks of cancer are suggested to have the same set of functional capabilities during development. These include; evading apoptosis, self-
sufficiency in growth signals, insensitivity to anti-growth signals, tissue invasion & metastasis, limitless replication potential, and sustained angiogenesis (Hanahan & Weinberg 2000). Several triggers of chronic inflammation may increase the risk of cancer, such as microbial infections, inflammatory conditions, and autoimmune diseases (Mantovani et al. 2008).

Several types of inflammation can promote cancer development and progression (Grivennikov et al. 2010). The associations between inflammatory markers and cancer may be site specific, and increasing levels of inflammation may have a stronger association with cancer death than cancer incidence (Il’yasova et al. 2005). In cancer mortality, leukocyte count has been shown to share an association (Erlinger et al. 2004), and high CRP has been observed to increase the risk for cancer (Allin et al. 2011) and lung cancer (Chaturvedi et al. 2010). Inflammation has been shown to increase cancer risk through two primary pathways; inflammatory conditions and genetic alterations that cause inflammation and neoplasia (Mantovani et al. 2008). Inflammation has a role across all phases of carcinogenesis, inflammation effects the initial genetic mutations or epigenetic mechanisms for cancer initiation and cell transformation (Trinchieri 2012).

2.2.8 Environment
Pollution and radiation are environmental factors which have been linked with several cancers (Anand et al. 2008). A reduction in air quality and long term exposure could be responsible for lung cancers, and may be a modifiable factor (Fajersztajn et al. 2013). The global burden of air pollution may become the leading factor of premature mortality by 2050 (Fajersztajn et al. 2013). In Europe, exposure to particulate matter air pollution has been associated with lung cancer (Raaschou-Nielsen et al. 2013). Ionizing and non-ionizing radiation have been linked with cancer (Anand et al. 2008). For example, the ionizing radiation of radon gas has been shown to be the second leading cause of lung cancer (Sethi et al. 2012).

2.2.9 Family history
In general, if a first degree relative (offspring, sibling or parent) has been affected by cancer, a subject has a higher cancer risk as compared to the general population for that cancer site. Colorectal, prostate, breast, and liver cancer been associated with family history (Turati et al. 2013). For lung cancer, epidemiological studies suggest an inherited susceptibility. A first degree relative has a 50% increased risk of lung cancer as compared with those without any family history (Coté et al. 2012). In a systemic review and meta-analysis, a consistent 2-fold increase in lung cancer was associated with familial aggregation (Matakidou et al. 2005.) An inherited susceptibility for lung cancer was observed among non-smoking lung cancer cases. After adjusting for smoking and other risk factors, the risk for developing lung cancer among relatives was (6.1-fold) and (7.2-fold) among offspring from ages (40-59 years) (Sekido et al. 1998).
<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Theoretical Minimum risk</th>
<th>Cancer sites Affected sites include:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overweight &amp; obesity</strong></td>
<td>For BMI (kg/m²) exposure variable is 21 Standard Deviation 1 kg/m²</td>
<td>corpus uteri cancer, colorectal cancer, post-menopausal breast cancer, gall bladder cancer, and kidney cancer</td>
</tr>
<tr>
<td>Body Mass Index (BMI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Low fruit &amp; vegetable intake</strong></td>
<td>600 Standard Deviation 50g</td>
<td>colorectal, stomach, lung and oesophageal cancer</td>
</tr>
<tr>
<td>Daily fruit and vegetable intake per day for adults</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Physical inactivity</strong></td>
<td>for &gt;2-5 hours per week of moderate-intensity activity or equivalent (400 kJ per week)</td>
<td>breast, colorectal and prostate cancers</td>
</tr>
<tr>
<td>Categories include (inactive, insufficiently inactive, sufficiently active) Activities during spare time, work and transport</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>No Smoking</td>
<td>lung, mouth and oropharynx, stomach, liver, pancreatic, cervix uteri, bladder, and leukaemia (&gt; 30 years) cancers</td>
</tr>
<tr>
<td>Current levels of smoking impact ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Alcohol use</strong></td>
<td>No alcohol use</td>
<td>liver, mouth and oropharynx, breast, oesophageal and other cancers (&gt; 15 years)</td>
</tr>
<tr>
<td>Current alcohol consumption volume and patterns</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Unsafe sex</strong></td>
<td>No unsafe sex</td>
<td>cervix uteri cancer (all ages)</td>
</tr>
<tr>
<td>Sex with an infected partner without any measures to prevent infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Urban air pollution</strong></td>
<td>7.5 ug/m³ for PM2₅, 15 ug/m³ for PM10</td>
<td>lung cancer (&gt; 30 years)</td>
</tr>
<tr>
<td>Estimated yearly average particulate matter concentration for particles with aerodynamic diameters &lt; 2.5 microns or 10 microns (PM₂₅ or PM₁₀)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Indoor smoke from household</strong></td>
<td>No household solid fuel use with limited ventilation</td>
<td>lung cancer (coal) (&gt;30 years)</td>
</tr>
<tr>
<td>Household use of solid fuels</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Contaminated injections in health-care settings</strong></td>
<td>No contaminated injections</td>
<td>Liver cancer (all ages)</td>
</tr>
<tr>
<td><strong>Exposure to &gt;1 contaminated injection</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2- Key factors associated with the risk of lung cancer

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Single most important causal determinant of individual and population risk, most valuable indicator of clinical risk a</strong></td>
<td><strong>Active smoking of cigarettes and other tobacco products:</strong> Individual risk increases with greater number of cigarettes smoked per day and greater number of years of smoking. Population risk increases with the prevalence of current smokers because population prevalence predicts lung cancer occurrence with a latency period of about 20-years</td>
</tr>
<tr>
<td><strong>B. Other risk factors causally associated with lung cancer a</strong></td>
<td>Secondhand smoke exposure Ionizing radiation, including radon Occupational exposures, eg, arsenic, chromium, nickel, asbestos, tar, and soot Indoor and outdoor air pollution</td>
</tr>
<tr>
<td><strong>C. Additional clinical risk indicators b</strong></td>
<td><strong>The risk factors noted above:</strong> Older age Male sex, particularly among those of African American ancestry Family history of lung cancer Acquired lung disease, COPD, TB, pneumoconiosis, idiopathic pulmonary fibrosis, and systemic sclerosis Occupational exposures, such as to inhalation of very small particles (silica dust)</td>
</tr>
<tr>
<td><strong>D. Examples of associations with consistent evidence but causal role not presently established</strong></td>
<td>HIV infection Fruit and vegetable intake (decreased risk) Physical activity (decreased risk) Marijuana smoking (not associated with risk)</td>
</tr>
</tbody>
</table>

*a The evidence for factors listed in these categories is extremely strong to meet epidemiologic criteria for causality.  
*b The factors listed under clinical risk indicators are all strongly associated with increased risk of lung cancer but are listed in this category either because they are intrinsic characteristics of the patient (age, sex, ethnic ancestry, family history) or are factors with consistent evidence of increased risk that presently falls short of being rated as causal.

Modified from Alberg et al. (2013)
2.3 COHORT STUDIES EXPLORING THE ROLE OF PHYSICAL ACTIVITY, CARDIORESPIRATORY FITNESS AND INFLAMMATION WITH LUNG CANCER RISK AND CANCER DEATH

The role of physical activity, CRF, (Robshahm et al. 2016) and inflammation (Sprague et al. 2008) may contribute to the risk of several cancers, including lung cancer. However, little is known about the interrelationship of these factors and their synergistic effects in relationship to lung cancer and cancer mortality risk. In the following cohort studies, the associations between physical activity, CRF, inflammation and cancer are described in detail. Observational studies describe associations, incidence, prevalence, causes and outcomes, which is a sufficient way to determine the cause of a disease, and the best way to establish incidence (Mann et al. 2003). In general, the criteria for the following studies include: 1) original prospective studies, 2) they investigated the effect of one or more variables of physical activity, CRF and inflammation on cancer 3) they reported a risk estimate with 95% confidence intervals. In addition, a brief description of study methodology.

2.3.1 Cardiorespiratory fitness and lung cancer

*The Cooper Center Longitudinal Study (CCLS)*

In this prospective, observational cohort study, the objective was to assess the associations between midlife CRF with incident cancer and survival after diagnosis. This included lung, prostate and colorectal cancers. Over an average follow-up of 6.5 years, there were 200 cases of lung cancer and CRF was associated with a reduced lung cancer risk (Lakoski et al. 2015). In a multivariate model, when comparing the low CRF (reference) to moderate CRF they observed a reduced risk HR 0.57 (95% confidence interval 0.41-0.81) for lung cancer, and a reduced risk for high CRF HR 0.45 (95% confidence interval 0.77-0.90). In addition, when comparing tertiles of CRF they showed a reduced risk for colon cancer. In a multivariate model, they observed a reduced risk for colon cancer when comparing the low CRF (reference) to moderate CRF, HR 0.67 (95% confidence interval 0.46-0.98), and a reduced risk for high CRF HR 0.56 (95% confidence interval 0.36-0.87). No association was observed between CRF and prostate cancer (Lakoski et al. 2015).

2.3.2 Physical activity and lung cancer

*European Investigation on Cancer and Nutrition (EPIC)*

This prospective cohort study was conducted in 23 centers that included 10 different European countries (France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden, Denmark and United Kingdom) (Steindorf et al. 2006). One of the primary aims for this study were to observe recreational and occupational physical activities as they relate to lung cancer risk. Of the 1,083 lung cancers cases, physical activity was not associated with lung cancer incidence (Steindorf et al. 2006). However, in the highest tertile (≥ 18.0 MET hours/week) for sport in men, and cycling for women was shown to reduce
lung cancer risk. Furthermore, vigorous non-occupational physical activity (< 33.5 MET hours/week) had reduced risk for lung cancer risk among women. In this study, Steindorf et al. 2006 did not observe that “physical activity” was clearly associated with a reduced lung cancer risk. However, evidence from this study suggests that specific physical activities may have preventative effects for lung cancer. Among men, in the category of recreational physical activity, the type of activity, “sport” shared an association with lung cancer risk. In a multivariate model, only the highest sport tertile of (≥ 18.0 MET hours/week) shared a reduced relative risk (RR) 0.71 (95% confidence interval 0.50-0.98) for lung cancer when compared to no sport, classified as none. Among women, physical activities had a slightly broader association for reducing lung cancer risk. The reduced risk for women was observed in vigorous non-occupational activities and cycling. For vigorous non-occupational activities, in a multivariate model the lowest tertile of (>0<13.5 MET hours/week) had shown a reduced risk of RR 0.65 (95% confidence interval 0.43-0.98) for lung cancer, as well as the middle tertile (13.5-33.5 MET hours/week) with a RR 0.60 (95% confidence interval 0.40-0.89) when compared with no activity. In recreational physical activity, women who were included in the highest tertile for cycling, had a RR 0.73 (95% confidence interval 0.54-0.99) reduced risk for lung cancer when compared to none (Steindorf et al. 2006).

2.3.3 Inflammation and lung cancer
Copenhagen General Population Study (CGPS)
In this prospective cohort study (Allin et al. 2016), the objective was to explore the associations of fibrinogen, CRP, and leukocyte count with colorectal, lung, prostate and breast cancers. Allin et al. 2016 examined if high plasma levels of CRP, leukocyte count and fibrinogen separately or combined were associated with common cancers in Denmark. Over a median follow-up of 4.8 years and maximum up to 9.1 years, 500 cases of lung cancer, 592 prostate, 822 breast, and 801 prostate cancers occurred. Individually, CRP, fibrinogen, and leukocyte count were associated with an increased risk of lung and colorectal cancers. An adjusted multivariate model consisted of age, sex, BMI, physical activity, smoking, alcohol consumption; for breast cancer, they adjusted for contraceptive therapy and hormone therapy. All of the biomarkers of inflammation were associated with lung cancer only when comparing the lowest tertile (reference) of CRP (<1.2 mg/l), fibrinogen (<9.9 umol/l), and leukocyte count (<6.5x10^9/l) with the highest tertile of CRP (>1.9 mg/l), fibrinogen (>11.9 umol/l), and leukocyte count (>7.9x10^9/l). In a multivariate model, which included light physical activity, an increased risk was observed when comparing the highest and lowest tertiles for CRP (HR 2.16 95 % confidence interval 1.67-2.78), fibrinogen HR (1.64 95 % confidence interval 1.25-2.16) and leukocyte count (HR 1.54 95 % confidence interval 1.22-1.94). When accumulated (combining the high inflammatory biomarkers into groups = 1+2+3), a linear relationship was observed for the risk of lung cancer for biomarker 1, with a HR 1.47 (95 % confidence interval 1.10-1.97) increased risk, and biomarkers 1+2 had a HR 2.07 (95 % confidence interval 1.55-2.76) increased risk and biomarkers 1+2+3 were associated with a HR 3.03 (95 % confidence interval 2.25-4.08) (Allin et al. 2016).
2.3.4 Physical activity, inflammation and lung cancer

*The Beaver Dam Eye Study (BDES)*

In this prospective cohort study, Sprague et al. 2008 had two primary aims, 1) to investigate the association between self-reported physical activity and lung cancer risk, and 2) to assess baseline inflammatory markers of white blood cell (WBC) count and serum albumin, and observe if these inflammatory markers mediate the relation between physical activity and lung cancer. An adjusted multivariate model included age, sex, pack-years of smoking, time since smoking cessation, BMI, alcohol intake, education and white blood cell count. Over an average follow-up of 12.8 years, 134 cases of lung cancer were diagnosed among 4,831 subjects. As a primary aim for this study, Sprague et al. 2008 observed that higher levels of baseline physical activity were associated with lung cancer incidence. After adjusting for lifestyle and demographic factors, the risk of lung cancer was reduced by 40% among participants in the highest tertile of total physical activity ≥ 875 (kcal/wk), and those who walked 12 or more city blocks per day as compared to no walking. In an adjusted multivariate model, when comparing the highest and lowest tertiles of total physical activity, they observed a reduced risk HR 0.56 (confidence interval 0.35-0.87) for lung cancer. The association between inflammatory biomarkers and lung cancer are as follows; in a multivariate model (excluding WBC), when comparing the lowest tertile < 6.4 x10³/uL of WBC to the highest tertile ≥ 8 (x10³/uL), they observed a 2.81-fold increased risk for lung cancer (95% confidence interval, 1.58-5.01, P=0.001 for trend across tertiles). Whereas, albumin shared no association with lung cancer risk. The second aim of the study was to assess if inflammation would mediate the associations between physical activity and lung cancer risk. In this study, white blood cell count did not appear to modify the relationship between total physical activity index and lung cancer risk (Sprague et al. 2008).

2.3.5 Cardiorespiratory fitness and cancer mortality

*The Copenhagen Male Study (CMS)*

The primary aim of this prospective cohort study was to examine the relationship between CRF with cancer and all-cause mortality (Jensen et al. 2016). Furthermore, they also assessed self-reported physical activity with questionnaires. With a follow-up period of 44.1 years, 4486 total deaths (87.4%) occurred, and over a 42.2-year follow-up, 1527 deaths were from cancer. An adjusted multivariate model included age, smoking, grams of tobacco per day, systolic and diastolic blood pressure, previous myocardial infarction, diabetes, self-reported physical activity, alcohol and social group. In a multivariate model, all tertiles of VO₂max were associated with cancer mortality. When comparing the first tertile (reference) with the second and third tertile of VO₂max, they observed a HR 0.88 (95% confidence interval 0.78-1.00) and HR 0.74 (95% confidence interval 0.64-0.84) reduced risk for cancer mortality, respectively. In addition, CRF was significantly associated across all tertiles of all-cause mortality over a follow-up of 44 years. However, in a multivariate model for self-
reported physical activity, no associations with cancer mortality were observed. For every 10 ml/kg/min increase in VO₂max, a decreased risk of HR 0.83 (95% confidence interval 0.77-0.90) in a multivariate model was observed. When comparing the reference, first tertile with the second tertile, they show a reduced risk of HR 0.88 (95% confidence interval 0.78-1.00). When comparing the first tertile with the third tertile, further reduction of cancer mortality was observed HR 0.74 (95% confidence interval 0.64-0.84). These results support the aims of the study from Jensen et al. (2016) and this study improves the current knowledge on the effects of CRF with cancer mortality (Jensen et al. 2016).

2.3.6 Physical activity, cardiorespiratory fitness with cancer risk and mortality
The Oslo Ischemia Study (OIS)
This prospective cohort study examined the associations between CRF, and self-reported physical activity with cancer risk, mortality and case fatality (Robsahm et al. 2016). At baseline, 1997 healthy Norwegian men from ages 40-59, were objectively measured for CRF and self-reported physical activity questionnaires (occupational, leisure time). Over an average follow-up of 26.2 years, 758 men were diagnosed with cancer and 433 died from cancer. Robsahm et al. 2016 showed that when comparing the highest and lowest tertiles of CRF, they observed HR 0.85 (95% confidence interval 0.68-1.00) a reduced risk for cancer, HR 0.68 (95% confidence interval 0.53-0.88) cancer death and HR 0.74 (95% confidence interval 0.57-0.96) for case fatality. Furthermore, they showed that leisure-time physical activity had modest associations with a HR 0.70 (95% confidence interval 0.56-0.86) reduced risk for cancer, HR 0.64 (95% confidence interval 0.49-0.83) cancer mortality, but not case fatality, when comparing “no activity” to a “light level”. In occupational physical activity, no associations were observed with cancer risk, death or case fatality (Robsahm et al. 2016).

2.3.7 Inflammation and cancer mortality
The Blue Mountains Eye Study (BMES)
The objective of this prospective cohort study was to examine the relationship between WBC and cancer mortality among residents near the Blue Mountains, west of Sydney (Shankar et al. 2006). In this cohort study, 212 cancer deaths occurred with a mean age of 66 years. White blood cell count was associated with cancer mortality only when comparing the lowest quartile of WBC referent (≤5300 Cells/ul)) with the highest quartile of WBC (≥7400 Cells/ul). When comparing the first and fourth quartiles of WBC, in a multivariate model including age and sex, they observed a RR 1.89-fold (95% confidence interval 1.29-2.75) increased risk for cancer mortality. On further analysis, they adjusted for education, BMI, hematocrit level, alcohol consumption, physical inactivity, smoking status, weekly aspirin use and diabetes status and observed a RR 1.76-fold (95% confidence interval 1.21-2.58) risk. Furthermore, they included fasting glucose levels and observed a RR 1.73-fold (95% confidence interval 1.18-2.55) increased risk. The results from Shankar et al. 2006.
suggest that higher baseline levels of WBC may increase the risk of cancer mortality (Shankar et al. 2006).

### 2.3.8 Other studies

In a case-control study (Ho et al. 2017), the objective was to assess the independent and combined impact of lifetime occupational history, and recreational activities with lung cancer risk among men and women. This study was conducted from 1996 to 2001. Recreational physical activity was assessed 20 years prior to diagnosis/interview, and occupational physical activity was assessed throughout life, which prevented the ability to combine into one variable. Histologically confirmed cases of lung cancer. Participation rate among cases was 84% (N=709 men, 422 women) and the randomly selected controls were 69% (N=889 men, 564 women). Unconditional logistic regression was used to estimate odds ratio (OR), separately for men and women. Increasing recreational physical activity was associated with a reduced lung cancer risk for men and women. In contrast, high occupational physical activity was associated with an increased risk for lung cancer among men, but not women. The odds ratio for high recreational physical activity versus low was 0.52 (95% CI 0.33-0.88%) for women and 0.77 (95% confidence interval 0.56-1.04) for men. For high versus low occupational physical activity, the odds ratio was 0.99 (95% confidence interval 0.62-1.58) in women and 1.57 (95% confidence interval 1.07-2.29) for men. A relationship between lung cancer and the joint effect of recreational and occupational physical activity was not observed (Ho et al. 2017).

In a meta-analysis (Li et al. 2016), the primary objective for this study was to observe the associations between physical activity and cancer mortality. The secondary objective was to compare the World Health Organization’s recommendations for physical activity with cancer death. Of the 71 prospective studies, this meta-analysis included 36 general population based studies and 35 studies conducted among cancer survivors. When comparing the lowest amount of physical activity with the highest amount of physical activity was observed to have a protective effect. With a pooled HR of 0.83 (95% confidence interval 0.79-0.87). The highest levels of physical activity were shown to reduce cancer death by 17% as compared to the lowest amount of physical activity. A non-linear association was observed between recreational physical activity of 5, 10, 15, 20 and 25 MET-h/week and had a HR 0.88, 0.86, 0.86, 0.85, 0.85. and 0.84 respectively, as compared to inactivity in the general population. Individuals who met the recommendations of the World Health Organization, of 7.5 MET-h/week, had a 14% lower risk of cancer death. In summary, high levels of physical activity may lower the risk for cancer mortality in the general population as compared to inactivity (Li et al. 2016).

In a prospective design, 118 patients completed a walking test to determine functional capacity and a self-reported exercise behavior questionnaire. The objective of this study was to determine the prognostic importance of functional capacity and exercise behavior among patients diagnosed with non-small cell lung cancer. Functional capacity of a patient was assessed by the distance covered in a six-minute walk test. During a median follow-up of 26.6 months, 77 deaths occurred and functional capacity was an independent predictor of survival. Every 50-meter improvement in the functional capacity was associated with a 13%
reduction in the risk for death. Compared with patients achieving a six-minute walk distance <358.5 m, the hazard ratio of all-cause mortality of HR 0.61 (95% confidence interval 0.34-1.07) for 6-minute walk test of 358.5-450 m, and HR 0.48 (95% confidence interval 0.24-0.93) for a six-minute walk test of >450 m. Furthermore, regular exercise behavior (>9 MET-hrs wk) was associated with a 33% reduced risk of death from non-small cell lung cancer relative to (<9 MET-hrs wk) (Jones et al. 2012).

2.3.9 Summary
To conclude, CRF, physical activity and inflammatory biomarkers, have been shown to have predictive value for the long-term outcome of cancer and/or cancer death (Table 3). These studies suggest that high levels of baseline fitness may reduce lung cancer and cancer mortality risk. For example, high CRF reduced lung cancer risk by 55% (HR 0.45, 95% CI 0.77-0.90) (Lakoski et al. 2015). With respect to physical activity and lung cancer, Steindorf et al. 2006 observed that specific physical activities may reduce the lung cancer risk. Among men, in recreational physical activity, the activity of, “sport” shared an association with lung cancer risk. They observed a reduced relative risk (RR) 0.71 (95% CI 0.50-0.98) for lung cancer when compared to no sport. Among women, vigorous non-occupational activities had a reduced risk of RR 0.65 (95% CI 0.43-0.98) and cycling RR 0.73 (95% CI 0.54-0.99) for lung cancer, when compared with no activity.

In these studies, high levels of inflammatory biomarkers shared an association with an increased risk for lung cancer and cancer death. However, frequent physical activity may reduce the odds of increased levels of inflammation (Abramson 2002). Sprauge et al. 2008 has shown that after adjusting for WBC in a multivariate model, physical activity was associated with lung cancer risk. White blood cell count increased lung cancer risk by 2.81-fold when comparing the lowest tertile (<6.4x10^3/μL) of WBC to the highest tertile (≥8 x10^3/μL) (Sprague et al. 2008). Furthermore, high plasma levels of CRP, fibrinogen and leukocyte count have shown an association with lung cancer (Allin et al. 2016). The highest risk was 2.16-fold for CRP, followed by 1.64-fold for fibrinogen and leukocyte count had a 1.54-fold increased risk (Allin et al. 2016). In the studies with cancer death, high CRF was associated with a 32% reduced risk (HR 0.68, 95% CI 0.53-0.88) (Robsahm et al. 2016) and a 26% reduction (HR 0.74, 95% CI 0.64-0.84) (Jensen et al. 2016). In contrast to high CRF, higher levels of baseline WBC increased cancer mortality risk by 1.89-fold (Shankar et al. 2006).

In summary, these prospective cohort studies suggest that physical activity, CRF and inflammation share an association with lung cancer and/or cancer death. Additionally, in a study among lung cancer patients, a case-control study, and a meta-analysis, physical activity reduces the risk for lung cancer and cancer death. Therefore, to improve the current literature on the role of physical activity in reducing cancer risk, this PhD thesis will explore the relationship between inflammatory biomarkers, physical activity, CRF with lung cancer and cancer mortality.
<table>
<thead>
<tr>
<th>First Author</th>
<th>Outcome</th>
<th>Study, sex</th>
<th>Country</th>
<th>Study design</th>
<th>Age, y</th>
<th>N. of cases/participants</th>
<th>Follow-up yrs</th>
<th>Measure</th>
<th>RR (95% CI) for multivariate models</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steindorf K, 2006</td>
<td>PA and lung cancer</td>
<td>EPIC, men and women</td>
<td>10 European countries</td>
<td>Prospective cohort study</td>
<td>Majority from 35-70 years</td>
<td>1,083 / 416,227</td>
<td>Average men 5.9 yrs, women 6.6 yrs</td>
<td>METs (hrs/wk)</td>
<td>Men &lt;9, 9-&lt;18, ≥ 18. Women &lt;6, 6-&lt;18, ≥ 18</td>
</tr>
<tr>
<td>Lakoski SG, 2015</td>
<td>CRF and incident cancer (Lung cancer)*</td>
<td>CCLS, men</td>
<td>Dallas, Texas</td>
<td>Prospective cohort study</td>
<td>mean 49 years</td>
<td>200 / 13,949</td>
<td>Average. 6.5 yrs</td>
<td>METs (peak) mean, Low (8.4), Mod (10.4), high (13). Estimated CRF.</td>
<td>Low vs mod, 0.57 (0.36-0.87), low vs high 0.45 (0.29-0.68)</td>
</tr>
<tr>
<td>Sprague BL, 2008</td>
<td>PA, inflammation, lung cancer</td>
<td>BDES, men and women</td>
<td>Beaver Dam, Wisconsin</td>
<td>Population-based cohort study</td>
<td>mean baseline, 58.7 years</td>
<td>134 / 4,831</td>
<td>Average. 12.8-yrs per person</td>
<td>Total PA (kcal/wk) &lt;174, 175-874, ≥ 875. WBC (x10^9/ul) &lt;6.4, 6.4-7.9, ≥.8. Total PA, Low vs high 0.55 (0.35-0.86). WBC, Low vs high 2.81 (1.58-5.01)</td>
<td>Total PA, Low vs high 0.55 (0.35-0.86). WBC, Low vs high 2.81 (1.58-5.01)</td>
</tr>
<tr>
<td>Robsahm TE, 2016</td>
<td>PA, CRF, cancer, cancer mortality</td>
<td>OIS, men</td>
<td>Oslo, Norway</td>
<td>Prospective cohort study</td>
<td>mean 49.3, 37-62</td>
<td>758 cancer risk, 433 cancer deaths/1997</td>
<td>Average, 26.2 yrs</td>
<td>CRF (kj/kg) &lt;118.9, 119-161.4, &gt;161.5. PA, no activity; light activity; Moderate/high. Cancer risk, Low vs high 0.85 (0.68-1.00). Cancer death, Low vs high 0.68 (0.53-0.88)</td>
<td>Cancer risk, Low vs high 0.85 (0.68-1.00). Cancer death, Low vs high 0.68 (0.53-0.88)</td>
</tr>
<tr>
<td>Allin KH, 2016</td>
<td>Inflammation and cancer (lung cancer)*</td>
<td>CGPS, men and women</td>
<td>Copenhagen, Denmark</td>
<td>Prospective cohort study</td>
<td>mean 58, 48-67</td>
<td>500 lung cancer/83,895</td>
<td>Median, 4.8 yrs</td>
<td>CRP (mg/l) &lt;1.2, 1.2-1.9, &gt;1.9. Fib. (umol/l) &lt; 9.9, 9.9-11.9, &gt; 11.9. Leukocyte (10^9/l) &lt; 6.5, 6.5-7.9, &gt; 7.9. CRP, Low vs High 2.16 (1.67-2.78). Fibrinogen 1.64 (1.25-2.16). Leukocyte 1.54</td>
<td>CRP, Low vs High 2.16 (1.67-2.78). Fibrinogen 1.64 (1.25-2.16). Leukocyte 1.54</td>
</tr>
<tr>
<td>Study</td>
<td>Cancer Site</td>
<td>Participants</td>
<td>Study Design</td>
<td>Mean Age</td>
<td>CRF (VO\textsubscript{2max}, ml/kg/min)</td>
<td>CRF (VO\textsubscript{2max}, ml/kg/min)</td>
<td>WBC Results</td>
<td>References</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>-------------</td>
<td>--------------</td>
<td>-------------</td>
<td>----------</td>
<td>---------------------------------------</td>
<td>---------------------------------------</td>
<td>-------------</td>
<td>------------</td>
<td></td>
</tr>
<tr>
<td>Jensen MT, 2016</td>
<td>CRF and cancer mortality</td>
<td>CMS, men</td>
<td>Copenhagen, Denmark</td>
<td>mean 48.8 yrs</td>
<td>1527 / 5131</td>
<td>Mean, 28.3 yrs</td>
<td>CRF (VO\textsubscript{2max}, ml/kg/min) 15-29, 30-35, 36-78.</td>
<td>Low vs mod 0.77 (0.68-0.87). Low vs high 0.64 (0.56-0.72).</td>
<td></td>
</tr>
<tr>
<td>Shankar A, 2006</td>
<td>Inflammation and cancer mortality</td>
<td>BMES, men and women</td>
<td>West of Sydney, Australia</td>
<td>mean 66 yrs, 49-84</td>
<td>212 / 3189</td>
<td>Dec 31, 1994 to Dec 31, 2001.</td>
<td>WBC quartiles (Cells/µL) ≤ 5300, 5400-6200, 6300-7300, ≥ 7400.</td>
<td>WBC, Results for Q1 (ref) vs Q4 1.76 (1.21-2.58).</td>
<td></td>
</tr>
</tbody>
</table>

(1.22-1.94).

2.4 MEASUREMENTS OF PHYSICAL ACTIVITY AND CARDIOVASCULAR FITNESS

2.4.1 Assessment of leisure-time physical activity
In order to reduce cancer risk, practitioners and researchers should understand the different methods used for measuring physical activity. When measuring physical activity, the physical activity dimensions are necessary, this includes; mode, frequency, duration and intensity (Strath et al. 2013). In epidemiological studies, physical activity measurements have included subjective and objective measurements. Subjective measures include self-reported questionnaires, diaries, personal journals (physical activity recall) and surveys, which are used to estimate energy expenditure (EE) and behavioral patterns. Subjective measures are commonly used and are cost effective for larger populations. Objective measurements may be used to estimate EE (accelerometers), calculate EE (doubly labeled water), and determine physical fitness levels with the physiological measure of maximum oxygen uptake (Bauman et al. 2006). These are only a few examples of assessment methods for physical activity, and choosing the appropriate physical activity assessment for public health research will depend on the desired outcome. Additional considerations in using physical activity measurements for research include feasibility and practicality (Strath et al. 2013).

Leisure-time physical activity is subjective measurement technique that requires the participant to self-recall the previous activities of his/herself. Therefore, self-reported questionnaires are commonly used to determine LTPA. In general, physical activity questionnaires are used to estimate EE. The relatively low cost of questionnaires have practical application in population health research. However, the disadvantages of individual self-reported physical activity include a poor estimation of intensity, or duration. (Loney et al. 2011). When compared with objective measurements, self-report shows more validity when used for population based estimation, rather than individual physical activity assessment (Loney et al. 2011).

2.4.2 Assessment of direct and indirect cardiorespiratory fitness
Cardiorespiratory fitness can be measured with indirect or directly methods. There are several indirect methods for estimating maximal oxygen uptake (VO₂max). Indirect methods may be a more viable choice for researchers, due to the relatively lower costs, availability, trained personnel and subject requirements (Grant et al. 1999). Therefore, for population studies, an indirect method may be more practical for assessing CRF. However, indirect exercise testing methods used for measuring (estimating) VO₂max, may have validity and inherent errors (Grant et al. 1999). Directly measured gas analyses to reach maximal oxygen uptake (VO₂max) is considered as the gold standard for CRF (Shepard et al. 1968).
At present, there are several procedures available for estimating VO\textsubscript{2}\text{max}. This measurement technique may be more suitable for a large number of individuals and reduce the health risk (Akalan et al. 2008). To estimate VO\textsubscript{2}\text{max}, there are several indirect testing methods available (Maximal Bruce, and 85% Bruce treadmill protocols, Astrand-Ryhming and heart-rate extrapolation cycle ergometer protocols, the Léger 20-m shuttle run, and Cooper’s 1.5-mile); these may have less than a 10% error. A 10% error range is generally expected for predictive tests (Grant et al. 1999). Due to expense, population group, and external factors, the practicality and feasibility for using directly measured VO\textsubscript{2}\text{max} may not be warranted. Therefore, a non-exercise method may be a better option. For example, a formulated regression equation based on non-exercise variables (age, body mass, and resting heart-rate) may reliably predict VO\textsubscript{2}\text{max} (Rexhepi & Brestovci 2014).

CRF provides information on the overall capacity of the aerobic energy system. Directly measured VO\textsubscript{2}\text{max} should be accepted as the absolute criterion (Shepard et al. 1968). CRF is described as the highest value or plateau of directly measured oxygen consumption by a respiratory gas analyzer (Laukkanen et al. 2010). The standardized criteria of VO\textsubscript{2}\text{max} includes; respiratory gas exchange data, the assessment of lactate threshold and pulse rate. Maximum oxygen intake is achieved when a further increase of workload, oxygen consumption has increased at a value lower than 2 ml/kg/min, and in most cases, the post-exercise lactate concentration > 100mg/100ml and pulse rate is within 2 standard deviations of the expected maximum value (Shepard et al. 1968).

2.4.3 Determinants of cardiorespiratory fitness
Cardiorespiratory endurance has been shown as a primary component for health related fitness. Regular endurance exercise can lead to permanent adaptations of the cardiorespiratory system, therefore improving physical fitness (Fahey 2015). Maximal oxygen uptake is dependent on physical activity exposure, which suggests that frequency, intensity, time and type of activities may impact CRF levels. However, age, gender, body size and genetics will influence CRF (Fletcher et al. 2001). Maintaining a physically active lifestyle may reduce the impact of age related decline of VO\textsubscript{2}\text{max}, whereas, CRF can influence quality of life and all-cause mortality (Hawkins & Wiswell 2003).

2.5 MEASUREMENT OF INFLAMMATORY BIOMARKERS

2.5.1 Assessment of inflammatory biomarkers
Baseline measurements of blood leukocyte count was measured with a cell counter (Coulter Counter Electronics, Luton, United Kingdom). The between-batch coefficient of variation (CV) was below 4% (Toriola, 2013). The Coulter counter is a device used for counting individual cells. Serum CRP concentration was measured using an immunometric assay (Immule High-Sensitivity CRP assay, DPC, Los Angeles, CA). The between batch CV was 3.1% at the CRP level of 3.2 mg/l.
2.5.2 Determinants of inflammatory biomarkers
High levels of inflammatory biomarkers may increase the risk for several chronic diseases, including cancer. Environmental and behavioral factors can influence individual levels of inflammation, however, CRP and WBC are partly determined through genetic factors (Pankow et al. 2001).

2.6 THE ROLE OF PHYSICAL ACTIVITY, CARDIORESPIRATORY FITNESS AND INFLAMMATORY BIOMARKERS IN RISK PREDICTION

2.6.1 The role of cardiorespiratory fitness in risk prediction
The health related benefits of CRF are well documented. CRF has shown to be a powerful predictor of disease and functional outcomes (Kaminsky et al. 2013). The health related physiological adaptations that occurs by improving CRF have immediate and long-term effects (Fahey 2015).

Presently, few longitudinal studies have focused on the associations between directly measured CRF (maximal exercise test) and cancer mortality (Schmid et al. 2014). Previous epidemiological evidence suggests that physical activity reduces the risk of several cancers, (Friedenreich et al. 2010) and high CRF reduces cancer mortality risk (Sawada et al. 2003) (Figure 4). Cardiorespiratory fitness may attenuate obesity related diseases (LaMonte & Blair 2006) and the mortality risk associated with an unhealthy diet (Heroux et al. 2009).
Figure 4. Meta-analysis of cancer mortality for individuals with high versus low cardiorespiratory fitness or intermediate versus low cardiorespiratory fitness; CI = confidence interval. Modified from Schmid & Leitzmann (2014)
2.6.2 The role of leisure-time physical activity in risk prediction

Leisure-time physical activity and CRF have been independently associated with a reduced disease risk among the same population (Lakka et al. 1994). Furthermore, the intensity (Lahti et al. 2014) and volume (Moore et al. 2012) of LTPA reduces mortality risk among middle-aged men and women (Lahti et al. 2014). Previous studies have also associated LTPA with reduced risk of mortality of those with familial factors (Kujala et al. 1998), and pre-diagnosed disease (Sone et al. 2013). In cancer related diseases, evidence suggests that higher levels of LTPA can reduce lung cancer (Tardon et al. 2005) and cancer mortality risk (Laukkanen et al. 2011).

Physical activity can reduce cancer risk through multiple pathways; maintaining a healthy body weight and energy expenditure may have positive affects for the immune system and regulate sex hormones, insulin, and prostaglandins (Kushi et al. 2012). Physical activity improves pulmonary efficiency and ventilation, therefore, limiting the exposure time of carcinogenic agents in the lungs (Brenner et al. 2016). High or moderate physical activity levels have been associated with a reduced risk in colon, endometrial and breast cancers (McTiernan 2008). Physical activity may modify cancer risk through various biological mechanisms, which include the immune system and steroid sex hormones. Physical activity effects the immune system in several ways, which includes; macrophages, natural killer cells, cytotoxic T lymphocytes and lymphonkine-activated killer cells. Steroid sex hormones have been associated with reproductive cancers in both genders and physical activities may have a protective role (Alberts & Hess 2013). Furthermore, physical activity may reduce the risk of cancer by reducing systemic inflammation, hyperinsulinemia and improving insulin resistance (McTiernan 2008).

2.6.3 The role of inflammatory biomarkers in risk prediction

Chronic inflammation is a strong risk factor for several cancers, and as inflammation persists, cancer risk increases (Shacter et al. 2002). Elevated levels of CRP increase the risk for all cancers (Allin et al. 2009). C-reactive protein has also been associated with all-cause mortality, although, the specific role of CRP as a marker, or causative factor is unclear (Zacho et al. 2010). There is lack of evidence suggesting that CRP has a causal role in malignancies, although, colorectal cancer may provide some evidence (Heikkilä et al. 2007). Among observational studies, three possible mechanisms may contribute to CRP and cancer risk. First, causality, CRP is the source of cancer pathogenesis. Second, reverse causality, i.e. cancer is the cause for increased CRP levels and confounding. The third mechanism involves a factor such as smoking which increases both cancer risk and CRP levels (Allin et al. 2011). However, CRP may be a better marker of an underlying disease, than the actual cause of the disease (Zacho et al. 2010).

In recent years, several epidemiological studies have suggested that inflammation is associated with many cancer types (Trinchieri et al. 2012). For example, a number of studies have examined the associations between leukocyte count (WBC) (Van Hemelryck et al.
2011) and incident cancers (Margolis et al. 2007). However, the role of leukocyte count in predicting cancer mortality is limited (Shankar et al. 2006).

2.6.4 The joint effect of inflammatory biomarkers and cardiorespiratory fitness in risk prediction
Previous research has shown an independent association between CRP (Allin et al. 2009), and CRF with cancer risk (Laukkanen et al. 2010). Cardiorespiratory fitness and CRP share an inverse relationship, independent of body mass index, waist girth, and percentage of body fat (Church et al. 2002). To date, few studies have focused on the risk associated with the joint effects of CRP combined with CRF to predict cancer morbidity and mortality.
In previous studies, physical activity (Geffken et al. 2001) and fitness (Church et al. 2002) were consistent in reducing leukocyte counts (WBC). Furthermore, leukocyte count (Shankar et al. 2006) and CRF (Sawada et al. 2003) have been associated with cancer death. To my knowledge, no prior studies have shown the joint impact of leukocyte count and CRF and their association with cancer mortality.

2.7 SUMMARY OF THE REVIEW OF LITERATURE
To reduce an individual’s risk of developing or dying from cancer, moderate to vigorous LTPA and high levels of CRF have shown long-term health benefits. Regular physical activity may reduce cancer rates by 46%, through a reduction in fat stores, changes in sex hormone levels, immune function and direct effects on the tumor (Warburton et al. 2006). Furthermore, CRF shares an inverse relationship with inflammation (Church et al. 2002) and frequent physical activities may significantly reduce the odds of increased levels of inflammation, (Abramson 2002) across all phases of carcinogenesis (Trinchieri 2012). In these previous studies, physical activity, CRF, and inflammation have all been associated with cancer risk and death. However, their independent role and interrelationship with cancer is limited in previous literature. Only a few studies have examined the long-term effects of directly measured CRF with lung cancer risk. Furthermore, few studies have evaluated the associations between cancer outcomes and the joint impact of inflammatory biomarkers (leukocyte count, CRP) and CRF. Therefore, to bridge the gap in literature, this PhD thesis will explore the relationship between inflammatory biomarkers, physical activity, CRF with lung cancer and cancer mortality.
3 Aims of the Study

The specific aims of the present study include:

I. To investigate the association of cardiorespiratory fitness and leisure-time physical activity with lung cancer risk.

II. To examine the combined and independent associations of cardiorespiratory fitness and C-reactive protein with lung cancer risk.

III. To examine the combined and independent associations of cardiorespiratory fitness and inflammatory biomarkers (leukocyte count, C-reactive protein) and with cancer mortality.
4 Methods

4.1 STUDY POPULATION

The study participants were a part of the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD). This study was designed to examine risk factors (age, smoking, alcohol) (Table 5), which also includes physical fitness (Table 6), for atherosclerotic CVD and cancers (Laukkanen et al. 2010). The first prospective analysis of all of the participants in KIHD at baseline included a randomly selected sample of 3235 men from Eastern Finland (Salonen et al. 1992). Among these, 2,682 (82.6%) participated. These men resided in the town of Kuopio or the surrounding communities and were 42, 48, 54, or 60 years of age at baseline examinations, which were conducted from March 20, 1984 to December 5, 1989 (Kurl et al. 2003). The KIHD was approved by the Research Ethics Committee of the University of Kuopio, Kuopio, Finland. Each participant gave written informed consent.

Table 4. The description of the study population and main variables in studies I-III.

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Population</th>
<th>Exposure</th>
<th>Follow-up time</th>
<th>Main Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>2305</td>
<td>Without cancer</td>
<td>CRF, LTPA</td>
<td>20 years</td>
<td>73 cases of lung cancer</td>
</tr>
<tr>
<td>II</td>
<td>2276</td>
<td>Without cancer</td>
<td>CRP, CRF</td>
<td>21 years</td>
<td>73 cases of lung cancer</td>
</tr>
<tr>
<td>III</td>
<td>2270</td>
<td>Without cancer</td>
<td>Leukocyte count, CRP, CRF</td>
<td>22 years</td>
<td>272 cases of cancer death</td>
</tr>
</tbody>
</table>

(CRF) cardiorespiratory fitness, (LTPA) Leisure-time physical activity, (CRP) C-reactive protein
Table 5- Baseline characteristics of men from KIHD whom were followed for an average of 22 years.

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Cancer Decedents</th>
<th>Lung Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>N</td>
<td>2302</td>
<td>278</td>
<td>79</td>
</tr>
<tr>
<td>Age</td>
<td>52.82 (5.05)</td>
<td>54.11 (3.75)</td>
<td>54.35 (4.31)</td>
</tr>
<tr>
<td>Years of Education</td>
<td>8.69 (3.48)</td>
<td>8.22 (3.33)</td>
<td>8.03 (3.50)</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td>12.16 (5.12)</td>
<td>12.69 (5.19)</td>
<td>13.62 (4.71)</td>
</tr>
<tr>
<td>Fruit and berries intake (4 days, g)</td>
<td>162.69 (145.29)</td>
<td>141.90 (137.70)</td>
<td>115.41 (118.64)</td>
</tr>
<tr>
<td>Vegetable intake (4 days, g)</td>
<td>289.12 (124.57)</td>
<td>279.45 (123.43)</td>
<td>244.47 (100.84)</td>
</tr>
<tr>
<td>Body mass index (kg/m2)</td>
<td>26.87 (3.45)</td>
<td>26.73 (3.27)</td>
<td>25.88 (3.22)</td>
</tr>
<tr>
<td>Cancer in family, (%)</td>
<td>25</td>
<td>29</td>
<td>32</td>
</tr>
<tr>
<td>Smoking (cig/day)</td>
<td>5.40 (9.88)</td>
<td>8.15 (11.17)</td>
<td>16.78 (13.00)</td>
</tr>
<tr>
<td>Smoking (pack/year)</td>
<td>8.18 (16.16)</td>
<td>13.39 (19.73)</td>
<td>29.54 (24.49)</td>
</tr>
<tr>
<td>Alcohol (g/week)</td>
<td>74.29 (133.61)</td>
<td>87.23 (182.95)</td>
<td>126.73 (278.80)</td>
</tr>
<tr>
<td>Alcohol (g/day)</td>
<td>10.61 (19.08)</td>
<td>12.46 (26.13)</td>
<td>18.10 (39.82)</td>
</tr>
<tr>
<td>Waist to hip ratio</td>
<td>0.94 (0.05)</td>
<td>0.95 (0.04)</td>
<td>0.94 (0.04)</td>
</tr>
<tr>
<td>LDL-chol* (mmol/l)</td>
<td>4.04 (1.01)</td>
<td>4.12 (1.05)</td>
<td>4.31 (1.27)</td>
</tr>
<tr>
<td>HDL-chol* (mmol/l)</td>
<td>1.29 (0.30)</td>
<td>1.28 (0.28)</td>
<td>1.27 (0.25)</td>
</tr>
<tr>
<td>Mean systolic blood pressure</td>
<td>134.01 (16.74)</td>
<td>134.56 (18.32)</td>
<td>132.57 (15.12)</td>
</tr>
<tr>
<td>Mean diastolic blood pressure</td>
<td>88.86 (10.43)</td>
<td>88.80 (11.39)</td>
<td>87.30 (11.24)</td>
</tr>
<tr>
<td>B-Glucose (mmol/l)</td>
<td>4.76 (1.07)</td>
<td>4.74 (1.04)</td>
<td>4.79 (1.13)</td>
</tr>
<tr>
<td>S-Insulin (mU/l)</td>
<td>11.61 (6.98)</td>
<td>11.73 (7.66)</td>
<td>10.48 (5.08)</td>
</tr>
</tbody>
</table>

Data are means and standard deviations (SD)

*HDL cholesterol: High density lipoprotein

*LDL cholesterol: Low density lipoprotein
Table 6- Cardiorespiratory fitness, physical activity and inflammatory biomarkers of men from KIHD whom were followed for an average of 22 years.

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Cancer Decedents</th>
<th>Lung Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>2302</td>
<td>278</td>
<td>79</td>
</tr>
<tr>
<td>VO₂max* (ml/kg/min)</td>
<td>30.28 (7.93)</td>
<td>28.94 (7.56)</td>
<td>27.68 (6.24)</td>
</tr>
<tr>
<td>Energy expenditure in OPA* (kcal/day)</td>
<td>1610.45 (1193.84)</td>
<td>1596.47 (1232.33)</td>
<td>1289.45 (1274.52)</td>
</tr>
<tr>
<td>Energy expenditure in CLTPA* (kcal/day)</td>
<td>139.63 (173.22)</td>
<td>130.17 (169.36)</td>
<td>120.65 (195.93)</td>
</tr>
<tr>
<td>Energy expenditure (kj/4-day mean)</td>
<td>9916.57 (2566.13)</td>
<td>9668.21 (2481.45)</td>
<td>9842.99 (2586.80)</td>
</tr>
<tr>
<td>Exercise capacity in watts (peak)</td>
<td>221.80 (51.99)</td>
<td>214.11 (47.45)</td>
<td>200.45 (44.63)</td>
</tr>
<tr>
<td>Leukocyte count (10⁹/L)</td>
<td>5.68 (1.58)</td>
<td>5.99 (1.81)</td>
<td>6.79 (1.62)</td>
</tr>
<tr>
<td>CRP* (mg/l)</td>
<td>2.28 (3.41)</td>
<td>2.17 (2.72)</td>
<td>3.45 (3.81)</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>3.01 (0.56) (n=2113)</td>
<td>3.05 (0.53) (n=248)</td>
<td>3.25 (0.65) (n=72)</td>
</tr>
</tbody>
</table>

Data are means and standard deviations (SD)

*CRP: C-reactive protein, *VO₂max: Maximal oxygen uptake
*OPA: Occupational physical activity, *CLTPA: leisure-time physical activity
4.2 ASSESSMENT OF CARDIORESPIRATORY FITNESS
Cardiorespiratory fitness includes the direct measurement of VO2max, which is recognized as the gold standard for measuring CRF (Kurl et al. 2003). Cardiorespiratory fitness is described as the highest value or plateau of directly measured oxygen consumption by a respiratory gas analyzer (Lakka et al. 1994). A maximal symptom-limited exercise tolerance test was performed between 8:00 a.m. and 10:00 a.m. using an electrically braked cycle ergometer. The standardized testing protocol comprised of an increase in the workload of 20 W/min. These tests were supervised by an experienced physician with the assistance of an experienced nurse (Laukkanen et al. 2010). A detailed description of CRF data collection has been previously published (Lakka et al. 1994). In brief, respiratory gas exchange was used for 612 men by the mixing-chamber method, whereas the remaining 1693 men had the breath-by-breath method. The common reasons for stopping the exercise included; leg fatigue (1163 men), exhaustion (356), breathlessness (202), pain in the leg muscles, joints or back (117). Discontinuing the test was due to cardiorespiratory symptoms or abnormalities of (361) men, which included arrhythmias (69), dyspnea (108), systolic or diastolic blood pressure (51), dizziness (14), chest pain (84) and ischemic electrocardiographic changes (35).

4.3 ASSESSMENT OF LEISURE-TIME PHYSICAL ACTIVITY
Leisure-time physical activity was assessed using the 12-month physical activity questionnaire, which is modified from the Minnesota Leisure Time Physical Activity Questionnaire. This questionnaire included the most common physical activities of middle-aged Finnish men (Lakka et al. 1994). For every type of physical activity, the subjects were required to indicate the frequency (session per month), average duration (hours and minutes per session) and intensity (0 no activity, 1 conditioning, 2 brisk, and 3 competitive). The intensity of physical activity was expressed in metabolic units (MET, or metabolic equivalents of oxygen consumption). Leisure-time physical activity was categorized according to type: (1) conditioning physical activity—walking (mean intensity, 4.2 MET), jogging (10.1 MET, skiing (9.6 MET), bicycling (5.8 MET), ect., (2) nonconditioning physical activity—crafts, repairs, or building (2.7 MET), yard work, gardening, farming, or snow shoveling (4.3 MET), ect., and (3) walking (3.5 MET) or bicycling (5.1 MET) to work (Lakka et al. 1994).

4.4 BIOCHEMICAL ANALYSES
The subjects were asked to abstain from alcohol consumption for 3 days, smoking for 12 hours, and fasting for 12 hours. The blood specimens were collected between 8:00 and 10:00 AM. After resting in a supine position for 30mins, the subject’s blood was withdrawn with a Terumo Venoject VT-100PZ (Terumo Corp., Tokyo) without the use of a tourniquet (Salonen et al. 1992). Blood leukocyte count was measured with a cell counter (Coulter Counter Electronics, Luton, United Kingdom). The between-batch coefficient of variation was below 4% (Toriola et al. 2013). Serum hs-CRP concentration was measured using an
immunometric assay (Immulite High-Sensitivity CRP assay, DPC, Los Angeles, CA). The between batch coefficient of variation was 3.1% at the CRP level of 3.2 mg/l.

4.5 OBESITY
Body mass index was calculated as body weight in kilograms divided by the square of height in meters. Subjects with a BMI greater than 25 m/kg² were considered overweight, and greater than 30 m/kg² were obese.

4.6 SMOKING AND ALCOHOL CONSUMPTION
The subjects who smoked cigarettes regularly, cigars or a pipe within the last 30 days were considered a smoker. The daily frequency and duration in years were recorded on a self-administered questionnaire, which was checked by an interviewer. An estimation of lifelong exposure to smoking was determined by the number of smoking years and daily use of tobacco products on the date of examination (Salonen et al. 1992). Alcohol consumption was determined by the quantity and frequency method for the Nordic alcohol consumption inventory (Toriola et al. 2013). Frequency, quantity (dose), and type of drink were recorded onto a response form. This assessment of alcohol intake and drinking patterns were then averaged into a weekly intake, based on the alcohol content of the drink and reported doses and frequencies (Toriola et al. 2013).

4.7 EDUCATION
To describe lifetime education, the participants where classified into one of four categories: less than an elementary education, completion of elementary education, completion of elementary school, completion of middle school, and completion of high school or above (Wilson et al. 1993).

4.8 FRUITS AND VEGETABLES
Food and nutrient assessment was taken at baseline. Subjects were instructed on the use of household measures for quantitative recording of their food intake over 4 days of data collection. A nutritionist gave instructions and checked the completed food intake records. Dietary food and nutrient intake was calculated using the NUTRICA software (Rissanen et al. 2003), which used the quantitative recording of 4 days of data collection. NUTRICA is capable of determining the vitamins in fruits and vegetables (Toriola et al. 2013).

4.9 BLOOD PRESSURE
Resting blood pressure was measured between 8:00 and 10:00 AM on the first examination day by one nurse with a random-zero mercury sphygmomanometer. The measuring protocol included, after a supine rest of 5 minutes, three measurements in supine, one in standing, and two in a sitting position with 5 minute intervals. The mean of all six systolic pressure values was used in the present analyses as the systolic blood pressure and the mean of all six diastolic measurements as diastolic blood pressure (Salonen et al. 1992).
4.10 BASELINE DISEASES
The family history of cancer was defined as the immediate family members including father, mother, sister or brother, have previously had, or currently have cancer. The subjects answered a self-administered questionnaire which was checked by an interviewer (Karppi et al. 2009).

4.11 COLLECTION AND CLASSIFICATION OF FOLLOW-UP EVENTS
Lung cancer diagnoses were coded according to the ICD-9 (International Classification of Diseases, Ninth Revision, Codes 160-165) or ICD 10 (code C34). Incident cancer cases in Finland are derived from the Finnish Cancer Registry (Laukkanen et al. 2010). Finnish personal identification codes are given to all Finnish residents, Finnish Cancer Registry has access to virtually all follow-up data on cancer diagnosis. There was no loss to follow-up. Follow-up started at baseline and ended on 31 Dec 2011. Men were excluded in the first 2 years of follow-up if they had lung cancer or history of cancer. Cancer deaths were ascertained by linkage to the National Death Registry using the Finnish personal identification codes. Follow-up started at baseline and ended on 31 Dec 2015. Men were excluded from the follow-up if they had died within the first 5 years or had a history of any cancer (Laukkanen et al. 2011).

4.12 STATISTICAL METHODS
Statistical analyses were performed with SPSS software, version 19.0 for Windows (SPSS, Inc, Chicago, Illinois). Descriptive data was organized to show the continuous data as mean and standard deviations, and categorical data is shown as percentages. To investigate the conventional risk factors for main outcomes, we analyzed Cox proportional hazards models. Relative hazards which were adjusted for risk factors were estimated as antilogarithms of coefficients from multivariable models. All tests for statistical significance were defined as p-values of < 0.05 and were 2-sided p-values. Spearman’s correlation was used for biomarkers and selected characteristics. The Kaplan-Meijer method was used to calculate the cumulative incidence of lung cancer and cancer mortality. The Kaplan-Meijer survival curve estimates are frequently used to assess the proportion hazards assumption (Xue et al. 2013).

4.13 STUDY I
In this population-based cohort, a sample of 2305 men from eastern Finland were randomly selected and had no history of cancer. The average follow-up time was 20 years. Energy expenditure and CRF were entered into Cox models as continuous variables and also classified into quartiles. In these models the reference group was the highest quartile. Three sets of covariates were used: model 1) age and examination year model 2) cigarette smoking, alcohol consumption, and cancer in family model 3) education, fruits and vegetables. The association of conventional risk factors and the risk for lung cancer was analyzed using Cox proportional hazards model. Relative hazards which were adjusted for
risk factors and estimated as antilogarithms of coefficients from multivariable models (Table 4).

**4.14 STUDY II**
In this cohort, 2276 men from eastern Finland were randomly selected and had no history of cancer. An average follow-up time was 21 years. C-reactive protein, CRF and the other risk factors for lung cancer were examined by covariate analyses and the risk of lung cancer with Cox proportional hazard modeling. To investigate the joint associations of CRP and CRF to lung cancer risk, median values of CRP and VO2max were classified into four categories of low/high, where low CRP and high CRF were used as the reference. On the basis of previous studies, a CRP cut-off >3.0 (mg/l) was used in a subsidiary analysis (Siemes C et al 2006). Three sets of covariates were used: model 1) age and cigarette smoking model 2) BMI, fruits and berries, and alcohol consumption, and model 3) education and cancer in family. The association of conventional risk factors and the risk for lung cancer was analyzed using proportional hazards Cox model. Relative hazards which were adjusted for risk factors and estimated as antilogarithms of coefficients from multivariable models.

**4.15 STUDY III**
In this population-based cohort of 2270 men from eastern Finland, had no history of cancer and an average follow-up time was 22 years. We examined leukocyte count, CRP, CRF and the other risk factors for cancer mortality by covariate analysis and the risk of cancer mortality with Cox proportional hazard modeling. In this population, common cancer deaths included lung, prostate, and GI tract (excluding pancreatic). To investigate the joint associations of inflammatory markers of (CRP, leukocyte count) and CRF with cancer mortality risk, the median values of CRP, leukocyte count and CRF were divided into four categories of low/high. Low leukocyte count and high CRF were used as a reference category. In addition, low CRP and high CRF were used as the reference category. Three sets of covariates were used: model 1) age and examination year, model 2) cancer in family and alcohol consumption, cigarette smoking and model 3) BMI and fruits and berries. Relative hazards which were adjusted for risk factors and estimated as antilogarithms of coefficients from multivariable models.
5 Results

5.1 STUDY 1: LTPA, CRF AND LUNG CANCER RISK

5.1.1 Leisure-time physical activity and lung cancer risk
At baseline, the mean LTPA was 139.9 kcal/day (range 0.01-2492.7, kcal/day). Men with lung cancer had lower mean LTPA, (125.8 kcal/day) as compared to men without lung cancer (140.3 kcal/day). The risk factors for lung cancer included smoking (p<0.001), alcohol consumption (p=0.047) and age (p=0.011). Men in the lowest quartile 10.67 (kcal/day) of LTPA had a 2.6-fold increased risk (p=0.01) for lung cancer as compared to the highest quartile 367.4 (kcal/day) after adjusting for age and examination year. After further adjustment for cancer in the family, smoking and alcohol, LTPA was not associated with the risk of lung cancer. Increasing LTPA by 0.80 kcal/day (1 SD) shared no association (RR 1.04, 95% CI 0.82 to 1.30) with lung cancer risk. After adjusting for CRF and LTPA into a multivariate model, CRF remained a significant predictor for lung cancer risk, whereas, LTPA shared no association.

5.1.2 Cardiorespiratory fitness and lung cancer risk
The mean CRF was 30.28 ml/kg/min (range 6.4-65.4 ml/kg/min) at baseline. Men with lung cancer had lower mean CRF, (27.0 ml/kg/min) as compared to men without lung cancer, (30.3 ml/kg/min) (p=0.001). Low CRF <25.0 ml/kg/min (lowest quartile) was associated with 4.3-fold risk of lung cancer after adjustment for age and examination year, when compared to the highest quartile. After further adjustment for cigarette smoking, alcohol consumption, and cancer in the family, there was a 3-fold risk for lung cancer when comparing the lowest and highest quartiles of CRF. Men with a low CRF <25.0 ml/kg/min (lowest quartile) had a 2.8-fold increased risk for lung cancer as compared with men with CRF of ≥35.1 ml/kg/min (referent) in a multivariate model. Excluding lung cancer events in the first 2 years of follow-up had no effect on results (Figure 5).
5.2 STUDY 2: CRF, CRP, AND LUNG CANCER RISK

5.2.1 Cardiorespiratory fitness and lung cancer risk
At baseline, the mean CRF was 30.28 ml/kg/min (range 6.4-65.4 ml/kg/min). Men with lung cancer had lower levels of CRF 27.6 ml/kg/min as compared to men without lung cancer 30.3 (ml/kg/min) (p<0.01). In a multivariate model, CRF had a 3-fold risk (RR 3.53, 95% CI 1.35-9.23, p=0.01) when comparing the highest and lowest quartiles of CRF.

5.2.2 C-reactive protein and lung cancer risk
The mean CRP concentration was 2.2 mg/l (range 0.1-53.5 mg/l) at baseline. Men with lung cancer had higher levels of CRP 3.6 mg/l as compared to men without lung cancer 2.2 mg/l (p<0.01). In this study, the independent predictive value of CRP shared a linear trend with lung cancer risk. A 3-fold (RR 3.22, 95% CI 1.44-7.20 p<0.01) risk was observed when comparing the highest and lowest quartiles of CRP. Furthermore, in a sub-analysis of CRP
>3.0 (mg/l) in a multivariate model, the association between CRP and lung cancer risk remained significant (RR 2.06, 95% CI 1.26-3.38, p<0.01).

5.2.3 C-reactive protein, cardiorespiratory fitness and lung cancer risk

To investigate the joint associations of CRP and CRF, we combined the median values of CRP and VO₂max into four categories. At baseline, the median CRP concentration was 1.24 mg/l (range 0.1-53.5 mg/l). The median CRF was 30.08 ml/kg/min (range 6.4-65.4 ml/kg/min). In a model adjusting for age and smoking, the joint impact for of high CRP (>1.24 mg/l) combined with low CRF (VO₂max < 30.08 ml/kg/min) was 3-fold (RR 3.34, 95% CI 1.36-8.18, p<0.01) the risk for lung cancer when compared to the reference group low CRP (<1.24 mg/l) and high CRF (VO₂max > 30.08 ml/kg/min). After further adjustment for intake of fruits and berries, alcohol consumption and BMI, the risk of lung cancer remained 4-fold (RR 4.22, 95% CI 1.67-10.64, p<0.01) as compared to the reference group. Further adjustment for family history of cancer and education, the risk of lung cancer was 4-fold (RR 4.19, 95% CI 1.66-10.57, p<0.01) among men with high CRP (>1.24 mg/l) combined with low CRF (VO₂max < 30.08 ml/kg/min) as compared to the reference group. The joint impact for men categorized with high CRP (>1.24 mg/l) and combined with either low/high CRF (VO₂max < > 30.08 ml/kg/min), had an increased risk for lung cancer as compared to the reference group (Figure 6). In a multivariate model, the interaction between CRP and CRF was almost statistically significant (p=0.054). In further analysis, after adjusting for pack-years in the multivariate model, the relative risk was statistically significant (RR 4.45, 95% CI 1.77-11.22, p<0.01) when we compared the joint impact of high CRP (>1.24 mg/l) combined with low CRF (VO₂max < 30.08 ml/kg/min) to the reference group. Furthermore, when we included smoking status (smoker/non-smoker) into the model, the results remained statistically significant (RR 3.45, 95% CI 1.36-8.75, p<0.01).
Figure 6. A multivariate adjusted model for lung cancer risk according to categories of low/high, low CRP and high CRF was used as the reference.

5.3 STUDY 3: INFLAMMATORY MARKERS, CRF AND CANCER MORTALITY RISK

5.3.1 Cardiorespiratory fitness and cancer mortality
Men who died from cancer had lower baseline CRF (28.91 ml/kg/min) as compared to other participants (30.47 ml/kg/min) (p<0.01). In a multivariate model for CRF, every 1 SD (7.9 ml/kg/min) increase in CRF was related to a 21 % decrease in cancer death. We observed a 2-fold (RR 2.01, 95% CI 1.33-3.04, p<0.01) risk for cancer mortality when comparing the highest (Q4 > 35.01-65.40 ml/kg/min (referent)) and lowest (Q1 < 25.10 ml/kg/min) quartiles of CRF.
5.3.2 C-reactive protein and cancer mortality
The mean CRP concentrations were 2.2 mg/l (range 0.10-53.50 mg/l) at baseline. Men who died from cancer had lower concentrations of CRP (2.18 mg/l) as compared to other participants (CRP 2.30 mg/l) (p=0.59). Elevated concentrations of CRP were not associated with cancer death. In a multivariate model, when we compared the highest (Q4 > 2.37-53.50 mg/l) quartile of CRP to the lowest quartile, (Q1 < 0.10-0.68 mg/l (referent)) no association with cancer mortality was observed (RR 0.96, 95% CI 0.66-1.38, p=0.83).

5.3.3 C-reactive protein, cardiorespiratory fitness and cancer mortality
The median concentration was 1.24 mg/l (range 0.1-53.5 mg/l) at baseline for CRP. The median CRF was 30.19 ml/kg/min (range 6.4-65.4 ml/kg/min). CRP and CRF were combined into four categories, to investigate the joint associations of CRP and CRF. After adjusting for age and examination year, the joint impact of high CRP (> 1.24 mg/l) combined with low CRF (VO\textsubscript{max} < 30.08 ml/kg/min) was a 1.60-fold (95% CI 1.17-2.18, p<0.01) risk for cancer mortality when compared to the reference group (low CRP (< 1.24 mg/l) combined with normal CRF (VO\textsubscript{max} ≥ 30.08 ml/kg/min)).
mg/l) and high CRF (VO_{2max} > 30.08 ml/kg/min). After further adjusting for smoking (cigarette-days), alcohol consumption and family history of cancer, the joint impact of high CRP combined with low CRF was not associated with cancer mortality (RR 1.28, 95% CI 0.93-1.75, p=0.12). In further adjustment for BMI, fruits and berries intake, the results were not statistically significant (RR 1.28, 95% CI 0.91–1.81, p=0.14). In a multivariate model, the interaction between CRP and CRF was not statistically significant (p=0.58). In a multivariate model, among men who died from cancer, the joint impact of CRP and CRF shared no association with cancer risk.

5.3.4 Leukocyte count and cancer mortality
At baseline, leukocyte count was 5.68x10^9/L (range 2.40-18.9x10^9/L) and men who died from cancer had higher leukocyte count (5.99x10^9/L) as compared to other participants (5.63x10^9/L) (p<0.01). An elevated prediagnostic leukocyte count was associated with cancer mortality. In a multivariate model, when we compared the highest (Q4 > 6.50-18.90x10^9/L) quartile of leukocyte count with the lowest quartile (Q1 < 2.40-4.60x10^9/L) (referent), we observed an association with cancer mortality (RR 1.50, 95% CI 1.06-2.14, p=0.02).

5.3.5 Leukocyte count, cardiorespiratory fitness and cancer mortality
At baseline, the median leukocyte count concentration was 5.40x10^9/L (range 2.4-18.9 x10^9/L). The median CRF was 30.19 ml/kg/min (range 6.4-65.4 ml/kg/min). The median values of leukocyte count and CRF were combined into four categories, to investigate the joint associations of leukocyte count and CRF. After adjusting for age and examination year, the joint impact of high leukocyte count (>5.40x10^9/L) combined with low CRF (VO_{2max} < 30.08 ml/kg/min) was a risk for cancer mortality when compared to the reference group (low leukocyte count (<5.40x10^9/L)) and high CRF (VO_{2max} > 30.08 ml/kg/min). After further adjusting for smoking (cigarette-days), alcohol consumption and family history of cancer, the joint impact of high leukocyte count (>5.40x10^9/L) combined with low CRF was a risk for cancer mortality when compared to the reference group. After further adjustment for BMI, fruits and berries intake, the results remained statistically significant (RR 1.85, 95% CI 1.30–2.63, p<0.01). The relative risk of cancer death according to categories of leukocytes and CRF are shown in Figure 7. After excluding cancer mortality deaths (N=22) during the first 5 years of follow-up, the results did not change (RR 1.85, 95% CI 1.28-2.67, p<0.01) in a multivariate model of high leukocyte count (>5.40x10^9/L) combined with low CRF (VO_{2max} < 30.08 ml/kg/min) as compared to the reference group. Excluding cancer deaths in the first 5 years of follow-up may help reduce the chance of asymptomatic cancer from baseline. In a multivariate model, the interaction between leukocyte count and CRF was not statistically significant (p=0.91). In a multivariate model, among men who died from cancer, the joint impact of leukocyte count and CRF had no significant interaction with cancer risk.
5.3.6 Summary of main findings

In study 1, after adjusting for risk factors, CRF had an association with lung cancer, whereas, LTPA showed no association. Furthermore, CRF was a stronger predictor of lung cancer than LTPA. Study 2 revealed that CRP and CRF were independently associated with lung cancer after adjusting for traditional risk factors. In addition, the joint impact of CRP and CRF increased the risk of lung cancer further than their independent predictive values. Study 3 has shown that leukocyte count was associated with cancer death, and CRP had no association. The results of this study also suggest that the joint impact of leukocyte count and CRF were associated with cancer death.
Table 7. Summary of main findings in studies 1, 2, and 3

<table>
<thead>
<tr>
<th>Study 1</th>
<th>Multivariate models</th>
<th>Quartiles of CRF RR (95% CI)</th>
<th>*p ≤ 0.05</th>
<th>Quartiles of LTPA RR (95% CI)</th>
<th>*p ≤ 0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Cancer Incidence</td>
<td></td>
<td>Q4 1 (referent) Q3 3.45 (1.39-8.56) * Q2 2.96 (1.17-7.50) * Q1 4.36 (1.75-10.80) *</td>
<td></td>
<td>Q4 1 (referent) Q3 1.83 (0.84-3.96) Q2 2.01 (0.94-4.30) Q1 2.60 (0.84-3.96) *</td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>Age, date of examination year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q4 1 (referent) Q3 3.04 (1.22-7.56) * Q2 2.48 (1.00-7.50) * Q1 2.97 (1.18-7.45) *</td>
<td></td>
<td>Q4 1 (referent) Q3 1.65 (0.63-3.96) Q2 1.37 (0.63-2.96) Q1 1.66 (0.79-3.49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>Age, date of examination year, cancer in the family, smoking (cig/years), alcohol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q4 1 (referent) Q3 2.91 (1.17-7.23) * Q2 2.30 (0.91-5.82) Q1 2.88 (1.14-7.22) *</td>
<td></td>
<td>Q4 1 (referent) Q3 1.72 (0.78-3.77) Q2 1.34 (0.62-2.89) Q1 1.56 (0.73-3.30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>Age, date of examination year, cancer in the family, smoking (cig/years), alcohol, education, fruits and vegetable intake</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q4 1 (referent) Q3 2.91 (1.17-7.23) * Q2 2.30 (0.91-5.82) Q1 2.88 (1.14-7.22) *</td>
<td></td>
<td>Q4 1 (referent) Q3 1.72 (0.78-3.77) Q2 1.34 (0.62-2.89) Q1 1.56 (0.73-3.30)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CRF Q4 (>35.17-65.40) Q3 (>30.03-55.10), Q2 (>25.03-30.02), Q1 (6.36-25.03)
LTPA Q4 (>187.4-2492), Q3 (>83.42-186.9), Q2 (>29.31-83.34), Q1 (00.00-29.25)

<table>
<thead>
<tr>
<th>Study 2</th>
<th>Multivariate models</th>
<th>Quartiles of CRP RR (95% CI)</th>
<th>*p ≤ 0.05</th>
<th>Quartiles of CRF RR (95% CI)</th>
<th>*p ≤ 0.05</th>
<th>Categories of CRP &amp; CRF RR (95% CI)</th>
<th>*p ≤ 0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Cancer Incidence</td>
<td></td>
<td>Q4 1 (referent) Q3 3.19 (1.30-7.86) Q2 2.40 (0.95-6.07) Q1 2.93 (1.15-7.41)</td>
<td></td>
<td>1) 1 (referent) 2) 2.83 (1.06-7.55) * 3) 4.62 (1.88-11.36) * 4) 3.34 (1.36-8.18) *</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>Age, smoking (smoker)</td>
<td>Q1 1 (referent) Q2 1.20 (0.48-3.00) Q3 2.01 (0.88-4.56) Q4 2.75 (1.26-6.02) *</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q4 1 (referent) Q3 3.19 (1.30-7.86) Q2 2.40 (0.95-6.07) Q1 2.93 (1.15-7.41)</td>
<td></td>
<td>1) 1 (referent) 2) 2.83 (1.06-7.55) * 3) 4.62 (1.88-11.36) * 4) 3.34 (1.36-8.18) *</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>Age, smoking (smoker), fruits and berries intake, BMI, alcohol</td>
<td>Q1 1 (referent) Q2 1.36 (0.54-3.40) Q3 2.29 (1.00-5.26) Q4 3.32 (1.49-7.39)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q4 1 (referent) Q3 3.19 (1.30-7.86) Q2 2.40 (0.95-6.07) Q1 2.93 (1.15-7.41)</td>
<td></td>
<td>1) 1 (referent) 2) 2.83 (1.06-7.55) * 3) 4.62 (1.88-11.36) * 4) 3.34 (1.36-8.18) *</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>Age, smoking (smoker), fruits and berries intake, BMI, alcohol, education, family history of cancer</td>
<td>Q1 1 (referent) Q2 1.33 (0.53-3.33) Q3 2.23 (0.97-5.13) Q4 3.22 (1.44-7.20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q4 1 (referent) Q3 3.15 (1.27-7.78) Q2 2.71 (1.06-6.97) Q1 3.53 (1.35-9.23)</td>
<td></td>
<td>1) 1 (referent) 2) 2.83 (1.06-7.55) * 3) 4.62 (1.88-11.36) * 4) 3.34 (1.36-8.18) *</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CRP Q1 (0.10-0.68), Q2 (0.69-1.24), Q3 (>1.25-2.37), Q4 (2.38-53.50)
CRF Q4 (>35.17-65.40) Q3 (>30.03-55.10), Q2 (>25.03-30.02), Q1 (6.36-25.10)
1) CRP < 50% & VO2max > 50% (referent)
2) CRP < 50% & VO2max < 50%
3) CRP > 50% & VO2max > 50%
4) CRP > 50% & VO2max < 50%
<table>
<thead>
<tr>
<th>Study 3 Cancer Mortality</th>
<th>Multivariate models</th>
<th>Quartiles of CRP RR (95% CI) *p ≤ 0.05</th>
<th>Quartiles of CRF RR (95% CI) *p ≤ 0.05</th>
<th>Quartiles of Leukocyte count RR (95% CI) *p ≤ 0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>Age, date of examination year</td>
<td>Q1 1 (referent)</td>
<td>Q4 1 (referent)</td>
<td>Q1 1 (referent)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q2 1.04 (0.74-1.46)</td>
<td>Q3 1.89 (1.29-2.76) *</td>
<td>Q2 0.92 (0.63-1.34) *</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q3 1.25 (0.89-1.79)</td>
<td>Q2 1.91 (1.31-2.80) *</td>
<td>Q3 1.44 (1.02-2.03) *</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q4 1.26 (0.89-1.79)</td>
<td>Q1 2.23 (1.51-3.29) *</td>
<td>Q4 2.09 (1.51-2.89) *</td>
</tr>
</tbody>
</table>

Model 2 | Age, date of examination year, family history of cancer, smoking (cig/day), alcohol | Q1 1 (referent) | Q4 1 (referent) | Q1 1 (referent) |
| | | Q2 1.02 (0.73-1.42) | Q3 1.71 (1.16-2.50) * | Q2 0.85 (0.58-1.23) * |
| | | Q3 1.07 (0.76-1.51) | Q2 1.69 (1.15-2.47) * | Q3 1.26 (0.89-1.79) * |
| | | Q4 0.98 (0.69-1.40) | Q1 1.91 (1.29-2.83) * | Q4 1.52 (1.07-2.16) * |

Model 3 | Age, date of examination year, family history of cancer, smoking (cig/day), alcohol, fruits and berries intake, BMI | Q1 1 (referent) | Q4 1 (referent) | Q1 1 (referent) |
| | | Q2 1.01 (0.72-1.42) | Q3 1.73 (1.18-2.54) * | Q2 0.85 (0.58-1.24) * |
| | | Q3 1.04 (0.74-1.48) | Q2 1.74 (1.18-2.57) * | Q3 1.26 (0.89-1.78) * |
| | | Q4 0.96 (0.66-1.38) | Q1 2.01 (1.33-3.44) * | Q4 1.50 (1.06-2.14) * |

CRP Q1 (0.10-0.68), Q2 (>0.69-1.24), Q3 (>1.25-2.36), Q4 (2.37-53.50)
CRF Q4 (>35.01-65.40) Q3 (>30.15-35.01), Q2 (>25.08-30.15), Q1 (>6.36-25.08)
Leukocyte Q1 (2.40-4.60), Q2 (>4.70-5.40), Q3 (>5.50-6.40), Q4 (>6.50-18.90)

<table>
<thead>
<tr>
<th>Study 3 Cancer Mortality</th>
<th>Multivariate models</th>
<th>Categories of CRP &amp; CRF RR (95% CI), *p ≤ 0.05</th>
<th>Categories of Leukocyte count &amp; CRF RR (95% CI), *p ≤ 0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>Age, date of examination year</td>
<td>1) 1 (referent)</td>
<td>1) 1 (referent)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2) 1.32 (0.94-1.86)</td>
<td>2) 1.39 (0.96-2.03) *</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3) 1.07 (0.74-1.56)</td>
<td>3) 1.83 (1.27-2.63) *</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4) 1.60 (1.17-2.18) *</td>
<td>4) 2.31 (1.66-3.22) *</td>
</tr>
</tbody>
</table>

Model 2 | Age, date of examination year, family history of cancer, smoking (cig/day), alcohol | 1) 1 (referent) | 1) 1 (referent) |
| | | 2) 1.25 (0.89-1.77) | 2) 1.32 (0.90-1.92) |
| | | 3) 0.90 (0.62-1.32) | 3) 1.52 (1.05-2.20) * |
| | | 4) 1.28 (0.93-1.75) | 4) 1.84 (1.30-2.58) * |

Model 3 | Age, date of examination year, family history of cancer, smoking (cig/day), alcohol, fruits and berries intake, BMI | 1) 1 (referent) | 1) 1 (referent) |
| | | 2) 1.27 (0.89-1.81) | 2) 1.34 (0.91-1.96) |
| | | 3) 0.90 (0.61-1.32) | 3) 1.51 (1.04-2.18) * |
| | | 4) 1.28 (0.91-1.81) | 4) 1.85 (1.30-2.63) * |

1) CRP < 50% & VO2max > 50% (referent)
2) CRP < 50% & VO2max < 50%
3) CRP > 50% & VO2max > 50%
4) CRP > 50% & VO2max < 50%
1) Leukocyte < 50% & VO2max > 50% (referent)
2) Leukocyte < 50% & VO2max < 50%
3) Leukocyte > 50% & VO2max > 50%
4) Leukocyte > 50% & VO2max < 50%
6 Discussion

This doctoral thesis examined the associations between CRF, inflammation and cancer outcomes. Specifically, 1) the prognostic value of CRF and LTPA with lung cancer risk, 2) the joint impact of the CRF and CRP with the risk of lung cancer and 3) the joint impact of inflammatory markers and CRF with cancer mortality.

6.1 LEISURE-TIME PHYSICAL ACTIVITY, CARDIORESPIRATORY FITNESS AND LUNG CANCER RISK

In this prospective population based study, directly measured VO₂max, a powerful measure for CRF, was a strong predictor of lung cancer risk. After adjusting for conventional risk factors which include; smoking, alcohol consumption, education, family history of cancer, fruits and vegetables, CRF, but not LTPA, was associated with lung cancer.

At present, only a few studies have looked at directly measured VO₂max as a prognostic measure for predicting lung cancer. In addition, the prognostic value of CRF and LTPA for predicting lung cancer was compared. Previous studies suggest that CRF is a strong prognostic measure for adverse health outcomes (Kaminsky et al. 2013). As an objective measure, CRF may be more reliable for estimating physical activity exposures, than the subjective method used for LTPA. In this study, the results suggest that baseline CRF is a stronger prognostic marker for predicting lung cancer than LTPA.

Smoking is considered a strong risk factor for lung cancer, and may be responsible for nearly 90% of lung cancers (Freedman et al. 2008). Smoking has also been shown to significantly reduce VO₂max, as compared to non-smokers (Tzani et al. 2008). Therefore, increasing lung function/capacity may impede the smoking-related declines in lung function. Physical activity may reduce lung cancer risk through biological mechanisms, by increasing pulmonary ventilation and perfusion could reduce the time for carcinogenic effects (Leitzmann et al. 2009). In this study, LTPA was not associated with lung cancer after adjusting for smoking. Whereas, CRF had a strong association with lung cancer after adjusting for all risk factors. After including BMI into a fully adjusted multivariate models, CRF had an association with lung cancer, whereas, LTPA had none. CRF and LTPA may provide different associations of risk for predicting health and disease outcomes. The physiological component of CRF may be more sensitive for predicting lung cancers, as compared to the estimation of energy expenditure of LTPA. In addition, an accurate assessment of LTPA may be a challenge in epidemiological studies, due to the inherent imprecision of physical activity questionnaires (Laaksonen et al. 2002). To improve the current knowledge, this study has shown that high levels of directly measured CRF reduces lung cancer risk. Similarly, a previous study suggest that indirectly measured CRF has shown a reduced risk for lung cancer (Lakoski et al. 2015). In contrast to previous studies (Tardon et al. 2005), this study did not show any association between LTPA and lung
cancer risk. Although CRF and LTPA are correlated, they provide specific information (Lakoski et al. 2015) and could result in inconsistent observations since physical activity measures may not have the same prognostic power as CRF (Kaminsky et al. 2013). This may suggest that LTPA has a poor correlation with CRF as described by Tager et al. 1998. For this study, LTPA was subjectively measured and required the participants to estimate by self-report their previous physical activities. However, CRF was objectively measured, and it is influenced by age, gender, BMI and physical activity (Lakoski et al. 2011). CRF and LTPA may provide different associations of risk prediction due to the precision of objective measures, and physiological component of CRF. When comparing the predictability of CRF and LTPA with all-cause mortality, Lee et al. 2011 observed an association between CRF and mortality, while LTPA showed no such association. The present study supports the sensitivity of CRF when compared to LTPA. This study suggest that objectively measured CRF has stronger associations with lung cancer risk than the subjective method of LTPA.

6.2 C-REACTIVE PROTEIN, CARDIORESPIRATORY FITNESS AND LUNG CANCER RISK
In the present study, we observed that CRP and CRF were independent predictors of lung cancer, furthermore, the joint association of CRP and CRF had increased the risk of lung cancer further than their independent predictive values. To our knowledge, this is the first study to show the joint association of CRP and CRF with respect to lung cancer. In previous studies, high levels of CRF share an inverse relationship with CRP (Church et al. 2002) and men with low levels of CRF (Lakoski et al. 2015) and high CRP (Chaturvedi et al. 2010) had an increased risk for lung cancer.

Smoking is a strong risk factor for lung cancer, and has been shown elevate CRP (Chaturvedi et al. 2010) and reduce CRF (Misigoj-Durakovic et al. 2012). However, among non-smokers, CRP levels are lower (Chaturvedi et al. 2010) and high CRF may reduce lung cancer risk (Lakoski et al. 2015). High CRF may indirectly reduce CRP (Lavie et al. 2011) inflammation/oxidative injury, and lung cancer risk by inhibiting tumor progression, lower circulating concentrations of metabolic and sex steroid hormones, and improving immune function (Jones et al. 2010).

As previously described, high CRF may reduce the lung cancer risk (Lakoski et al. 2015), whereas, high CRP may increase risk (Chaturvedi et al. 2010). Therefore, improving CRF may have anti-inflammatory effects that positively influence CRP. This is consistent with the inverse relationship between CRP and CRF (Church et al. 2002). However, the precise mechanism, which reduces CRP, remains unclear. Infection, reduced pulmonary function, and smoking may be confounders, which influence the levels of CRP, CRF and their associations with lung cancer. The effects of regular exercise may be able to mediate the association between CRF and CRP (Church et al. 2002). As described in this study, the relationship between CRF and CRP has an effect on lung cancer risk. To improve the current knowledge, this study describes the independent and joint impact of CRP and CRF,
and their relationship with lung cancer. Previous studies have shown that high CRP increases lung cancer risk (Chaturvedi et al. 2010) and low CRF increases death from lung cancer (Sui et al. 2010). Currently missing from literature is the combined effect of CRP and CRF in association with lung cancer. This study contributes to the current literature by showing that CRP and CRF have a powerful effect on lung cancer risk.

6.3 INFLAMMATORY BIOMARKERS, CARDIORESPIRATORY FITNESS, AND THE RISK OF CANCER MORTALITY
Lung cancer is the most common cancer and leading cause of cancer death overall (Brenner et al. 2011). Programs to reduce lung cancer risk and death may include tobacco cessation campaigns, limiting exposure to occupational and environmental hazards, and promoting healthier lifestyles for an aging population (de Groot & Munden 2012). Individuals who wish to reduce lung cancer risk may do so by increasing their CRF levels (Lakoski et al. 2015), since this has shown positive effects on inflammatory markers (Lavie et al. 2011). Furthermore, inflammatory biomarkers could increase the risk for cancer death (Shankar et al. 2006) and CRF has shown an inverse relationship to inflammatory markers (Lin et al. 2010). To prevent cancer mortality, the aim of this study was to examine the risks associated with the joint impact of inflammatory markers and CRF.

Our study revealed the significant risk factors for cancer death to include CRF, leukocytes, smoking and alcohol consumption. The men who died from cancer had lower baseline CRF as compared to other participants, lower concentrations of CRP compared to other participants, but a higher leukocyte count as compared to other participants. Men who died from cancer smoked more cigarettes, consumed more alcohol, had a family history of cancer and lower education status. Among the men who had died from cancer, nearly half of them were smokers. The most common cancers that resulted in death were lung, prostate, and GI tract cancers excluding pancreatic cancer.

To our knowledge, no prior studies have observed the joint effects of prediagnostic inflammatory biomarkers (leukocyte count, CRP) and CRF with cancer mortality. When we examined the joint impact of leukocyte count and CRF with cancer mortality, we observed an association with cancer death. In addition, the predictive capacity for the joint impact of leukocyte count and CRF is slightly stronger than for leukocyte count alone. However, as shown in previous cancer mortality studies, we noted that leukocyte count (Shankar et al. 2006) and CRF (Sawada et al. 2003) are independent predictors of death.

Inflammation has been shown to have a strong relationship with cancer development (Trinchieri 2012) and a greater volume of physical activity is reported to lower the risk of elevated levels of inflammatory biomarkers (Beavers et al. 2010). Our results support previous evidence as described, improving CRF is beneficial for reducing disease risk (Kaminsky et al. 2013) and high CRF is effective for preventing cancer death (Sawada et al. 2003). We show that higher levels of CRF share an inverse relationship with cancer mortality risk. In contrast to the benefits of high CRF (Sawada et al. 2003), elevated levels of
leukocyte count (Shankar et al. 2006) and CRP may increase the cancer mortality risk (Ko et al. 2012). Unlike previous studies on cancer death, our results do not suggest that elevated levels of CRP share any association (Wulaningsih et al. 2016). However, in this study leukocyte count was found to be a factor contributing the increased risk. As described in several previous studies, high levels of baseline CRF is effective for reducing the risk for cancer death, although the biological mechanisms that directly reduce the risk remain unclear. The role of inflammation in the development of cancer is well documented. Therefore, to examine the role of inflammation and CRF, the joint impact of high CRF and inflammatory biomarkers on cancer risks, requires further investigation. This study suggests that elevated levels of inflammation and low levels of CRF increase cancer mortality risk.

To date, few studies have observed an association between inflammatory biomarkers and cancer mortality. Alternatively, the relationship between CRF and cancer death has been more extensive in literature. This study contributes to the current body of literature by showing that high leukocyte count combined with low CRF increases the risk of cancer death. In contrast, high CRP and low CRF share no association. Consistent with previous studies, this study shows that the leukocyte count (Ruggiero et al. 2007) and CRF (Lee et al. 2010) are independently associated with cancer death. The contribution of this study to the current literature is to show that the leukocyte count, in combination with CRF, increases the risk of cancer mortality.

6.4 STRENGTHS AND LIMITATIONS OF THIS STUDY

The strengths of this study include the prospective study design, with a representative population-based sample of middle-aged men. This study had a follow-up period of up to 22 years, and excluded all men with any history of cancer at baseline. The participation rate was high and there were no losses despite the long follow-up of the study population. Another strength for this study is the reliable data on mortality because deaths were ascertained by Finnish National Death and Cancer Registry using personal identification codes. Furthermore, incident cancer cases were derived from the Finnish Cancer Registry. The study had the reliability of anthropometric measures, exercise test variables and detailed assessment of risk factors. Another strength includes the direct measurement of VO₂max, which is recognized as the gold standard for measuring CRF (Kurl et al. 2003).

This study has a few limitations. Firstly, several lifestyle factors that include physical activity and genetic susceptibility, may interact in the etiology of cancers. This could limit the ability to show how one factor can independently contribute to risk reduction. Secondly, self-report of physical activity may be subject to misclassification. Thirdly, this study was based on a genetically and ethnically population of homogeneous males, this may limit the generalization of our results. Further investigations may wish to include women or other ethnic groups. Fourthly, there is a possibility for residual confounding, and risk factors may not be fully controlled in the multivariate models. Lastly, the genetic
component of CRF is about 70%, but CRF can be improved to some extent by physical activity.
7 Conclusions

The conclusions for this thesis are as follows.

1. Cardiorespiratory fitness was inversely and independently associated with the risk of lung cancer. However, leisure-time physical activity was not associated with the risk of lung cancer. In lung cancer prevention, methods for improving cardiorespiratory fitness may limit risks more effectively than leisure-time physical activity. Our results show that cardiorespiratory fitness is a strong predictor of lung cancer.

2. The joint impact of C-reactive protein and cardiorespiratory fitness was a strong risk marker for lung cancer. Furthermore, men with high C-reactive protein levels had an increased risk for lung cancer than men with low C-reactive protein levels. High cardiorespiratory fitness was associated with a reduced risk for lung cancer.

3. Men with high prediagnostic leukocytes count, combined with low cardiorespiratory fitness are at an increased risk for cancer death. The joint impact of prediagnostic leukocyte count and cardiorespiratory fitness is a better predictor of cancer death than the joint impact of C-reactive protein and cardiorespiratory fitness.
8 Recommendations

8.1 RECOMMENDATION FOR CANCER PREVENTION
In this thesis, high levels of CRF were associated with reduced lung cancer risk and cancer death. Physical activity exerted has a proportionate effect on individual CRF, and high CRF had shown positive effects for reducing the cancer risk. The mechanisms for reducing cancer risk and death included high CRF and low levels of inflammation (leukocyte count, CRP).

In order to reduce lung cancer risk, participation in aerobic physical activities (running, cross-country skiing) which improve CRF, may limit risk more effectively than LTPA. In our cohort of men, increasing levels CRF were associated with an increased reduction in the lung cancer risk. We show that CRF and CRP independently predicted the lung cancer risk. The lung cancer risk was observed to be lower among men with lower quartiles of CRP, or men with high quartiles of CRF. However, when we combined CRF with CRP, the joint effect of high CRP and low CRF was associated with an increased risk for lung cancer. Therefore, maintaining healthy levels of CRP and high CRF during middle age may be an effective way to prevent lung cancer and attenuate the risk.

This thesis shows that cancer mortality was independently associated with high leukocyte count. As suggested in the published literature, inflammatory markers may represent one of the hallmarks of cancer. Therefore, improving the current methods for reducing inflammation may be worthwhile for limiting cancer risk and reduce the associated mortality. The anti-inflammatory effects that result from high CRF, may reduce the risk for cancer mortality among men with an elevated leukocyte count. This thesis also suggests that the joint impact of high leukocyte count and low CRF increases the risk for cancer death. If one wishes to control one’s cancer risk, retaining high levels of CRF and maintaining low levels of leukocyte count would be advisable.

8.2 RECOMMENDATION FOR FUTURE RESEARCH
In the future, investigations into LTPA that directly support behaviors to improve CRF, may identify successful methods for improving fitness among high risk populations. Investigators may choose from several modern physical activity measurement devices which provide accuracy and data storage. These devices are generally user friendly and may be useful for estimating a participant’s daily energy expenditure, e.g. a step counter or heart-rate monitor. Modern devices have become easier for individuals to collect, track, and reflect on their physical activities. Physical activity data can be easily collected and stored to record distance, intensity, and duration. For researchers, the ability to identify and distinguish physical activity behaviors with these devices has created a powerful tool to address population health concerns with physical activity. As a whole, the population can benefit from the advancements in current technology and may prove to be useful for improving population health.
To improve population health, future investigations into the relationship between CRF and inflammatory markers would be necessary among populations of women and ethnic minorities. Further investigations into women and minority populations may utilize the current knowledge to improve cancer prevention among these groups. Lastly, future investigations with larger cohorts may reflect the role of inflammation, CRF and LTPA among the non-smoking population. This may support the current knowledge and provide more reliable conclusions about the effects of inflammation, CRF and LTPA and risks associated with lung cancer.
9 References


Allin KH, Bojesen SE, Nordestgaard BG. Inflammatory biomarkers and risk of cancer in 84,000 individuals from the general population. Int J Cancer. 2016;139(7):1493-500.


Heikkilä K., Ebrahim S, Lawlor DA. A systematic review of the association between circulating concentrations of C reactive protein and cancer. J Epidemiol Comm H 2007;61(9);824-833.


The role of cardiorespiratory fitness, leisure-time physical activity and inflammatory biomarkers in lung cancer risk, and cancer death is limited. Among men, this follow-up study suggests that high levels of cardiorespiratory fitness reduces the risk for lung cancer and cancer death. Whereas, high levels of C-reactive protein and leukocyte count increase lung cancer risk and cancer death. Furthermore, poor cardiorespiratory fitness combined with high C-reactive protein had a four-fold increased risk for lung cancer.