PHYSICAL ACTIVITY AND LYNCH SYNDROME

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ABSTRACT

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Physical activity promotes health and well-being of an individual. It may help to reduce the onset of various chronic diseases such as diabetes, cardiovascular diseases, and cancer. This study is a part of the research project called "Lynch syndrome and lifestyle" by Central Finland Health Care District and the University of Jyväskylä. Lynch syndrome or Hereditary Nonpolyposis Colorectal Cancer (HNPCC) is caused by an inherited mutation of mismatch repair genes and is associated with increased risk of developing cancer in one's lifetime. The purpose of this study is to analyze the physical activity profile of people with Lynch syndrome in Finland. Additionally, it investigates the association between physical activity and cancer in people with Lynch syndrome.

According to the Lynch syndrome registry in Finland, the questionnaires were sent to 952 family members with Lynch syndrome. Total 414 participants responded. Among them 47% participants have cancer and 53% do not have cancer. The data were analyzed by independent t-test, chi-square test and logistic regression using IBM SPSS statistics.

The study found an association between current physical activity and cancer occurrence (odds ratio [OR] 2.71, 95% confidence interval [CI] $1.50 - 4.92$). About two-thirds of the participants with Lynch syndrome have meet WHO physical activity guidelines from both groups (cancer and without cancer). The study indicated a statistically significant difference of current physical activity between cancer and without cancer people with Lynch syndrome ($p = 0.008$).

Apart from considerable health benefits, physical activity can aid to spread the knowledge of Lynch syndrome among young people. Very few studies have observed the influence of physical activity on the development of cancer in people with Lynch syndrome. This study has a high potential for further research on physical activity, evidence-based guidance, and hereditary cancer. Furthermore, the study findings would add value for physical activity promotion among Lynch syndrome families.

Keywords: Leisure time physical activity, Lifestyle factors, Colorectal cancer, Lynch syndrome, MET, Cancer prevention

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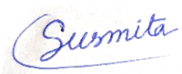
Preface

Physical activity and cancer prevention is an ongoing research area. The broad impacts of physical activity on our society has inspired me to work on this. This Master thesis has been an amazing journey where I have utilized the knowledge from medicine, health care and social science of sport. During this work, I have dig down the concepts of physical activity, risk factors for cancer and health benefits of physical activity in reducing the risk of cancer. The evidence-based guidance of physical activity may offer a cost-effective tool towards a healthy society.

I am grateful to Prof. Sarianna Sipilä (Gerontology Research Center, JYU) for giving me the opportunity to take part in this research project and for her beliefs in me. I would also like to thank Eija Laakkonen and Anna-Katriina Salmikangas for always been keen to help me whenever I have struggled. I am thankful to Hanna Vehmas for her encouragement in the early phase of the thesis. Special thanks to my husband, Ramkrishna Ghosh, for his constant criticism and helping hand. Last but not least, I would like to thank my parents, sister, brother and friends for their moral support and infinite encouragement.

I hope that you will enjoy reading the thesis.



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Date May 7, 2018

1 Introduction

"Prevention is better than cure."

Lynch syndrome (Hereditary Nonpolyposis Colorectal Cancer) is generated by the mutation of Mismatch Repair Gene (MMR) in DNA (Aaltonen et al., 1998). It is the most common cause of hereditary colorectal cancer (around 3%). The Finnish population has a 10% risk of colon cancer during their lifetime and the risk increases in cases of hereditary colorectal cancer. About 0.1% Finns carry Lynch syndrome (Cancer Society of Finland, 2016).

Typically, due to the changes of genes or its functions cancer develops. In 2015, cancer caused 8.8 million deaths (World Health Organization, 2018a). Colorectal cancer, which is the third most common, occurs in the tissue of colon and rectum. Lifestyle, genetic, and environmental components are the main factors of Colorectal cancer development (Skyrud et al., 2017). People with this genetic disorder have a greater risk of developing colorectal cancer, endometrial cancer and other types of disruptive cancers (Lynch, 2003).

Evidence-based risk-reducing strategies are getting popular, such as imposing higher taxes on tobacco and alcohol and promoting physical activity and healthy diets. These strategies may prevent up to 30–50% of cancers (World Health Organization, 2018a). Even though active living and healthy eating is a popular trend, sedentary lifestyle causes obese young and chronically ill older generation. Sedentary lifestyle affects metabolism and health, compared to an active lifestyle with moderate to vigorous physical activity (Tremblay et al., 2010). Lack of physical activity, obesity, smoking, alcohol, low fruit, and vegetable consumption are mainly responsible for one-third of cancer deaths (World Health Organization, 2018a).

Recent studies (Blanchard & Courneya, 2010; Laukkanen et al., 2011; Walter et al., 2017) have shown that physical activity may decline the risk of cancer and its effects. Moderate to vigorous physical activity has substantial health benefits and might decrease the risk of certain cancers such as colorectal cancer (Friedenreich et al., 2010; Vrieling et al., 2010).

Therefore, evidence-based physical activity guidelines can be used as a tool to promote health and well-being of the society.

However, only a few studies have focused on the physical activity of people with Lynch syndrome and their family (Moore et al., 2016). This study will fill the gap by analyzing physical activity profile of the people with Lynch syndrome. This study also emphasis on finding the possible relation between physical activity and cancer of people with this hereditary condition. The hypothesis for this research is that there is a relationship between physical activity and cancer. This study is valuable as it illuminates the relationship between the physical activity and cancer among people with Lynch syndrome. This thesis work has been done in collaboration with Gerontology Research Center.

2 Lynch syndrome and cancer risk

Lynch syndrome is associated with DNA gene mutation, which influences on increased cancer risk (“Lynch cancers”, 2015). These cancer risks may be reduced by adopting healthy lifestyles, including physical activity, diet, weight control and excluding smoking (World Health Organization, 2018a).

2.1 Lynch syndrome

Familial Adenomatous Polyposis (FAP) and Hereditary Nonpolyposis Colorectal Cancer (HNPCC) are two forms of hereditary colorectal cancer. The most common type is HNPCC, also known as Lynch syndrome, covers 2-4% of colorectal cancer. The APC gene mutation trigger FAP and covers 1% colon cancer (“Lynch syndrome”, 2018). In general, Lynch syndrome results from germline mutation inactivation in one of the DNA MMR gene (MMR genes are MLH1, MSH2, MSH6, and PMS2) (Aaltonen et al., 1998; Mecklin et al., 2007). EPCAM gene, which does not belong to the MMR gene family, has now being implicated with Lynch syndrome (Sehgal et al., 2014). Lynch syndrome is an autosomal dominant syndrome, in which a child has a risk for cancer by receiving a normal gene from one parent and a defective gene from the other parent (Sehgal et al., 2014). People with mutated MMR gene have a tendency to develop cancer at a younger age than the general population (Aarnio et al., 1999).

Typically, an individual has 50% chance of inheriting MMR mutation, which increases the susceptibility of developing cancers in their lifetime (“Lynch cancers”, 2015). Since Lynch syndrome is inherited via direct family relations, knowing and documenting the family medical history is one of the best available diagnosis tools at present (Lynch & Chapelle, 2003). Figure 1 illustrates the classic characteristics of a family with Lynch syndrome. The affected family members suffer from colon cancer and endometrial cancer with a random rate of occurrence and young cancer age. The example shows one child has colon cancer (at 37 years), even though parents have no cancer (Sehgal et al., 2014).

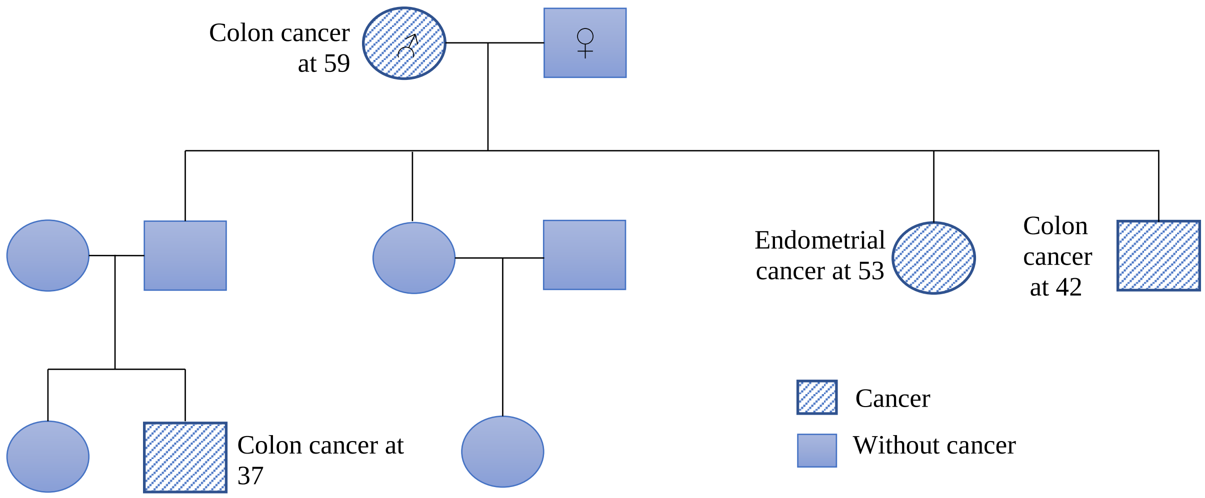

Figure 1 Pedigree of Lynch Syndrome showing the age and type of cancer in three generations, adopted from (Sehgal et al., 2014)

2.2 Risk of cancer

An individual with Lynch syndrome has 12.5 times more lifetime risk (70–80 %) for developing colorectal cancer compared to the general population (6% risk) (Aaltonen et al., 1998; Aarnio et al., 1999). In addition, people with Lynch syndrome have increased risk of extracolonic cancers such as endometrium (20-60%), ovary (9-12%), stomach (11-19%), small intestine (1-4%), pancreas, hepatobiliary tract (2-7%), brain (1-3%), urinary tract cancers (4-5%) and certain skin tumors (up to 80%), as shown in Figure 2 ("Lynch syndrome", 2018; "Lynch cancers", 2015).

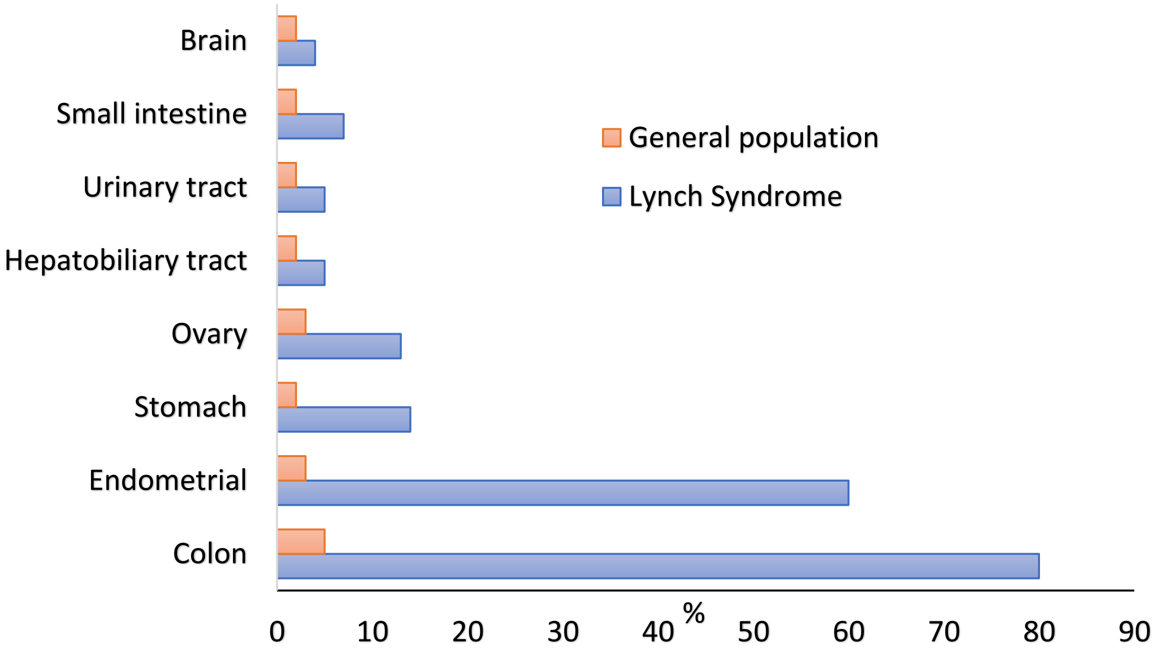

Figure 2 Lifetime risk of cancers in people with Lynch syndrome (Lynch Syndrome International, 2015)

The screening for colorectal cancer reduces the risk factors and prevents overall mortality rates by about 65% in families with MMR gene mutation ("Lynch cancers", 2015). Therefore, early detection and diagnosis are important for survival. For the identification of high-risk families, the Amsterdam criteria are used. This contains the following conditions: i. three or more cases of colorectal cancer over two or more generations; ii. with at least one diagnosed before age 50 years; and iii. no evidence of familial adenomatous polyposis (FAP) (Sehgal et al., 2014). Amsterdam criteria can also be used to identify microsatellite instability, which is a potential marker of hereditary nonpolyposis colorectal cancer (Lynch & Chapelle, 2003). Microsatellites are repetitive DNA fragments which have high mutation rate. A deficiency of this protein can express microsatellite instability in the case of hereditary nonpolyposis colorectal cancer (Sehgal et al., 2014). In other words, germline mutation of MMR genes is a primary marker for patients with Lynch syndrome (Lynch & Chapelle, 2003).

Bethesda guidelines, which covers clinical, pathological and family history for the clinical diagnosis of Lynch syndrome, are being introduced to overcome the low sensitivity of Amsterdam criteria (Umar et al., 2004). Nevertheless, this guideline still misses approximately 30% of Lynch syndrome families (Sehgal et al.,2014). In addition, genetic counseling and screening are recommended for the better identification (Mecklin et al., 2007). Alternatively, the morbidity (prevalence of the disease) and mortality (death) of cancer patients may improve through regular cancer screening and surgical treatments (Lynch & Chapelle, 2003; Mecklin et al., 2007).

3 Physical activity and lifestyle

Health and wellbeing of an individual depend on their lifestyle and socio-economic status. The higher cost of sports services and facilities may cause disparities in the society (Myllyniemi & Berg, 2013). Smoking, alcohol intake, physical activity, and dietary pattern have been recognized as crucial lifestyle risk factors for cancer (Blanchard et al., 2010; World Health Organization, 2018a). Lifestyle factors may have an influence on developing cancer among people with Lynch syndrome, for example, colorectal cancer (Duijnhoven et al., 2013). However, only a few studies have explored in case of Lynch syndrome and physical activity. This study mainly focused on physical activity as a lifestyle risk factor for developing cancer of people with Lynch syndrome. Whether or not, physical activity influence on the onset of cancer, people with Lynch syndrome will benefit with regular physical activity. In addition, it can also improve colon function, weight control, and balanced blood sugar level (World Health Organization, 2018a).

3.1 Physical activity

Physical activity takes into consideration of any physical movement by skeletal muscles that consume more energy expenditure than resting (World Health Organization, 2018b). Leisure-time physical activity is a type of physical activity that occurred throughout a person's discretionary time which results in substantial energy expenditure (Motl & Klaren, 2017). An individual can participate in physical activity for fun or/and enjoyment, however, the main drive is to improve health outcomes (for instance, obesity, cardiac function and depression) (Motl & Klaren, 2017). The intensity of physical activity is measured by Metabolic Equivalent, also known as MET or MET values (Gunn et al., 2004). Typically, MET is calculated by the energy expenditure of activities, where 1 MET corresponds to resting metabolic rate (also known as rest MET) (Tremblay et al., 2010). For instance, running is equivalent to at least 8 MET, whereas, moderate-pace walking is equivalent to 3-4 MET (Bushman, 2012). It is possible to attain $4 \times 30 = 120$ MET-minutes (or 2.0 MET-hours) of physical activity when a 4 MET activity is done for 30 minutes. Similarly, 120 MET-minutes can be achieved by doing an 8 MET activity for 15 minutes (Office of Disease Prevention and Health Promotion, 2018a).

In an absolute scale, a moderate intensity refers to the physical activity performed at $3 - 6$ times the intensity of rest MET, and a vigorous intensity refers to the physical activity performed at 6 or more times for an adult (Kokko et al., 2009). For example, according to the metabolic index chart, walking at 4.8 kilometers per hour involves 3.3 MET of energy expenditure (moderate intensity) and running at 9.6 kilometers per hour requires 10 MET activity of energy expenditure (vigorous intensity) (Bushman, 2012). To achieve substantial health benefit of physical activity, moderate to vigorous intensity physical activities are recommended (Office of Disease Prevention and Health Promotion, 2018b).

According to the physical activity WHO guidelines, to attain health benefits, adults should do 150 minutes of moderate-intensity aerobic physical activity (such as brisk walking or tennis) per week or 75 minutes (1 hour and 15 minutes) of vigorous-intensity aerobic physical activity (such as jogging) per week or an equal combination of both (World Health Organization, 2018b). In terms of energy expenditure, that can be translated in 500–1000 MET-minutes/week, estimated based on the standard MET thresholds (3 MET for moderate and 6 MET for vigorous activity) (Tucker et al., 2011). Furthermore, older adults are recommended to perform a moderate-intensity aerobic physical activity for a minimum of 30 minutes on five days each week or vigorous-intensity aerobic activity for a minimum of 20 min on three days each week. Even though physical activity guidelines are based on people's age and functional capabilities, the physical condition varies person to person. Furthermore, these guidelines are usually more followed by physically active people compare to those who are not motivated enough to perform the regular leisure-time physical activity. Therefore, customized physical activity recommendations by healthcare professional/ physical trainer, based on individual's ability, might be beneficial. Using technology and internet could be a useful tool to motivate people to lead an active lifestyle (for example, educational mobile games).

3.2 Health and sedentary lifestyle

Over the past centuries, required physical activities have decreased in day to day life due to technological advancements and digital transformation (Kaleta & Jegier, 2005). On the other hand, chronic diseases have increased as a result of unprecedented social and economic changes, which in turn have an effect on physical activity and dietary habits. The study suggests a low physical activity and a sedentary lifestyle can be the essential risk factor for noncommunicable diseases such as cardiovascular diseases, overweight, diabetes and certain cancers. The weight of chronic diseases has been predicted to rise 57% by 2020 (Kaleta & Jegier, 2005).

Sedentary behavior (≤1.5 MET energy expenditure) can influence metabolic function by increasing plasma triglyceride levels and decreasing levels of high-density lipoprotein (HDL) cholesterol (Tremblay et al., 2010). Additionally, it can lead to insulin resistance and increase the risk of various chronic diseases. An individual can show sedentary behavior by sitting for a long time at home or at work. Hence, sedentary behavior during the lifespan can be a key factor in the onset of cancer development (Gierach et al., 2009; Simons et al., 2013; Tremblay et al., 2010).

In Europe, about $9 - 19\%$ cancer cases might be associated with physical inactivity (Friedenreich et al., 2010). The majority are at higher risk of sedentary behavior due to an increased rate of office work and sedentary leisure time habits, resulting 9 to 11 hours of total sitting time per day (Pesola et al., 2017). Among Finns, about 29% sits 5 to 8.5 hours and about 12% sits more than 8.5 hours in a day (European Commission, 2018). It has been estimated that in the USA 25% people are not engaged in any kind of exercise and only 15% of the adult population participate in a leisure-time physical activity (Kaleta & Jegier, 2005). Nevertheless, people can have sedentary behavior even after performing moderate to vigorous physical activity (Tremblay et al., 2010). More than 1.5 hours of moderate-intensity physical activity is required to balance the premature mortality risk because of more than 8 hours sitting time per day (Pesola et al., 2017).

3.3 Health benefits of physical activity

Leisure time physical activity may have a positive impact on health status at any age. Skeletal muscle mass and strength can be increased by doing a regular physical activity (Leskinen et al., 2013). Furthermore, the regular physical activity can delay the progression of multiple diseases (King et al., 2001; Martinez et al., 1997). Leisure time a physical activity can be associated with reducing the risk of type II diabetes, certain cancers (esophageal, rectal, lung) and other chronic diseases such as obesity and hypertension (Honda et al., 2015; Moore et al., 2016). The risk of premature death can be reduced by of 500 MET-minutes per week activity and the activity of more than 500 MET-minutes per week may result in risk reduction of breast cancer (Office of Disease Prevention and Health Promotion, 2018b).

Regular physical activity controls glucose homeostasis and muscle fat infiltration (Leskinen et al., 2013). Generally, chronic diseases trigger at middle age and therefore, preventive and therapeutic physical activity recommendations are vital for adults and elderly people. Regular aerobic and muscle-strengthening activities may reduce the risk of chronic diseases, premature mortality and functional limitations (Nelson et al., 2007). Leisure time physical activity can promote healthy living.

4 Physical activity and Lynch syndrome

4.1 Role of physical activity in reducing the risk of cancers

Regular physical activity (moderate and vigorous) can have an effect on reducing the risk of cancer by affecting glucose hemostasis and fat metabolism (shown in figure 3). Long-term physical activity is associated with lipid metabolism and plasma glucose levels (Leskinen et al., 2010). Most of the glucose is consumed by the skeletal muscle volume (Leskinen et al., 2013). Thus, physical activity improves insulin sensitivity, which can increase antioxidant enzymes and enhance DNA repair system. For the beneficial effect against cancer, physical activity might play a vital role in decreasing adipokines (body fat) and inflammatory markers (C- reactive protein, TNF-α) (Friedenreich et al., 2010). The result of physical activity can be linked with few nonhormonal mechanisms such as inflammation, immune function and oxidative stress that are responsible for reducing cancer risk (Laukkanen et al., 2011). Further, physical activity can assist in reducing colon cancer by lowering gastrointestinal transit time, however, this effect may depend on the tumor characteristics (Friedenreich et al., 2016).

Previous studies have estimated that polymorphisms in genes may interact with physical activity or other diet and lifestyle factors to alter risks. It has been suggested that both p53

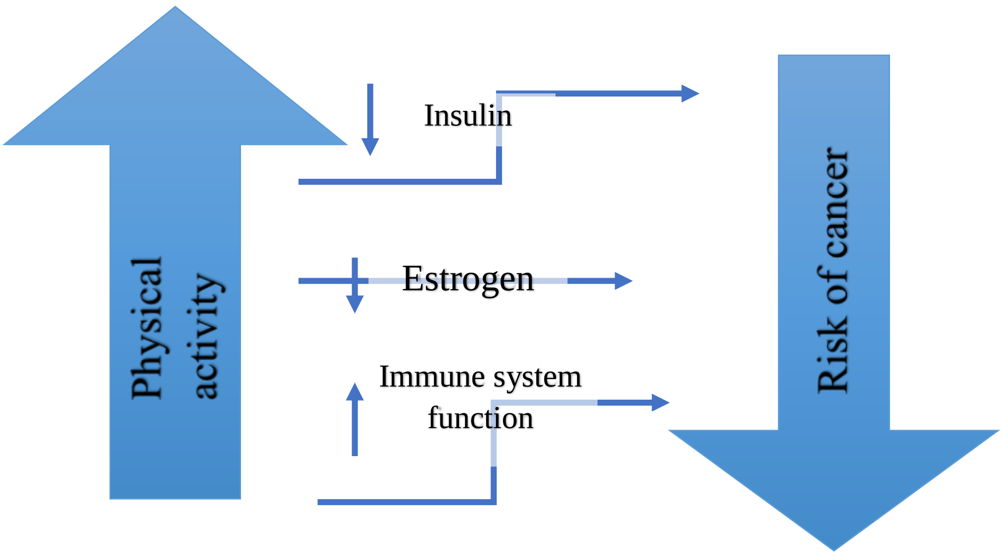

Figure 3 Biological effect of physical activity - modified from (Friedenreich et al., 2010)

and Ki-ras mutations in the gene may be associated with western diet and physical activity (Slattery, 2004). Previous studies have suggested that leisure-time physical activity could play a key role in reducing the risk of onset of few cancers and various chronic diseases (Moore et al., 2016). However, the influence of physical activity on cancer from Lynch syndrome yet to be thoroughly studied.

Vrieling & Kampman (2010) has stated that higher leisure-time physical activity after a cancer diagnosis can lower the chance of cancer-specific mortality. In these case, physical activity provides a better lifestyle and therefore better prognosis among colorectal cancer patients (Vrieling & Kampman, 2010). Laukkanen has reported that higher level of leisure time physical activity (at least 30 min per day) decreases the cancer mortality among male from eastern Finland (Laukkanen et al., 2011). Total leisure-time physical activity (moderate level 4.5 MET) of 1000–2500 kcal energy expenditure per week have been found to be enough to reduce the risk of prostate, colon and lung cancers. Moreover, more than 5.2 MET mean intensity of leisure-time physical activity may reduce the risk of cancer deaths among male (Laukkanen et al., 2011).

Obesity is found to be associated with increased colorectal cancer risk among people with Lynch syndrome, and it is more significant in men with Lynch syndrome (Movahedi et al., 2015). Obesity and overweight influence physiological changes (e.g. metabolism, insulin resistance etc.), which might increase the risk factors for developing cancers in the future (Vrieling & Kampman, 2010). Blanchard argues that there is a relationship between higher body mass index and lack of physical activity for obese and non-obese cancer patients (Blanchard et al., 2010). Vries et. al. have observed an association between BMI, physical activity, and colon cancer among male. With enhanced physical activity, a male individual may improve their BMI levels (de Vries et al., 2010). However, the relationship between physical activity and BMI of the female population has not been clearly established in the previous study (de Vries et al., 2010). On the other hand, another study has shown that physically active women have healthy BMI compare to physically inactive women (Laakkonen et al., 2017). Therefore, it can be stated that physical activity may have an effect on BMI for both male and female. On the other hand, the risk of developing colorectal adenoma can be associated with overweight ($\geq$25 kg/m^2) in male (Botma et al., 2010).

Similarly, Campbell et. al. has reported that colorectal cancer risk can be increased for overweight men (25%) and for obese men (83%) (Campbell et al., 2010). However, significant associations between weight and colorectal cancer incidence have not been found among women (Campbell et al., 2010).

Furthermore, Simons et al., (2013) have argued that higher occupational energy expenditure and lower sitting time at work may decrease the risk of colorectal cancer in male, whereas, the non-occupational physical activity can be associated with reduced colorectal cancer risks for female. Nevertheless, the regular long-term physical activity may act as a protective factor for decreasing colorectal cancer risk for both genders (Simons et al., 2013).

According to Slattery, the frequency, duration, and intensity of activity are the key components of a public health message to decrease the risk of colon cancer through physical activity (Slattery, 2004). Moderate to vigorous physical activity can lower the colorectal cancer recurrence and mortality risk by lowering the insulin resistance and the concentration of insulin-like growth factor I (Friedenreich et al., 2010; Rock et al., 2012; Vrieling & Kampman, 2010). Thus, substantial health benefits can be achieved by doing the regular medium-vigorous physical activity. The overall health benefits of physical activity have already been well studied, whereas, the specific pathway of the function of physical activity in reducing hereditary cancer still demands more research.

4.2 Physical activity promotion among Lynch syndrome families

Cancer screening may decrease cancer incidence and improve life expectancy in a family with Lynch syndrome (Aaltonen et al., 1998; Mecklin et al., 2007; Wang et al., 2012). The cost-effectiveness of screening for hereditary cancer syndrome depends on understanding the value of screening, psychological needs, and management of quality of life in people with genetic cancer syndrome (Wang et al., 2012). The younger generation with a family history of Lynch syndrome might tend to become discouraged and uninterested during their lifetime to take preventive action (Aktan-Collan et al., 2013). The anxiety of cancer, fear of dying soon and worried about future have been the most common cause of concern of people who go through genetic testing (Aktan-Collan et al., 2011).

Awareness of hereditary predisposition for a specific type of cancer is particularly important for younger adults. Increasing awareness and recognition of a potential hereditary predisposition in individuals is required (Aktan-Collan et al., 2011). Consequently, Lynch syndrome families might feel supported and integrated into the society by knowing more about this genetic predisposition and preventive interventions including lifestyle modifications (Aktan-Collan et al., 2013). Thus, physical activity can play a role as a stimulator for early diagnosis and sustainable life in families with Lynch syndrome by urging young and adult people to go for genetic testing and cancer screening test ahead of time and by increasing physical fitness and muscle strength.

4.3 Other lifestyle factors in relation to cancer risks

Smoking and alcohol consumption has been recognized as an important risk factor for various cancer (Zisman et al., 2006). Previous studies have shown a strong association between colorectal cancer and smoking (Botteri et al., 2008; Zisman et al., 2006). It has been reported that earlier age of colorectal cancer incidence can be linked to smoking and drinking (Zisman et al., 2006). The exogenous environmental factor can influence the risk of colorectal cancer. Moreover, the risk of distal colon cancer among male has been reported to increase due to smoking and alcohol consumption. Interestingly, smoking can modulate the cancer onset age of both male and female, however, the consequence can be higher among female. Women are more prone to the carcinogenic effect of smoking (Zisman et al., 2006). Botteri reported that colorectal cancer-specific mortality can be significantly associated with smoking. Based on that, it has been claimed that smoking and drinking history should be considered when deciding cancer screening age (Botteri et al., 2008).

Previous researchers have suggested the effect of smoking and alcohol consumption on sporadic colon cancer (colon cancer due to other factors, but not genetics), however, there is minimal data on the impact of external lifestyle behavior on hereditary colorectal cancer (Burton et al., 2010). Although smoking and BMI have been considered a risk factor for the development of colorectal tumors in people with Lynch syndrome, moderate evidence has reported that both of those risk factors may increase the risk of tumors (Duijnhoven et al., 2013). However, the effect of smoking and alcohol consumption on other types of cancer need to be studied.

The studies on Lynch syndrome and related possible lifestyle risk factors have been summarized (as shown in table 1). Here few studies suggest strong correlations, and few are not. On the other hand, there is not much literature available on physical activity and possible interrelation with colorectal cancer in Lynch syndrome (Duijnhoven et al., 2013). Therefore, future research is needed to understand the role of physical activity and Lynch cancer. This study aims to fill the gap.

Table 1 Summary of the associated lifestyle factors on sporadic and Lynch syndrome-related colorectal cancer (recreated from (Duijnhoven et al., 2013))

Lifestyle factor	Sporadic colorectal cancer[1]		Colorectal cancer with Lynch syndrome[2]			
	Influence[3]	Reference	[4]Statistical correlation	Reference	Type of study	Type of population (N)[5]
Smoking status	↑	Botteri et al., 2008; Liang et al., 2009	++	Diergaarde et al., 2007	Case–control	Proven (29 %) and suspected (145 cases/103 controls)
			++	Watson et al., 2004	Retrospective cohort	Proven and inferred (360)
			++	Brand et al., 2006	Retrospective cohort	Proven (752)
			++	Pande et al., 2010	Retrospective cohort	Proven (386)
			++	Winkels et al., 2012	Prospective cohort	Proven and inferred (340)
Alcohol	↑	World Cancer Research Fund, 2011	0	Diergaarde et al., 2007	Case–control	Proven (29 %) and suspected (145 cases/103 controls)
			0	Watson et al., 2004	Retrospective cohort	Proven and inferred (271)
			+	Winkels et al., 2012	Prospective cohort	Proven (386)
Body fatness (BMI)	↑	World Cancer Research Fund, 2011	0	Diergaarde et al., 2007	Case–control	Proven (29 %) and suspected (145 cases/103 controls)
			+	Campbell et al., 2010	Case–control	Proven (36 cases/49 controls)
			++	Win et al., 2011	Retrospective cohort	Proven (1324)
			++	Botma et al., 2010	Prospective cohort	Proven (486)
Abdominal fatness (waist circumference and waist/hip ratio)	↑	World Cancer Research Fund, 2011				
Height	↑	World Cancer Research Fund, 2011	–	Botma et al., 2010	Prospective cohort	Proven (486)
Physical activity	↓	World Cancer Research Fund, 2011				

1=Review studies; 2=Single studies; 3(Arrow) = probable and 0 = limited-no conclusion; 4=Two signs (++statistically significant) One sign (+indicative) (0 no association); 5= Proven (genetically tested and confirmed MMR gene mutation carriers), Suspected (fulfilled Amsterdam criteria), Inferred (clinical HNPCC diagnosis and a family member with a confirmed MMR gene mutation)

5 Aims and research questions

The purpose of this study is to analyze the physical activity profile of people with Lynch syndrome in Finland. Additionally, it investigates the association between physical activity and cancer in people with Lynch syndrome.

By studying the intensity of the physical activity of the participants (MET-hours/week), it is possible to outline the features of physical activity level in their lifetime. This leads to the first research question,

- What is the characteristics of physical activity among people with family history of Lynch syndrome?

Like other health benefits, moderate to vigorous intensity physical activity may help to reduce the onset of chronic diseases. Therefore, by investigating the influence of leisure time physical activity along with other lifestyle habits would provide know-how of the association of physical activity with cancer in the Lynch syndrome families. This leads to the second research question,

- Is there any relationship between physical activity and cancer in people with Lynch syndrome?

6 Materials and methods

This thesis is part of a larger project called “Lynch syndrome and lifestyle” (“Lynch syndrooma”, 2016). The invitation to participate in the questionnaire survey was sent to families according to the Finnish Lynch syndrome registry. In addition, the intention of the research regarding hereditary cancer and the effect of lifestyle was explained. The whole dataset has been stored electronically under bigger database in gerontology research center. The confidentiality of the participants’ data has been maintained in this study. The study protocol has been approved by the ethics committee of the Central Finland Health Care District.

6.1 Study design and participants

The data has been collected using questionnaires during December 2016 - August 2017. The structured questionnaires were sent by post to altogether 952 people in December 2016. The answers from the questionnaires have been collected back in March-May 2017. Information on cancer diagnosis, age, sex and mutation type was obtained Jyväskylä Central Hospital. The questionnaires were mostly filled; however, in few occasions data were missing. Altogether 414 participants replied to the questionnaires. The data was organized in IBM SPSS database for running tests and further analysis.

6.2 Background variables

Background information of the participants has been analyzed in accordance with participants' medical record (age, sex, gender, MMR gene mutation type and cancer status). Study participants have been divided into two groups– cancer and without cancer, accordingly. The questionnaire contained queries about participant's anthropometric data (height, weight, waist circumference), self-reported health status, current medication list, smoking habit and alcohol consumption, along with few socioeconomic data (such as civil status, profession). Participants' were asked to measure their weight before breakfast and without clothes (if possible). BMI was calculated using height and weight in kg/m^2 unit. Participants were divided into three groups: namely, normal weight ($BMI \leq 25\ kg/m^2$), overweight ($BMI\ 25 - 30\ kg/m^2$), or obese ($BMI \geq 30\ kg/m^2$) (World Health Organization, 2018b). Measuring tapes were supplied with the questionnaire for examining the waist circumference along with an instruction set.

Participants' average sitting time in a day has been assessed by asking how long (in hrs.) they sit at work/study place, at home (in front of the television, computer, eating, reading, hobby), in transportation and others. Based on that, a total sitting hour of an individual has been calculated. Participant's smoking habit (namely never smokers, current smokers, and past smokers) has been accessed from their current and past smoking patterns. Participant, who has reported smoking cigarettes less than 100 times during their life, have been considered as never smokers. Past smokers were not smoking for last 10 years. Moderate and heavy alcohol consumers have been identified by frequency and portion of alcohol per month. Participants drinking habits were categorized as never, moderate and heavy; if consumes < 1 portion/month, if consumes $3 - 6$ portions $2 - 4$ times/month, and if consumes > 6 portions > 8 times/month, respectively.

6.3 Physical activity

Leisure-time physical activity includes physical activity, which doesn't occur in commuting to or during work/study, also mentioned in the questionnaire. Leisure time physical activity was assessed by four questions. The first question was about participant's perceived current physical activity status. Participant's self-reported current physical activity was assessed by using the seven-point scale, which is shown below:

1 = "do not participate in any kind of physical activity"

2 = "light physical activities 1-2 times /week"

3 = "light physical activities several times/week"

4 = "physical activities, causing shortness of breath and sweating 1-2 times/week."

5 = "physical activities, causing shortness of breath and sweating several times/week."

6 = "active sports"

7 = "competitive sports"

The answers were categorized as light (1-3 scale), moderate (4-5 scale) and vigorous (6-7 scale) physical activity. The second question asked about monthly frequency (how much leisure time physical activity occurred in each month): < 1 time/month, $1 - 2$ times/month, $3 - 5$ times/month, $6 - 10$ times/month, $11 - 19$ times/month and ≥ 20 times/month. The third question asked about intensity (whether the level of leisure time physical activity was as tiring as (equivalent to) walking, alternating walking and jogging, jogging, or running). The fourth question asked about duration (how long each session of physical activity generally lasted): < 15 minutes, $15 - 30$ min, $30 - 60$ min, $1 - 2$ h, or $\geq$ 2h and the answers were categorized accordingly. Additionally, participant's past physical activity performed during lifetime (e.g. in every decade) has also been included in the question sets.

Typically, an individual's physical activity levels are categorized on the base of MET level (King et al., 2001). The leisure-time physical activity MET value was calculated by multiplying the average intensity, duration, and frequency in a month. MET hours per month has been converted to MET-minutes per week for the analysis. Leisure time physical activity was divided into three categories in line with WHO guidelines; namely, ≤ 500 MET-minutes/week, 500-1000 MET-minutes/week and > 1000 MET-minutes/week (World Health Organization, 2018b). According to this guideline, at least 150 minutes of moderate-intensity physical activity or at least 75 minutes of vigorous-intensity physical activity throughout the week (can be interpreted as 500-1000 MET-minutes/week) is needed to get substantial health benefits (World Health Organization, 2018b).

6.4 Statistical methods

IBM SPSS statistics (version 24) and Microsoft Excel have been used for data analysis and data verifications. The chi-squared test is mostly utilized to determine if there is a significant difference between the expected frequencies and the observed frequencies in one or more categories (Fisher, 1922). The independent t-test is commonly used to test if two sets of data differ significantly from each other (Dodge, 2008). In this study, $\chi 2$ -test was used for categorical variables (perceived present physical activity status) and independent t-test for continuous variables (numeric data such as age, BMI, MET value). These tests are largely used to compare (statistical significance) physical activity between two groups, namely, cancer and without cancer. A logistic regression analysis can be used to summarize and study the relationships between a predictor variable and the dependent variable (Neter et al., 1996). In this study, logistic regression models were made to estimate the association of current physical activity and cancer of the participants.

The questionnaire contained closed questions including ranking, selected items, and categorical response. The questions were categorized and organized logically, which might have supported the participants to fill in. All most every participant has provided information about their physical activity level based on the conditions and ranking of the questions. Therefore, there is no reason to not to believe in the participant's response to the self-reported physical activity.

7 Results

Participants' questionnaire response rate was 43% (total 414 participants). Baseline characteristics of the participants (with cancer and without cancer) have been summarized in table 2. The age distribution of the participants was $21 - 87$ years, among them $50 - 70$ years has a majority. To represent the distribution of age among cancer and without cancer group, the study population was divided into four groups: ≤ 45 years, $45 - 59$ years, $60 - 70$ years and > 70 years. The mean age of participants with cancer was 65.74 ($SD = 9.6$) and without cancer was 50.75 ($SD = 13.65$). Independent t-test and chi-square test were conducted to investigate differences among groups for continuous and categorical variables. There was a statistically significant difference of age between cancer [$mean = 65.74$] and without cancer [$mean = 50.75$] groups ($p < 0.001$).

Employment status of the participants was accessed into economically active (paid or self-employed) or not active (student, unemployed, working occasionally, retired, parental leave). In the study population, 29% people were employed, 52% were retirement pensionaries and 17% were on maternity/parental leave and disability/sickness pensioner (as shown in table 2). Participants' socioeconomic status was significantly different between cancer and without cancer groups ($p < 0.05$), that might be due to cancer diagnosis age.

The mean Body Mass Index (BMI) did not differ significantly between cancer and without cancer group ($p = 0.298$). There was no significant difference of mean waist circumference for people with cancer and without cancer ($p = 0.064$). The difference in participants' average sitting time per day was not statistically significant. Furthermore, without statistical significance, smoking and alcohol consumption patterns slightly differ between the groups (shown in table 2).

Table 2 Baseline characteristics of the participants

Characteristics	Cancer	Without cancer	p-value[¥]
Total	n= 194	n= 220	
Female %[n]	56 [109]	54 [120]	
Male %[n]	43 [85]	45 [100]	
Age in years: Mean(SD)	65.74 (9.6)	50.75 (13.7)	**<0.001**
≤45 %[n]	1.5 [3]	37.3 [82]	
46 - 59 %[n]	24.3 [47]	32.2 [71]	
60 - 70 %[n]	43.3 [84]	24.1 [53]	
>70 %[n]	30.9 [60]	6.4 [14]	
WC in cm: Mean (SD)	95.22 (15.6)	92.55 (13.4)	0.064
BMI in kg/m2: Mean(SD)	27.13 (5.5)	26.60 (4.9)	0.298
Normal %[n]	41.2 [80]	40.9 [90]	
Overweight %[n]	31.4 [61]	38.6 [85]	
Obese %[n]	24.7 [48]	20 [44]	
Sitting time in hours: Mean(SD)	9.96 (3.23)	9.48 (3.0)	0.187
At work	2.50 (2.4)	3.27 (2.3)	
Travelling	0.74 (0.6)	0.90 (0.8)	
At home	5.17 (2.0)	4.45 (2.0)	
Others	0.67 (0.65)	0.66 (0.5)	
Smoking habits			0.503
Never %[n]	52.6 [102]	52.3 [115]	
Past %[n]	9.3 [18]	17.3 [38]	
Current %[n]	35.6 [69]	29.1 [64]	
Alcohol consumption			0.227
Never / rare (<1 portion/week) %[n]	45.4 [88]	40.9 [90]	
Weekly (1-5 portions/week) %[n]	37.1 [72]	33.2 [73]	
Often (>5 portions/week) %[n]	17.5 [34]	25.9 [57]	
Socio-economic status			**<0.001**
Working/employee %[n]	28.9 [56]	65 [143]	
Retired pension %[n]	52.6 [102]	19.5 [43]	
Others %[n]	17.4 [34]	15 [33]	

[¥] **χ2 -**test was used for categorical variables and independent **t-**test for continuous variables.

Participant’s self-reported current physical activity status have been summarized in table 3. The differences of current physical activity status among groups were investigated. In order to examine the participants’ self-perceived current physical activity status, it has been categorized as low, moderate and vigorous intensity physical activity. The purpose of this categorization was to illustrate the participant's current physical activity features. Majority of the participants from both groups reported being involved in a light or moderate physical activity. Only 13% people with cancer and 23% people without cancer reported being involved in regular strength training exercises or competitive sports. There was the statistically significant difference in perceived current physical activity status between the groups ($p = 0.008$). The study population size in table 2 and table 3 slightly differs due to the missing response of physical activity questions.

The mean MET-minutes per week for cancer participants were 1347 and for participants without cancer were 1431 (as shown in table 3). According to the guideline, the participants have done enough physical activity to get considerable health benefits (World Health Organization, 2018b). There was no statistically significant difference of mean MET value between the groups ($p = 0.564$). The results showed that participants with cancer and without cancer have took part in various levels of physical activity per week.

Table 3 Leisure-time physical activity characteristics (MET-minutes/week) in the study population

Physical activity (MET)	Cancer n = 180	Without cancer n = 215	p-value[¥]
Total: Mean (SD)	1347.16 (1380.45)	1431.39 (1493.34)	0.564
Male	n = 77	n = 96	
	1293.40 (1465.27)	1383.42 (1424.75)	
Female	n = 103	n = 119	
	1387.35 (1319.4)	1470.08 (1551.4)	
Physical activity level	% [n]	% [n]	
<500 MET minutes/week [†]	34.4 [62]	37.7 [81]	
500-1000 MET minutes/week	17.3 [31]	16.7 [36]	
>1000 MET minutes/week	48.3 [87]	45.6 [98]	
According to the participant's perception			
Current physical activity	Cancer	Without cancer	**0.008**
Light physical activity %[n]	43.5 [84]	31.8 [70]	
Moderate physical activity %[n]	43.5 [84]	45.0 [99]	
Vigorous physical activity %[n]	13 [25]	23.2 [51]	

[¥] Independent t-test was used for continuous variables and $\chi 2$ -test was used for categorical variables to compare means

[†] WHO physical activity guidelines 2018 recommend 150 min/week at moderate and 75 min/week at a vigorous intensity (translated as 500-1000 MET-minutes/week)

Results of the logistic regression analysis are presented in table 4. Binary logistic regression was performed to investigate the association between self-reported current physical activity status and presence of cancer. Three models were created, and all were adjusted for sex. In the first model, current physical activity variable was included. In the second model, smoking was included in addition to model 1. Alcohol consumption was further added in the model 3. All three models demonstrate an association between self-perceived current physical activity from vigorous to light and cancer occurrence (Model 1: OR 2.46 95% CI $(1.38-4.36)$). Both in Model 2 and Model 3, the added variables have changed the association between self-perceived current physical activity and cancer incidence (OR 2.71 95% CI $(1.49-4.92)$).

Table 4 Association between physical activity and presence of cancer among people with Lynch syndrome in logistic regression analysis sex-adjusted

Variables		Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
	Sex adjusted	0.91 (0.62-1.35)	0.89 (0.60-1.35)	0.94 (0.62-1.44)
Physical activity (self-perceived)	Vigorous vs Light	2.46 (1.38-4.36)	2.71(1.50-4.91)	2.71 (1.49-4.92)
	Vigorous vs Moderate	1.73 (.98-3.03)	1.81 (1.02-3.20)	1.79 (1.0-3.18)
	Smoking (Past vs Never)		0.79 (0.51-1.23)	0.74 (0.47-1.17)
	Smoking (Past vs Current)		0.39 (0.19-0.76)	0.40 (0.20-0.79)
Alcohol consumption (Heavy vs Light)				1.58 (0.89-2.79)
	Alcohol consumption (Heavy vs Moderate)			1.69 (0.96-2.95)

Note: Model 1 adjusted for sex; Model 2 adjusted for sex and smoking; Model 3: Model 1 + Model 2 + adjustment for alcohol consumption.

8 Discussion

The key findings of the study showed that there was an association between current physical activity and cancer. Participants, who were vigorously physically active, had 2.7 times the risk of being healthy (having no cancer) compared to those with a light level of physical activity $(OR\ 2.71\ 95\%\ CI\ (1.49 - 4.92)$, as shown in table 4. The self-perceived current physical activity level was significantly different between these two groups ($p = 0.008$, as shown in table 3). The mean MET-minutes per week for both groups were > 1000 MET-minutes per week. The finding suggested that in average two-third of the study population fulfill the WHO guideline (World Health Organization, 2018a).

Unlike other lifestyle factors, the association between physical activity and cancer among individuals with Lynch syndrome have not been explored much, as shown in Section 4.3. Hence, the study could not be compared with other related studies. The total physical activity during a lifetime along with cancer status of the participants would be an interesting study. In that way, the health benefits of physical activity can be estimated for predicting cancer status among people with Lynch syndrome. It is possible that other lifestyle factors (such as smoking, alcohol consumption) are more closely associated with cancer occurrence. As shown in table 4, adding smoking and alcohol consumption has changed the relationship between participant's current physical activity level with cancer. These findings are aligned with previous studies where it has been estimated that other lifestyle factors along with physical activity could help to reduce the onset of cancer (Friedenreich et al., 2010; Duijnhoven et al., 2013). An interesting fact has been observed during data analysis that there was a difference between the participant's self-perceived current physical activity status (7-point scale) and participant's MET value. Different question types may have caused these differences. The MET–values were calculated based on average frequency, time and intensity in a month. These may have created confusion among older populations to respond. In contrast, the 7- point scale considers more generally the participant's perceived impression of being physically active.

The present study suggests that the people with Lynch syndrome have overall active lifestyle with weekly MET value more than 1000 minutes. About two-thirds of the participants with Lynch syndrome have meet WHO physical activity guidelines from both groups (cancer and without cancer). This could be because sport and leisure time physical activity is part of the Finnish culture (Kaleta & Jegier, 2005); for example, more than two-third Finns do independent physical activities in nature (European Commission, 2018). Previous research has reported that the highest percentage of leisure time physical activity occurs in Finland (29.9%), followed by Germany (19.9%), Spain (17.6%), Russia (13.9%), and the lowest in Poland (6.4%) and Hungary (6.9%) (Kaleta & Jegier, 2005). However, according to ATH survey result reports (2013), about one-third (34% adults and 20% of older adults) among the general population in Finland, meet the WHO recommended physical activity levels (World Health Organization, 2016). Therefore, it can be concluded that the Finnish population with Lynch syndrome tend to lead an active lifestyle compared to rest. However, further studies on physical activity level before and after cancer diagnosis are required to see if there is any difference.

The participants of this study were physically active in average. This finding may lead to the fact that cancer-related death can be lower among physically active people in their later life. Earlier studies reported low mortality related to colorectal cancer and endometrial cancer in Finland (7.9% died from colorectal and 5% from endometrial cancer) (Pylvänäinen et al., 2012). Colorectal cancer mortality might be reduced through risk factor modification (lifestyle recommendations) along with screening, and improved treatment (Skyrud et al., 2017). In this case, higher leisure time physical activity might play a significant role along with screening and early diagnosing in cancer-specific mortality in Lynch syndrome. Previous studies have shown evidence that together with behavioral support interventions, moderate to vigorous physical activities can prevent recurrence of cancer at a later stage of life (Rock et al., 2012). Although it cannot be concluded from this study that physical activity alone makes a significant role, however, physical activity along with other lifestyle factors including smoking can improve the outcome of lowering the risk of cancer in people with Lynch syndrome (as shown in table 4).

The study findings reveal that only a few people with Lynch syndrome (2%) reported being diagnosed with cancer below age 45 years old (as shown in table 2). The data shows the cancer incidence gets higher in accordance with increasing age. Therefore, there might be a risk of underestimating the risk of developing cancer in future among people with Lynch syndrome. Even though genetic counseling, testing, and cancer surveillance have well-proven benefits in reducing mortality of Lynch syndrome mutation-positive carriers, it is essential to educate offspring about the risk of this syndrome and the possibility of genetic testing in an earlier age (Aktan-Collan et al., 2011). Communication among family members and mental support may help to overcome the fear and tension of genetic testing among young people. Previous studies have shown that increased physical activity is linked not only to behavioral and social skills but also to physical and social environmental support (Kahn et al., 2002). Therefore, people with an active lifestyle can be more prone to go for a screening test and genetic testing than people with a sedentary lifestyle.

Studies have shown that people might avoid going for genetic counseling and might not be motivated to take part in various physical activity due to lack of knowledge about the hereditary predisposed mutated gene (Aktan-Collan et al., 2013). Certainly, participants (with Lynch syndrome) without cancer have more chance to develop cancer in their lifetime compared to the general population. Therefore, physical activity might need to be integrated into their modified lifestyle from the early age (Burton et al., 2010; Friedenreich et al., 2010). Additionally, physical activity can significantly improve well-being and physical strength (Leskinen et al., 2013; Rock et al., 2012). Hence, it can be concluded that physical activity promotion may not alone reduce the cancer risk, but it may serve to lead a sustainable life before and after the cancer diagnosis.

Family with Lynch syndrome and their relatives can be benefitted by the promotion of health education through physical activity (Kahn et al., 2002). Family-based social support intervention may include health education which can encourage these families to cope up with healthy behavior change and to provide customized physical activity programs. This can be achieved by organizing community-based sports events which can attract people from different age to do outdoor activities such as running, jogging, swimming, Nordic walking as well as indoor activities such as going to the gym, ball games, gardening. The social awareness about Lynch syndrome might create better communication among people about getting to know their family history of any cancer occurrence and the type of medical surveillance including screening, genetic counseling.

One of the strengths of this study is the considerable number of participants. The collected data represents the overall physical activity trend among Lynch syndrome families. Based on that, a future improvement on the lifestyle modifications can be suggested. Furthermore, the quantitative questionnaire included detailed questions about the intensity of present physical activity which has permitted to assess various components of physical activity including duration, frequency, intensity and participants perception of present physical activity level. Historically, using survey have been a very common method of collecting data in the field of physical activity (Thomas et al., 2015). However, the self-reported physical activity status, frequency, and duration based on the questionnaire cannot always exhibit the accurate answer. According to Hagströmer (2006), selecting the right measurement for physical activity and energy expenditure could be an issue. Activity monitors have proven to be an instrument to track physical activity level in the literature (Hagströmer et al., 2006). However, this method is expensive and therefore, has not been conducted in this study. The study has some limitation. Firstly, numerous lifestyle factors including physical activity and genetic features might interact with the onset of cancer among Lynch syndrome families. Therefore, it is hard to show only one factor contribute independently to decrease the cancer risks.

Secondly, the lack of total physical activity data of the participants lifetime. This study has included only present physical activity level in the analysis. The questionnaire had included previous physical activity history question which includes the type of physical activity during participants lifetime. However, frequency, intensity and duration (three components) of past physical activities are not easy to collect and henceforth, has not been incorporated into the present study. These three components of participant’s previous physical activity can be essential for the calculating the total physical activity level during a lifetime. More explanations might be helpful to collect data in this regard (e.g. visual leaflets on physical activity guidelines and MET chart).

An updated cloud-based public health application can be initiated where physical activity data can be stored online, as illustrated in Figure 4. In this way, it will be easy to follow up lifetime physical activity pattern of the Lynch syndrome families. Consequently, it can help to run a more accurate analysis of the effect of the physical activity on cancer onset age (pre-diagnosis physical activity) as well as cancer recurrence and quality of life after cancer incidence (post-diagnosis physical activity). Finally, the physical activity measurement has been based on participants self-report, which might introduce bias in the study. Future study needs to include the physical activity level at a younger age in accordance with present age. In order to do that, a facility can be implemented where the physical activity data from the Lynch syndrome families can be collected yearly to study and follow up their physical activity level during the lifetime (as shown in figure 4).

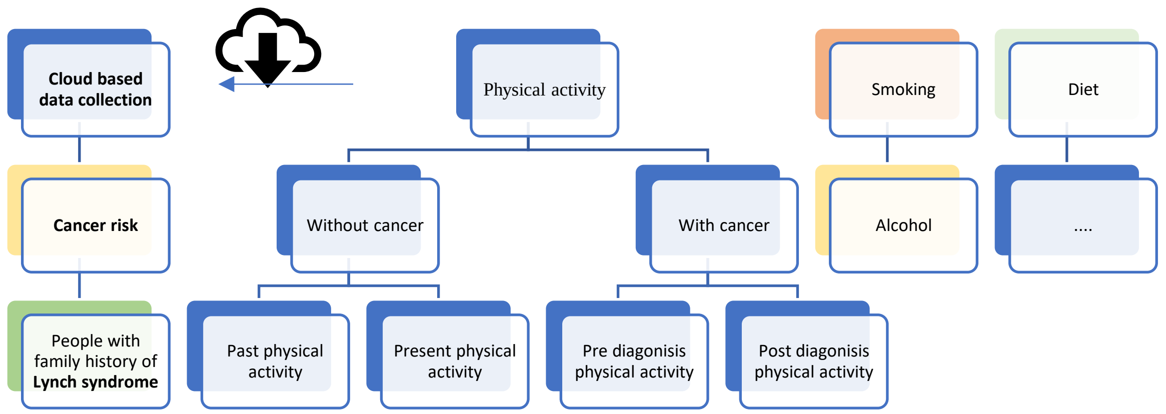

Figure 4 Cloud-based data collection and cancer risk factor analysis

9 Conclusion

With the formerly stated limitations in mind, the study concludes that both cancer and without cancer individuals with Lynch syndrome are associated with different physical activity levels. In line with earlier studies (Duijnhoven et al., 2013; Friedenreich et al., 2016) physical activity along with other lifestyle factors including a dietary factor, smoking, and alcohol consumption might be linked with lowering the risk of onset of cancer. Thus, there is an opportunity for the role of physical activity to modulate the risk of developing cancer in Lynch syndrome.

In this study, the difference of current physical activity level between cancer and without cancer have been reported (table 3). The association between cancer and physical activity along with smoking, alcohol consumption is also presented in this study (table 4). An association between current physical activity and cancer occurrence (odds ratio [OR] 2.71, 95% confidence interval [CI] 1.50-4.92) has been established in the study. People with Lynch syndrome are more physically active compared to an average Finns (only one-third meets guidelines). About two-thirds of the participants with Lynch syndrome have meet WHO physical activity guidelines from both groups (cancer and without cancer). Physical activity can provide a platform for them to learn more about this genetic syndrome and to engage in a regular independent physical activity (or through sports clubs) in their free time. Therefore, health care provider should include gender and age-specific physical activity guidelines to increase the quality of life and to decrease cancer-specific mortality in Lynch syndrome carriers. These findings are useful in the bigger context of promoting physical activity among Lynch syndrome families. Additionally, smoking history and physical activity history along with family history of cancers can be integrated while deciding for the age of cancer screening test in families with Lynch syndrome.

Future knowledge on the influence of total lifetime physical activity on cancer risk in Lynch syndrome families can lead to evidence-based lifestyle guidance for families with these mutated genes. This study provides the ground for that. Instead of “one size fits for all”, customized guidance on moderate to vigorous physical activity along with other lifestyle factors should be emphasized to reduce the risk of cancer and to increase the longevity of life after a cancer diagnosis among people with Lynch syndrome. Thus, physical activity promotion can be included in prevention strategies against hereditary cancer. This study has the potential to contribute to the further research on the effect of an environmental factor on developing cancer. Finally, connecting a strong link between physical activity and hereditary cancer prevention, a research challenge that remains to be tackled.

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