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Is there a different effect of excess body weight on cancer risk in type 1 and type 2 endometrial cancer?

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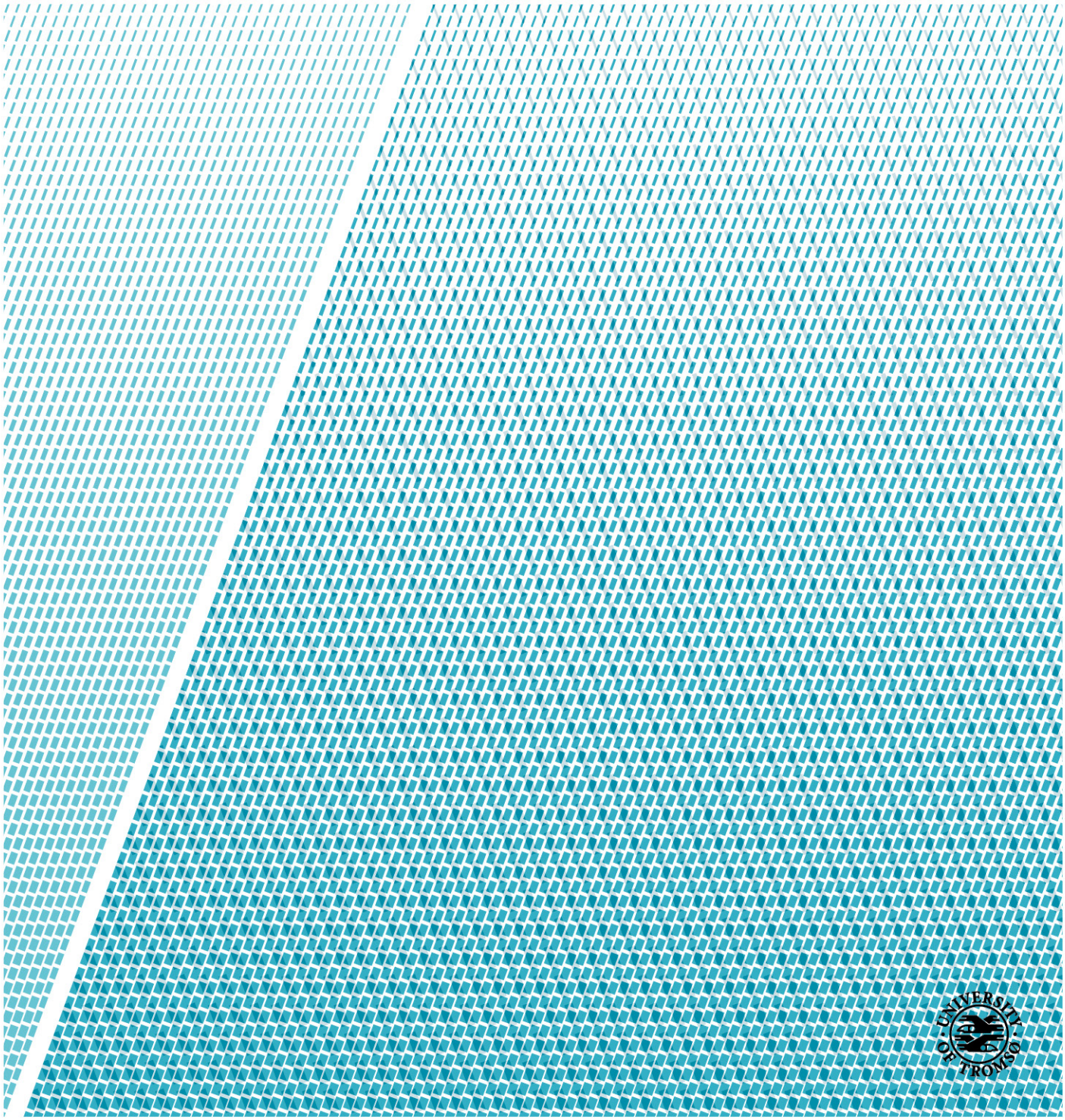

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Abstract

Background: Endometrial cancer (EC) is the fifth most common type of cancer in women worldwide being responsible for 4.8% of all cancers in women. From large cohort studies there is consistent evidence for a positive association between excess body weight and different cancer types. Women with excess body weight stands out as having a particularly high relative risk for EC. Excess body weight is an increasing health problem worldwide and a deeper understanding of the association between excess body weight and EC subtypes is needed.

Objective: The main aim of this master's thesis is to assess if the effect of excess body weight on cancer risk is different in type 1 and type 2 EC.

Material and methods: Data from the Norwegian Women and Cancer (NOWAC) study, a national population-based cohort study in Norway, was used. Participants were followed from 1991 until 2016. Cox proportional hazard regression was used to explore the effect of body mass index (BMI) on the risk of type 1 and type 2 EC. To evaluate whether the association between excess body weight and EC varied between type 1 and type 2 EC, the effect estimates were compared using a heterogeneity test, which follows an approximate chi square distribution.

Results: For every increase of two body mass index (BMI) units, the risk of type 1 EC increased significantly by 21% (HR=1.21, 95% CI: 1.71, 1.25). For type 2 EC, the corresponding number was 11% (HR=1.11, 95% CI: 1.03, 1.20). Women who were overweight (BMI $\geq$ 25.0 kg/m^2) had 35% increased risk of type 1 EC (HR=1.35, 95% CI: 1.07, 1.69) and women with obesity had a 3-fold higher risk of type 1 EC (HR=3.00, 95% CI: 2.25, 3.88) compared to women with normal weight. Women who were overweight had no increased risk of type 2 EC (HR=1.05, 95% CI: 0.70, 1.58), whereas women with obesity had a 95% higher risk of type 2 EC (HR=1.95, 95% CI: 1.15, 3.31), compared to women with normal weight. The associations between BMI and EC risk did not differ significantly between the two subtypes.

Conclusion: In summary, BMI was associated with type 1 and type 2 EC in a dose response manner. The association between excess body weight and type 1 and type 2 EC does not significantly differ according to subtypes, however, the association seems to be stronger in type 1. This could support the idea that estrogen plays a more important role in the development of type 1 ECs compared to type 2 EC.

Abbreviations

BMI	Body mass index
CI	Confidence interval
CUC	Cancer of the uterine corpus
DM	Diabetes mellitus
EC	Endometrial cancer
FIGO	International federation of obstetrics and gynecology
HR	Hazard ratio
HUNT study	The Nord-Trøndelag health study
IARC	International agency for research on cancer
ICD	International classification of diseases and related health problems
ICD-O	International classification of diseases for oncology
IUD	Intrauterine device
MOTNAC	Manual of tumor nomenclature and coding
MHT	Menopausal hormone therapy
NOS	Not otherwise specified
NOWAC study	Norwegian women and cancer study
OC	Oral contraceptives
PA	Physical activity
RR	Relative risk
SD	Standard deviation
WCRF	World cancer research fund

WHO	World Health Organization
Y	year

1 Introduction

Since 1950, the incidences of cancer of the uterine corpus (CUC) have increased, especially in high-income countries (1, 2), including North America and several countries in Europe (3). Low-income countries have low incidences of CUC and in countries undergoing the transition from low- to high-income economies an increasing trend of CUC has been observed (4). The worldwide estimated age-standardized incidence rate for CUC was 8.3 per 100 000 in 2012 (5).

In Norway, a constant increasing trend in CUC incidence was also observed until 2011, however after 2011 the increasing trend flattened out slightly (6). The age-adjusted incidence rate per 100 000 was 6.3 in 1953 and 16.5 in 2011 (2, 6). The increase in this period was most pronounced in postmenopausal women older than 55 but was also present in premenopausal women in the last decades of the observation period (2). Obesity is a well-known risk factor for CUC and the increasing prevalence of overweight and obesity may explain parts of the increasing risk in CUC (7). Another reason may be temporal changes in reproductive behavior and changes in composition of menopausal hormone therapy (MHT), as established risk factors are related to an imbalance between estrogen and progesterone exposure (8).

1.1 The definition of obesity

The World Health Organization (WHO) defines obesity as a condition of abnormal or excessive fat accumulation in adipose tissue so that health may be impaired (9). A common anthropometric measure of body composition is body mass index (BMI; formerly called Quetelet´s index), which is defined as the weight in kilograms divided by the square of the height in meters (kg/m^2) (9). Garrow et al showed in 1985 that BMI is a fairly good estimate of body fatness and obesity compared to other measures, for instance body density, total body water and total body potassium (10). The WHO definition for overweight in adults is BMI ≥ 25 kg/m^2 and for obesity BMI ≥ 30 kg/m^2 (11). In this master's thesis the WHO definition for overweight (25 kg/m^2 ≤ BMI < 30 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) will be used. To describe the group of overweight and obese participants combined, the term "excess body weight" will be used.

1.2 Prevalence and trends in obesity

Obesity is an increasing health problem worldwide. The WHO states that the prevalence of obesity worldwide has nearly tripled since 1975 (11) and reached 39% in adults aged > 18 years in 2016. Even more alarmingly; the prevalence of excess body weight among children and adolescents has risen dramatically since 1975, from 4% in 1975 to over 18% in 2016

(11). This will further heighten the epidemic of obesity in adults, since childhood obesity generally persists into adulthood, with all the associated health risks (9). Ward et al (12) showed in a simulation that about 50% of all children with obesity will also be overweight or obese as adults. This will be an enormous health challenge for the next generation.

The trend in excess body weight prevalence in Norway is the same as in most countries in the world. Data from the Global Health Observatory (WHO´s gateway to health related statistics) (13) shows that the prevalence of excess body weight among adults (age > 18 years) is increasing in Norway. In a national survey performed by Statistics Norway in 2015, the prevalence of self-reported overweight was 20% for men and 12% for women and the prevalence of obesity reached 13% for men and 11% for women in 2015 (age-standardized estimate) (14). The prevalence differed widely in different parts of the country. A longitudinal analysis of repeated cross-sections (1994-2008) of the population in Tromsø, Northern Norway, showed that the prevalence of obesity is increasing in the population there, and reached 20.9% in men and 18.5% in women in the years 2007/08. The observed increase was strongest among the youngest age groups (15, 16). Another population-based study in Norway, the Nord-Trøndelag Health Study (The HUNT Study) (17), also showed significant increasing prevalence of excess body weight during the observation period from 1984-2008. The greatest increase was seen in the age group of 20-29 years. All participants underwent a clinical examination where weight was measured. The prevalence for overweight was 52.4% in men and 37.7% in women and the prevalence of obesity was 22.1% in men and 23.1% in women in the last survey in 2006/2008. These results were generated from three cross-sectional surveys (17). In contrast to the national survey, where weight was self-reported, both studies, the Tromsø study and the HUNT study, used weight information from clinical examinations. Both regions, Tromsø (Northern Norway) and Nord-Trøndelag (Trøndelag), reported a higher prevalence of excess body weight than the average of the country in the national survey done by Statistics Norway (14).

1.3 Obesity and cancer risk

Obesity increases the risk of several important non-communicable diseases such as cardiovascular diseases, diabetes, musculoskeletal disorders and some cancers (11). From large cohort studies, there is consistent evidence of a positive association between obesity and increased risk of 12 to 13 cancer types (18, 19). However, some disagreements exists: Lauby-Secretan et al (18) mention 13 cancers in the International Agency for Research on Cancer (IARC) report from 2016, including endometrial cancer (EC), postmenopausal breast cancer, ovarian cancer, esophageal adenocarcinoma, gastric cardia cancer, colorectal cancer, liver and

gallbladder cancer, pancreatic cancer and renal-cell kidney cancer, meningioma, thyroid cancer and multiple myeloma (18) (random order). In the latest report from the World Cancer Research Fund (WCRF) from 2018 (19), the expert group mentions seven cancer types with convincing evidence and five cancer types with probable evidence of an association with excess body weight. The seven cancer types with convincing evidence included esophageal adenocarcinoma, pancreatic cancer, liver cancer, colorectal cancer, kidney cancer, postmenopausal breast cancer and EC.

The global burden of all cancers attributable to high BMI was estimated to be 3.6% by Arnold et al in 2012 (20). The population attributable fraction for CUC due to high BMI, was estimated to be 4% (20). Another study in Europe estimated that 60% of all new CUC cases each year were attributed to excess body weight (21). Thus, CUC stands out as having a particularly strong association with obesity. Shaw et al (22) found in over twenty cohort studies that the overall pooled risk estimate for CUC in relation to obesity was 2.65 (95% CI: 2.42 to2.90). Severe obesity was associated with a 4.8-fold increase (overall pooled risk estimate 4.84, 95% CI: 3.92 to 5.97) in CUC risk compared to women with normal-weight (22).

1.4 Definition of CUC and EC

CUC and EC are often used synonymously; one can also find the name “cancer of the corpus uterus”, “cancer of the uterus” or “uterine corpus tumors”. A clear definition of these terms is essential. The uterus is the reproductive organ in a woman, in which the fetus grows and develops when the woman is pregnant. It has two parts: the upper part is called the “corpus uterus” (or in English “the body of the uterus” or more popularly “the womb”) and the lower part is named the “cervix uteri” (“Cervix” in Figure 1). Tumors arising from the body of the uterus are called CUC and tumors arising from the cervix uteri are called “tumors of the uterine cervix” or “cervical cancer” (see Figure 1).

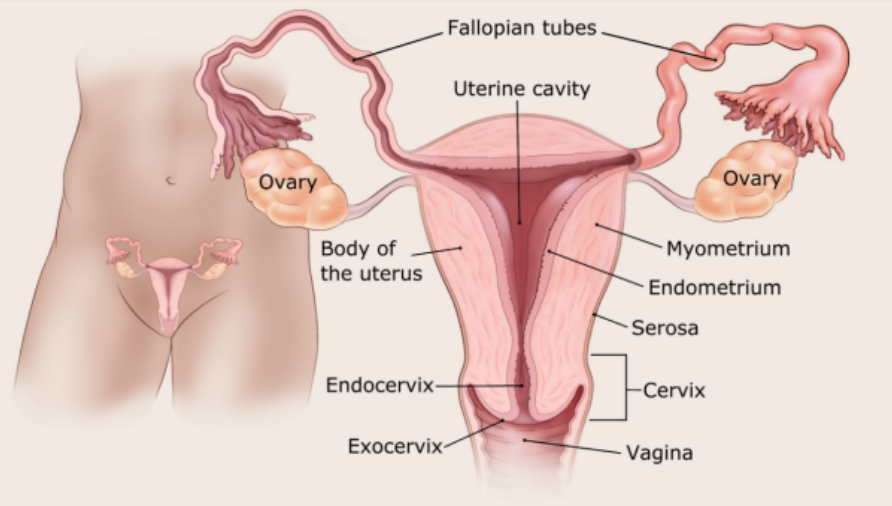

Figure 1 - Anatomy of the uterus
© American cancer society (23)

Depending on which cell type the tumor originates from, it can be divided into different groups: epithelial, mesenchymal, mixed epithelial/mesenchymal and trophoblastic tumors. Epithelial tumor cells in the endometrium, the inner lining of the uterus, are defined as EC lesions. EC accounts for the majority of all CUC (24). Therefore the name EC is often used to describe all CUC and hence is often used synonymously. Mesenchymal tumors and mixed epithelial/mesenchymal tumors arise from the middle layer of the body of the uterus called the myometrium. These tumors are, by definition, not ECs, but are usually referred to as EC as described above. Trophoblastic tumors are a group of pregnancy-related tumors in the corpus uteri, however this is a specific disease with its own identification code and thus is not included when CUC are discussed. In this master's thesis, CUC refers to all tumors arising from the body of the uterus and EC refers only to cancers arising from the endometrium of the body of the uterus.

1.5 WHO classification systems of CUC and EC

The International Classification of Disease (ICD) is a medical classification list released by the WHO, which defines all diseases, disorders, injuries and other health conditions in order to harmonize health information. There are two coding systems that describe a specific tumor. ICD-10 is the 10th revision and was completed in 1992 (25). All neoplasms are coded by their anatomical site of origin. This is also called the topographical code. For example all neoplasms of the corpus uteri are coded with C54 (see Appendix A for more detailed ICD-10 classification of malignant neoplasm of the corpus uteri depending on its anatomical origin). The International Classification of Disease for Oncology ICD-O-3 (the 3rd revision available since 2000) (26) is a domain-specific oncological extension of the ICD-10 coding system This

classification code is widely used by cancer registries and is called the morphological code. It contains six digits and describes the histology, the behavior (malignant or benign) and the histological grading of the tumor. The structure of the morphological code is as follows: the first four digits describe the histology of the tumor, the 5th digit indicates the dignity of the tumor (behavior code) and the 6th digit describes the histological grading and differentiation of the tumor. The differentiation of a tumor (26) describes to what extent the histology of the tumor resembles the normal tissue from which it arises. The degree of differentiation is often described as "well", "moderate" or "poorly", where well differentiated means that it resembles the normal tissue a lot (Grade 1) and "poorly" means that it resembles the normal tissue very little (Grade 3). "Undifferentiated" or "anaplastic" tissue have nothing in common with normal tissue and correspond usually to Grade 4 (26). Poorly differentiated tumors are more aggressive than well differentiated. The significance of the two last digits (the behavior code and the histological grading code) are shown in Table 1 and 2. Adapted to the endometrial tissue the grading of ECs has its own specific denomination based on the percentage of solid (non-squamous) growth and is in three categories. The definition of the specific grading for ECs is shown in parenthesis in Table 2 (27).

Table 1 - Behavior code (5th digit) WHO adapted †

_ _ _ _/ 0	Benign
_ _ _ _/ 1	Uncertain whether benign or malignant
_ _ _ _/ 2	In situ; non-invasive
_ _ _ _/ 3	Malignant, primary
_ _ _ _/ 6	Malignant , metastatic *
_ _ _ _/ 9	Malignant, uncertain whether primary or metastatic *
	* not used by cancer registries

† (26)

Table 2 - Code for histological grading and differentiation (6th digit) WHO adapted †

_ _ _ _/ _ 1	Well differentiated; differentiated, not other specified (NOS) (EC: <5% of solid growth)
_ _ _ _/ _ 2	Moderately differentiated; intermediate differentiation (EC: 5% - <50% of solid growth)
_ _ _ _/ _ 3	Poorly differentiated (EC: > 50% of solid growth)
_ _ _ _/ _ 4	Undifferentiated; anaplastic
_ _ _ _/ _ 9	Grade or differentiation not determined

† (26)

In Appendix B an adaption from the official WHO classification for the different subtypes of CUC (C54) and their histological codes from ICD-O-3 (27) is showed.

1.5.1 **Type 1 and type 2 EC**

Introduced by Bokhman in 1983 (28), EC have been divided into two main subtypes (type 1 and type 2 EC) on the basis of differences in clinical and histological observations (28-30). This dualistic model, which concerns only EC, describes in general two pathways of carcinogenesis of EC. Historically, type 1 EC was thought to follow the "classic" pathway, where indolent tumors develop from endometrial hyperplasia (cell proliferation in the endometrial layer) in an estrogen-rich milieu, whereas type 2 ECs represent the "alternative" pathway in which aggressive tumors arise from an atrophic endometrium (decrease of tissue in the endometrial layer) and seems to be less associated with an excess of estrogen (31). About 80% of all ECs are classified as type 1. These are mostly endometrioid adenocarcinomas, which are a subgroup of type 1 EC (see Appendix C for classification of CUC subtypes). Endometrioid adenocarcinomas have good prognosis (unless high-grade forms), whereas type 2 EC are more rare and occur in about 20% of EC cases. Type 2 ECs are often serous and clear cell carcinomas with poorer prognosis (29). This dualistic model has been discussed a lot and new methods like immunohistochemical analysis and genetic analyses challenge this simplistic categorization into type 1 and type 2 EC. It is often not clear to which group a tumor, especially grade 3 of type 1 EC, belongs (29, 30, 32) and in several studies about type 1 and type 2 ECs and obesity, different classification has been used.

Nevertheless, the assessment of the classification of EC is important in the clinical practice. It is used as a prognostic factor and as a criterion to guide the treatment of the cancerous disease. The management of treatment depends on different factors like age, stage indicated by the FIGO (Federation of Gynecology and Obstetrics) Classification, lympho-vascular invasion, and histological subtype and grade. The decision as to whether if a simple hysterectomy or a full staging (including lymph node dissection) is undertaken or if an adjuvant chemotherapy and radiotherapy is needed or not, depends on these factors (33-35).

1.6 Risk factors

1.6.1 Risk factors for CUC and EC

Age, high BMI, metabolic syndrome, diabetes mellitus (DM) and polycystic ovarian syndrome increase the risk of CUC and EC (4, 36-42). Intake of coffee and tea, smoking and physical activity are known to decrease the risk of CUC and EC (4, 43-47). Reproductive factors like early menarche, late menopause, nulliparity, increased lifetime number of menstruations and chronic anovulation leads to prolonged endogenous exposure to estrogen and increases the risk of CUC and EC (48, 49). The effect of exogeneous hormone use is similar: long-term exposure to unopposed estrogens and high postmenopausal concentration of estrogens through medication increases the CUC and EC risk (36, 50-53). However, the use of oral contraceptives pills (OC) and intrauterine devices (IUD; levonorgestrel) decrease the risk of EC (54, 55). Tibolon, a synthetic steroid derivate and Tamoxifen, a chemotherapeutic substance, increases the risk of CUC and EC (51, 56-58).

1.6.2 Risk factors for type 1 and type 2 ECs

The association between excess body weight and type 1 and type 2 of ECs has been investigated in several studies. Setiawan et al made a pooled analysis in 2013 (8), in which individual results from 10 cohorts and 14 case-control studies were included. The results showed that high BMI had a greater effect on type 1 EC, but was also a risk factor for type 2 EC. In Norway, two previous studies have investigated the association between obesity and subtypes of EC (59, 60). Bjørge et al (59) used data about height and weight measurements from several health surveys in Norway collected between 1963 and 2001. In total 1036909 women were included and followed over a period up to 41 years (average follow-up 25 years and 25 million person-years). With linkage to the Cancer Registry of Norway they identified 9227 women with incident CUC (7164 with type 1 EC, 992 with type 2 EC and 837 with either sarcomas or mixed tumors and others). An increased relative risk (RR) was seen in both types of EC, but was more pronounced in type 1 EC. They could not control for possible

confounder like parity, diabetes, use of OC or MHT. The second study was conducted by Lindemann et al (60) in 2009. This prospective study (HUNT-I Study) in Nord-Trøndelag County in Norway included 36755 women aged 20 years and older between 1984 and 1986. During the period of follow-up 263 women developed CUC and 224 of them were classified as EC, among whom 166 were classified as endometrioid adenocarcinomas (subgroup of type 1 EC). When comparing risk estimates of excess body weight in endometrioid adenocarcinomas, overall EC and CUC, the association was strongest in endometrioid adenocarcinomas but also present in the two other groups. This study could adjust for prevalent diabetes, smoking and physical activity, but no information about reproductive factors or intake of OCs or MHT was available. Several other studies concluded that they had not enough cases to assess the association between excess body weight and risk type 2 ECs (31, 61, 62).

Other factors that increase/decrease the risk for type 1 EC includes sugar-sweetened beverages and two rare genetic predispositions (Lynch syndrome and Cowden syndrome (63-66)), whereas coffee consumption was negatively associated with EC type 1, particularly among obese women (67). Type 2 EC was associated with high intake of folate, vitamin B2 and vitamin B6 (68). Type 2 EC is more often diagnosed in older women, in non-white women and in women with postmenopausal status (69). Furthermore women with type 2 EC, which were compared to women with type 1 EC, were more often multiparous, current cigarette smokers or had a history of breast cancer diagnosis (which was treated with tamoxifen) (69).

1.7 Endometrial carcinogenesis in relation to excess body weight and ECs

Three mechanisms underlying the association between excess body weight and cancer have been suggested: alteration of sex hormone metabolism, insulin resistance (increased insulin level) and systemic inflammation (7, 29, 70-72). For ECs an excess amount of estrogen produced in fat tissue has been proposed as the main mechanism. Kaaks et al (73) showed that the risk of CUC and EC is increased in women with high plasma level of bioavailable estrogen or low plasma level of progesterone. This idea of carcinogenesis by an excess of "unopposed estrogens" (73) is supported by the risk factors mentioned in the section before: early menarche, late menopause, parity and use of exogenous estrogens for OC and MHT (69). In regards to the influence of estrogens on CUC and EC it is important to distinguish between CUC and EC. The endometrium is the layer of the corpus uterus which is receptive to estrogens (19). As the two different subtypes of EC arise in two different environments

(endometrial hyperplasia versus endometrial atrophy), it is of importance to investigate differences in risk factors between type 1 and type 2 EC. The hypothesis that an excess amount of estrogen leads to EC, will be strengthened if a differential risk profile related to excess body weight could be found. Lax et al showed already in 1998 (74) that estrogen and progesterone receptors are only expressed in type1 EC. Several studies showed also an association between excess body weight and type 2 EC although to a minor degree (8, 59, 60). These results challenge the hypothesis of the estrogen-related pathway; either the risk factors associated with estrogen-driven proliferation are also important for type 2 tumors, or other mechanisms than those involving estrogen are more important and can at least partly explain the association between body fatness and EC risk. One pathway of carcinogenesis does not necessarily exclude another pathway. Several theories of carcinogenesis can coexist and the development of ECs could be multifactorial with more or less pronounced mechanisms in each subtype. Investigating the difference in risk factors between type 1 and type 2 EC will contribute to a deeper understanding of carcinogenesis of these two types. As increasing incidences of excess body weight is expected worldwide, this knowledge is important in order to prevent EC.

1.8 Objective

The main aim of this master's thesis is to assess if the effect of excess body weight on cancer risk is different in type 1 and type 2 EC.

2 Material and methods

2.1 Study population

The Norwegian Women and Cancer (NOWAC) study is a national population-based cohort study in Norway, which was initiated in 1991 (75). NOWAC is representative for the female population of Norway born during the years 1927-1965. Over 320 000 women aged 27 to 65 years have been randomly sampled from the Norwegian Central Person Register, which contains information on all Norwegian inhabitants. Each inhabitant can be identified with a unique identity number, which allows linkage to national registries, such as the Cancer Registry of Norway and the National Registry of Norway. The selected women were invited to participate in the study by completing a detailed questionnaire regarding lifestyle, diet, health and use of medicines and exogeneous hormones such as OC and MHT. As shown in Figure 1 about 172000 women completed the first questionnaire in the period 1991-2007 (red boxes). Most women were followed-up after a period of 6 to 13 years if they agreed to get a subsequent questionnaire. Some women have completed up to 4 questionnaires since 1991.

The overall response rate in NOWAC was 53% (13-15). The external validity of the NOWAC study has been investigated in different studies (76-78) and has been proven to be good.

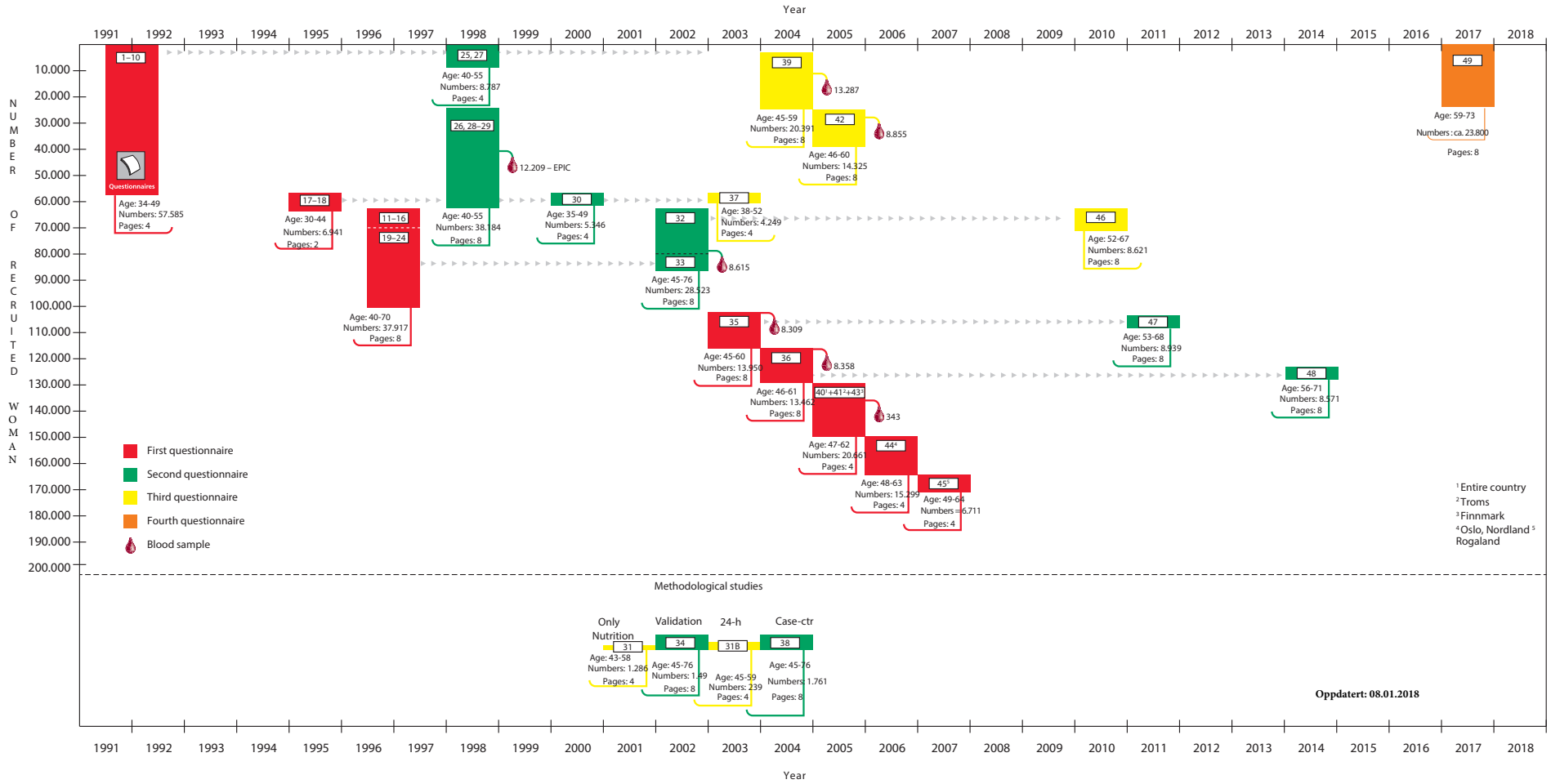

Figure 2 - Timeline of the questionnaires answered by the participants in the NOWAC study

2.2 Ethical considerations

The NOWAC Study has been approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate and all included participants gave a written informed consent (46). The data used in this master's thesis were anonymized and no information about the identity number of the participants was available for researchers. The key, which was used to link the personal identification number to the data of the cohort and the Cancer registry of Norway were kept at Statistics Norway, an external and independent agency.

2.3 Inclusion and exclusion criteria

172 472 women completed the first questionnaire and were qualified for inclusion in the study. Information from all completed baseline questionnaires in the period between 1991 to 2007 (figure 1: all red boxes) were used. Women who died or emigrated before the start of follow-up of the study (n=31), as well as those with prevalent cancer diagnosis (first primary cancer except non-melanoma skin cancer) at the start of follow-up (n=6681) were excluded from this study. Women who had missing information on height and/or weight at baseline were also excluded (n=4124). Women with implausible information about the age at menarche (< 8 year or > 20 year), age at first birth (< 12 years) and age at menopause (< 25 year or > 60 years) were excluded too (n=108) as well as participants with implausible values of both height and weight (height< 100 cm or > 230 cm; weight < 30 kg or > 200 kg) (n=4). Further women with known hysterectomy (n=9992) were excluded too.

The final sample included 151 532 women from whom completed information about BMI at the baseline was available. Figure 2 summarises the exclusion procedure described above.

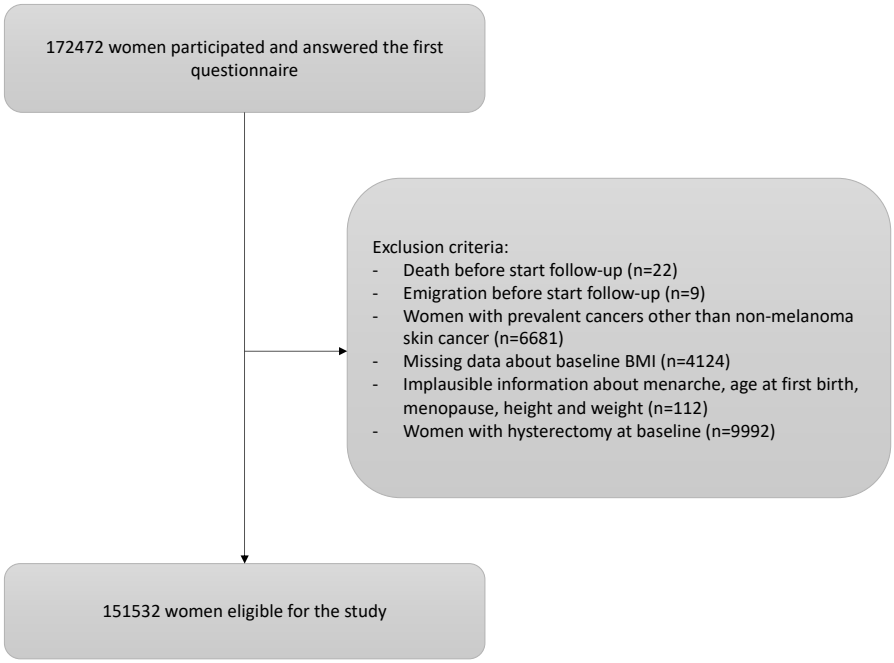

Figure 3 - Flowcharts of *study participants*

2.4 Outcome variable: type 1 and type 2 EC

Incident CUC cases were identified through linkage of the NOWAC data to data from the Cancer Registry of Norway. The diagnosis of CUC was defined by the ICD-10 topographical code C54 (=primary neoplasm of the uterine corpus). Only first primary CUC were included. The cancer registry provides also the ICD-O-3 morphological codes for all identified cases of CUC. With these histology codes it was possible to define EC and subtypes. The FIGO Cancer report about cancer of the corpus uteri (79) and the WHO Classification of Tumors (27) were the main sources of information for the classification. Further information on classification was based on different reviews and articles from pathologists doing research in the field of ECs (32, 33, 80, 81). Several previous studies, which assessed subtypes of EC were reviewed and their classification of type 1 and type 2 EC were compared (Table 3) (8, 31, 59, 60, 62, 68, 82, 83).

Table 3 - Morphological code (ICD-0-3) and its classification in type 1 and type 2 EC in several studies

	ICD-O-3	Setiawan (8)	McCullough (31)	Bjørg (59)	Uccella (68)	Yang (62)	Lindemann (60)	Amankwah (82)	Stevens (83)	Borch (46)
Epithelial tumours and related lesions										
Endometrial carcinoma										
Endometrioid adenocarcinoma	8380/3	Type 1	Type 1	Type 1	Type 1	Type 1	endometrioid	Type 1	Type 1	Type 1
Adenocarcinoma with squamous metaplasia	8570/3	Type 1	Type 1	Type 1	Type 1	Type 1	endometrioid	Type 1	Type 1	Type 1
Villous adeno Ca	8262/3			Type 1	Type 1		endometrioid		Type 1	
Endometrioid adenofibroma	8381/3	Type 1	Overall							Type 1
Endometrioid adenocarcinoma, secretory variant	8382/3	Type 1	Type 1	Type 1		Type 1	endometrioid		Type 1	Type 1
Endometrioid adenocarcinoma, ciliated cell variant	8383/3	Type 1	Type 1	Type 1		Type 1	endometrioid		Type 1	Type 1
Mucinous adeno Ca	8480/3	?		Type 1	Type 1	Type 1	EC	Type 1		
Mucin-producing adeno Ca	8481/3	?		Type 1		Type 1	EC			
Mucinous adenoCa, endocervical type	8482/3	?		Type 1		Type 1	EC			
Serous cystadenocarcinoma, NOS (C56.9)	8441/3	Type 2	Type 2	Type 2	Type 2	Type 2	EC	Type 2		
Clear cell adenocarcinoma NOS	8310/3	?	Type 2	Type 2	Type 2	Type 2	EC	Type 2	Type 2	
Mixed cell adenocarcinoma	8323/3	Type 2			Type 2	Type 2	EC	Type 2		
Squamous cell Ca NOS	8070/3		Type 2			Type 2	EC	Type 2	Type 2	
Transitional cell carcinoma	8120/3						EC			
Small cell carcinoma, NOS	8041/3				Type 1	Type 2	EC			
Undifferentiated carcinoma, NOS	8020/3						EC			
Others										
Mucoepidermoid tumor	8430/3									
Mullerian mixed tumor	8950/3		Overall		Type 2					
Neoplasm, malignant	8000/3				Type 1	Overall				
Carcinoma, NOS	8010/3				Type 1	Overall				
Papillary carcinoma, NOS	8050/3				Type 2	Overall				
Adenocarcinoma in adenomatous polyp	8210/3				Type 1	Type 1				
Papillary adeno Ca, NOS	8260/3				Type 2	Overall		Type 2		
Adenocarcioma in tubulovillous adenoma	8263/3				Type 1					
Mesodermial mixed tumor	8951/3				Type 2					
Cystadenocarcinoma, NOS	8440/3					Type 2				
Squamous cell carcinoma, keratinizing, NOS	8071/3					Type 2				
Squamous cell carcinoma, microinvasive	8076/3					Type 2				
Adenocarcinoma, NOS	8140/3	Type 1			Type 1					Type 1
Adenosquamous carcinoma	8560/3	Type 1								Type 1
Neuroendocrine carcinoma, NOS	8246/3									
Combined small cell carcinoma	8045/3									
		†‡	†				*		†	

NOS = Not other specified

† Endometrioid carcinoma Grade 3^{+} classified as type 2 EC

* MOTNAC before 1993, ICD-O-2 after 1993

‡ ? = classification is unclear (included in the analysis about type 1 and type 2 EC, but no information about classification)

Based on a review of the previous literature and communication with pathologists, the following classification was used in this master's thesis: endometrioid adenocarcinoma (ICD-O3 code: 8380/3) and its secretory variant (8382/3), adenocarcinoma with squamous differentiation (8570/3), adenosquamous carcinoma (8560/3), mucin-producing adenocarcinoma (848173) and mucinous adenocarcinoma (8480/3) were grouped as type 1 tumours if their grade was 1 or 2. If their grade was 3 or 4, they were coded as type 2 EC. Grade 9's (unknown) of these histological subtypes were excluded. Serous/papillary serous cystadenocarcinoma (8441/3 and 8460/3), small cell carcinoma NOS (8041/3), mixed cell adenocarcinoma (8323/3), clear cell adenocarcinoma NOS (8310/3), combined small cell carcinoma (8045/3) and adenocarcinoma with mixed subtypes (8255/3) were grouped as type 2 EC. Table 4 shows the final classification of ECs in type 1 and type 2 used in this master's thesis. In Appendix C, the classification of all CUCs is shown in detail.

Table 4 - Classification of ECs into type 1 and type 2

Type 1	Type 2
8380 (8380/31; 8380/32)	8380 (8380/33; 8380/34)
8382 (8382/31; 8382/32)	8382 (8382/33; 8382/34)
8480 (8480/31; 8480/32)	8480 (8480/33; 8480/34)
8481 (8481/31; 8481/32)	8481 (8481/33; 8481/34)
8560 (8560/31; 8560/32)	8560 (8560/33; 8560/34)
8570 (8570/31; 8570/32)	8570 (8570/33; 8570/34)
	8041 (8041/3x)
	8045 (8045/3x)
	8255 (8255/3x)
	8310 (8310/3x)
	8441 (8310/3x)
	8460 (8460/3x)
	8323 (8323/3x)

x means that every grade (1,2,3,4 and 9) was included.

2.5 Exposure variable: BMI

In the questionnaires, the participants were asked to recall their weight in kilogram and their height in centimetres, and from this information BMI was calculated. The accuracy of the self-reported information on weight and height in NOWAC has been validated in a study by Skeie et al. (76). That study showed that the discrepancies between self-reported and directly

measured BMI in women were small. Despite of under-reporting in the overweight and obese group, they concluded that the self-reported weight and height data provide a valid ranking of BMI for middle-aged Norwegian women.

In this study, BMI was analysed both as a categorical variable and as a continuous variable (per 2 kg/m^2 increase). Corresponding to WHOs definition of under- normal- and overweight and obese (84) four categories (kg/m^2) were created: <18.5 underweight, 18.5 to <25 normal weight, 25 to <30 overweight and ≥30 obese.

2.6 Covariates

Age was integrated as the timescale of the survival analysis. Thus, all risk estimates were automatically age-adjusted.

2.6.1 Lifestyle, nutrition, and education

Cigarette smoking at baseline was categorised into three groups (never, ever and current smoking). The variable DM was categorised in two groups (no, yes). The validity of self-reported DM has been analysed by Rylander et al (85) in a cross-sectional validation study: the positive predictive value of the questionnaire about DM type 2 was 83%. Physical activity (PA) level was reported on a 10-point scale from 1 to 10, with 1 being a very low and 10 being a very high PA level. The original data were regrouped into three categories of PA level (low, medium and high). Self-reported PA level has been validated by Borch et al (78) against objectives measure of PA level (8 minute step-test). The validation showed moderate correlation (Spearman´s rank correlation coefficient in the range of 0.36-0.46. $p<0.001$) and a linear trend. The correlation was evaluated to be valid to rank PA levels in a female Norwegian population. Coffee consumption was grouped into 4 groups based on reported frequency (≤1 to <4, ≥4 to <8, ≥8 cups/day). The food frequency questionnaire which was used to evaluate the coffee consumption was validated by 24-h recalls, which showed good validity with information on coffee consumption (Spearman´s rank correlation coefficient=0.82, 95% CI: 0.77, 0.86) (86). Education was categorised into three groups: < 10 years, 10-12 years and >12 years. A validation study from Lund et al (77) about the information of education in NOWAC showed only minor differences to the national register of education.

2.6.2 Reproductive factors and intake of hormones

Age at menarche was categorised into three groups: ≤ 12 years, 13-14 years and ≥ 15 years. To examine age at first full term pregnancy and parity, a new variable was created, which

combines these two variables: nullipara, age at first birth < 30 years and one child, age at first birth ≥ 30 years and one child, two or more children and age at first birth < 30 years and two or more children and age at first birth ≥ 30 years. The external validity of the variable parity in the NOWAC study has been proven to be good and there was no significant difference between responder and non-responder ($p<0.001$) (77). The variable menopausal status was created from information from the questionnaire about menstruation, age, hysterectomy and ovariectomy, age at menopause and MHT. Six groups were formed: premenopausal, perimenopausal, postmenopausal, unknown, hysterectomy/under 53 years old and MHT/under 53 years old. As women in the 5th group met the exclusion criterion "hysterectomy", they were excluded at the beginning. The group 4 and 6 was merged to one new group and was called "unknown". Thus, four groups were used in the analysis: premenopausal, perimenopausal, postmenopausal and unknown menopausal status. Waaseth et al (87) assessed the validity of the menopausal status categorisation by measuring plasma concentrations of sex hormone in a subsample of women and concluded that the NOWAC study questionnaires provide valid information on menopausal status among women who were 42 to 62 years old (87). Use of OC (never, ever) and use of hormonal IUD (never, ever) were also included in this study. MHT (never, ever) was used as covariate.

2.7 Statistical methods

Differences in demographics and lifestyle across BMI categories at baseline were assessed with one-way ANOVA, t-testing and chi-square. Cox proportional hazard regression was used to explore the effect of BMI on the risk of type 1 and type 2 EC while controlling for potential confounding variables. The follow-up started when the study participants completed the baseline questionnaire. Age was used as the timescale. Reasons for censoring during the observation time were: diagnosis of another cancer (first primary non-melanoma cancer), emigration or death of the participant, hysterectomy or end of follow-up (31st December 2016) – whichever came first. Only the subtype of interest (type 1 or type 2 EC) was counted as an event and all other cancer diagnoses (including the other subtypes of CUC) were censored. For instance, to explore the risk of type 1 EC, all women with type 2 EC, another CUC, or another primary cancer diagnosis were censored at the time of diagnosis. The result of a cox regression analysis is presented by hazard ratios (HR). A HR was considered significant, if its 95% confidence interval (CI) did not include 1, which corresponds to a p-value of <0.05.

Each covariate was first analysed separately with cox regression (Breslow method) assessing the association with type 1 or type 2 EC. In order to construct a multivariable cox regression

model, the "purposeful selection of covariates" described by Hosmer and Lemeshow (88) was used. Briefly, all covariates were initially tested in a univariate cox regression and were included in a multivariable regression model if the p-value was < 0.25. The remaining covariates were removed stepwise until all included covariates were significant ($p \leq 0.05$). At every step the change of the regression coefficient was registered and if it was more than 20%, the covariate was left in the multivariable model. Additionally a likelihood-ratio test was performed after every step between the full and the reduced model (when one or two covariates were excluded) to make sure that the two models did not differ significantly from each other. The covariates which did not enter the first multivariable cox regression model were finally refitted in the final model to make sure that they did not contribute significantly to the final model. The proportional hazards assumptions were tested with Nelson-Aalen plots and the Schoenfeld residual test. BMI was assessed both as categorical and continuous variable. To explore whether there was a linear trend across the BMI groups, values in every BMI group was replaced by the median value of its respectively BMI group. These new BMI values were tested in a cox regression as a continuous variable. Further analysis to detect interactions between the covariates were not performed, because of limited statistical power (there were only few cases in each category). To evaluate whether the association between excess body weight and EC varied between type 1 and type 2 EC, the effect estimates were compared using a heterogeneity test recommended by Wang et al (89) in an article about studying disease subtype heterogeneity (subsection on unconstrained models page 5 and 6).

In general, a two-sided p value of 0.05 or less was considered statistically significant. All statistical analyses were performed using STATA Version 15.1 (Stata Corp LLC, Texas, USA).

2.7.1 **Missing data**

Participants were excluded from the analysis if they had missing information on included variables. Hence complete case analysis was performed. Questions about the use of hormonal IUD was not included in every questionnaire as it was not introduced in Norway until 1994 (90). Thus, women who answered questionnaires before 1994, were classified as non-user of hormonal IUD. As the definition of use of IUD was "ever" or "never", we assumed that no women got an IUD after a CUC diagnosis and used the information from the second questionnaire regarding ever use of IUD as baseline information in order to minimize missing data for this variable.

2.7.2 Sensitivity analysis

One discrepancy in the classification of type 1 and type 2 EC across previous studies were related to the morphological code "8140/3". These tumors are called "adenocarcinoma, NOS", which means that additional information is needed to make a conclusion about the affiliation to type 1 or type 2 EC. However, further information about immunohistochemical analysis were not available from the Cancer Registry of Norway. Several other studies included these cases as type 1 EC. In this study, two sensitivity analyses were performed, in which different definitions of type 1 and type 2 EC were assessed. The first sensitivity analysis included all tumors with histological code "8140" as type 1 EC (all grade 3^+ were classified as type 2 EC, see Appendix E). The second sensitivity analysis included all type 1 EC with grade 3^+ as type 1 EC instead of type 2 EC (see Appendix G).

3 Results

3.1 Population characteristics

The study sample consisted of 151 532 women. Characteristics of the study subjects at baseline across the four BMI groups are shown in Table 5. The majority (63.8%) of the study subjects had normal weight, 2.1 % were underweight, 26.0% were overweight and 8.1% were obese. The mean age increased with increasing BMI and was 47.7 years in the group with normal weight, 51.4 years in the group with overweight and 52.2 years in the group with obesity. Participant with excess body weight were less often current smokers and were more often never smokers than women with normal weight. They were less often physically active, reported higher prevalence of DM and had lower coffee consumption. The education level was lower in the group with excess weight. Women with excess body weight had in general earlier menarche than women with normal weight. More women in the group with excess body weight were postmenopausal than women in the group with normal weight. Women with excess bodyweight used less often OC however they used MHT more often. All differences between BMI groups were statistically significant. There was one exception: there was no difference in use of IUD between the group with normal weight and the two groups with excess body weight.

Table 5 - Demographic characteristics of the study sample at baseline.

		N ‡	Underweight	Normal	Overweight	Obesity
Number of women, n (%)		151532	3265 (2.1)	96654 (63.8)	39350 (26.0)	12263 (8.1)
Incident CUC cases †	Overall n	1489	13	739	450	287
Incident CUC subtype, (%) *	Type 1 EC	935	69	60	62	70
	Type 2 EC	263	23	19	17	15
	Others	291	8	21	20	15
Characteristics at baseline						
Age	Mean age (SD)		45.2 (8.8)	47.7 (8.4)	51.4 (8.1)	52.2 (7.7)
Smoking %		149755				
	Never		27.3	33.9	36.1	37.6
	Ex		20.5	32.8	37.5	38.4
	Current		52.2	33.3	26.4	24.0
Physical activity %		139047				
	Low		25.1	20.1	29.4	44.9
	Medium		37.0	41.5	42.5	36.9
	High		37.9	38.4	28.1	18.1
Diabetes mellitus %		119773				
	Yes		1.22	1.06	2.66	9.26
Coffee consumption, cup/day %		105501				
	≤ 1		19.2	16.4	15.2	19.9
	>1 and < 4		28.9	32.8	32.7	31.8
	≥ 4 and < 8		32.5	37.0	39.7	36.0
	≥ 8		19.4	13.8	12.5	12.3
Education (y) %		143993				
	< 10		22.7	20.3	27.5	31.3
	10 – 12		32.2	33.8	35.0	34.7
	> 12		45.1	46.0	37.5	34.0
Age at menarche (y) %		149234				
	≤ 12		21.0	25.1	32.2	41.2
	13 - 14		51.3	54.8	51.9	46.8
	≥ 15		27.7	20.1	15.9	12.0
Combination age at first birth and parity (number of children/age at first birth in y) %		151532				
	nullparity		14.3	9.9	8.7	11.6
	1 / < 30		10.2	8.2	7.4	7.8
	1 / ≥ 30		5.5	4.2	3.6	3.8
	≥ 2 / < 30		63.1	71.1	74.5	71.3
	≥ 2 / ≥ 30		6.9	6.7	5.8	5.5
Menopausal status %		151532				
	Premenopausal		60.2	51.8	34.7	29.0
	Perimenopausal		4.9	6.5	7.8	8.6
	Postmenopausal		31.3	37.4	53.6	58.8
	Unknown		3.6	4.3	3.9	3.6
Oral contraceptive use %		146457				
	Ever		62.2	60.4	52.4	48.2
IUD use %		108182				
	Ever		7.0	10.0	10.2	9.9
MHT use %		142570				
	Ever		16.1	21.7	27.7	26.2

y (years), SD (standard deviation)

‡ N: the total amount for the specific variable

† Incident CUC cases among the study population in the observation period from 1991 until December 31st 2016.

* Percent of total CUC in each BMI category

For all variables differences between BMI category were statistically significant ($p<0.05$) with the exception of IUD use

During the observation period from 1991 until 31st December 2016, 1489 incident cases of CUC (first primary CUC) were diagnosed. The mean follow-up time was 18 years. Among the 1489 CUC cases, 935 were classified as type 1 EC, 263 as type 2 EC and 291 were other CUCs. The age at diagnosis of CUC ranged from 37 to 89 years with a mean age of 62 years. The mean age at diagnosis for type 1 EC was 62 years and 63 years for type 2 EC.

The most common CUC subtypes were endometrioid adenocarcinoma (ICD-O-3 code: 8380), adenocarcinoma with squamous differentiation (8570), adenocarcinoma with mixed subtypes (8255), clear cell adenocarcinoma (8310) and serous/papillary serous cystadenocarcinoma (8441, 8460). Figure 3 shows the number of cases for every morphological code after grouping them into type 1 and type 2 ECs.

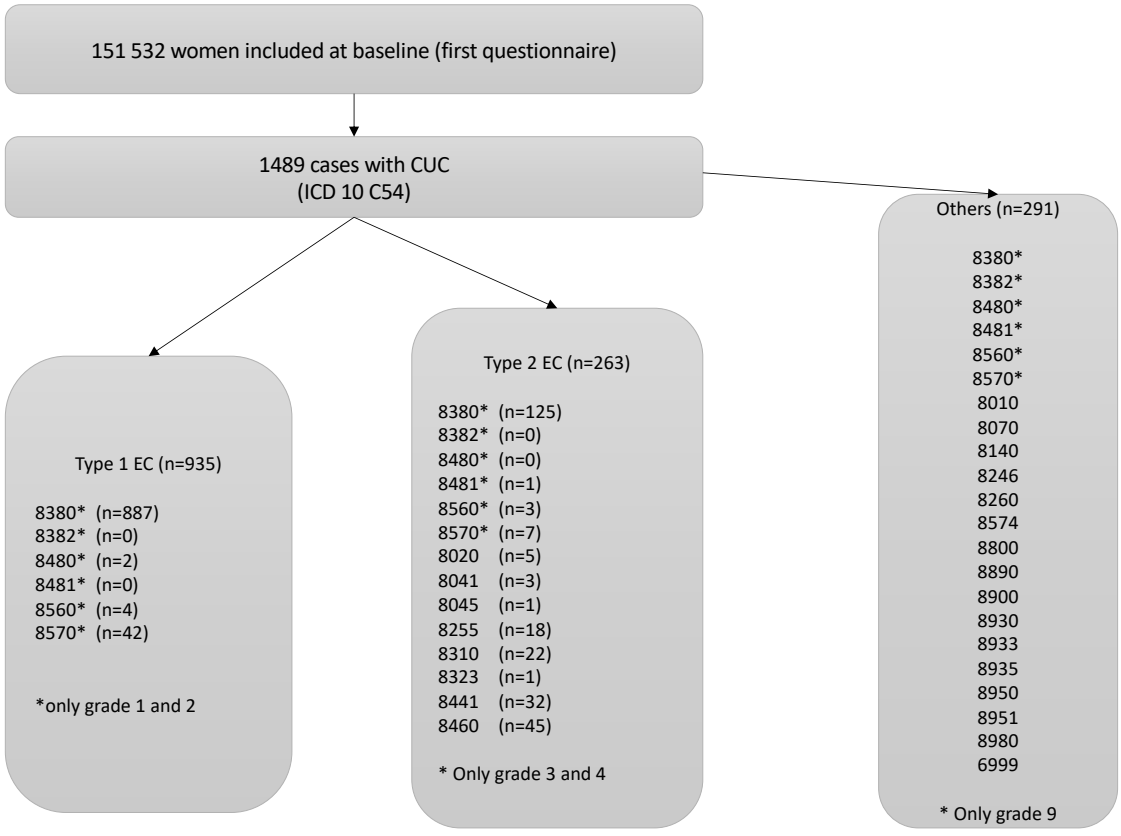

Figure 4 - CUC and subtypes (type 1 EC, type 2 EC and other CUC) which occurred in the study population between 1991 and December 31st 2016.

3.2 Survival analysis of type 1 and type 2 EC

3.2.1 Multivariable cox regression

Table 6 shows the results of the final multivariable analyses. Age-adjusted HR for each assessed covariate is presented in Appendix D. All models fulfilled the assumption of proportional hazards. In the final model for type 1 EC, 63 871 women were included, which totalled 1 160 300 person-years and 431 incident cases of type 1 EC. Women with overweight had 35% increased risk of type 1 EC compared to women with normal weight (HR=1.35, 95% CI: 1.07, 1.69. p=0.010). Compared to women with normal weight, women with obesity had a 3-fold higher risk of type 1 EC (HR=3.00, 95% CI: 2.25, 3.88. p<0.001). The risk of type 1 EC increased linearly from the women with underweight to women with obesity (p_{trend}<0.001). When modelling BMI as a continuous variable, for every increase of 2 kg/m^2 of BMI, the risk of type 1 EC increased by 21% (HR=1.21, 95% CI: 1.17, 1.25. P<0.001).

In the final model for type 2 EC, 73109 women were included, which totalled with 1318810 person-years and 134 incident cases of type 2 EC. Women with overweight had no increased risk of type 2 EC compared to women with normal weight (HR=1.05, 95% CI: 0.70, 1.55. p=0.800). However, women with obesity had a 95% higher risk of type 2 EC (HR=1.95, 95% CI: 1.15, 3.31. P=0.014), compared to women with normal weight. There was a linear trend in risk estimates of type 2 EC across the BMI groups (p_{trend}=0.037). Per 2 kg/m^2 increase of BMI, there was a significant increase of risk (11%) of type 2 EC (HR=1.11, 95% CI: 1.03, 1.20. P=0.007).

The analyses displayed no evidence of differential effects of excess body weight on the two types of EC among women with overweight ($p_{heterogeneity}$ = 0.306), or obesity ($p_{heterogeneity}$ = 0.171). Likewise, there was no significant difference in risk estimates across EC types according to BMI when modelled in continuous form (per 2 kg/m^2) ($p_{heterogeneity}$ = 0.055).

Table 6 - Multivariable adjusted HRs (95% CI) for association between excess body weight and risk of type 1 and type 2 EC

	Type 1 EC [1]					Type 2 EC [2]					$P_{heterogneity}$ [3]
	No of subjects	No of failures	Time at risk [4]	HR (95% CI)	p [5]	No of subjects	No of failures	Time at risk[4]	HR (95% CI)	p [5]	
BMI (kg/m2)											
<18.5	1517	2	30957	0.25 (0.06, 1.02)	0.053	1697	2	34276	0.81 (0.20, 3.28)	0.762	
18.5 – 24.9	42878	235	807171	1.00		48442	81	905450	1.00		
25.0 – 29.9	15177	119	253725	1.35 (1.07, 1.69)	0.010	17819	34	297086	1.05 (0.70, 1.58)	0.800	0.306
≥ 30	4299	75	68447	3.00 (2.25, 3.88)	<0.001	5151	17	81997	1.95 (1.15, 3.31)	0.014	0.171
P_{trend} [6]				<0.001					0.037		
BMI (per 2 kg/m2)	63871	431	1160300	1.21 (1.17, 1.25)	<0.001	73109	134	1318809	1.11 (1.03, 1.20)	0.007	0.055

[1] multivariable cox regression model adjusted for physical activity, combination term between age at first birth and parity, oral contraception, education level, menopausal status, use of IUD and consumption of coffee.

[2] multivariable cox regression model adjusted for use of IUD, consumption of coffee and menopausal status

[3] $p_{heterogeneity}$ between estimate for type 1 and type 2 EC

[4] person-years

[5] p for H_0: HR = 1

[6] p_{trend} for HR trend across BMI category (underweight, normal weight, overweight and obese)

3.2.2 **Results of the two sensitivity analysis**

In the first sensitivity analysis, all tumours with histological code "8140" (adenocarcinoma, NOS) were included as type 1 EC. The analysis showed the same results as the main analysis. Compared to women with normal weight, women with overweight had 35% higher risk of type 1 EC (HR 1.35, 95% CI: 1.09, 1.69. p=0.007) and women with obesity had 190% higher risk of type 1 EC (HR 2.91, 95% CI: 2.23, 3.80. p<0.001). Women with overweight had no significant higher risk of type 2 EC, but women with obesity had a 105% higher risk of type 2 EC (HR 2.05, 95% CI: 1.24, 3.39. p=0.005). There was a significant trend across the BMI groups in both type 1 and type 2 EC (type 1 EC: p<0.001 and type 2 EC p=0.017). All heterogeneity analyses were not significant indicating that BMI has similar effect on the two groups of ECs according to this classification (see Appendix F).

In the second sensitivity analysis, all type 1 EC with grad 3^{+} were classified as type 1 EC. Details about classification are shown in Appendix G. The second sensitivity analysis gave a slightly different result (Appendix I). A significant difference in effect estimates across type 1 and type 2 EC was observed when modelling BMI as a continuous variable ($p_{heterogeneity}$=0.041). Per 2 kg/m^2 increase in BMI, there was a significant increase in risk of both types (type 1 EC: HR=1.20, 95% CI: 1.16, 1.23. P<0.001 and type 2 EC: HR=1.10, 95% CI: 1.02, 1.19. p=0.019). Otherwise the results were similar to the main analysis. Women with overweight had 36 % higher risk of type 1 EC (HR 1.36, 95% CI: 1.11, 1.65. p=0.002) and women with obesity had 188% higher risk of type 1 EC (HR 1.88, 95% CI: 2.26, 3.66. p<0.001). Women with overweight had no significant higher risk of type 2 EC, but women with obesity had a 110% higher risk of type 2 EC (HR 2.10, 95% CI: 1.25, 3.52. p=0.005). The remaining heterogeneity tests in the second sensitivity analysis were not significant as in the main analysis.

4 Discussion

The relationship between excess body weight and risk of type 1 and type 2 EC was investigated in this master´s thesis and the main aim was to assess if the effect of excess body weight on cancer risk is different in type 1 and type 2 EC.

In this study, excess body weight increased the risk of both type 1 EC and type 2 EC. The results suggest no significant difference in effect of excess body weight on the risk of type 1 and type 2 ECs. Although not statistically significant, type 1 EC provided higher risk estimate in relation to BMI than type 2 EC. However, for type 2 EC, only obesity was associated with a significant increased risk when assessing the effect of BMI categories on EC risk, but in this

groups only a few (n=16) women developed type 2 EC. These results support the findings of other studies about excess body weight and type 1 and type 2 ECs. Most previous studies showed a stronger association between excess body weight and type 1 EC compared with type 2 EC (31, 39, 59-61, 82, 83), but a positive association was also present in type 2 ECs. Crosbie et al (39) made a meta-analysis in which cases from three studies (31, 59, 60) were analysed, stratifying by histological type. The conclusion was that combined RR for type 1 was higher compared with type 2, but that this difference was not statistically significant. The authors of the three included studies in the meta-analysis made the same conclusion. Bjørge et al (59) concluded that there was an increasing risk of CUC with increasing BMI and that this increased risk was most pronounced for type 1, but also existing for type 2 tumors, sarcomas and mixed tumors. Lindemann et al (60) found that there was a positive association of BMI with all subtypes of CUC, but with strongest association for endometrioid adenocarcinomas. Collough et al (31) found that the association was driven by high-grade endometrioid tumors and that the small number of cases in other subtypes precluded a meaningful analysis. The conclusions of the three studies points out two important problems, which arises when analysing the association of excess body weight and type 1 and type 2 ECs. First of all, the classification of EC into type 1 and type 2 is important. The presumption that the association is driven by type 1 grade 3 tumors (high-grade endometrioid tumors) shows that the classification may influence the results and it seems that there is certain uncertainty about the right classification. Another important point is that most studies have only a small number of cases of type 2 EC cases, which makes it difficult to analyse risk differences between the two types. To overcome the problem with the small number of cases in type 2 EC, Setiawan et al (8) made a pooled analysis with individual-level data from 24 epidemiological studies. The result from this study showed that BMI was significantly and positively associated with both type 1 and type 2 ECs, but the association was weaker in type 2. However, they found a significant heterogeneity between type 1 and 2 EC when analysing BMI as a continuous variable. The conclusion of the pooled analysis by Setiawan et al was that "the risk factor profile for type 2 and type 1 tumors are quite similar, suggesting that they share some common etiologic pathway". In contrast to that study, the results of this master's thesis showed no significant heterogeneity between type 1 and type 2 ECs when analysing the association of BMI and ECs, modelling BMI both in categorical and continuous form.

The classification of ECs into type 1 and type 2 is an important challenge when studying the two types of EC. The literature review conducted as a part of this master's thesis revealed that there is no common definition. A crucial first step for the classification is the histological

determination from a pathologist. Already at this step the agreement between different pathologists was shown by Scholten to be moderate (the interobserver agreement for the FIGO system $\kappa = 0.41$) (81) and other authors could confirm that the reproducibility was limited when it comes to defining the histological code and grading of ECs (33, 91, 92). From a clinical point of view, grade 3+ behave like type 2 ECs, as they are more aggressive than grade 1 and grade 2 endometrioid EC. The reproducibility was improved when a binary grading system was used that divided tumors into low-grade and high-grade lesions (81). As Scholten et al concluded in the article (81) that "a simple architectural binary grading system that divided tumors into low-grade lesions and high-grade lesions based on the proportion of solid growth (≤ 50% versus > 50%) had superior prognostic power and greater reproducibility". Several pathologists (33, 91-93), the American Cancer Society and the FIGO recommend to classify EC with grade 3^+ as type 2 EC. But still the cut-off between grade 2 and 3 is not always clear and Prat describes this problem well in an article in 2004 (94): "….it has become progressively apparent that both groups overlap to some extent, making the dualistic model a guideline at best…". In this master's thesis all type 1 EC with grade 3^+ were classified as type 2 EC based on the abovementioned discussion. The results of the sensitivity analyses illustrate that the classification is important. The principal conclusion from the first sensitivity analysis when 8140 (adenocarcinoma NOS) tumors were included as type 1 EC (in the main analysis they were excluded) was the same. The main conclusion from the second sensitivity analysis (see Appendix E) was different. When modelling BMI as a continuous variable, there was evidence of a different effect of excess body weight on type 1 and type 2 ECs. Therefore, it needs to be emphasized how important it is to report, which histological code was classified as type 1 or type 2 EC. Not all researchers described the histological codes and its classification in detail (often only the histological description is named) and this may lead to misunderstanding and misclassification. It was difficult to reproduce how several previously published studies classified type 1 and type 2 EC in their research. One implication of this study could be that researchers should describe their classification in type 1 and type 2 EC by means of ICD-O-3 codes. This simplifies the reproducibility of the results, makes it easier to investigate the subtypes of CUC and allows for a proper comparison of results.

4.1 Strengths of the study

The strengths of this study was that the NOWAC study is a large population-based study which is representative for women between 31- 70 years old, living in Norway. Participants have been followed over a period of 35 years. Information about the most important confounders such as lifestyle, nutrition, education, reproductive factors and status and

hormonal intake were available, which allowed us to control our estimates for these variables. The unique personal identification number and the linkage to the Cancer Registry of Norway provide information about CUC cases with high quality. Additionally, the external validity of NOWAC was proven to be good. Two sensitivity analyses were done and showed that the discussion about classification is important. Most known risk and protective factors of type1 and type 2 EC were included. Strong evidence of the protective effect of coffee was described recently in the World Cancer Research Fund of 2018. We included this confounder in our analysis; until now most studies about CUC, type 1 and type 2 EC did not correct for this factor.

4.2 Weaknesses of the study

In the NOWAC study, height and weight are self-reported which could introduce potential misclassification as the main exposure BMI was calculated from information on height and weight. However, it could be assumed that misclassification is non-differential, as the information about height and weight was collected prior to the development or the diagnosis of the disease. In this case the risk estimate is likely biased towards the null.

BMI as a measure of obesity has its own limitations. BMI is a proxy for obesity and it does not measure the percentage of body fat, the amount of adipose tissue or the distribution of adipose tissue. It is known that the distribution of adipose tissue is important as abdominal visceral adipocytes are metabolically more active than subcutaneous fat tissue (10, 95, 96). Therefore, waste-to-hip ratio would be more appropriate to take this accepted fact into account. In addition, the information about BMI were collected at the beginning of the follow-up, possible weight change over time were not analysed.

The information from the Cancer Registry of Norway were limited to the histological and morphological codes. There were no possibilities to review the histological slides and discuss the classification and determination of type 1 and type 2 EC with help of this information. Missing data could also be a source of information bias. In this master's thesis a complete case analysis was performed. To confirm that the missing data did not bias our results multiple imputations could be performed under the assumption that the data was missing at random. This was beyond of the scope of this master's thesis.

5 Conclusion

In summary, BMI is associated in a dose response manner with both type 1 and type 2 EC. The association between excess body weight and type 1 and type 2 EC does not significantly differ according to subtypes, however, the association seems to be stronger in type 1. This

potential higher risk estimate in type 1 EC could support the idea that estrogen plays a more important role in the development of type 1 ECs compared to type 2 EC.

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Appendix

Appendix A. ICD-10 Classification of malignant neoplasm corpus uteri (C54)

C 54.0	Isthmus uteri (lower uterine segment)
C 54.1	Endometrium
C 54.2	Myometrium
C 54.3	Fundus uteri
C 54.8	Overlapping lesion of corpus uteri
C 54.9	Corpus uteri, unspecified

Appendix B. Adaption of WHO classification for different subtypes of CUC and corresponding ICD-3-codes (only malignant tumors included) (27).

Epithelial tumours and related lesions			
Endometrial carcinoma			
	Endometrioid adenocarcinoma		8380/3
		AdenoCa with squamous metaplasia	8570/3
		Villous adeno Ca	8262/3
		Endometrioid adeno Ca, secretory variant	8382/3
	Mucinous adeno Ca		8480/3
	Mucin-producing adeno Ca		8481/3
	Mucinous adenoCa, endocervical type		8482/3
	Serous cystadenoCa		8441/3
	Clear cell adeno Ca NOS		8310/3
	Mixed cell adeno Ca		8323/3
	Squamous cell Ca NOS		8070/3
	Transitional cell carcinoma		8120/3
	Small-cell carcinoma NOS		8041/3
	Undifferentiated carcinoma, NOS		8020/3
Mesenchymal tumours			
Endometrial stromal and related tumours			
	Endometrial stromal sarcoma, low grade		8931/3
	Undifferentiated endometrial sarcoma		8930/3
Smooth muscle tumours			
	Leiomyosarcoma		8890/3
Mixed epithelial and mesenchymal tumours			
	Carcinosarcoma NOS		8980/3
	Adenosarcoma		8933/3
	Carcinofibroma		8934/3

Appendix C. CUC (ICD C54), type 1 and type 2 EC classification; main analysis.

CUC

EC		Others	
Type 1	Type 2		
8380 (8380/31; 8380/32)	8380 (8380/33; 8380/34)	8380 (8380/39)	8890 (8890/3x)
8382 (8382/31; 8382/32)	8382 (8382/33; 8382/34)	8382 (8382/39)	8900 (8900/3x)
8480 (8480/31; 8480/32)	8480 (8480/33; 8480/34)	8480 (8480/39)	8900 (8900/3x)
8481 (8481/31; 8481/32)	8481 (8481/33; 8481/34)	8481 (8481/39)	8930 (8930/3x)
8560 (8560/31; 8560/32)	8560 (8560/33; 8560/34)	8560 (8560/39)	8933 (8933/3x)
8570 (8570/31; 8570/32)	8570 (8570/33; 8570/34)	8570 (8570/39)	8935 (8935/3x)
	8041 (8041/3x)	6999 (6999/3x)	8950 (8950/3x)
	8045 (8045/3x)	8010 (8010/3x)	8951 (8951/3x)
	8255 (8255/3x)	8070 (8070/3x)	8980 (8980/3x)
	8310 (8310/3x)	8140 (8140/3x)	
	8441 (8310/3x)	8246 (8246/3x)	
	8460 (8460/3x)	8260 (8260/3x)	
	8323 (8323/3x)	8574 (8574/3x)	

x means that every grade (1,2,3,4 and 9) was included.

Appendix D. Age-adjusted HR with 95% CI for CUC, type 1 and type2 in relation to exposure variable and co-variates

		CUC			Type 1			Type 2		
	Person-years	No of failure	Age-adjusted HR (95% CI)	p-value	No of failure	Age-adjusted HR (95% CI)	p-value	No of failure	Ageadjusted HR (95% CI)	p-value
BMI (kg/m2)										
<18.5	59720	13	0.56 (0.32, 0.97)	0.039	9	0.65 (0.34, 1.27)	0.208	3	0.70 (0.22, 2.21)	0.547
18.5 – 24.9	1632971	739	1.00		444	1.00		140	1.00	
25.0 – 29.9	585217	450	1.41 (1.26, 1.59)	<0.001	281	1.46 (1.25, 1.69)	<0.001	78	1.24 (0.94, 1.63)	0.137
≥ 30	171433	287	3.00 (2.62, 3.44)	<0.001	201	3.46 (2.92, 4.09)	<0.001	42	2.21 (1.57, 3.13)	<0.001
Smoking										
Never	846471	647	1.00		404	1.00		119	1.00	
Ever	785107	486	0.84 (0.74, 0.94)	0.003	318	0.88 (0.76, 1.02)	0.083	78	0.74 (0.56, 0.99)	0.041
Current	786211	340	0.65 (0.57, 0.74)	<0.001	203	0.63 (0.53, 0.75)	<0.001	63	0.69 (0.50, 0.93)	0.016
Physical activity										
Low	558102	424	1.00		278	1.00		74	1.00	
Medium	931729	515	0.74 (0.65, 0.84)	<0.001	328	0.72 (0.61, 0.85)	<0.001	93	0.77 (0.57, 1.05)	0.098
High	742677	386	0.70 (0.61, 0.80)	<0.001	231	0.64 (0.54, 0.77)	<0.001	67	0.71 (0.51, 0.99)	0.041
Diabetes mellitus										
No	1876181	1111	1.00		691	1.00		190	1.00	
Yes	32117	46	1.88 (1.34, 2.53)	<0.001	33	2.12 (1.49, 3.01)	<0.001	9	2.09 (1.07, 4.08)	0.032
Coffee consumption (cup/day)										
≤ 1	305796	189	1.00		128	1.00		24	1.00	
>1 and < 4	608681	399	0.95 (0.80, 1.13)	0.539	249	0.87 (0.70, 1.07)	0.191	81	1.47 (0.93, 2.33)	0.095
≥4 and < 8	717147	399	0.81 (0.20, 0.97)	0.020	235	0.70 (0.57, 0.87)	0.001	67	1.06 (0.67, 1.69)	0.805
≥ 8	288405	107	0.68 (0.53, 0.86)	0.001	64	0.60 (0.45, 0.81)	0.001	17	0.89 (0.48, 1.65)	0.700

Education (years)										
< 10	562126	367	1.00		209	1.00		75	1.00	
10 - 12	808815	475	1.10 (0.95, 1.26)	0.199	303	1.25 (1.04, 1.50)	0.014	86	1.02 (0.74, 1.39)	0.920
> 12	970526	566	1.15 (1.00, 1.32)	0.039	375	1.38 (1.16, 1.64)	<0.001	87	0.92 (0.67, 1.27)	0.617
Age at menarche (years)										
≤ 12	674400	469	1.00		301	1.00		82	1.00	
13 - 14	1293687	775	0.82 (0.73, 0.92)	0.001	486	0.80 (0.69, 0.92)	0.002	139	0.83 (0.63, 1.09)	0.173
≥ 15	443411	230	0.66 (0.56, 0.77)	<0.001	141	0.63 (0.51, 0.77)	<0.001	36	0.57 (0.38, 0.84)	0.005
Combination age at first birth and parity (number of children/age at first birth)										
nullparity	233781	196	1.00		134	1.00		23	1.00	
1 / < 30y	195932	136	0.83 (0.67, 1.03)	0.096	93	0.83 (0.64, 1.08)	0.171	21	1.10 (0.61, 1.99)	0.750
1 / ≥ 30y	98030	45	0.57 (0.41, 0.78)	0.001	27	0.50 (0.33, 0.75)	<0.001	12	1.30 (0.65, 2.62)	0.456
≥ 2 / < 30y	1771846	1040	0.63 (0.54, 0.74)	<0.001	635	0.56 (0.47, 0.68)	<0.001	191	0.98 (0.63, 1.51)	0.922
≥ 2 / ≥ 30y	149764	72	0.53 (0.41, 0.70)	<0.001	46	0.50 (0.36, 0.70)	<0.001	16	1.00 (0.53, 1.90)	0.997
Menopausal status										
Premenopausal	1368725	645	1.00		404	1.00		107	1.00	
Perimenopausal	136932	111	1.27 (1.03, 1.55)	0.023	77	1.37 (1.07, 1.75)	0.012	18	1.20 (0.73, 1.99)	0.465
Postmenopausal	837296	689	0.80 (0.71, 0.91)	0.001	429	0.76 (0.65, 0.88)	<0.001	132	0.78 (0.58, 1.05)	0.103
Unknown	106388	44	0.72 (0.53, 0.98)	0.039	25	0.65 (0.43, 0.97)	0.033	6	0.58 (0.26, 1.33)	0.201
OC use										
Never	995023	823	1.00		503	1.00		154	1.00	
Ever	1382860	610	0.69 (0.62, 0.77)	<0.001	396	0.75 (0.65, 0.86)	<0.001	103	0.68 (0.52, 0.88)	0.003
IUD use										
Never	1549281	1055	1.00		680	1.00		186	1.00	
Ever	155752	45	0.46 (0.34, 0.63)	<0.001	31	0.50 (0.35, 0.71)	<0.001	6	0.37 (0.16, 0.83)	0.016
MHT use										
Never	1856205	1094	1.00		696	1.00		183	1.00	
Ever	421638	343	0.95 (0.84, 1.08)	0.449	205	0.88 (0.75, 1.03)	0.101	73	1.16 (0.88, 1.53)	0.290

Appendix E. First Sensitivity analysis: CUC (ICD C54), type 1 and type 2 EC classification; morphological code “8140” is classified as type I EC (grade 3+ are classified as type 2 EC)

CUC

EC		Others	
Type 1	Type 2		
8380 (8380/31; 8380/32)	8380 (8380/33; 8380/34)	8380 (8380/39)	8890 (8890/3x)
8382 (8382/31; 8382/32)	8382 (8382/33; 8382/34)	8382 (8382/39)	8900 (8900/3x)
8480 (8480/31; 8480/32)	8480 (8480/33; 8480/34)	8480 (8480/39)	8900 (8900/3x)
8481 (8481/31; 8481/32)	8481 (8481/33; 8481/34)	8481 (8481/39)	8930 (8930/3x)
8560 (8560/31; 8560/32)	8560 (8560/33; 8560/34)	8560 (8560/39)	8933 (8933/3x)
8570 (8570/31; 8570/32)	8570 (8570/33; 8570/34)	8570 (8570/39)	8935 (8935/3x)
8140 (8140/31; 8140/32)	8140 (8140/33; 8140/34)	8140 (8140/39)	8950 (8950/3x)
	8041 (8041/3x)	6999 (6999/3x)	8951 (8951/3x)
	8045 (8045/3x)	8010 (8010/3x)	8980 (8980/3x)
	8255 (8255/3x)	8070 (8070/3x)	
	8310 (8310/3x)	8140 (8140/3x)	
	8441 (8310/3x)	8246 (8246/3x)	
	8460 (8460/3x)	8260 (8260/3x)	
	8323 (8323/3x)	8574 (8574/3x)	

x means that every grade (1,2,3,4 and 9) was included.

Appendix F. Multivariable adjusted HRs (95% CI) for the first sensitivity analysis

	Type 1 EC [1]					Type 2 EC [2]					$P_{heterogneity}$ [3]
	No of subjects	No of failures	Time at risk [4]	HR (95% CI)	p [5]	No of subjects	No of failures	Time at risk[4]	HR (95% CI)	p [5]	
BMI (kg/m2)											
<18.5	1517	2	30957	0.24 (0.06, 0.96)	0.044	1697	2	34276	0.73 (0.18, 2.96)	0.658	
18.5 – 24.9	42878	247	807171	1.00		48442	88	905450	1.00		
25.0 – 29.9	15177	126	253725	1.35 (1.09, 1.69)	0.007	17819	36	297086	1.05 (0.71, 1.56)	0.810	0.270
≥ 30	4299	78	68447	2.91 (2.23, 3.80)	<0.001	5151	19	81997	2.05 (1.24, 3.39)	0.005	0.228
P_{trend} [6]				<0.001					0.017		
BMI (per 2 kg/m2)	63871	453	1160300	1.20 (1.17, 1.24)	<0.001	73109	145	1318810	1.12 (1.04, 1.20)	0.002	0.075

[1] multivariable cox regression model adjusted for physical activity, combination term between age at first birth and parity, oral contraception, education level, menopausal status, use of IUD and consumption of coffee.

[2] multivariable cox regression model adjusted for use of IUD, consumption of coffee and menopausal status

[3] $p_{heterogeneity}$ between estimate for type 1 and type 2 EC

[4] person-years

[5] p for H_0: HR = 1

[6] p_{trend} for HR trend across BMI category (underweight, normal weight, overweight and obesity)

Appendix G. Second Sensitivity analysis: CUC (ICD C54), type 1 and type 2 EC classification; grade 3+ classified as type 1 EC.

CUC

EC		Others	
Type 1	Type 2		
8380 (8380/3x)	8041 (8041/3x)	6999 (6999/3x)	8900 (8900/3x)
8382 (8382/3x)	8045 (8045/3x)	8010 (8010/3x)	8900 (8900/3x)
8480 (8480/3x)	8255 (8255/3x)	8070 (8070/3x)	8930 (8930/3x)
8481 (8481/3x)	8310 (8310/3x)	8140 (8140/3x)	8933 (8933/3x)
8560 (8560/3x)	8441 (8310/3x)	8246 (8246/3x)	8935 (8935/3x)
8570 (8570/3x)	8460 (8460/3x)	8260 (8260/3x)	8950 (8950/3x)
8140 (8140/3x)	8323 (8323/3x)	8574 (8574/3x)	8951 (8951/3x)
		8890 (8890/3x)	8980 (8980/3x)

x means that every grade (1,2,3,4 and 9) was included

Appendix H. Multivariable adjusted HRs (95% CI) for the second sensitivity analysis

	Type 1 EC [1]					Type 2 EC [2]					$P_{heterogneity}$ [3]
	No of subjects	No of failures	Time at risk [4]	HR (95% CI)	p [5]	No of subjects	No of failures	Time at risk[4]	HR (95% CI)	p [5]	
BMI (kg/m2)											
<18.5	1517	3	30957	0.29 (0.09, 0.89)	0.031	3209	2	58539	1.09 (0.27, 4.45)	0.908	
18.5 – 24.9	42878	309	807171	1.00		95546	67	1612384	1.00		
25.0 – 29.9	15177	157	253725	1.36 (1.11, 1.65)	0.002	38896	36	577835	1.18 (0.78, 1.78)	0.437	0.543
≥ 30	4299	95	68447	2.88 (2.26, 3.66)	<0.001	12109	19	169109	2.10 (1.25, 3.52)	0.005	0.277
P_{trend} [6]				<0.001					0.012		
BMI (per 2 kg/m2)	63871	564	1160300	1.20 (1.16, 1.23)	<0.001	149760	124	2417866	1.10 (1.02, 1.19)	0.019	0.041

[1] multivariable cox regression model adjusted for physical activity, combination term between age at first birth and parity, oral contraception, education level, menopausal status, use of IUD and consumption of coffee.

[2] multivariable cox regression model adjusted for use of IUD, consumption of coffee and menopausal status

[3] $p_{heterogeneity}$ between estimate for type 1 and type 2 EC

[4] person-years

[5] p for H_0: HR = 1

[6] p_{trend} for HR trend across BMI category (underweight, normal weight, overweight and obesity)