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High intake of Ultra-Processed Foods and risk of Colorectal Cancer: The Norwegian Women and Cancer study

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Master's thesis in clinical nutrition, ERN-3900, May 2022

Acknowledgments

First and foremost, I would like to thank those who made this project possible. I would like to express my sincere gratitude to Professor Guri Skeie for being there through the entire process, providing valuable guidance and feedback, challenging me to help me grow. I feel lucky to have been able to have you as my supervisor both during writing my bachelor's and master's thesis. I would also like to thank the Norwegian Women and Cancer (NOWAC) study for providing access to the data material and John Martin Fredriksen for helping with the NOVA classification process.

Further, I would like to thank Dr. Inge Huybrechts for giving valuable feedback and Dr. Helle Margrete Meltzer for sharing her knowledge about the NOVA system that together inspired new thoughts and reflections.

Lastly, I would like to thank my family and friends for their continuous support and encouragement throughout the year.

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Norway, May 2022

Abstract

Background: Norway is one of the countries with the highest rate of colorectal cancer (CRC). Previous research on diet and CRC has been heavily based on nutrients and foods, but new findings indicate that the way we process food may be of importance. However, the findings are contradictory. Further, new findings indicate that CRC risk factors might affect colorectal subsites differently. As the modern diet is changing towards including more ultra-processed food (UPF), a better understanding of how food processing affects CRC might be a new approach to prevent CRC. This raises the question: is there an association between high intake of UPF and CRC risk?

Method: 77,100 women (1625 cases) from the Norwegian Women and Cancer study were included in this prospective cohort analysis. Dietary intakes were collected using validated semi-quantitative food frequency questionnaires. The foods were categorized based on the degree they had been processed by using the NOVA classification system. Multivariable Cox proportional hazard models were used to assess the association between high intake of UPF and CRC risk.

Results: A high UPF intake, compared to a low UPF intake, was not significantly significant associated with increased total CRC risk after adjusting for all covariates, including energy intake(HR=1.21; 95% CI 1.01-1.46, P-trend = 0.08). However, a high UPF intake, compared to a low UPF intake, was statistically significant associated with right-sided colon cancer when adjusting for covariates(HR=1.28; 95% CI 1.03-1.60, P-trend = 0.04). The average follow-up time was 17.4 years.

Conclusions: Results in this large prospective cohort suggest no overall association between a high UPF intake and risk of CRC. However, an association between a high UPF intake and right-sided colon cancer was found. These findings indicate that UPF affects colorectal subsites differently. Further research investigating the association between UPF and CRC is needed to determine causality.

Keywords: Ultra-processed food, colorectal cancer, NOWAC, Norway.

Abstrakt

Bakgrunn: Norge er at av landene i verden med høyest forekomst av kolorektalkreft(CRC). Tidligere forskning på kosthold og CRC er sterkt basert på næringsstoffer og matvarer, men nye funn tyder på at måten vi prosesserer mat på også har en betydning. Funne er i midlertidig motstridende. Videre indikerer nye funn at risikofaktorer for CRC påvirker tarmavsnittene ulikt. Ettersom kostholdet endres mot å inkludere mer ultra-prosessert mat(UPF), kan en bedre forståelse av hvordan prosessering av mat påvirker kolorektalkreft være viktig i forebyggingsarbeidet mot kolorektalkreft. Dette legger grunnlaget for forskningsspørsmålet: er det en assosiasjon mellom høyt inntak av UPF og økt risiko før CRC?

Metode: 77 100 kvinner(1625 cases) fra den norske kvinner og kreftstudien ble inkludert i denne prospektive kohorten. Informasjon om kostholdsdata ble samlet inn ved hjelp av validerte semi-kvantitative matfrekvens spørreskjemaer. NOVA-klassifiseringssystemet ble brukt for å klassifisere matvarene etter hvilken grad de var prosessert. Multivariabel cox regresjon ble brukt til å vurdere sammenhengen mellom høyt UPF inntak og risiko for CRC.

Resultat: Et høyt inntak av UPF, sammenlignet med et lavt inntak av UPF, var ikke statistisk signifikant assosiert med økt risiko for total CRC i den multivariable og energi-justerte modellen (HR=1.21; 95% CI 1.01-1.46, P-trend = 0.08). Derimot var et høyt inntak av UPF, sammenliknet med et lavt inntak av UPF, statistisk signifikant assosiert med kreft i høyre side av kolon i den multivariable-justerte modellen (HR=1.28; 95% CI 1.03-1.60, P-trend = 0.04). Gjennomsnittlig oppfølgingstid var 17.4 år.

Konklusjon: Ingen sammenheng ble funnet mellom et høyt inntak av UPF og CRC, men en sammenheng ble funnet mellom et høyt inntak av UPF og kreft i høyre side av kolon. Dette indikerer at UPF påvirker risikoen for kreft i tarmavsnittene ulikt. Ytterligere forskning som undersøker sammenhengen mellom UPF og CRC er nødvendig for å fastslå kausalitet.

List of abbreviations

BMI	Body mass index
CI	Confidence interval
CIN	Chromosomal instability
CRC	Colorectal cancer
CUP	Continuous Update Project
EPIC	The European Prospective Investigation into Cancer and Nutrition
FFQ	Food Frequency Questionnaire
HAA	Heterocyclic aromatic amines
HR	Hazard ratio
IARC	International Agency for Research on Cancer
ICD-10	International Classification of Diseases, 10th revision
kJ	Kilojoule
MAR	Missing at random
MCAR	Missing completely at random
MSI	Microsatellite instability
NCD	Noncommunicable diseases
NCI	National Cancer Institute
NNR2012	Nordic Nutrition Recommendations 2012
NNR2023	Nordic Nutrition Recommendations 2023
NOWAC	The Norwegian Women and Cancer Study
PAH	Polycyclic aromatic hydrocarbons
UPF	Ultra-processed food
WCRF	World Cancer Research Fund

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1 Introduction

1.1 The importance of diet for health

Noncommunicable diseases (NCDs), also called chronic diseases, is the biggest contributor to all death globally, making up 71% of total mortality(1). NCDs have been recognized as a major challenge for sustainable development and were, in 2015, included in the Sustainable Development Goals (SDG) with an aim to reduce premature mortality from NCDs through prevention and treatment by one-third by 2030 (SDG target 3.4)(2). Cancer is the second most deadly disease among NCDs, accounting for 9.3 million deaths per year(1). Various modifiable lifestyle factors such as diet can influence the risk of developing cancer. This means many cases of cancer can be prevented. By implementing a healthy diet and other existing evidence-based prevention strategies, such as avoiding tobacco use, maintaining a healthy weight, and exercising regularly, 30-50% of cancer death can be prevented(3). This emphasizes the importance of lifestyle, including diet, in preventative cancer treatment.

The current dietary recommendations for cancer prevention are based on World Cancer Research Fund(WCRF) Continuous Update Project(CUP) panel systematic reviews of the evidence regarding diet, nutrition, physical activity, and incidence of cancer(4). The recommendations for cancer prevention from WCRFs reports are further included in the Nordic Nutrition Recommendations (NNR2012) and the Norwegian national dietary guidelines(5, 6). It is to be noticed that NNR2012 was published in 2012 and thus used WCRFs second report from 2007 and not the third report published in 2018. However, the recommendations from the 2007 report still stand strong(7).

A healthy diet is associated with a decrease in cancer risk(5). In NNR2012, a healthy diet is characterized by being rich in vegetables, pulses, fruits and berries, nuts and seeds, whole grains, fish and seafood, vegetable oils and vegetable oil-based spreads, and low-fat dairy products(5). In contrast, the Western diet pattern, characterized by red and processed meats, foods low in essential nutrients, high in added sugar and fats and salt, has been associated with a higher risk of developing cancer compared to a healthy diet(5). Furthermore, NNR2012 also write that food preparation and manufacturing methods that include treatment at very high heat over an extended period of time might increase the risk of adverse health

effects(5). This underlines that food processing is a possible new aspect that should be considered when discussing a healthy diet to prevent cancer.

1.1.1 The evolution of food processing

The way we process food has developed over time. The first origins of food processing trace back to the hunter-gather society, where heat over fire was used to boil water and cook meat and vegetables to increase palatability(8). From there, further development of processing techniques were developed. By 3000-1500BC, the Egyptians had created further processing techniques, including sun drying, fermentation to produce alcohol, and cereal grinding(8). Then, during the first two millennium AD, there was a rapid increase in trade and exchange of foods and technologies.

Further, the industrial way of food processing escalated during the Industrial Revolution(8). During the first part of the Industrial Revolution in the 1700s, food processing was still heavily based on craft skills, but the first scientific discoveries were invented, such as chlorine to purify water and citric acid to flavor and preserve food(8). Then in the 1900s, the scientific understanding increased, and after electricity was invented, the food industry and food processing were revolutionized(8). During the World Wars, the development of processed foods increased further, partly stimulated by the need to preserve food for military rations. After World War II, the production of ready-to-go meals and snacks we know today began. Since then, new technologies, products, and packaging methods have been developed and continued to be advanced, resulting in the food processing market we know today where convenience food are an important part of our daily diets(8).

1.2 What is food processing and why emphasize it

Food processing can be defined as '*any deliberate change made in a food from the time of origin to the time of consumption*'(9)(s.2066S). One or multiple methods are used to turn fresh foods into food products during the processing. This can include methods such as chopping, freezing, fermenting, or adding additives(10). Five purposes of food processing can be highlighted(11):

1. To make food edible or more pleasant to eat, such as milling and grinding grain crops to make flour.

2. To make food more convenient, such as making meals that are fast to prepare or ready to go.
3. Improve nutritional quality, such as fortifying non-dairy milk with calcium.
4. Extend the product's shelf-life and improve food safety, for example, by removing harmful microorganisms.
5. Decrease the cost of food, for example, by producing foods in bulk, such as precut frozen broccoli.

According to Monteiro et al., almost all the food we eat is processed in one form or another(12). One type of food processing can be picking an apple from a tree and washing it before eating. Another type of processing can be adding additives to add a particular purpose, such as increasing nutritional value or improving the food quality(12). These food additives can help keep bread free of mold for longer and function as emulsifiers, in for example peanut butter, to prevent fats and oils from separating(13). Other food processing methods can be chopping and cooking of foods when preparing food at home, not to mention the more industrialized processing methods such as hydrogenation and hydrolyzation(12).

As to why food processing is important to emphasize, two reasons can be highlighted. 1) The development of food processing has resulted in a change in food systems, which has contributed to a change in availability, resulting in a change in purchases and consumption of more processed foods(14). 2) Though food processing has many benefits, such as preserving foods and increasing the shelf-life, some food processing methods such as hydrogenation of vegetable oil and cooking of meat at high temperatures over an extended period have shown to have adverse health effects(15, 16). As such, the overall health impact of these highly processed foods on our health is largely unknown and may be differential for different population groups and eating cultures.

1.2.1 Classification systems for food processing

As there are a wide variety of food processing methods and a big difference in how they affect our health, several classification systems have been developed to distinguish between the different degrees of food processing(17-19). This, to make it easier to understand how to judge food supplies and distinguish between different types of processing terms such as minimally processed and highly processed. In a study from 2014 that examined five different

food processing classification systems, a classification system called NOVA was deemed the most specific, coherent, and comprehensive classification system(20).

1.3 The NOVA classification system

1.3.1 Description of the NOVA classification

The NOVA classification system was developed by researchers at the University of São Paolo, who argued that there was a need for a new system that distinguished between the variety of food processing methods to better analyze and assess how food processing affects human health(14). To fulfill this need, they developed a categorizations system called NOVA that categorizes foods according to their extent and purpose of food processing rather than in terms of nutrients(21). The first version of NOVA was published in 2010(22) and was later adjusted and refined(19). Now NOVA has become a recognized tool for nutrition and public health research(21).

NOVA identifies food processing as 'physical, biological and chemical processes that occur after foods are separated from nature, and before they are consumed or used in the preparation of dishes and meals'(21) (s.30). NOVA categorizes foods in groups from 1 to 4, 4 being the most processed, based on the extent and purpose of the food processing. In short: The first group, referred to as Group 1, includes unprocessed or minimally processed foods, which are the edible part of plants, animals and fungi, algae and water (e.g. fruit and eggs), and unprocessed foods that have gone through physical transformation(e.g. pressed juice and dried fruits)(21). Group 2 includes processed culinary ingredients and are substances derived from Group 1 foods (e.g. salt, sugar, and honey)(21). Group 3 includes processed foods and is made by adding substances from Group 2 to Group 1 foods (e.g. cheese and homemade bread)(21). Group 4 includes UPF, which are '*formulations made mostly or entirely from substances derived from foods and additive, with little if any intact Group 1 food*' (e.g. mass-produced bread, margarine, and breakfast cereals)(14)(s.9). Further information and specifications of the four NOVA groups can be found in Table 1.

Table 1. Overview of the definitions in the NOVA classification system*

	Group 1		Group 2	Group 3	Group 4
	Unprocessed foods	Minimally processed foods	Processed culinary ingredients	Processed foods	Ultra-processed foods
Definition	*Unprocessed foods*: Edible parts of plants, animals, fungi, algae, and water. *Minimally processed foods*: Physical transformation of unprocessed foods.		Substances derived from nature or Group 1 foods.	Foods made by adding Group 2 substances to Group 1 foods.	Formulations made mostly or entirely from substances derived from foods and additives, with little intact Group 1 foods.
Purpose	To extend storage life and make foods more edible, safe, and diverse to prepare.		To make products used to prepare, season, and cook group 1 foods. This to make more enjoyable and varied dishes.	To increase durability, modify or enhance sensory qualities of Group 1 foods.	To create ready to eat meals and drink products that are low-cost, convenient, attractive, and hyper-palatable with extended storage life.
Prosessing technique	*Unprocessed foods:* Edible parts of plants, animals, fungi, algae, and water are separated from nature. *Minimally processed foods:* Unwanted parts from foods are removed, drying, crushing, grinding, roasting, boiling, pasteurization, freezing, placing in containers, vacuum packaging, non-alcoholic fermentation, or other methods without adding salt, sugar, oils, fats, or other food substances.		Pressing, refining, grinding, milling and spray drying.	Cooking or preservation methods and non-alcoholic fermentation. Additives may be used to preserve original properties or to resist microbial contamination.	Goes through a series of processes, where high-level equipment and technology often are used. In addition to including additives found in Group 3 (e.g., salt, sugar, antioxidants), Group 4 also contains other substances directly extracted from food. Examples of such substances are lactose, casein, and gluten, in addition further processed substances, such hydrogenated oils, hydrolyzed proteins and maltodextrin.

	Group 1		Group 2	Group 3	Group 4
	Unprocessed foods	Minimally processed foods	Processed culinary ingredients	Processed foods	Ultra-processed foods
Examples	*Unprocessed foods:* Fresh fruit, vegetables, eggs, meat, fish, grains, seeds, and legumes. *Minimally processed foods:* Dried, frozen, or chilled vegetables, meats, fruit; vegetable and fruit juices without added sugar; pasteurized milk.		Salt, sugar, honey, syrup, vegetable oils, butter, and starches. Products such as salted butter or group 2 foods with added vitamins and minerals remain in this group.	Canned or bottled vegetables, fruit, and legumes; salted or sugared nuts and seeds; salted, cured, or smoked meats; canned fish; fruit in syrup; cheeses and unpackaged freshly made bread.	Carbonated drinks; sweet and savory packaged snacks; ice cream, chocolate; mass-produced bread and buns; margarine and spreads; breakfast 'cereals', 'energy' bars; milk drinks, 'fruit' yogurt and 'fruit' drinks; 'instant' sauces; sausages, burgers, and other reconstitutes meat products; 'instant' soups and noodles.

*An adapted and modified version of the NOVA classification system made by Monteiro et. al.(14, 21)

1.3.2 Strengths and limitations of the NOVA classification system

NOVA has previously been revised and compared to four other food processing classification systems in a systematic review(20). In the review the quality and relevance in use of the classification systems were evaluated. The four other classification systems reviewed were developed by the International Food Policy Research Institute (IFPRI) in Guatemala, the National Institute of Public Health in Mexico, the International Food Information Council Foundation (IFIC) in the US, and the International Agency for Research on Cancer (IARC) in Europe(20). These four classifications systems did not have any names and will thus be referred to by the country they were developed in.

From the review, several strengths of NOVA were pinned forward. Firstly, NOVA was considered to have the highest quality as it was the only system that was derived from a comprehensive definition of food processing that differentiated between industrial processing methods and artisanal types of processing. In addition, it was pinned forward that NOVA, since first published, had been updated to make the definitions clearer(20).

Among the other classification systems, the Mexican system was also rated high. However, it was considered only partly specific, one of the reasons being that it distinguished between industrialized and local foods by evaluating the scale the foods had been marked and not by the properties and nature(20). The European system was rated a bit lower as it among others, did not completely distinguish between domestic and industrial processing. The US and Guatemalan systems were rated the lowest as they were considered to have incomplete lists of food and products and overlapping criteria used to define food categories. Overall, NOVA was viewed as completely specific, coherent, and comprehensive as both the nature, extent, and purpose were considered, as the NOVA groups were viewed as conceptually different with specific food processing methods defined, and as all food and food products were covered in the system(20).

Though NOVA has become more accepted for addressing the level of food processing in our diet, the classification system has been criticized. The two main topics on which NOVA has been criticized are 1) Whether or not NOVA is helpful in terms of examining food's effect on health(23) and 2) Having too heterogeneous and imprecise definitions(23). Despite the

criticism, this thesis is still going to use NOVA. This decision is based on the following reasons. Firstly, many of the critics are according to Monteiro based on misconception of the purpose behind NOVA(24), which is to 'categorize food according to the extent and purpose of food processing, rather than in terms of nutrition' (21)(s.28). Secondly, it can be questioned whether the critics were objective or had conflicts of interest(25). Thirdly, in the review mentioned above, NOVA was deemed to be the most specific, coherent, and comprehensive classification system for food processing compared to four other identified classification systems(20). It is to be noted that co-authors of the review also are members of the NOVA research team. Lastly, that NOVA efficiently evaluates the quality of diet and a diet's negative effect on health has been shown in multiple studies(26). In addition, NOVAs usefulness can be demonstrated by Brazil, Uruguay, Ecuador, Peru, and Belgium, which have included the NOVA classification system in their national dietary guidelines(27-31).

1.4 Ultra-processed food and health

1.4.1 Dietary share of UPF and changes in UPF consumption

That UPF makes up a large part of the modern diet is shown in previous studies(32, 33). How the consumption of UPF is estimated in the studies varies. UPF consumption is both estimated at a household level and an individual level. Further, the consumption is calculated using different units, such as money, energy, and weight. In Norway, the proportion of UPF in the diet has only been measured at a household level. In a previous study that investigated the household availability of UPF among 19 European countries, Norway was placed 6th, with an average household availability of 37% UPF measured by purchased dietary energy(1998)(32). In the study the average household availability ranged from 10% in Portugal (2000) to 50% in the UK(2008)(32). Further, a master thesis that examined the consumption of UPF in the Norwegian diet between 2013 and 2019 found that UPF accounted for 49% of all food purchased in grocery stores and 46% of all food expenditures at household level in 2013(33). In 2019, a slight increase in purchases and expenditure of UPF was seen, UPF making up 50% and 47%, respectively(33). Overall, the results show that the general household availability of UPF is high and that UPF accounts for half of the food sales in Norway(32, 33). This indicates a high consumption of UPF in the Norwegian population.

1.4.2 UPF and health outcomes

As the modern diet is changing towards including more UPFs, it is important to look further into how UPFs can affect our health. Among 43 studies reviewed in a metanalysis from 2020, 37 studies found an association between consumption of UPF and at least one adverse health outcome, some of them being obesity, type 2 diabetes, cardiovascular disease, depression, and cancer(34). Among different cancer types, high UPF consumption has been associated with an increased risk of overall cancer(35), breast cancer(35), and colorectal cancer (CRC)(36). The influence of diet on the incidence of CRC has previously been heavily based on the nutrients in food. However, new research indicates that the way we process food may be of importance as well(36, 37).

1.5 Colorectal cancer

1.5.1 Location of colorectal cancer

CRC refers to a cancer tumor located in the last part of the digestive system called the large intestines, which consists of the colon and rectum(38). The colon is further divided into four main sections. The first section is colon ascending, which is located on the right side of the abdomen, continuing upwards from the end of the small intestines were undigested food enters from. The second section is called colon transversum, which goes across the abdomen from the right to the left side. The third section is called colon descending, which descends (travels down) on the left side. The fourth section is called colon sigmoid, named after its 'S' shape. Colon sigmoid then travels down and connects with the rectum and the anus(38).

In research, when examining different subsites, the colorectal tract is further divided into larger sections. The colorectal tract is typically divided in two, total colon and rectum(39), or three, right-sided colon(colon ascending and colon transversum), left-sided colon (colon descending), and total rectum(37). An illustration of the main segments of the colorectal tract and the corresponding subsites groups is shown in Figure 1.

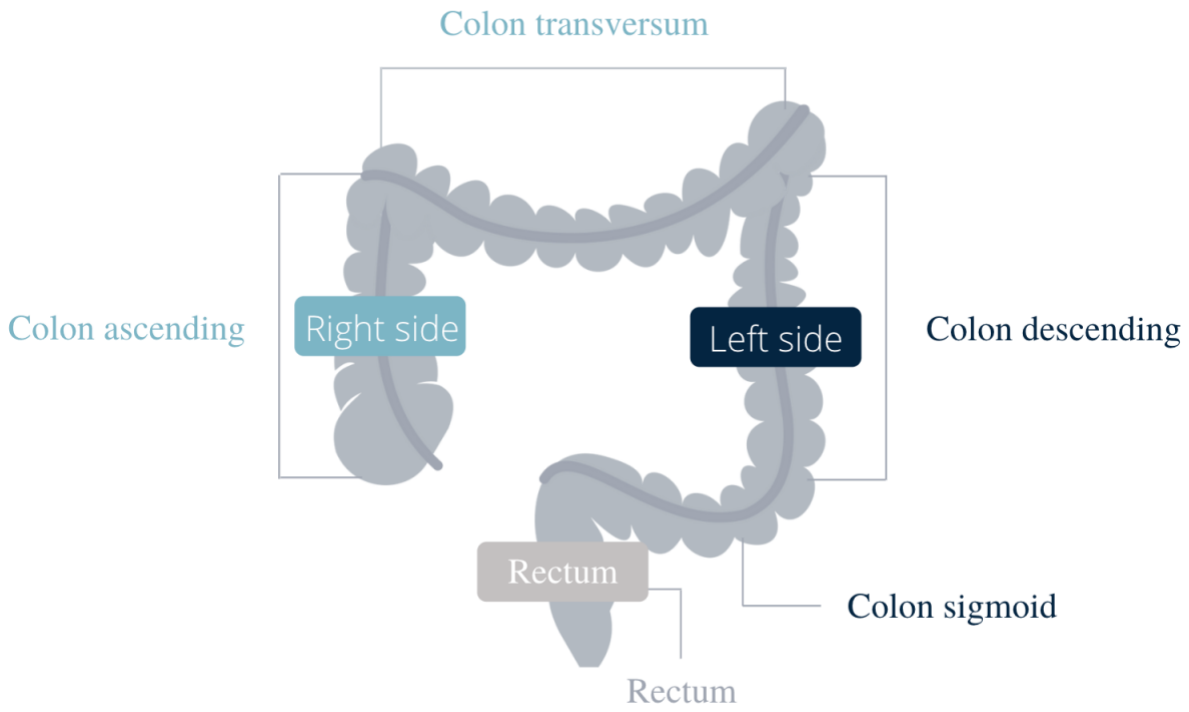

Figure 1. Illustration of the main segments of the colorectal tract and the corresponding subsites groups (Illustration created with use of a modified figure(40)).

1.5.2 Functions of the colon and rectum

The colon plays an essential role in absorbing water and salts from intestinal content after the content has passed through the small intestines, where most of the nutrients are absorbed. The colon further passes waste to rectum, where it is stored until it passes out of the body through anus(41). Within the colon, a complex ecosystem of bacteria exists, often referred to as the gut microbiota. The gut microbiota has multiple functions, some of the them to defend against harmful microorganisms, digest food like dietary fiber that humans cannot digest, produce molecules that have important functions in the body(e.g., short-chain fatty acids), and synthesize vitamins and amino acids(42).

1.5.3 Pathology of CRC

98% of the CRC cases are adenocarcinoma, meaning cancer develops from an adenoma(43). The name adenoma is derived from the word 'adeno', meaning 'pertaining to a gland', which is related to the adenoma origin in the glandular tissue(44). The glandular tissue is the thin layer of tissue that covers organs, glands, and other structures within the body. A tumor can be

either benign or malignant(cancerous). An adenoma is a benign tumor, meaning it is not cancerous, but it is an abnormal mass of cells in the body caused by cells dividing more than usual or not dying when they should(44). The abnormal cells grow slowly in one location without spreading to other local structures or body sites. Over time an adenoma can become an adenocarcinoma, a malignant (cancerous) tumor. In contrast to a benign tumor, a malignant tumor proliferates, can invade surrounding tissue, and spread to other body parts(44). From here, colon cancer can occur, and symptoms can start.

1.5.4 CRC symptoms

The kind of symptoms that occur depends on the tumor´s location(43). To simplify the tumor´s location, one can distinguish between tumors that occur in the right side of the colon, the left side of the colon, and the rectum(45). The general symptoms are stool changes, feeling of incomplete emptying, symptoms of anemia, blood or mucus in the stool, and defecation pain(43). Symptoms more specific to tumors in the left and last part of the bowel are stool changes, feeling of incomplete emptying, and blood or mucus in the stool(45). Symptoms more specific for the right side of the colon are anemia, lethargy, decreased appetite, weight loss, and fever(45). Symptoms on the left and last part of the bowel are usually easier to detect and are generally spotted earlier than symptoms on the right side(45).

1.5.5 Diagnosis of CRC

CRC is diagnosed by tests of blood in the stool, hemoglobin, liver function, and colonoscopy(43). The diagnosis is further confirmed by histology(43). When CRC is confirmed, the diagnosis is coded with an International Classification of Diseases, 10th revision (ICD-10) codes C18-C20 (ICD-10 C18-C20). The division of the ICD-codes will be further described in chapter 3.2.2.

1.5.6 Incidence, mortality, and survival rates of CRC in Norway

Norway is one of the countries with the highest rate of CRC, and when looking at the incidence rate among women, Norway is on top(46). In Norway, ten new men or women are diagnosed with CRC every day, accounting for about 3500 new cases every year(47). The

incidence rate for colon and rectal cancer are often presented together, though the rates differ(48).

Colon cancer has, since 1965, increased steadily and fortunately we now see a decrease in men and a flattening in women(48). For rectal cancer, the incidence has been stable since 1990, and a decline for both sexes has been seen in the recent years(48). When looking at the mortality rate in Norway, a decrease is seen for both colon and rectal cancer(48). In addition, the five-year survival rate for total CRC has increased from 30 percent to 70 since the 70s(49). The increase seen in the five-year survival rate may be due to better treatment(50). Though the incidence, mortality, and five-year relative survival rates are changing toward the positive, Norway is still ine of the countries with the highest rate of CRC(49), and by 2030 the incidence is expected to increase by 40% for men and 25% for women(51). However, only a small part of the increase is due to a real increase in cancer risk, while most is due to the changing population size and age structure(51).

1.5.7 Current established risk factors for CRC

What directly causes CRC is currently unknown, but age, genes, diseases, medication, and lifestyle are factors of importance(52). Among the non-lifestyle factors, an increased risk of CRC is seen with increased age, inflammatory bowel disease (such as Crohn´s disease or ulcerative colitis), a personal or a family history of CRC or colorectal polyps, genetic syndromes such as familial adenomatous polyposis or Lynch syndrome(52). Among lifestyle factors, WCRF has found strong evidence that physical activity, whole grains, foods containing dietary fiber, dairy products, and calcium supplements decrease the risk of CRC(53). In addition, WCRF has found that processed meat, alcoholic drinks, smoking, body fatness, and red meat are strongly associated with increased risk of CRC(53). Further, new research suggests that CRC risk factors only increases the risk of cancer in specific subsites and not along the whole colorectal tract(54). This indicate that one risk factor might increase cancer risk in one area, such as in the ascending colon, while another risk factor might not increase risk in the ascending colon but in the rectum.

1.6 High UPF intake and CRC

Previous research on diet and CRC has been heavily based on nutrients and foods, but new findings indicate that the way we process food may be a new direction of importance. In a case-control study from 2021, a 10% increase (g/day) in UPF was associated with an 11% increase in odds of CRC(36). Further, results from another case-control also showed that a high UPF intake was statistically significant associated with CRC compared to a low UPF intake(39). In addition, results from a case-control study with 652 participants found a statistical significant association between a high UPF intake and colorectal adenomas compared to low UPF intake(37). However, results from the NutriNet-Santé prospective cohort, with 104 980 participants, found no association between high intake of UPF and risk of CRC compared to the lowest UPF intake group(35). Nevertheless, this NutriNet-Santé cohort is young and does not have much power yet. As the findings are opposing it cannot be concluded whether or not a high UPF intake is statistically significant associated with CRC risk. Further investigation on the association between UPF and CRC is important to contribute to filling this gap in knowledge.

1.6.1 Mechanisms by which UPF influences CRC risk

The mechanisms by which UPF might influence the risk of CRC are not yet known. From the current literature, some hypotheses can be noticed and divided into two main pathways as to how they increase CRC risk: 1) Through a direct pathway and 2) Through an indirect pathway. The direct pathways include poor nutritional quality and substances added or formed during processing(53). The indirect pathways include overweight and obesity(55).

Though the NOVA classification does not categorize foods according to their nutritional quality, foods in the UPF category are often high in total fat, saturated fat, trans fat, free sugars, salt, and low in dietary fiber and various micronutrients(14). As shown earlier WCRF has implied strong evidence that dietary fiber has a protective effect on CRC(53). This potentially through reducing transit time, preventing insulin resistance, and dietary fiber being available for gut microbiota to digest and produce butyrate which can increase apoptosis and decrease proliferation(53). Further, the UPF category include processed meat which convincingly is associated with CRC(53). When meat is treated at high temperatures,

molecules called polycyclic aromatic hydrocarbons (PAHs) are formed. These PAHs are associated with an increased risk of CRC through causing DNA damage(15).

UPF may also contain other potentially carcinogenic substances added or formed during processing such as 1) Sodium nitrites, a compound used to preserve, which can react with other compounds and form N-nitroso compounds when treated over high heat. These N-nitroso compounds may damage DNA and lead to cancerous cells(56). 2) Trans fatty acids, unsaturated fatty acid transformed under hydrogenation, which have been hypothesized to irritate the colon and rectal mucosa and promote inflammation and oxidative stress when present in the fecal matter(57). 3) Bisphenol A(BPA), a chemical used in polycarbonate plastics, epoxy resins, and thermal paper typically used for packaging, which can cause oxidative stress(58). Oxidative stress is caused by an elevated intracellular level of reactive oxygen species (ROS). Research has shown that oxidative stress can affect cell proliferation and apoptosis and lead to DNA mutations, which play an essential part in the development of cancer(59).

Furthermore, UPFs association with CRC may be explained by an indirect effect on body fatness, which has strongly been associated with an increased risk of CRC(53). That a high intake of UPF is associated with body fatness has been shown in multiple studies(55). In the litterateur, many hypotheses have been made to understand the mechanisms as to why UPF might cause weight gain. Three of the leading hypotheses are 1) UPF tends to be energy-dense(14), and as the body regulates food intake by volume rather than calories, consuming a high amount of UPF may lead to excess energy intake, which can lead to weight gain(60). 2) UPF may adversely affect the gut microbiota, among other things, through micronutrient deficiency, emulsifiers, additives (such as artificial sweeteners), and preservatives, which can cause weight gain(61). 3) UPF might have a negative effect on appetite regulation. In a study from 2019 results showed that participants consumed 500 more calories per day when eating UPF than when eating minimally processed foods(62). Moreover, participants exposed to a high UPF diet gained 0.9 kg (mostly fat mass) over a two-week period compared to when exposed to a non-UPF diet(62). In addition, the study saw a lower increase in the appetite-suppressing hormone PYY when the participants consumed UPF than when they consumed unprocessed food, supporting the hypothesis that UPF might negatively affect appetite regulation(62). Overall, the previous findings indicate that body fatness may be an underlying

mechanism as to why UPF might increase risk of CRC. Potential mechanisms that drive the association between high consumption of UPF and increased risk of CRC are summarized and illustrated in Figure 2.

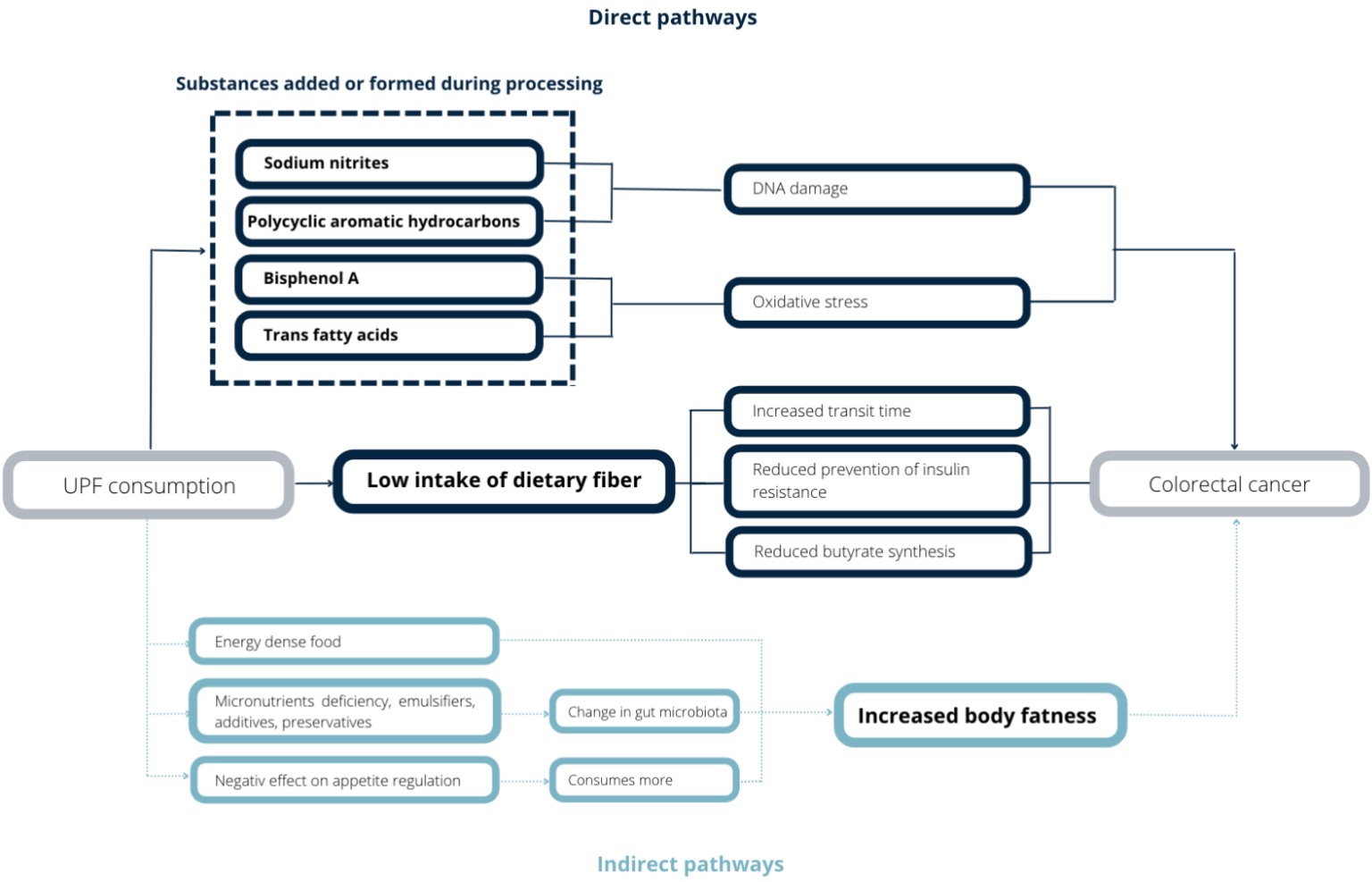

Figure 2. Overview of direct and indirect mechanisms - association between UPF and CRC

2 Aims of the thesis

The aim of this study is to investigate if there is an association between high consumption of ultra-processed food and the risk of CRC in the Norwegian Women and Cancer study. In more detail, the specific objectives are to answer these questions:

1. Do those who have a high intake of UPF differ on important lifestyle and demographic variables compared to those who have low intake of UPF?

2. Is a high intake of UPF associated with CRC among Norwegian women that participated in the Norwegian women and cancer study?

3. Is there an association between a high intake of UPF and cancer in colorectal subsites?

3 Material and Methods

3.1 Study design

This master thesis has a prospective cohort study design and uses data from the Norwegian Women and Cancer Study (NOWAC). Follow-up time was calculated from date the first questionnaire was answered till emigration, death, diagnosis with any form of cancer, or end of follow-up. The end of follow-up was 31. December 2018.

3.1.1 The Norwegian Women and Cancer Study

NOWAC is an ongoing national population-based prospective cohort with more than 170,000 participants, with parts of it being incorporated under a large multinational study called the European Prospective Investigation into Cancer and Nutrition (EPIC)(63). NOWAC was initiated in 1991 with the aim to investigate the use of oral contraceptives and other risk factors for breast cancer(63). Over a period of 11 years (from 1991 until 2007), women aged between 30 and 70 were randomly recruited from the Norwegian national population register. Invitations and all questionnaires were sent by mail. Dietary data was collected through semi-quantitative food frequency questionnaires (FFQ). In addition, participants were also asked questions about lifestyle and health, such as smoking, physical activity, alcohol consumption, anthropometry, their health, and socioeconomic status. Incidence of cancer was registered in the Cancer Registry of Norway, to which NOWAC is linked(63).

Women in NOWAC have all answered one baseline questionnaire, and participants recruited between 1991-92 have answered up to three follow-up questionnaires. In Figure 3, an overview of each questionnaire completed is represented with a color, date, and number of participants. The box is colored blue for first-time questionnaires, green for second-time questionnaires, yellow for third-time questionnaires, and red for fourth-time questionnaires. In this thesis, no repeated measurements were included. The first-time questionnaires from 1996, 2004, and 2006, and the secondary questionnaire from 1998, were used. These are all marked with a black square in Figure 3. The secondary questionnaires from 1998 were used for participants who answered the first-time questionnaires in 1991-92. This was done as the secondary questionnaires were more compatible with the later ones, than the first questionnaires which were shorter and had fewer diet-related questions.

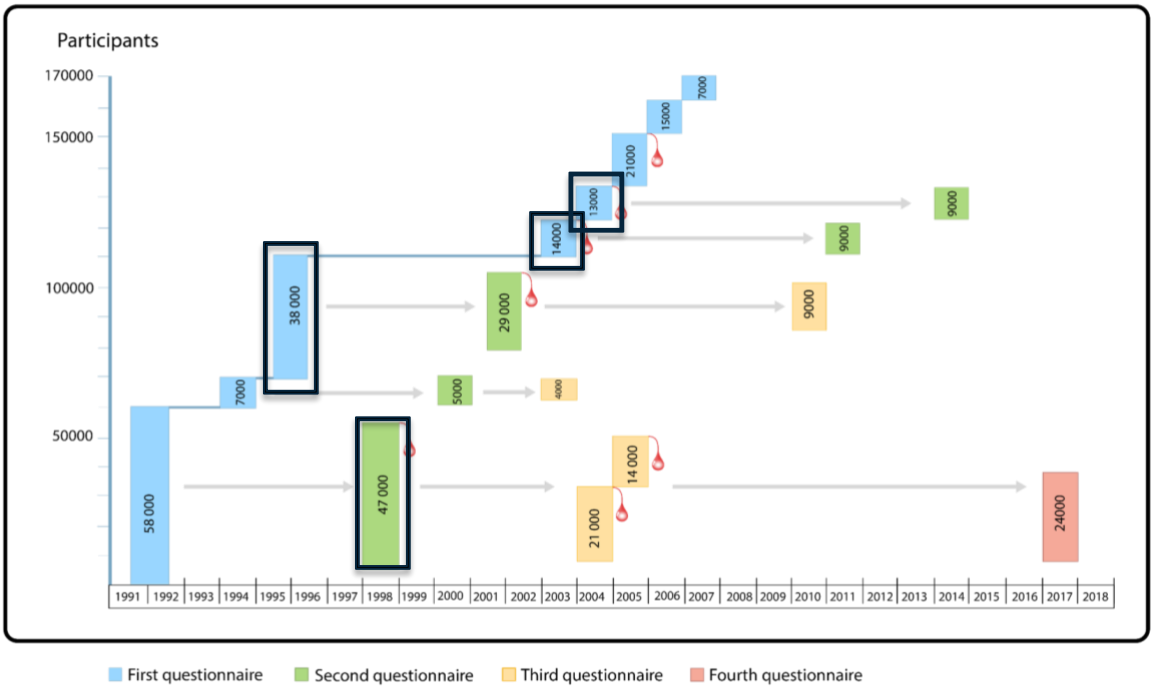

Figure 3. Overview of the enrolment in NOWAC (adopted from an unpublished document in NOWAC)

The NOWAC study has undertaken validity and reproducibility studies to examine the accuracy of collected data and to which extent the findings can be generalized. A study from 2003 that examined the external validity in NOWAC found no major source of selection bias, indicating the collected data to be representative for the population studied(64). In the same year, the validity of the FFQs were also examined. In the validation study, the FFQs were compared with four repeated 24-h recalls(65). 238 women participated and were interviewed over the phone once every season. The results from the validation study showed that the FFQs ability to rank participants was good for foods eaten frequently(65). However, the ranking ability was weaker for foods less frequently eaten and some micronutrients(65). Nevertheless, this may be due to limitations of the 24h recalls in capturing less frequently consumed foods rather than a limitation of the FFQs. Further the reproducibility of the FFQ has also been examined. In the reproducibility study, where 2000 women were retested, the kappa estimator of agreement was 0.5-0.7 for the dietary questions, which shows moderate to substantial agreement, meaning the diet collected data was acceptably consistent(66). Overall, the studies show that the collected diet data through the FFQ in NOWAC is acceptable and reliable, and that the data can be used to rank the participants.

3.1.2 Inclusion and exclusion criteria

All women that participated in the NOWAC study who had completed the FFQs were included from the NOWAC study (n=95,937, cases= 2357). Participants were excluded from the analysis if they were diagnosed with any form of cancer (n=4018, cases= 302), had died or emigrated before entry or at entry (n=10, cases= 0), had extreme energy intake (≤2500kJ and ≥15000kJ) (n=1,007, cases= 24), or had missing on confounding or mediating variables (13,802, cases= 406). Out of the 95,937 (2357 cases) participants, 18,837 (732 cases) were excluded. In total, 77,100 participants and 1625 cases of CRC were included in this study. See Figure 4.

The background for excluding participants that had any form of cancer, had died, or emigrated before or at baseline was to exclude those who were not at risk of getting their first cancer diagnosis in Norway. Participants with extreme energy intake were excluded to avoid reporting, coding, or estimation errors that could potentially influence the results derived from the dataset. The cut-off for extreme energy intake was set to ≤2500kJ and ≥15000kJ based on NOWAC standards(67). Lastly, participants with missing on confounding and mediating variables were excluded as they would have fallen out in the cox regression resulting in two different datasets before and after exclusion.

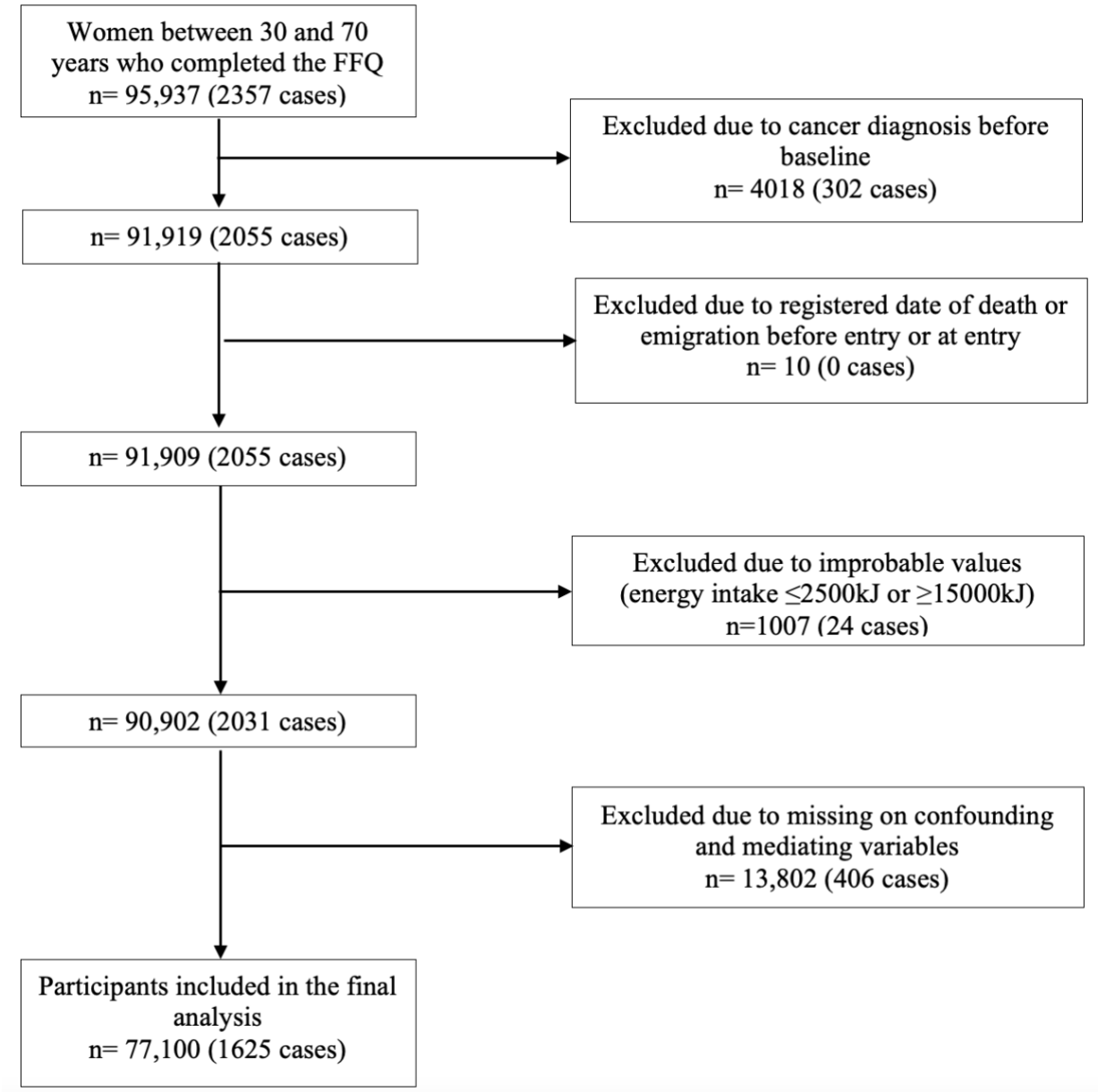

Figure 4. Flowchart of the exclusion process

3.1.3 Missing data

All confounding and mediating variables with missing values are reported in Table 2. The missing values were excluded stepwise, and the number of reported missing values represents the number of missing values at the time the variables were excluded. Missing values on the dietary variables have previously been imputed to the lowest frequency (0) and lowest portion and did thus not have any missing. Hormone therapy did not have any missing either.

Table 2. Missing data on confounding and mediating variables

Variables	Number of missing values
Energy (kJ)	1007
BMI	1981
Educational level	4744
Physical activity	6370
Smoking status	707
Total missing	14809

3.2 Statistical analysis

All statistical analyses were performed in SPSS Statistics (Release 28.0.0.0). To evaluate the association between the proportion of UPF in the diet and the incidence of CRC, Cox proportional hazard models were used with follow-up time as the primary timescale. Hazard ratios and 95% confidence intervals with the lowest quartile as a reference group were estimated. P-values under 0.05 were considered significant.

Descriptive statistic was used to summarize and describe data, detect patterns, and find missing data. The SPSS tools such as frequency tables and crosstabs were used to report baseline characteristics and missing data. Median intake and percentiles were used to evaluate food items and means, and standard deviation was used to evaluate other continuous variables.

3.2.1 Exposure

The exposure variable was the intake of UPF. Data on the intake of UPF was generated by recoding the dietary data collected through a semi-quantitative FFQ. The FFQ was designed to assess the participant's diet from the past year, with emphasis on typical Norwegian food items and fish consumption(66). Each food item had fixed frequencies, and some additionally had quantity questions. Participants could choose one checkbox from what they found most representative of their diet. For further information about FFQ, see Appendix 2. The intake of foods that did not have separate quantity questions were converted into grams by using the standardized portion sizes and weights from the Norwegian Weight and Measurement Table. (68).

3.2.1.1 Estimation of UPF consumption

To classify the foods from the FFQs according to the degree they had been processed, the NOVA classification system was used. As an aid in classifying the food items, an unpublished protocol created by IARC was used. The protocol was made in cooperation with Monteiro and was designed to standardize the use of NOVA across different countries in the EPIC study.

A total of 433 foods were registered in the NOWAC FFQs and transferred to a spreadsheet. As some foods appeared multiple times under different names or food codes a clean-up process was done so a food only appeared once. After the clean-up, 277 foods were left. The 277 foods were then gone through independently by two nutrition students and matched to the relevant composition table, and further grouped into a food group based on the food grouping system of the Norwegian Food Composition Database(69). Further, the foods were classified into one of the four NOVA groups. The classification was done based on the NOVA guidelines from EPIC, papers from the NOVA creators(14, 19), and knowledge about Norwegian food consumption.

Because of some generic questions and complex foods during the NOVA classification process, the 277 foods were further treated in one of three ways: 1) as single components, 2) as food with fat, or 3) as recipes. Foods treated as single components were defined as whole single standing foods (e.g. a piece of fruit, a cod filet) or commercial food products (e.g. jam,

cheese, store-bought bread, meat, and fish products, canned fruit). These single components were categorized into a NOVA group directly. Foods treated as food with fat were defined as food prepared with a source of fat (e.g. cod prepared with fat, meatballs prepared with fat). Foods treated as food with fat were split up as 'food item' (e.g. chicken) + 'source of fat' (e.g. oil) and classified into a NOVA group separately. Foods treated as a recipe were defined as homemade or presumably homemade foods (e.g. homemade bread, fish cakes, cauliflower soup). Foods treated as a recipe were decomposed and broken down into ingredients (e.g. homemade bread= flour + water + yeast + salt). Each ingredient was then classified into a NOVA group.

Further, three scenarios were made because of some uncertainties about which NOVA group some foods were most likely to belong to. In scenario one, 'best scenario', the food was given the most likely suitable NOVA code. In the second scenario, 'NOVA-low', the food was given the lowest suitable NOVA code. In the third scenario, 'NOVA-high', the food item was given the highest suitable NOVA code. For example, bread was placed in group 3 in the NOVA-low scenario because the bread might be home-baked. However, as bread also could be store-bought it was placed in NOVA 4 in the NOVA-high scenario. Lastly, as most participants had reported consuming store-bought bread in later questionnaires, bread was placed in group 4 in the best scenario. To assess which NOVA group a food was most likely to have in the best scenario, information of usual consumption from NOWAC FFQs or data from 24h recall based on EPIC's calibration study(65, 70), knowledge of the Norwegian food market/culture, recipes and information from producers were used. After the students had classified the foods separately, the classification was compared and discussed with the supervisor. To delimit the thesis, only the best scenario was used in this paper. An overview of the steps in the classification process can be found in Figure 5.

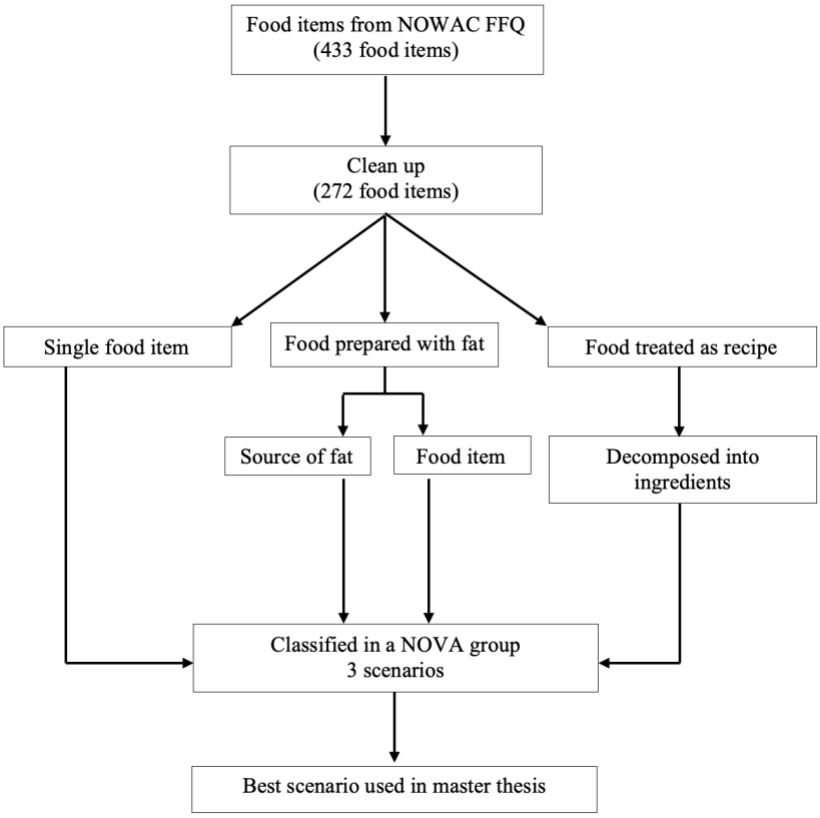

Figure 5. Overview of the NOVA classification process

Further, nutrition calculations were re-run, including the NOVA coding. Lastly, new data files, including NOVA information in g/day and kJ (kilojoule)/day per food group and in total, were generated for the NOVA best scenario. In the thesis, the calculations of the proportion of UPF by weight (percentage g/day) was used. The choice of using the calculated proportion of UPF by weight instead of energy was made to consider UPFs that do not provide any energy (such as artificially sweetened beverages) and components that are added or created during processing, such as food additives and neo-formed components. Further, the participants were divided into quartiles based on their UPF intake. The quartiles were defined as low intake(<=274g/d), medium low intake (275-361g/d), medium high intake (362-465g/d) and high intake (>466g/d).

3.2.2 Outcome

The outcome variable was defined as the incidence of CRC. Cases were defined using the ICD-10 code C18-C20 (ICD-10 C18-C20). The ICD-10 codes were further classified into five groups, total CRC, total colon, right-sided colon, left-sided colon, and rectal cancer. The grouping of the ICD-codes was based on definitions from the National Cancer Institute dictionary(71, 72), an earlier publication(73), and discussions with the supervisor. In Figure 6, each CRC section is represented with a color and their corresponding ICD-10 codes grouped inside. The total CRC section is represented by a dark blue color, which groups all the ICD-10 codes, meaning when we look at total CRC, we look at all the sections of the colon and rectum. Further, the ICD-10 codes were divided into total colon, represented with a dark purple color, and rectum, represented with a light blue color. Total colon was further divided into the right-sided colon, surrounded by a bright pink color, and the left-sided colon, surrounded by a gray color.

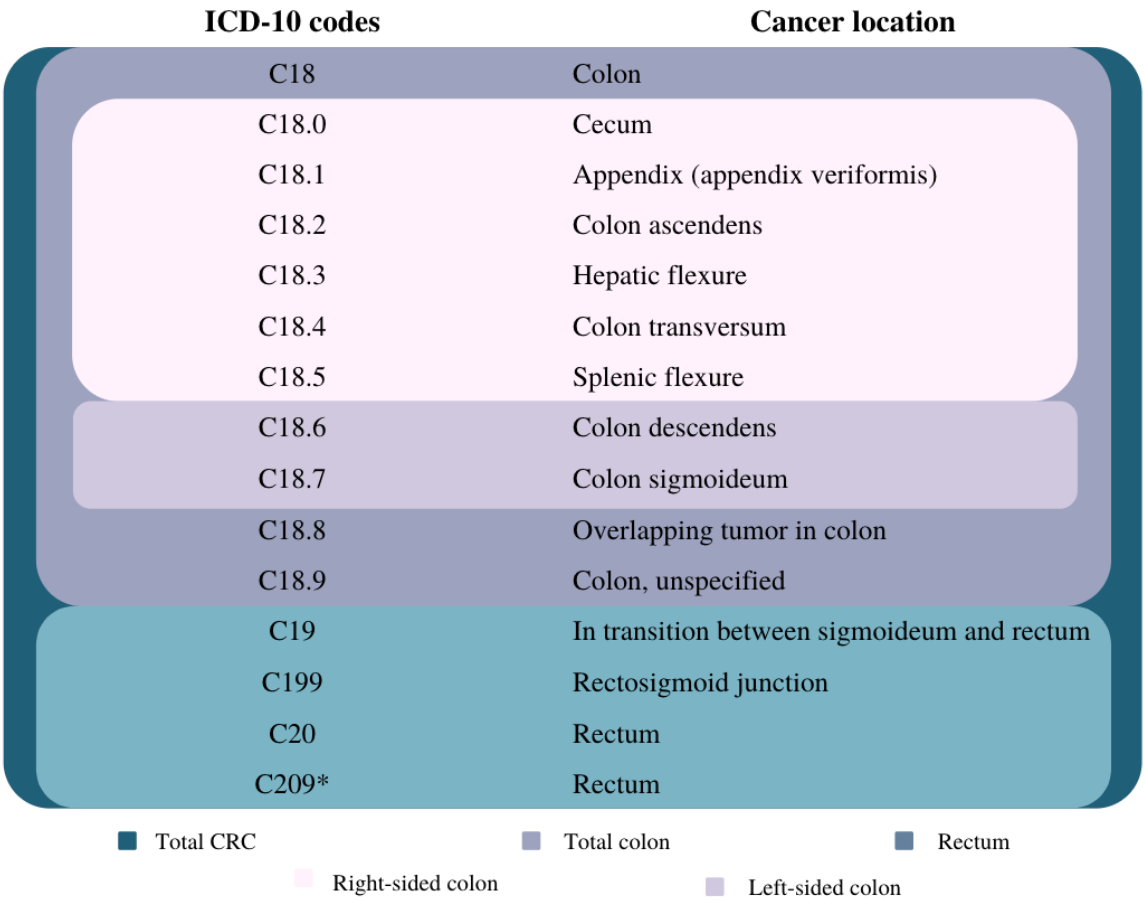

Figure 6. Overview of the ICD-10 codes and the grouping of the colorectal subsites.

*Classified using the International Classification of Diseases for Oncology, third edition (ICD-O-3) which is an extension of ICD-10, used primarily in tumor and cancer registries for coding the location and the histology(74).

3.2.3 Covariates

All covariates were chosen based on the litterateur and available data. The WCRF CUP panel concluded physical activity to be convincingly protective against colon cancer(75). Body fatness, adult attained height, alcoholic drinks, and consumption of processed meat were concluded to be convincing causes of CRC(75). Wholegrains, dietary fiber, dairy products, and calcium supplements were concluded to be probable protective factors against CRC, while red meat was concluded to be a probable cause of CRC(75).

In addition to dietary findings, nutrition, and physical activity, other causes for CRC have been established. Smoking and inflammatory bowel disease have been shown to increase the risk of CRC, while long-term use of aspirin, a non-steroidal anti-inflammatory drug, and hormone therapy in postmenopausal women have shown to be protective against CRC(75). However, as NOWAC did not have data on the use of aspirin, calcium supplements, and inflammatory bowel disease, these potential covariates were not included in the analysis.

Further, total energy intake was additionally included as a confounding factor as it is usually used in epidemiologic studies to adjust for confounding(76). Body mass index (BMI), processed meat, and dietary fiber were not included as covariates as they were thought to be mediators(53, 55).

The covariates included were age (scale: years), height (scale: cm), smoking status (ordinal: 1= never, 2=former 3=current), physical activity score as ordinal data (1-10 grouped; 1= inactive [1-4], 2= moderately active [5-6], 3= active [7-10]), educational level as ordinal data (1= <10 years, 2= 10-12 years, 3= >12 years), hormone therapy (HRT) as ordinal data (0=current, 1= previous, 2= never) alcohol as ordinal data per day (1= 0g, 2= 1-2g, 3= 3-5g, 4= 6g+), and total energy intake(kJ/day), and dietary intake variables as continuous data (gram per day; total intake of red meat and dairy products).

3.2.4 Model building

All covariates and mediators were tested in the proportional hazard model independently against the dependent variable, with a cut-off significance level at P<= 0.2. To check for linear trends, which is a prerequisite for regression, continuous variables were tested as both

continuous and categorical variables. In the univariate analyses, the variables were included as categorical if there were a lot of variation in the results. Because of uncertainties of whether total energy intake was correlated with consumption of UPF, multicollinearity was checked. The VIF value was under 10.00 and energy was thus kept in the model. Based on the univariate analysis, age, educational level, hormone therapy, energy, smoking status, activity level, alcohol, dairy products, and UPF were statistically significant. Height and red meat were not considered significant and were therefore excluded. The remaining covariates, except for energy, were included in a multivariable model to construct the final model. Covariates with a p-value higher than 0.05 were excluded one at a time, highest to lowest, until every covariate was statistically significant. After excluding covariates that were not statistically significant in the multivariable model, the remaining covariates were age, educational level, smoking status, and dairy products.

The proportional hazard assumption was evaluated graphically by checking the Log (-log) plot. Three models were constructed: a crude model (adjusted for age), a multivariable model adjusted for all covariates (age, educational level, smoking status, and dairy products), and a multivariable model adjusted for all covariates and energy. Sensitivity analysis based on the multivariable energy-adjusted model was performed by excluding the first three years of each participant's follow-up period. This was done for two reasons: 1) To limit reverse causality as participants might unconsciously have made changes in dietary habits due to subclinical symptoms, and 2) To take into consideration that CRC takes a long time to develop, and therefore it is unlikely that cases that were diagnosed during the first three years were associated with baseline UPF intake. To evaluate the association between the proportion of UPF in the diet and the incidence of cancer in colorectal subsites, a new analysis using both the multivariable-adjusted and the multivariable energy-adjusted models was done on the total colon, right-sided colon, left-sided colon, and rectum.

Lastly, the multivariable energy-adjusted model on CRC was further stratified by BMI (over and under 25kg/m2), dietary fiber (over and under median intake), and processed meat (over and under median intake). The stratification was undertaken to examine if the effect was equal in both the high and low groups of the mediators, as they may be potential important factors behind the mechanism of UPF association with CRC.

3.3 Ethical considerations

The NOWAC study has previously obtained ethical approval from the Regional Committee for Medical and Health Ethics (REK). All participants provided informed consent before study enrollment in NOWAC. Participants have been informed that participation is voluntary and that they at any time can withdraw from the study.

3.3.1 Privacy and confidentiality

The dataset used in this thesis did not contain any sensitive personal data and was kept on a two-factor identification OneDrive account throughout the research period. Once the research has been published, all data will be safely removed from the online storage area.

3.3.2 Conflict of interest

There are no conflicts of interest.

4 Results

A total of 95,937 women aged 30-70, who had completed the FFQs were included from the NOWAC study. Out of the 95,937 participants, 2357 were cases. After exclusion 77,100 woman and 1625 cases were included in the study. All participants were followed up for an average of 17.4 years.

4.1 Baseline characteristics in the UPF quartiles

In Table 3 the distribution of the NOVA groups across UPF quartiles is presented. When looking at the median intake of NOVA (g/day), the amount consumed in all NOVA groups increased steadily from those with a low UPF intake to those with a high up intake. Among participants with a low UPF intake, NOVA 1 constituted 83% of the diet, and NOVA 4 constituted 10%. Among participants with a high intake of UPF, NOVA 1 constituted 70% of the diet, while NOVA 4 constituted 24% of the diet.

Table 3. Distribution of the NOVA groups across quartiles of UPF intake.

NOVA intake (g/d median)(p25/p75)	Low (<=274g)	Medium low (275-361g)	Medium high (362-465g)	High (>466g)
NOVA 1	1653 (1233-2121)	1760 (1354-2227)	1837 (1411-2319)	1904 (1427-2425)
NOVA 2	9 (5-15)	11 (7-18)	12 (8-20)	13 (8-22)
NOVA 3	102 (68-150)	112 (77-156)	118 (83-162)	122 (86-168)
NOVA 4	223 (185-250)	318 (296-339)	407 (383-433)	569 (507-731)
NOVA intake (%)				
NOVA 1	83	80	77	70
NOVA 2	0.6	0.6	0.6	0.6
NOVA 3	6	6	5	5
NOVA 4	10	14	17	24

4.1.1 Main food groups contribution to UPF intake

In Figure 7 an overview of the Norwegian food groups contribution to UPF intake (% of g/day) is presented. The main food groups that contributed to the UPF intake (g/d) were food group 5 (35.5%; Grains, baked goods, seeds, and nuts), food group 9 (21.3%; beverages), food group 4 (12.0%; fish and shellfish), and food group 3 (8.7%; meat and poultry), followed by food group 1 (7.0%; milk and dairy products), food group 8 (5.2%; margarine, butter, oil), food group 10 (4.7%; various dishes, products, and ingredients), food group 6 (4.0%; potatoes, vegetables, fruit, and berries), food group 7 (1.7%; chocolate and other sweets), and food group 2 (egg; 0%). A more detailed overview of the food items in each food group can be found in Appendix 3.

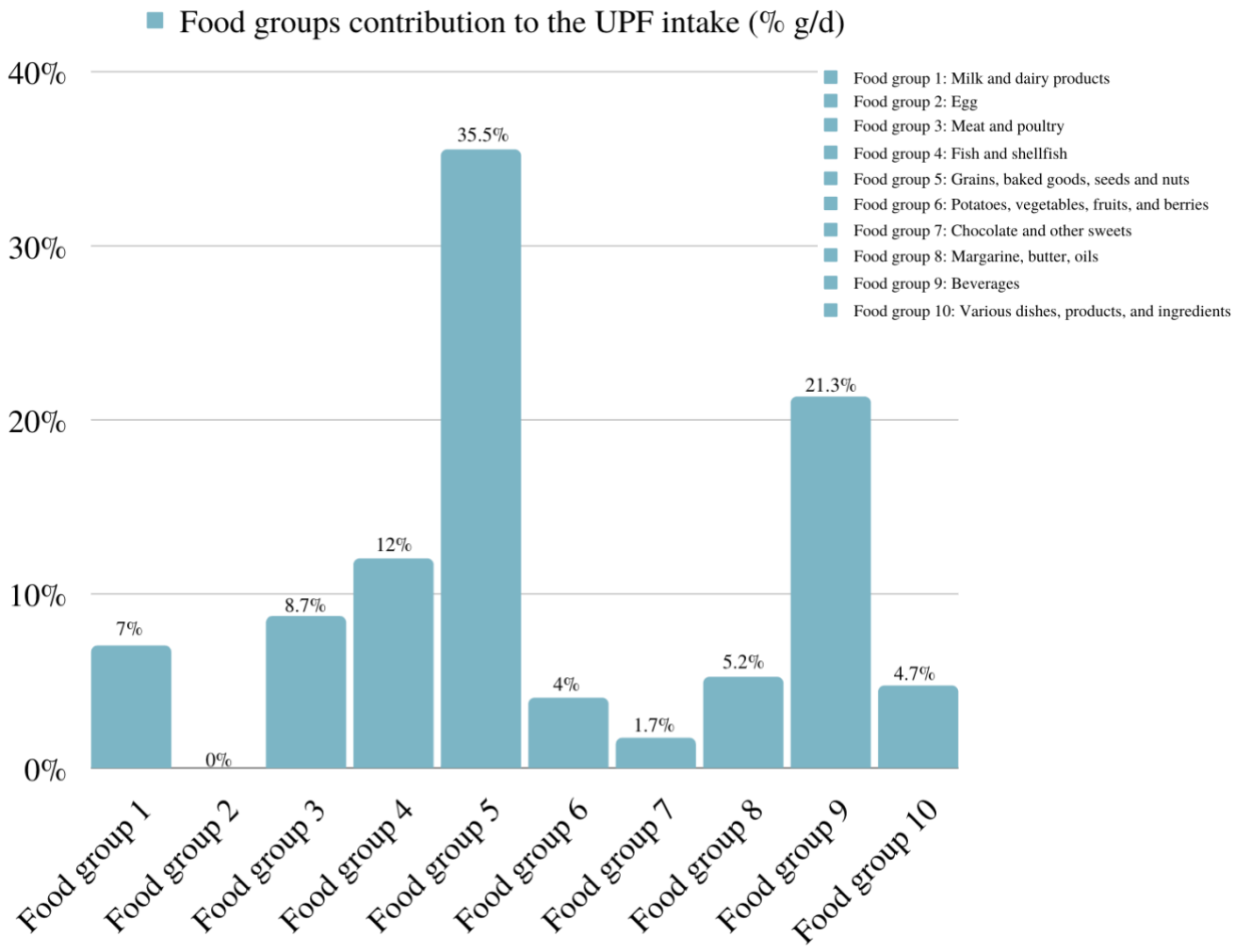

Figure 7. Norwegian food groups contribution to UPF intake (% of g/day)

4.1.2 Lifestyle characteristics

The main lifestyle characteristics of the participants according to the UPF intake quartiles are reported in Table 4. Participants with a high UPF intake compared to participants with a low UPF intake were younger, taller, current smokers, and higher educated, with a higher physical activity level. In addition, participants with a high UPF intake used hormone therapy less compared to participants with a low UPF intake. Further, no differences were observed in bad and very bad self-reported health between participants with a high UPF intake and participants with a low UPF intake. However, 64% of participants with a high UPF intake reported having good health, while 60% of participants with a low UPF intake reported having good health. 29% of participants with a high UPF intake, reported having very good health, while 33% of participants with a low UPF intake reported having very good health. When looking at BMI, 8% of participants with a high UPF intake were underweight, and 12% were obese. In contrast, 6% of participants with a low UPF intake were underweight, and 9% were obese. Further, 30% of participants with a low UPF intake were overweight and 55% had a normal weight. Whereas 28% of participant with a high UPF intake were overweight and 52% had a normal weight.

Table 4. Baseline lifestyle characteristics according to UPF quartiles

	Proportion of UPF consumption in the diet			
	Low (<=274g)	**Medium low** (275-361g)	**Medium high** (362-465g)	**High** (>466g)
Characteristics				
N	19275	19275	19275	19275
Age (years) (sd)	53 (6)	52 (6)	51 (6)	49 (5)
Height (cm) (sd)	165.7 (6)	166.2 (6)	166.5 (6)	166.8 (6)
Weight (kg) (sd)	67.9 (11)	68.2 (11)	68.0 (11)	69.2 (13)
Number of children (mean)(sd)	2.4 (1)	2.6 (1)	2.7 (1)	2.8 (1)
Smoking status				
Current % (n)	32.5 (6267)	35.1 (6763)	36.3 (6992)	35.0 (6737)
Former % (n)	38.4 (7394)	37.7 (7273)	36.0 (6932)	33.4 (6445)
Never % (n)	29.1 (5614)	27.2 (5239)	27.8 (5351)	31.6 (6093)
Number of pack years (mean)(sd)	20 (7)	20 (6)	19 (5)	19 (5)
Smoking age (mean)(sd)	11 (9)	10 (9)	10 (9)	11 (9)
BMI (kg/m2) (%)(n)				
Underweight < 20	6 (1160)	6 (1101)	7.0 (1345)	8 (1493)
Normal weight 20-25	55 (10308)	56 (10500)	56 (10657)	52 (1493)
Overweight 25.1-30	30 (5795)	30 (5628)	28 (5262)	28 (5358)
Obese > 30.1	9 (1640)	9 (1661)	9 (1644)	12 (2206)
Education level (%)(n)				
<9 years	27 (5175)	24 (4679)	23 (4466)	21 (3953)
10-12 years	34 (6464)	35 (6648)	34 (6541)	37 (7031)
> 12 years	40 (7636)	41 (7948)	43 (8268)	43 (8291)
Hormone therapy (%)(n)				
Current	23 (4394)	22 (4228)	20 (3932)	20 (3755)
Former	12 (2335)	11 (2162)	11 (2065)	11 (2131)
Never	65 (12275)	67 (12885)	69 (13278)	70 (13389)
Physical activity (%)(n)				
Inactive (1-4)	29 (5598)	26 (5004)	25 (4732)	25 (4801)
Moderatly active (5-6)	42 (8075)	44 (8471)	44 (8517)	43 (8350)
Active (7-10)	29 (5602)	30 (5800)	31 (6026)	32 (6124)
Self-reported health (%)(n)				
Very good	33 (5106)	33 (5394)	32 (5454)	29 (5329)
Good	60 (9378)	60 (9713)	62 (10553)	64 (11680)
Bad	7 (1159)	6 (1031)	6 (1012)	7 (1272)
Very bad	0.4 (65)	0.3 (49)	0.3 (44)	0.3 (54)

4.1.3 Dietary characteristics

Generally, the intake of red meat, dairy products, processed meat, and dietary fiber increased with the UPF quartiles from lowest to highest. Participants with a high UPF intake compared to participants with a low UPF intake had a higher intake of energy, red meat, processed meat, dairy products, and dietary fiber, along with a lower intake of alcohol. See Table 5.

Table 5. Baseline dietary characteristics according to UPF quartiles

	Proportion of UPF consumption in the diet			
Characteristics	**Low** (<=274g)	**Medium low** (275-361g)	**Medium high** (362-465g)	**High** (>466g)
Alcohol (%)(n)				
0g	19 (3730)	19 (3701)	20 (3838)	21 (3997)
1-2g	27 (5219)	27 (5268)	28 (5427)	29 (5517)
3-5g	27 (5125)	28 (5359)	27(5286)	27 (5281)
6g+	27 (5201)	26 (4947)	25 (4724)	23 (4480)
Dietary intake (g/d median)(p25/p75)				
Red meat	11 (6-19)	13 (7-20)	14 (8-22)	15 (9-23)
Dairy products	175 (82-277)	216 (106-338)	233 (123-447)	234 (118-483)
Processed meat	21 (13-32)	28 (18-41)	35 (22-49)	41 (26-59)
Dietary fiber	17 (13-21)	20 (17-24)	23 (19-27)	24 (20-29)
Total energy	5386 (4606-6176)	6657 (5913-7424)	7631 (6743-8520)	8478 (7248-9740)

4.2 Cox proportional hazards: assumption of proportional hazards

To check the assumption of proportional hazards, a log minus log plot was generated, and the interaction between UPF and time was examined, see Appendix 4. The log minus log plot showed that the hazards were parallel over time. Further, the association between UPF and time was statistically insignificant (sig. = 0.169), meaning UPF does not interact with time. The proportional hazard assumption was fulfilled.

4.3 The association between a high UPF intake and risk of CRC

Table 6 shows the association between the portion of UPF in the diet and CRC risk. In the crude model, a high UPF intake was statistically insignificant associated with CRC risk compared to a low UPF intake (HR= 1.08; 95% confidence interval [CI]: 0.94-1.25). In the multivariable model adjusted for age, educational level, smoking status, and intake of dairy products, a high UPF intake was statistically insignificant associated with CRC risk compared to a low UPF intake (HR= 1.12; 95% CI: 0.97-1.30). The overall P-trend in the crude and multivariable-adjusted models were statistically insignificant (p= 0.51 and 0.25, respectively). In the multivariable and energy-adjusted model, a high UPF intake was borderline statistically significant associated with CRC risk compared to a low UPF intake (HR= 1.21; 95% CI: 1.01-1.46). The P-trend in the multivariable and energy-adjusted model was borderline statistically insignificant (P= 0.08).

Table 6. Cox proportional HRs (95% CI) for the association between UPF intake and CRC risk

	Proportion of UPF consumption in the diet				
	Low (<=274g) HR	**Medium low** (275-361g) HR (95% CI)	**Medium high** (362-465g) HR (95% CI)	**High** (>466g) HR (95% CI)	**P for trend**
Colorectal cancer					
N	467	437	373	348	
Crude model	1 [Ref.]	1.00 (0.88-1.14)	0.95 (0.83-1.09)	1.08 (0.94-1.25)	0.51
Multivariate-adjusted*	1 [Ref.]	1.03 (0.90-1.72)	0.98 (0.86-1.13)	1.12 (0.97-1.30)	0.25
Multivariate and energy-adjusted**	1 [Ref.]	1.06 (0.92-1.22)	1.04 (0.88-1.22)	1.21 (1.01-1.46)	0.08

HR= hazard ratio.
* Multivariable-adjusted = multivariable Cox proportional hazard model adjusted for age, educational level, smoking status and intakes of dairy products.
** Multivariable and energy-adjusted = Multivariable-adjusted + adjusted for energy intake.

4.3.1 Association between UPF and risk of cancer in colorectal subsites

Table 7 shows the association between the proportion of UPF in the diet and cancer risk in colorectal subsites. In the left side of the colon and rectum, a high UPF intake was statistically insignificant associated with cancer risk compared to a low UPF intake in the multivariable-adjusted and the multivariable and energy-adjusted model. In total colon, a high UPF intake was statistically insignificant associated with cancer risk compared to a low UPF intake in the multivariable model (HR 1.16 (95% CI: 0.97-1.38). However, in the multivariable and energy-adjusted model a high UPF intake was statistically significant associated with risk of colon cancer compared to a low UPF intake (HR 1.29 (95% CI: 1.03-1.61)). The P-trend in the multivariable and energy-adjusted model was statistically significant (P= 0.04). In the right side of colon, a high UPF intake was statistically significant associated with cancer risk compared to a low UPF intake in both the multivariable-adjusted and multivariable and energy-adjusted model (HR= 1.28; 95% CI:1.03-1.60, and HR= 1.53; 95% CI: 1.15-2.03, respectively). The p-trend in the multivariable-adjusted and multivariable and energy-adjusted models for right-sided colon cancer was statistically significant (P= 0.04 and 0.004, respectively).

Table 7. Cox proportional HRs (95% CI) for the association between UPF intake and cancer risk in colorectal subsites

	Proportion of UPF consumption in the diet				
	Low (<=274g) HR	**Medium low** (275-361g) HR (95% CI)	**Medium high** (362-465g) HR (95% CI)	**High** (>466g) HR (95% CI)	**P for trend**
Total colon					
N	320	291	256	235	
Multivariate-adjusted*	1 [Ref.]	1.01 (0.86-1.18)	1.00 (0.85-1.19)	1.16 (0.97-1.38)	0.17
Multivariate and energy-adjusted**	1 [Ref.]	1.05 (0.89-1.25)	1.08 (0.89-1.32)	1.29 (1.03-1.61)	0.04
Right side colon					
N	201	175	159	148	
Multivariate-adjusted*	1 [Ref.]	0.99 (0.81-1.21)	1.05 (0.85-1.3)	1.28 (1.03-1.60)	0.04
Multivariate and energy-adjusted**	1 [Ref.]	1.06 (0.86-1.32)	1.19 (0.93-1.52)	1.53 (1.15-2.03)	0.004
Left side colon					
N	105	105	92	80	
Multivariate-adjusted*	1 [Ref.]	1.05 (0.80-1.34)	0.99 (0.75-1.32)	1.00 (0.74-1.35)	0.91
Multivariate and energy-adjusted**	1 [Ref.]	1.09 (0.82-1.45)	1.05 (0.76-1.46)	1.09 (0.74-1.60)	0.74
Rectal					
N	147	146	117	113	
Multivariate-adjusted*	1 [Ref.]	1.07 (0.85-1.35)	0.94 (0.74-1.20)	1.06 (0.82-1.36)	0.96
Multivariate and energy-adjusted**	1 [Ref.]	1.08 (0.85-1.38)	0.95 (0.72-1.27)	1.08 (0.78-1.49)	0.89

HR= hazard ratio.
* Multivariable-adjusted = Multivariable Cox proportional hazard model adjusted for age, educational level, smoking status and intakes of dairy products.
** Multivariable and energy-adjusted = Multivariable-adjusted + adjusted for energy intake.

4.3.2 Stratified analyses

Stratified analyses were done to assess the risk of cancer within groups of high and low BMI (cut-off point 25), high and low intake of dietary fiber (median 21g/day), and high and low intake of processed meat (median 30g/day). All estimates are presented in Table 8. A high UPF intake and low BMI (<25 kg/m2) was statistically insignificant associated with CRC risk compared to a low UFP intake and low BMI in the multivariable and energy-adjusted model (HR 1.10; 95% CI: 0.86-1.42) and the P-trend was statistically insignificant (P-trend= 0.50). A high UPF intake and a high BMI (>25 kg/m2) was statistically significant associated with CRC risk compared to a low UPF intake and high BMI (HR 1.33; 95% CI: 1.02- 1.75), the P-trend being borderline statistically insignificant (P-trend= 0.08).

A high UPF intake and a low dietary fiber intake (<21g/day) was borderline statistically significant associated with CRC risk, compared to a low UPF and dietary fiber, in the multivariable and energy-adjusted model (HR 1.28; 95% CI: 0.99-1.66). A medium-low UPF intake and a low dietary fiber intake was borderline statistically significant associated with CRC risk compared to a low UPF intake and low dietary fiber intake (HR 1.20; 95% CI: 1.00-1.43), the P-trend being borderline statistical insignificant (P-trend= 0.08). A high UPF intake and a high dietary fiber intake (>21g/day) was statistically insignificant associated with CRC risk, compared to a low UPF intake and high dietary fiber intake, in the multivariable and energy-adjusted model (HR 1.02; 95% CI: 0.77-1.34), P-trend being statistically insignificant (P-trend= 0.58).

A high UPF intake and a low processed meat intake (<30g/day) was statistically significantly associated with CRC risk compared to a low UPF intake and low processed meat intake in the multivariable and energy-adjusted model (HR1.34; 95% CI: 1.03-1.74), P-trend being borderline statistically insignificant (P-trend=0.07). A high UPF intake and a high processed meat intake(>30g/day) was statistically insignificant associated with CRC risk compared to a low UPF intake and high processed meat intake in the multivariable and energy-adjusted model (HR 1.06; 95% CI:0.81-1.38), P-trend being statistically insignificant (P-trend=0.61).

Table 8. Stratified analysis: Cox proportional HRs (95% CI) for the association between UPF intake and CRC risk

	Proportion of UPF consumption in the diet				
	Low (<=274g) HR	**Medium low** (275-361g) HR (95% CI)	**Medium high** (362-465g) HR (95% CI)	**High** (>466g) HR (95% CI)	**P for trend**
Colorectal cancer					
BMI < 25*	1	1.06 (0.86-1.28)	1.05 (0.85-1.30)	1.10 (0.86-1.42)	0.50
BMI > 25*	1	1.06 (0.86-1.31)	1.01 (0.79-1.29)	1.33 (1.02-1.75)	0.08
Fibre < 21*	1	1.20 (1.00-1.43)	1.14 (0.90-1.43)	1.28 (0.99-1.66)	0.08
Fibre > 21*	1	0.82 (0.65-1.04)	0.86 (0.67-1.09)	1.02 (0.77-1.34)	0.58
Processed meat < 30*	1	1.10 (0.92-1.32)	1.05 (0.84-1.32)	1.34 (1.03-1.74)	0.07
Processed meat > 30*	1	0.94 (0.76-1.17)	0.94 (0.74-1.19)	1.06 (0.81-1.38)	0.61

HR= hazard ratio.
* Multivariable Cox proportional hazard model adjusted for age, educational level, smoking status, and intakes of dairy products and total energy.

4.3.3 Sensitivity analyses

Sensitivity analyses, omitting the first three years of follow-up for all participants, were performed on the primary analysis and the analysis on colorectal subsites. The sensitivity analyses provided similar effect estimates as the previous models with no follow-up time removed. Estimates for the crude, multivariable-adjusted, and multivariable and energy-adjusted models of the primary analysis can be found in Table 9. Estimates for the multivariable-adjusted and multivariable and energy-adjusted models of the colorectal subsites can be found in Table 10.

Table 9. Sensitivity analysis: Cox proportional HRs (95% CI) for the association between UPF intake and CRC risk

	Proportion of UPF consumption in the diet				
	Low (<=274g) HR	**Medium low** (275-361g) HR (95% CI)	**Medium high** (362-465g) HR (95% CI)	**High** (>466g) HR (95% CI)	**P for trend**
Colorectal cancer					
N	467	437	373	348	
Crude model	1 [Ref.]	1.01 (0.88-1.16)	0.96 (0.83-1.12)	1.10 (0.94-1.27)	0.42
Multivariate-adjusted*	1 [Ref.]	1.03 (0.90-1.18)	0.99 (0.86-1.15)	1.13 (0.97-1.31)	0.22
Multivariate and energy-adjusted**	1 [Ref.]	1.06 (0.92-1.23)	1.04 (0.88-1.23)	1.21 (1.00-1.47)	0.09

HR= hazard ratio.
* Multivariable-adjusted = multivariable Cox proportional hazard model adjusted for age, educational level, smoking status and intakes of dairy.
** Multivariable and energy-adjusted = Multivariable-adjusted + adjusted for energy intake.

Table 10. Sensitive analysis: Cox proportional HRs (95% CI) for the association between UPF intake cancer risk in colorectal subsites

	Proportion of UPF consumption in the diet				
	Low (<=274g) HR	**Medium low** (275-361g) HR (95% CI)	**Medium high** (362-465g) HR (95% CI)	**High** (>466g) HR (95% CI)	**P for trend**
Total colon					
N	320	291	256	235	
Multivariate-adjusted*	1 [Ref.]	0.99 (0.84-1.17)	1.02 (0.86-1.21)	1.14 (0.95-1.37)	0.2
Multivariate and energy-adjusted**	1 [Ref.]	1.03 (0.86-1.23)	1.10 (0.89-1.34)	1.26 (1.00-1.60)	0.06
Right side colon					
N	201	175	159	149	
Multivariate-adjusted*	1 [Ref.]	0.99 (0.80-1.23)	1.08 (0.87-1.34)	1.29 (1.02-1.63)	0.04
Multivariate and energy-adjusted**	1 [Ref.]	1.07 (0.85-1.34)	1.23 (0.95-1.59)	1.54 (1.14-2.07)	0.004
Left side colon					
N	105	105	92	80	
Multivariate-adjusted*	1 [Ref.]	0.97 (0.73-1.28)	0.96 (0.72-1.29)	0.92 (0.67-1.26)	0.62
Multivariate and energy-adjusted**	1 [Ref.]	0.99 (0.73-1.34)	1.01 (0.71-1.42)	0.98 (0.65-1.47)	0.95
Rectal					
N	147	146	117	113	
Multivariate-adjusted*	1 [Ref.]	1.13 (0.88-1.43)	0.94 (0.72-1.22)	1.12 (0.86-1.46)	0.74
Multivariate and energy-adjusted**	1 [Ref.]	1.12 (0.87-1.45)	0.94 (0.69-1.26)	1.11 (0.79-1.56)	0.85

HR= hazard ratio.
* Multivariable-adjusted = multivariable Cox proportional hazard model adjusted for age, educational level, smoking status and intakes of dairy.
** Multivariable and energy-adjusted = Multivariable-adjusted + adjusted for energy intake.

5 Discussion

This thesis aimed to examine the association between a high UPF intake and risk of CRC in NOWAC and is the first study to investigate the association between a high intake of UPF and the risk of cancer in colorectal subsites.

Overall, a high UPF intake was not statistically significant associated with increased CRC risk compared to a low UPF intake. However, after adjusting for total energy intake and all covariates a borderline statistical insignificant trend was found. Further, right-sided colon cancer was statistically significant associated with a high UPF intake compared to a low UPF intake. Total colon cancer was also statistically significant associated with a high UPF intake compared to a low UPF intake, but only after adjusting for all covariates and total energy intake. No statistically significant associations were found between a high UPF intake and cancer on the left side of colon or in the rectum compared to low UPF intake. Summarized, these findings suggest that a high UPF intake is associated with right-sided colon cancer and that the right-sided colon cancer drives the association between high UPF intake and CRC risk.

In the stratified analysis, a high UPF intake and a high BMI or low processed meat intake were borderline statistically significant associated with increased CRC risk compared to a low UPF intake and a high BMI or low processed meat intake. Further, those with a medium-low or high UPF intake and low dietary fiber intake were borderline significant associated with an increased risk of CRC compared to those with a low UPF intake and low dietary fiber intake. Overall, these findings indicates that a high BMI and low dietary fiber intake, but not intake of processed meat, may be potential drivers behind the association between a high UPF intake and increased risk of CRC.

When looking at demographic and lifestyle characteristics differences were observed between participants with high and low UPF intake. Participants with a high UPF intake compared to a low UPF intake tended to be younger, taller, current smokers, and more underweight or obese. In addition, they tended to be higher educated, have a higher physical activity level, and use hormone therapy less. No differences were found in bad and very bad self-reported health, but differences were observed in good and very good self-reported health between groups with a high and low UPF intake. For the dietary characteristics, the intake (g/d)

increased from participants who had low UPF intake to participants who had high UPF intake. Overall, no healthy or unhealthy profile was identified.

UPF made up 24% (g/d) of the total diet among individuals with a high UPF intake. If the UPF intake had been calculated for the total study population the estimate would likely have been lower. The UPF intake in Norway has previously been measured on household availability calculated using money(33) and energy (kcal/d)(32). No measurements have been calculated on an individual level or by weight. Thus, the previous estimates and the estimates of UPF intake in this thesis cannot be directly compared. When comparing the estimate of UPF intake in this thesis to other countries in Europe, the estimates are generally the same or lower(35, 36). The possible lower UPF intake observed in Norway might be due to older dietary data or differences in food culture and gender roles. However, as this discussion is outside of this thesis's specific objectives, it will not be further discussed.

As Norway is one of the countries with the highest incidence of CRC(46), one may ask if Norway also is one of the countries with the highest consumption of UPF. However, Norway is placed 6th (37%) compared to other European countries average household availability of UPF. The top five countries are the UK (51%), Ireland (46%), Germany (46%), Belgium (45%), and Finland (41%)(32), which Norway all has a higher incidence of CRC than(46).

5.1 Interpretation and comparison with other studies

To my knowledge, four earlier studies have examined the association between UPF and CRC, one cohort(35) and three case-controls(36, 37, 39). All the previous studies used NOVA to classify food and food items according to what extent the foods are processed. As the findings in earlier studies are conflicting, the findings of this study are both consistent and inconsistent with previous results.

5.1.1 Differences in demographic and lifestyle characteristics

This and all four previous studies suggest that there is a difference in demographic and lifestyle characteristics among high and low UPF consumers(35-37, 39). In general, participants with a high UPF intake compared to a low UPF intake tend to be younger, current smokers, and have higher energy intake(35-37, 39). As mentioned earlier, participants with a

high UPF intake were more physical active and higher educated than participants with a low UPF intake in this thesis. However, these findings are inconsistent with the previous studies (35-37). The inconsistent findings might indicate that the characteristics of those consuming UPF may differ between regions. As the results are inconsistent, no general healthy or unhealthy profile among individuals with a high UPF intake can be concluded.

That individuals with a high UPF intake might be more physically active and educated than participants with a low UPF intake can be surprising as these characteristics often are associated with a healthier diet(77, 78). A possible explanation might be that the convenience and misleading health claims of certain UPF foods, like zero calories, are attractive for the highly educated population as they may have busy schedules due to responsible jobs and extra activities. This time constraint might contribute to the extra use of convenience foods. However, as the purpose of NOVA is to categorize foods according to the extent and purpose of the food processing and not by nutritional composition(21), not all UPFs might be unhealthy as such. In a recent study, UPF accounted for 26% of foods considered healthy(79). Thus, participants with a higher level of physical activity and education might choose UPF because of their convenience but at the same time evaluate UPFs nutritional composition.

On the other hand, the failed attempt to find an overall healthy or unhealthy profile might be due to the time at which the studies were conducted, as the society and trends of food consumption can have changed over time. Further, the inconsistent findings can result from studies being conducted in different countries with different study populations, as the food cultures and gender roles may vary.

5.1.2 The association between a high UPF intake and CRC

In 2018, the first study that examined the association between a high UPF intake and increased risk of CRC was published(35). The study had a cohort study design and was based on the French NutriNet-Santé prospective cohort with 105,000 participants and 153 CRC cases. The result from the cohort showed no overall association between high UPF intake and increased risk of CRC compared low UPF intake(35). However, a borderline non-significant trend was seen after adjusting for further covariates(35). The French cohort used 24h recalls to collect dietary data, which is a strength compared to FFQs used in this thesis. The fact that

the French cohort failed to reach the standard threshold for statistical significance may be due to a low number of incidences, as the cohort only had 153 cases(35). Overall, the findings are in line with the results in this thesis.

In contrast to the French cohort and the current thesis, all three case-controls found that a high UPF intake was statistically significantly associated with CRC(36, 39) or colorectal adenomas(37) compared to a low UPF intake. All the case controls used FFQ to collect dietary data. However, how the studies measured the NOVA groups contribution to the diet differed. The NOVA groups contribution was either calculated by weight (g/d)(36, 39), similar to this thesis, or by energy (kcal/d)(37). Both calculations methods have pros and cons which will be discussed in chapter 5.2.7.

Though the case-controls found that a high UPF intake was statistically significantly associated with CRC(36, 39) or colorectal adenomas(37) compared to a low UPF intake, the strength of the estimates varies. In the case-control that studied a high UPF intake and colorectal adenomas the odds ratio (OR) was high, but the confidence intervals (CI) was wide(OR 1.75; 95% CI 1.14-2.68)(37), which weakens the precision of the estimates. The wide CI may be a result of the low sample size as the study only had 652 participants and 294 cases(37). In the case-controls that studied the association between a high UPF intake and CRC, the ORs were lower, but the CI was narrower, which indicates more precise estimates (odds ratio(OR) 1.11; 95% CI 1.04–1.18(36) and OR 1.40; 95% CI = 1.22–1.61(39)). In addition, the studies had 1453(39) and 1852(36) cases, which are considered substantial and strengthens the estimates. Generally, the findings from the case-controls indicates that there is an association between a high UPF intake and CRC.

The current thesis failed attempt to find an overall association between high UPF intake and risk of CRC may be explained by the fact that there is no association. With that being said, some methodical approaches might also explain the lack of association. Firstly, the FFQs from NOWAC was not designed to assess how foods were processed, and thus foods might have been categorized in the wrong NOVA groups. Secondly, NOVAs definitions might have been misinterpreted during the coding, leading to misclassification of foods. Lastly, the lack of association may be due to foods included in the study, which represent the typical

Norwegian diet. The Norwegian diet might differ in terms of foods and processing methods compared to the other studies that took place in Morocco(39), Spain(36), and Israel(37).

5.1.3 A high UPF intake and cancer in colorectal subsites

In this thesis, a high UPF intake was statistically significant associated with right-sided colon cancer and total colon cancer compared to a low UPF intake. No statistically significant association were found between a high UPF intake and left-sided colon cancer or rectal cancer compared to low UPF intake. Similar findings were found in one of the case-controls were a high UPF intake, compared to a low UPF intake, only was statistically significant associated with right-sided colon adenomas and not left-sided colon adenomas (37). The two other case controls did not examine subsites but examined the difference between the colon and rectum(36, 39). In contrast to previous findings, both studies found that a high UPF intake was statistically significantly associated with cancer in colon and in rectum compared to low UPF intake(36, 39). The lack of association between high UPF intake and cancer in the left side of the colon and rectum in this thesis might be due to fewer cases. In this thesis left-sided colon and rectal cancer only had 382 and 523 cases, respectively, while the case-controls had 724 and 700 rectal cancers, respectively(36, 39).

Nevertheless, a high UPF intake might affect colorectal subsites differently. Colorectal subsites have shown to differ in physiology, anatomy, environmental carcinogens, genetic mechanisms, and prognosis, which can explain why associations between high UPF intake and colorectal subsites might differ(80). Further, two main pathways of genomic instability have been observed in the colon. These genomic instability pathways are called chromosomal instability (CIN) and microsatellite instability (MSI)(81). Through the CIN pathway, typically associated with left-sided CRC tumors, cancer is developed due to errors in chromosome segregation, by causing abnormalities in the chromosomes(81, 82). Through the MSI pathway, typically associated with right-sided CRC, cancer is developed due to a defect in the DNA mismatch repair (MMR) system(81). MMR is a system that repairs errors in the DNA, and a defect in MMR can cause errors in the DNA which further can result in cancer development(81).

Interestingly, an earlier study found an association between MSI colon cancer and dietary heterocyclic aromatic amines (HAA), which are molecules produced during cooking of meat at high temperatures(83). That HAA is associated with the MSI colon cancer, typically seen on the right side of the colon, might partly explain why UPF is associated with right-sided colon cancer. However, BPA, which mentioned earlier has been associated with CRC risk, may be associated with CIN colon cancer by inducing centrosome changes that disturb the chromosome segregation(84). Thus, substances in UPF might increase the risk of cancer in both the left and right sides of the colon. Whether high UPF intake affects colorectal subsites differently or not is too early to say as there are too few studies available, and the findings are opposing.

5.1.4 Mechanisms behind the association between a high UPF intake and CRC

The specific mechanisms that drive the possible association between high UPF intake and risk of CRC are unknown, but potential mechanisms can be discussed. According to the WCRF report dietary fiber is convincingly associated with decreasing the risk of CRC by reducing transit time, preventing insulin resistance, and playing an essential part in butyrate synthesis(53), see Figure 2 for more details. In this thesis, a high UPF intake and low dietary fiber intake was borderline statistically significant associated with an increased risk of CRC compared to low UPF intake and high dietary fiber intake. In addition, the initial statistically significant association between high UPF intake and CRC was attenuated after adjusting for dietary fiber in the Moroccan case-control, meaning the association was no longer statistically significant(39). As UPFs are generally characterized by being low in dietary fiber(14), a high UPF intake might cause a low dietary fiber intake. When having a low dietary fiber intake, the protective effects of dietary fiber are reduced, which might explain why the risk for CRC increases when having a high UPF intake.

In this thesis, the Norwegian food group 5 (grains, baked goods, seeds, and nuts) made up 35.5% of the UPF group. As bread consumed among participants was thought to be mostly store-bought, bread was classified as UPF. In Norway, bread is consumed in large amounts and is the most important source of whole grains(85, 86). As bread make up a large part of UPF in this thesis, the dietary fiber content can have contributed to the nonsignificant association found between a high intake of UPF and risk of CRC. If breads were placed in

NOVA 3 and not NOVA 4, it would have been interesting to see if the association between UPF and CRC still would have remained statistically insignificant or if the association would have change to become statistically significant.

Further, a diet high in UPF might be high in processed meat. In the WCRF report processed meat is convincingly associated with increased CRC risk(53). Processed meat contains substances added or formed during processing that can be carcinogenic. Examples of such substances are sodium nitrites and polycyclic aromatic hydrocarbons, which might cause DNA damage and further lead to CRC (15, 56), see Figure 2. Contradictory to the findings, a UPF intake and high processed meat intake was not statistically significantly associated with CRC risk compared to a low UPF intake and high processed meat intake. What is even more interesting is that those with a high UPF intake, but a low processed meat intake, had a borderline significant association with increased risk of CRC compared to those with a low UPF intake and low processed meat intake. These findings further align with the case-control study investigating a high UPF intake and colorectal adenomas(37) but contradicts a previous study that found an positive association between processed meat and risk of CRC in NOWAC(87).

Several factors can explain this thesis failed attempt to find a statistically significant association between a high intake of UPF and processed meat and risk of CRC. Firstly, NOWACs findings on processed meat and health effects are generally limited(88). The limited findings on processed meat and health effects might be a result of inadequate data on processed meat, as the FFQ in NOWAC focuses more on intake of fish than meat(66). Further, the additives used in Norway are strictly regulated and are only approved if they are scientifically proven not to be harmful to health(89). Whether or not processed meat is a mediator behind the association between a high UPF intake and risk of CRC remains unclear.

High BMI is another established risk factor for CRC(53). That a high UPF intake is associated with a high BMI has been shown in multiple studies(55), and many hypotheses have been suggested as to why a high intake of UPF causes weight gain or increases obesity(61, 62), see Figure 2 for further details. In this thesis, a high UPF intake and high BMI was borderline significantly associated with CRC risk compared to a low UPF intake and high BMI. In contrast, a high UPF intake and low BMI was not statistically significantly

associated with CRC risk compared to low BMI and low UPF intake. These results support that high BMI is a driver behind the association between high UPF intake and risk of CRC. However, all the four previous studies adjusted for BMI, and the two case-controls that investigated a high UPF intake and CRC still got statistically significant estimates(36, 39). Thus, there might be something else besides BMI, or in addition to BMI, that drives the association between a high UPF intake and CRC.

Further, the current thesis and the French cohort found a borderline non-significant trend among individuals with a high UPF intake and risk of CRC after adjusting for covariates and total energy intake or covariates plus intake of lipids, sodium, and carbohydrates and Western dietary pattern(35). Similar results was found in the Spanish case-control, where the association between a high intake of UPF and CRC risk was attenuated after adjusting for daily energy density, total saturated fat, or simple carbohydrate intake(36). These findings could potentially be explained by non-nutrient components often added or formed during processing of UPF, such as additives, molecules formed during the preparation over high heat, and molecules from packaging, as these have been shown to cause oxidative stress or damage to the DNA and further lead to CRC(15, 56, 58), see Figure 2. Thus, the mechanisms that drive the association between high UPF intake and CRC risk may go beyond dietary quality and total energy intake.

5.2 Assessment of the methodical quality

In epidemiological studies there are many possibilities of errors occurring. These errors can be either random or systematic and can lead to estimates deviating from the true results(90).

5.2.1 Random error

Random errors are chance differences between an observed and true value of a population(90). The dietary data and the calculated UPF intake in this thesis might be subject to random errors because of human error in reading or typing during the NOVA calcification process and when the participants answered the FFQ. Further, random error might have occurred due to individual variations(90). However, this thesis has a large sample size, and

two students compared their work during the NOVA classification process, which reduces the possibility of random errors.

5.2.2 Systematic error and validity

Systematic errors, or bias, are errors that systematically differ from the true value, which causes the results to be moved in one direction(90). In this thesis, systematic errors might have occurred as dietary data was collected using broad questionnaire surveys. When using broad questionnaire surveys, decisions on regular intake might be based on general consumption standards. For example, because most participants in NOWAC consumed store-bought bread (Group 4) instead of homemade bread (Group 3), bread was classified in Group 4. Thus, the standardization of the consumption can have led to a measured UPF intake that systematically differs from the true intake.

Further systematic errors that might be present in this thesis are recall bias and selection bias. Recall bias occurs when participants do not accurately remember previous events or experiences or omit details(91). The FFQ from NOWAC collected data on the usual consumption from the past year. Thus, participants had to think back a year when answering the questionnaires. This might have caused participants to remember incorrectly or forget their actual intake, resulting in bias in the collected dietary data. However, NOWACs dietary data has been assessed against repeated 24 h recalls, and the results show that the dietary data collected through the FFQ is acceptable and reliable and can be used to rank the participants(65).

Lastly, selection bias, which occurs when there is a systematic difference between those who participated in the study and those who did not(90), might be present as NOWAC is volunteer-based. Subjects who chose to participate in NOWAC might have a healthier lifestyle than those who did not, resulting in a lower UPF intake than the general population. However, this thesis has a cohort study design, and women in NOWAC were randomly selected from the Norwegian Population Register, reducing the risk of selection bias. In addition, a previous study has examined the reproducibility of the collected data in NOWAC and found no major source of selection bias(66). However, the exclusion of participants with missing values can have led to selection bias and incorrect inferences about associations

between UPF intake and CRC. Thus, the chance of selection bias cannot be entirely overlooked.

5.2.3 Assessment of the study design

This thesis has a cohort design which is considered among the superior epidemiological study designs, as it can measure the incidence and are less exposed to selection and recall bias(92). Many previous studies on UPF intake and CRC have used the case-control study design. However, as the case-controls define the study population on the background of the disease, the case-controls cannot measure the incidence and are more prone to selection bias, recall bias, and confounding(92). Thus, case-controls are less adept at showing causal relationships than cohorts. When determining causality, randomized control studies are seen as the gold standard because of their potential to limit bias (93). However, when studying risk factors for diseases such as CRC, exposing individuals to possible harmful exposures is not ethical. Thus, cohorts are thought to be the most robust study design when examining the relationship between UPF intake and the risk of CRC.

5.2.4 Handling of missing data

In this thesis, there were 14,809 missing values, most of which were present in the physical activity, BMI, and education variables, see Table 2. In NOWAC, there were also missing data in the dietary variables, but these variables had previously been imputed using the null value(94). Missing data can reduce statistical power, cause bias in the estimation of the parameters, and reduce the sample's representativeness(95). Each of these problems may threaten the study's validity and lead to invalid conclusions. Based on the types of missing data present in a study different strategies for handling missing data are recommended (95). In this thesis, there may both be missing completely at random (MCAR) and missing at random (MAR). When MAR is present, multiple imputation is seen as the best strategy to reduce bias from the missing values(95). However, as imputation is advanced, time-consuming, and seen as outside the expectations of a master thesis, exclusion was chosen as a strategy to handle missing data. As missing on confounding and mediating variables was excluded, bias might be present in this thesis.

5.2.5 The choice of covariates to limit confounding

When investigating a cause-and-effect relationship confounding can occur. Confounding is when a third variable, called a confounding variable, is associated with the exposure and also influences the disease outcome(96). When a confounder is present, it can be challenging to separate the actual effect of the exposure variable and the effect from the covariate. Thus, covariates are important to adjust for to minimize bias in the estimate(96).

In this study, an attempt to minimize potential confounding was done by adjusting for covariates in the multivariable analysis. The choice of covariates was based on the literature and available data. As NOWAC did not have data on inflammatory bowel disease, aspirin, and calcium supplements, these potential confounders were not adjusted for in the multivariable analysis. Thus, residual confounding may still exist. Some of the previous studies that examined the association between high UPF intake and CRC have adjusted for additional dietary variables such as saturated fat, trans fat, and western dietary pattern(35, 36). However, in this thesis, these factors were not adjusted for as they were not established risk factors for CRC in the WCRF report(53). Including variables that are not established risk factors might not contribute with more explanatory value and might make the results more challenging to interpret(97).

Though total energy intake is not an established risk factor for CRC in the WCRF report(53), total energy intake was still included as a covariate in a separate analysis as it can cause confounding in epidemiologic studies(76). The descriptive statistics showed that the intake of total energy, dietary characteristics, and the intake of all NOVA groups (g/day) increased with the increased proportion of UPF in the diet. In addition, after including total energy intake in the model, the association between high UPF intake and risk of CRC went from being non-significant to being borderline significant. These findings support that total energy intake should be treated as a covariate, as excluding total energy intake from the model might lead to bias in the estimates.

5.2.6 Division of CRC subsites

This thesis divided the colorectal tract into three subsites: right-sided colon cancer, left-sided colon cancer, and rectal cancer. Recently, a new study found that different risk factors of CRC

have different effects across subsites and this even in the right-sided and left-sided colon(54). Thus, dividing the colorectal tract into more than three subsites might be important. With the current division used in this thesis, the detected associations between a high UPF intake and CRC compared to a low UPF intake might have become less significant. Further, certain effects of high UPF intake in some areas in the colorectal tract might be undetected.

5.2.7 Methods for calculating the UPF intake

In previous studies, the UPF intake has been calculated by money(33), weight (g/d)(35, 36, 39), and energy (kcal/day)(37). When assessing the UPF intake effect on health, estimating UPF proportion in the diet by weight or energy may be better than by money, as they measure UPF intake at an individual level. Whether weight or energy is the best method to calculate the contribution of UPF in the diet can be further discussed. When calculating UPF by energy, UPFs that do not contribute to energy intake, such as artificially sweetened beverages and substances added or formed under processing, are not considered (e.g., additives and neo-formed components). Thus, calculating the UPF intake by weight may reflect more aspects of UPF as non-energy components are considered. However, measuring by weight can cause some foods to be weighted more than they should. Beverages, such as diet coke, which is artificially sweetened and categorized as UPF, are often consumed in large amounts. The artificial sweetener only makes up a small percentage of the weight in diet coke, as most of the diet coke is water. Thus, calculating UPF intake by weight may lead to skewed distribution. Nevertheless, this could partly be adjusted for by adjusting for water intake. Which method that calculates the UPF intake the best remains unclear.

5.2.8 Strengths

There are several strengths in this study. Firstly, this study has a prospective cohort design with a large sample size and long follow-up time, which gives more stable risk estimates. Secondly, foods are classified according to NOVA, using guidelines developed by IARC and Monteiro (unpublished), which reduces the chances of misclassification. Thirdly, this thesis examines UPF intake against cancer in colorectal subsites. Further, NOWAC has good cancer registry data(98), and dietary data from NOWAC is considered good for ranking the participants(66). Lastly, this cohort has 1625 cases, which is a relatively high number compared to the other cohort and one case-control, who only had 135(35) and 294(37) cases,

respectively, and similar to the Moroccan and Spanish case-controls who had 1453(39) and 1852(36) cases, respectively.

5.2.9 Limitations

Some limitations should be acknowledged. Firstly, dietary data was collected using self-reporting FFQs which are less detailed than 24h recalls. In addition, this thesis did not use FFQs designed to look at food processing. Thus, own judgment was used to classify foods into NOVA groups, which can have resulted in some degree of misclassification. Different scenarios were made and could have been examined, but this was not done to delimit the thesis. Secondly, the FFQs can have caused social desirability bias as participants might have underestimated food they considered unhealthy and overestimated foods they considered healthy. Thirdly, though the collected dietary data from the FFQ has been validated, the study only assessed foods and nutrients and not processing methods(66). Thus, the validation for food processing might be poorer.

Further, it should be put forward that the NOVA system may not be the optimal classification system as it has been criticized for being too heterogenous and imprecise(23). However, NOVA can be thought to be the most established food processing classification system today as it is acknowledged in reports from FAO(99) and included in dietary guidelines in multiple countries(27-29). For further discussion of NOVA, see chapter 5.3. Further, this study includes only women, and the nutritional data was collected in only one country, limiting the generalizability to men and across populations with different diets. Lastly, residual confounding might still occur due to lack of data on covariates, unmeasured behavioral factors, and/or imprecision in the measures of the included covariates. Thus, residual confounding cannot be entirely excluded.

5.3 Is NOVA an effective tool for assessing foods effect on health?

One of the main aims of nutrition research is to understand how our food affects our health(100). As mentioned in chapter 1.3.2, researchers have previously criticized NOVA for being too heterogenous and imprecise and questioned whether NOVA is helpful in examining foods effect on health(23). In short, it was argued in chapter 1.3.2 that NOVA was viewed as the most specific and comprehensive classification system and that it was helpful in terms of

examining foods effect on health, as UPF has been associated with adverse negative health effects(26). Further, both findings in this paper and findings in previous papers implies that there is an association between high UPF intake and risk of CRC or CRC subsites(36, 39), supporting Monteiro's statement that the way we process food is an important aspect of nutritional research to look further into(34).

Though NOVA might be a good food processing classification system and the most used classification system in research today(101), it cannot overlook that NOVA still might have flaws. As mentioned earlier, a new study found that the overall consistency of assigning foods to the same NOVA group was low among evaluators(102), supporting the critic that the NOVA definitions are not clear or precise enough(23). This can further cause uncertainties in the estimates in studies, as foods might be misplaced in the NOVA groups.

Furthermore, about 26% of foods considered good for health are classified as UPF(79). This indicates that not all UPF causes health problems but might also be health beneficial. That some UPFs can be health beneficial is supported by a previous study that redesigned processed meat by adding inulin which decreased the risk of CRC in rats(103). With the NOVA classification system, this food would be categorized as UPF(21). In an article by Monteiro et al., they write that the NOVA classification system 'groups foods according to the extent and purpose of the processing they undergo'(21 p. 30). As the researchers wanted to make inulin-rich meat that reduced CRC risk, the purpose behind the processing could be thought to make a food item healthier. However, with the current NOVA definitions, it is unclear how a food should be categorized when assessing both the processing methods and the purpose behind the food processing.

To summarize, Monteiro et al. have opened a new direction in dietary research, which has been shown to be important. However, the NOVA system today might have a few shortcomings, as mentioned above. Further development of NOVA might be suggested to make the classification system even more precise. How to further develop NOVA needs to be carefully considered. However, a few suggestions could be made, such as 1) Making the definitions more precise to reduce misclassification and better the overall consistency among evaluators when they assign foods to NOVA groups. 2) Include more groups to distinguish between UPF that might be considered healthy and UPF that can be considered unhealthy.

This could further help to understand which processing methods that potentially are beneficial for health and which that are harmful. Lastly, as some healthy foods are classified as UPF(79), it might be beneficial to develop a guideline on how to interpret the healthiness of foods when assessing nutrients, foods, and food processing combined.

5.4 Implications for public health

UPF is currently a hot topic among researchers, and the awareness of UPF is also increasing among consumers. As UPF is getting more attention and research has shown that UPF might have various health effects(34), it is said that UPF will be mentioned in the new Nordic Nutrition Recommendations 2023 (NNR2023)(104). With the current evidence and attention towards UPF, it can be discussed if the term should be used in public communication and dietary guidelines, such as the dietary guidelines for the prevention of CRC, as a strategy to reduce the risk of CRC and reach the SDG target 3.4 by 2030(2). However, as foods with both beneficial and adverse health effects are classified together in the UPF category(79), it might be confusing for consumers to interpret whether UPF is healthy or unhealthy. Thus, the NOVA system might need further development before being used in public communication and dietary guidelines in Norway.

5.5 Suggestions for further research

Previous studies suggest an association between a high intake of UPF and CRC(36, 39). However, the results are still inconsistent, and few studies are available. Before it can be said that a high UPF intake increases the risk of CRC, there is a need for more longitudinal studies with larger sample sizes that study different populations in different countries and different diets. Furthermore, as the NOVA definition might cause confusion and thus misclassification of foods, further development of a universally accepted definition of UPF that is clear, precise, and easy to interpret might be needed to decrease bias and increase the correspondence of UPF classification across studies(102). In addition, to get more precise information on how foods have been processed and reduce the chance of misclassification, there is a need for better dietary assessment methods such as 24h recalls or FFQs designed to assess food processing.

Further, the mechanisms behind the potential association between UPF and CRC risk are not yet known. Thus, more studies examining both the nutritional composition and non-nutrient components are needed to better understand the mechanisms that drive the association. Furthermore, to better understand how the different NOVA groups affect the risk of CRC, more studies examining all NOVA groups and scenarios in relation to CRC are needed. Substitution analyses might also be worthwhile exploring to understand better how much replacing a certain percentage of UPF with non-processed food would prevent development of CRC.

Furthermore, studies calculating UPF by weight and energy are needed to determine which method measures UPF most precisely. Lastly, the current division of the colorectal tract is generally limited to colon and rectum, and few studies have examined the association between high UPF intake and cancer in more refined colorectal subsites. As new research suggests that different risk factors for CRC have different effects across colorectal subsites, even within the right-sided and left-sided colon(54), the importance of studying colorectal subsites can be highlighted. New research on refined subsites may reduce the risk of offset estimates and lead to discovery of new associations between UPF and cancer in some areas in the colorectal tract that might be undetected.

6 Conclusion

In summary, evidence in this thesis shows no overall association between high UPF intake and increased risk of CRC among women in the NOWAC study. However, the results suggest a statistically significant association between high UPF intake and increased risk of cancer in the right side of the colon. The results also show a difference in lifestyle and demographic variables between participants with a high and low UPF intake. As the results from previous studies are contradictory, the results from this study are both consistent and inconsistent with earlier findings. Though the studies are contradictory, the results still indicate that UPF is a potential risk factor for CRC that is important to investigate further. What the association is driven by is not yet known. Results suggest that a low dietary fiber intake and high BMI might be mechanisms of importance, but the result also indicate that the mechanisms go beyond a high BMI and poor dietary quality. Due to few studies and the previous limitation mentioned, it is too early to say if there is a causal relationship between a high UPF intake and CRC risk. Further longitudinal studies investigating the relationship between a high UPF intake and CRC risk are needed to determine causality.

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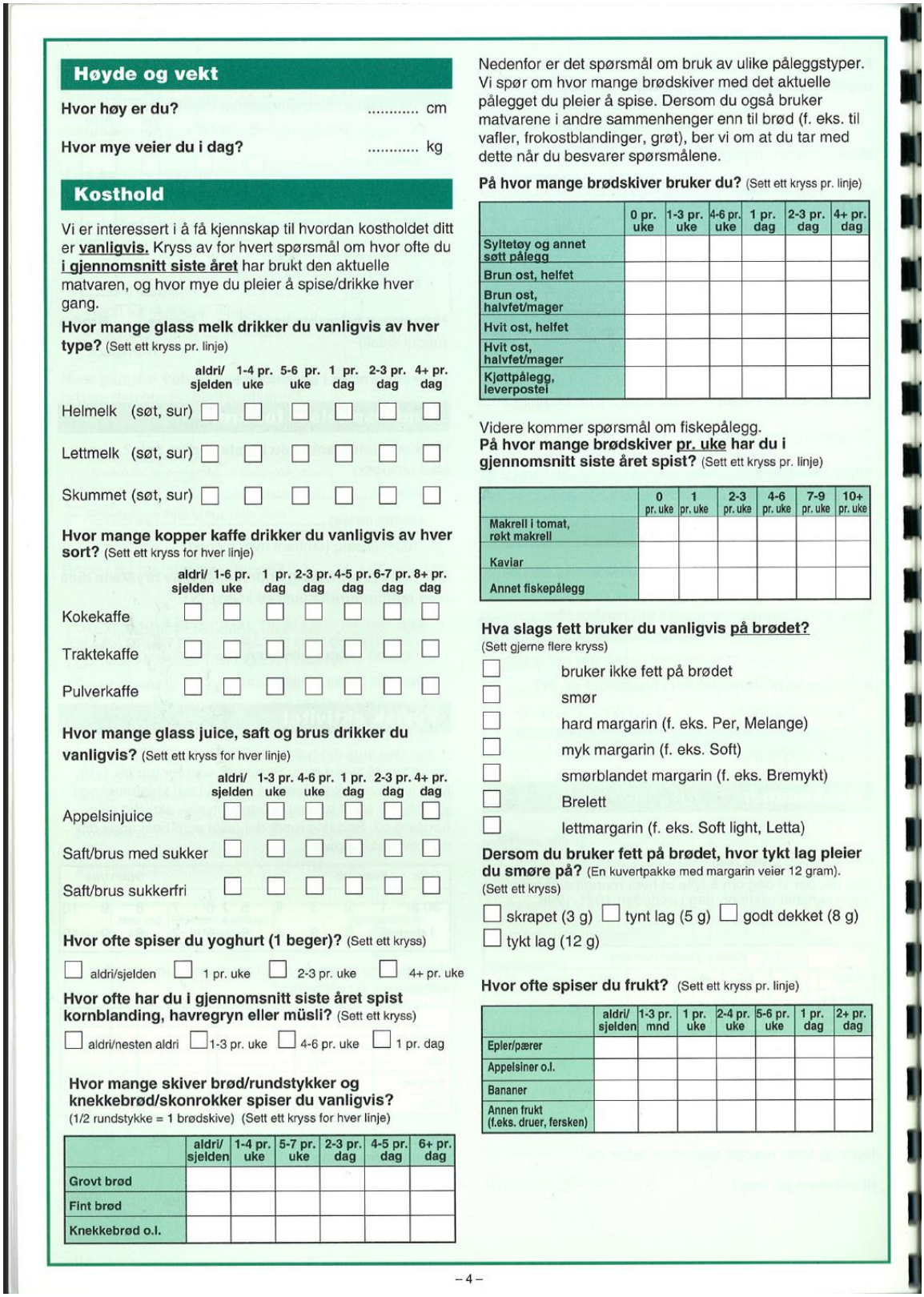
Appendix 1

Literature search

Database	Search terms	Filters	Results	Date
PubMed	((((((food) OR foods) OR product) OR products)) AND ((("ultraprocessed") OR "ultra processed") OR "ultra-processed")) AND ((Colorectal neoplasms [MeSH] OR intestinal polyps [MeSH]) OR ((colon [tiab] OR rectum [tiab] OR rectal [tiab] OR colorectum [tiab] OR colorectal [tiab] OR large bowel [tiab] OR large intestine [tiab] OR gut [tiab]) AND (malign* [tiab] OR neoplasm* [tiab] OR carcinoma* [tiab] OR cancer* [tiab] OR tumor* [tiab] OR tumour* [tiab] OR polyp* [tiab])))	No filter	11 articles After update: 13 articles	22. October Updated: 10. April
Medline		No filter	12 articles	10. April
Google scholar	Ultraprocessed food, ultra-processed food, ultra processed food, colorectal cancer, colorectal neoplasms	No filter	42 articles	12. April
Web of Science	(AB=(food*)) OR AB=(product*) AND ((AB=(ultraprocessed)) OR AB=(ultra-processed)) OR AB=(ultra processed) AND (AB=(Colorectal neoplasms)) OR AB=(intestinal polyps) OR ((((((((AB=(malign*)) OR AB=(neoplasm*)) OR AB=(carcinoma*)) OR AB=(cancer*)) OR AB=(neoplasm*)) OR AB=(carcinoma*)) OR AB=(tumor*)) OR AB=(tumour*)) OR AB=(polyp*) AND 6 (((((((AB=(colon)) OR AB=(rectum)) OR AB=(rectal)) OR AB=(colorectum)) OR AB=(colorectal)) OR AB=(large bowel)) OR AB=(large intestine)) OR AB=(gut)	No filter	15 articles	10. April

Appendix 2

Examples of questions from the questionnaires



Høyde og vekt

Hvor høy er du? ..... cm

Hvor mye veier du i dag? ..... kg

Kosthold

Vi er interessert i å få kjennskap til hvordan kostholdet ditt er **vanligvis.** Kryss av for hvert spørsmål om hvor ofte du **i gjennomsnitt siste året** har brukt den aktuelle matvaren, og hvor mye du pleier å spise/drikke hver gang.

Hvor mange glass melk drikker du vanligvis av hver type? (Sett ett kryss pr. linje)

	aldri/ sjelden	1-4 pr. uke	5-6 pr. uke	1 pr. dag	2-3 pr. dag	4+ pr. dag
Helmelk (søt, sur)	☐	☐	☐	☐	☐	☐
Lettmelk (søt, sur)	☐	☐	☐	☐	☐	☐
Skummet (søt, sur)	☐	☐	☐	☐	☐	☐

Hvor mange kopper kaffe drikker du vanligvis av hver sort? (Sett ett kryss for hver linje)

	aldri/ sjelden	1-6 pr. uke	1 pr. dag	2-3 pr. dag	4-5 pr. dag	6-7 pr. dag	8+ pr. dag
Kokekaffe	☐	☐	☐	☐	☐	☐	☐
Traktekaffe	☐	☐	☐	☐	☐	☐	☐
Pulverkaffe	☐	☐	☐	☐	☐	☐	☐

Hvor mange glass juice, saft og brus drikker du vanligvis? (Sett ett kryss for hver linje)

	aldri/ sjelden	1-3 pr. uke	4-6 pr. uke	1 pr. dag	2-3 pr. dag	4+ pr. dag
Appelsinjuice	☐	☐	☐	☐	☐	☐
Saft/brus med sukker	☐	☐	☐	☐	☐	☐
Saft/brus sukkerfri	☐	☐	☐	☐	☐	☐

Hvor ofte spiser du yoghurt (1 beger)? (Sett ett kryss)

☐ aldri/sjelden ☐ 1 pr. uke ☐ 2-3 pr. uke ☐ 4+ pr. uke

Hvor ofte har du i gjennomsnitt siste året spist kornblanding, havregryn eller müsli? (Sett ett kryss)

☐ aldri/nesten aldri ☐ 1-3 pr. uke ☐ 4-6 pr. uke ☐ 1 pr. dag

Hvor mange skiver brød/rundstykker og knekkebrød/skonrokker spiser du vanligvis?
(1/2 rundstykke = 1 brødskive) (Sett ett kryss for hver linje)

	aldri/ sjelden	1-4 pr. uke	5-7 pr. uke	2-3 pr. dag	4-5 pr. dag	6+ pr. dag
Grovt brød						
Fint brød						
Knekkebrød o.l.						

Nedenfor er det spørsmål om bruk av ulike påleggstyper. Vi spør om hvor mange brødskiver med det aktuelle pålegget du pleier å spise. Dersom du også bruker matvarene i andre sammenhenger enn til brød (f. eks. til vafler, frokostblandinger, grøt), ber vi om at du tar med dette når du besvarer spørsmålene.

På hvor mange brødskiver bruker du? (Sett ett kryss pr. linje)

	0 pr. uke	1-3 pr. uke	4-6 pr. uke	1 pr. dag	2-3 pr. dag	4+ pr. dag
Syltetøy og annet søtt pålegg						
Brun ost, helfet						
Brun ost, halvfet/mager						
Hvit ost, helfet						
Hvit ost, halvfet/mager						
Kjøttpålegg, leverpostei						

Videre kommer spørsmål om fiskepålegg.
På hvor mange brødskiver pr. uke har du i gjennomsnitt siste året spist? (Sett ett kryss pr. linje)

	0 pr. uke	1 pr. uke	2-3 pr. uke	4-6 pr. uke	7-9 pr. uke	10+ pr. uke
Makrell i tomat, røkt makrell						
Kaviar						
Annet fiskepålegg						

Hva slags fett bruker du vanligvis på brødet?
(Sett gjerne flere kryss)

☐ bruker ikke fett på brødet
☐ smør
☐ hard margarin (f. eks. Per, Melange)
☐ myk margarin (f. eks. Soft)
☐ smørblandet margarin (f. eks. Bremykt)
☐ Brelett
☐ lettmargarin (f. eks. Soft light, Letta)

Dersom du bruker fett på brødet, hvor tykt lag pleier du smøre på? (En kuvertpakke med margarin veier 12 gram).
(Sett ett kryss)

☐ skrapet (3 g) ☐ tynt lag (5 g) ☐ godt dekket (8 g)
☐ tykt lag (12 g)

Hvor ofte spiser du frukt? (Sett ett kryss pr. linje)

	aldri/ sjelden	1-3 pr. mnd	1 pr. uke	2-4 pr. uke	5-6 pr. uke	1 pr. dag	2+ pr. dag
Epler/pærer							
Appelsiner o.l.							
Bananer							
Annen frukt (f.eks. druer, fersken)							

– 4 –

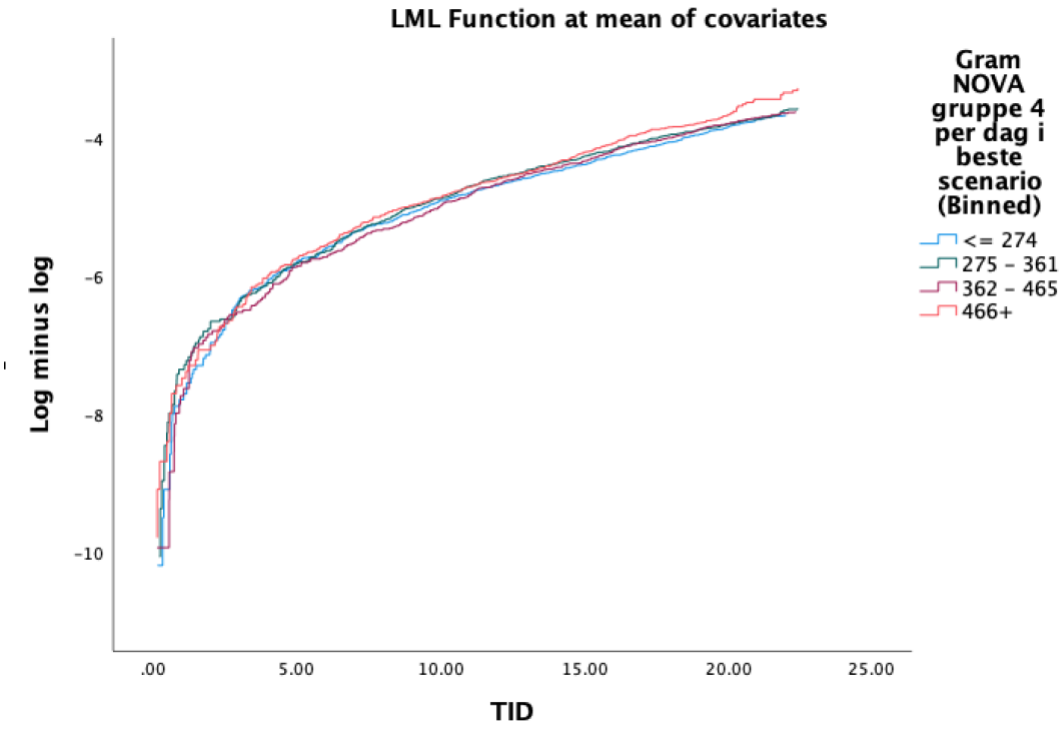
Appendix 3

Detailed overview of the Norwegian food groups

Norwegian food groups	Foods
Milk and dairy products	Milk and milk-based drinks Yogurt Heavy cream, sour cream, cream substitutes Cheese
Egg	Egg, raw Egg, cooked
Meat and poultry	Poultry Lamb and mutton Beef and veal Pork Various meat products Lamb, beef, pork (cooked) Dishes with poultry and meat
Fish and shellfish	Fish and fish products Dishes with fish, shellfish, etc. Shellfish, fish offal
Grains, baked goods, seeds, and nuts	Grains, rice, pasta Cereal, breakfast cereals Bread products, homemade Bread products, industrial made Crispbread, etc. Cookies, sweet biscuits, waffled, etc. Other cakes, etc. Nuts, almonds, and seeds
Potatoes, vegetables, fruits, and berries	Potatoes Vegetables Legumes Fruit and berries Herbs and spices
Chocolate and other sweets	Sugar, honey, and sweet spreads Chocolate and other sweets
Margarine, butter, oils etc.	Margarine and butter Cooking oil, fat for frying, etc. Mayonnaise, dressing, etc. Fish oil
Beverages	Water, coffee, tea Juice, soda, etc. Alcoholic beverages
Various dishes, products, and ingredients	Pizza, pai, taco, etc. Porridge Soups, stews, bases Dessert, ice cream and side dishes Snacks Vegetarian products and dishes Various ingredients Powder, dry products

Appendix 4

Log minus log plot and interaction between UPF and time



Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)
T_COV_	.005	.004	1.895	1	.169	1.005
Gram NOVA gruppe 4 per dag i beste scenario (Binned)	-.148	.051	8.382	1	.004	.862