Recognizing patients with (a higher risk of) endometrial cancer; the rol of fat distribution and inflammation in the origin of endometrial cancer, a study that focuses on prevention and prediction

Published: 20-07-2021
Last updated: 04-04-2024

We expect the BMI and the type of fat distribution to have a significant influence on the change in hormone levels, fat metabolism and systemic inflammation levels after bilateral salpingo-oophorectomy (BSO). In patients with endometrial cancer,...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Reproductive neoplasms female malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON52042

Source
ToetsingOnline

Brief title
ENDOCRINE (ENDOmetrial Cancer pReventIon aNd prEdiction)

Condition

- Reproductive neoplasms female malignant and unspecified

Synonym
cancer of the womb, Uterine cancer

Research involving

Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: endometrial cancer, fat distribution, inflammation, prevention

Outcome measures

Primary outcome

Hormone levels and inflammation markers after BSO depending on BMI

Secondary outcome

Effect of fat distribution on hormone levels and inflammation markers

Effect of BSO on subjects complaints (depending on BMI)

Study description

Background summary

Endometrial cancer is the most common malignancy in women in the higher developed countries. The incidence of endometrial carcinoma is increasing because of the influence of increasing life expectancy and increasing obesity. Of all the malignancies, the endometrial cancer is most positively correlated to a body mass index (BMI) and with each increase of 5 BMI units, there is 50% higher risk of developing endometrial cancer. The underlying mechanisms between obesity and cancer are complex. For endometrial cancer, prolonged estrogen stimulation plays a role due to, among other things, increased aromatase activity in peripheral fat. In addition, obesity-related inflammation and insulin resistance appear to be important. The latter may also explain that not only the endometrioid (traditionally considered as estrogen sensitive) subtype, but also the non- endometrioid subtypes of endometrial cancer show an increased incidence in weight gain. This obesity-related inflammation also plays a role in the onset of other diseases, such as cardiovascular disease and type 2 diabetes.

Due to increasing obesity worldwide and in the more developed countries in

particular, it is expected that the incidence of endometrial cancer will continue to increase significantly, also in premenopausal women. Most women with endometrial cancer have a favorable prognosis because the disease leads to symptoms of abnormal blood loss at an early stage. However, endometrial cancer, especially in obese women, can also be seen as an expression of unhealthy patient environment, and is associated with co-morbidities such as diabetes and hypertension. This is explained by overlap in underlying mechanisms such as the above mentioned inflammation. The increase in non- endometrioid endometrial cancer, which is insufficiently explained by estrogens and characterized by poorer prognosis, illustrates the knowledge gap on the relationship between obesity and endometrial cancer.
Obesity is often expressed in BMI (WHO), an easily applicable but coarse indicator that does not do justice to the complexity of obesity and weight distribution (apple/pear figure) and the distribution between subcutaneous and visceral fat. Internationally, the importance of fat distribution within the origin of endometrial cancer research is more recognized, as is research of both applicants, in which BMI and fat distribution on CT appear to be correlated to hormonal levels and tumor inflammation as well as tumor pathway activation.
However, regardless of the degree of overweight, there is agreement in the literature regarding the strong, positive relationship between BMI and endometrial carcinoma incidence.
The adipose tissue is a very complex cereal that produces hormones such as adiponectin and leptin, as well as steroids that influence the development and course of endometrial cancer. The visceral fat is metabolic more active, and therefore possibly a worse prognostic than subcutaneous fat, while the subcutaneous fat seems more important for estrogen production in women with normal BMI. However, after menopause, peripheral adipose tissue is the main producer due to the presence of aromatase, an enzyme that converts androgens into estrogens. Finally also the uterus itself partly regulates its local estrogen metabolism (intracrinology), consisting of a complex mechanism of and interaction between multiple enzymes, which plays an important role in the endometrial cancer. This expertise is specifically present within the MUMC+ in clinical and pre-clinical research.

In light of the differences in the type of fat (visceral versus subcutaneous), the shift towards a relative increase in central adiposity (visceral fat) due to the menopausal transition seems important.

The primary treatment of the endometrial carcinoma consists of hysterectomy with removal of the ovaries (bilateral salpingo-oophorectomy, BSO). Removal of the ovaries has a dual purpose; 1. It is part of the urbanization of the endometrial carcinoma. It leads to a reduction of the remaining estrogen and androgen production and thus reduces the risk of recurrence.
However, the impact of BMI and fat distribution (subcutaneous versus visceral) on hormone levels, metabolism and inflammation at onset and progression of enometrial carcinoma is not clear, but is directly relevant for better

understanding and treatment of the endometrial carcinoma in obese patients. The routine surgical treatment of the endometrial carcinoma, in which one has direct access to both subcutaneous and visceral adipose tissue in addition to access to the tumor, however, allows to investigate these important relationships.

Study objective

We expect the BMI and the type of fat distribution to have a significant influence on the change in hormone levels, fat metabolism and systemic inflammation levels after bilateral salpingo-oophorectomy (BSO). In patients with endometrial cancer, systemic inflammation is expected to be higher compared to controls, and proportionally more visceral than subcutaneous fat is present. It is also expected that bso in obese patients only leads to a relatively small decrease in estrogen levels.

The results help to better understand the impact of inflammation and obesity on endometrial cancer. This is a large knowledge gap and, given the huge increase in obesity, very relevant for the future.
This knowledge can contribute to the decision making regarding the routine removal of ovaries in obese women with endometrial cancer and gives opportunities for innovation in the treatment of endometrial cancer.
In addition, these insights can facilitate better risk stratification in obese women with abnormal vaginal blood loss. For this group, targeted preventive measures such as weight reduction and promotion of physical activity can be advised. Especially because there is a large overlay with the underlying mechanisms of obesity and obesity-related inflammation with cardiovascular disease and type 2 diabetes, this knowledge can be applied on a broader level.

Study design

This is a prospective observational study (pilot)
Inclusion criteria
-CASES (n=80): Subjects with endometrial carncer and atypical endometrial hyperplasia undergoing hysterectomy including BSO upon inclusion will be stratified by BMI and menopausal status.
- pre- and perimenopausal BMI >=32 (n=20)
- pre- and perimenopausal BMI 18-25 (n=20)
- postmenopausal BMI >=32 (n=20)
- postmenopausal BMI 18-25(n=20)

CONTROLS (n=80): Subjects undergoing bilateral salpingo-oophorectomy (BSO) for non-oncological reasons. For this purpose, patients undergoing a trial laparotomy in which the ovaries are removed and eventually will be diagnosed as benign, will be approached. Age >40 years due to matchability with cases.
- Pre- and perimenopausal BMI >=32 (n=20)

- pre- and perimenopausal BMI <25 (n=20)
- postmenopausal BMI >=32 (n=20)
- postmenopausal BMI <25(n=20)

Exclusion criteria:
Other malignancy <5 years prior to inclusion, except basal cell carcinoma
Use of hormonal therapy <12 months
Insufficient understanding of the Dutch language
Subjects not allowed to undergo CT-scan

Study activities
Preoperative
-Blood collection for estrogen levels and systemic inflammation markers
-CT for fat segmentation
-Waist / hip circumference and BMI
-Questionnaire on comorbidity, physical activity level, and presence of menopausal symptoms.
-if still recognizable cycle present: ask cycle day.

Per operative
Collection of adipose tissue subcutaneously, omentum and intestinal epiploica + tumor

Postoperative (6 weeks)
Collect clinical data on tumor (subtype, stage and treatment)
-Estrogen levels, systemic inflammation markers
-Questionnaire on (changes in) menopausal complaints (hot flashes)
-Follow up for oncological outcome measures for three years

Analyses:
The analyses are aimed at comparing the serum estrogen levels and inflammation markers before and after removal of the ovaries and comparing the different groups:
- Pre-/perimenopausal and postmenopausal
- BMI 18-25 and >=32
- Endometrial cancer patients and controls
Characterization of the systemic estrogens (by multiplex system steroid analysis) and systemic inflammation markers and cytokines (C-reactive protein (CRP), interleukin 1 beta (IL1β), interleukin 6 (IL6), tumor necrosis factor alpha (TNFα), insulin-like growth factor 1(IGF1) before and after surgery. In addition, spijtserum is stored for possible further analyses.
Analyze the fat and fat metabolism that have been shown in the literature to be important for inflammation and hormone production (macrophages, T cells): TNF-α, IL-6, and IL-1β, oestron, aromatase, adiponectin, resistin, leptin).
Correlate the results to the different types of fat distribution (visceral and subcutaneous) as visualized on CT. Hip waist circumference and body image

(apple/pear figure) are also included.

Study burden and risks

The load and risks for the subjects are minimal.
Extra hospital visit: No.
Extra invasive procedures (including blood draw): Yes, one additional blood draw at the time of post-OK visit.
Biological material collection:
- Blood: At the same time as routine blood draw and during post-OK visit.
- Tissue: During routine surgery:
- Tumor/metastasis: residual material.
- Subcutaneous fat biopsy: achieved when opening abdomen: biopsy without risk.
- Ometal biopsy: Routine in aggressive subtypes; non-aggressive subtypes: decrease biopsy. risk: small: minimal blood loss.
- The intestinal fat biopsies: no routine action at the endometrium carcinoma: emphatically no biopsy of the intestine itself.
Risks:1. small: blood loss; 2. minimal/negligible: intestinal damage (nb If there is no fat rich spot, no biopsy is taken).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Cases: Subjects with endometrial cancer/hyperplasia with atypia, who are planned for hysterectomy with bilateral salpingo-oophorectomy.
Controls: Subjects who are planned for bilateral salpingo-oophorectomy without malignancy and are older than 40

Exclusion criteria

Malignancy 5 years prior to inclusion (basal cell carcinoma excluded)
Use of systemic hormonale therapy the past 12 months
inadequate knowledge of the Dutch language
Contra-indication for ct-scan

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	08-11-2021
Enrollment:	160

Type:	Actual

Ethics review

Approved WMO Date:	20-07-2021
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-05-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL76255.068.21
Other	NL9622