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Prevention of breast and endometrial cancer using total dietary replacement

Submission date
08/01/2020

Recruitment status
No longer recruiting

Registration date
11/05/2020

Overall study status
Completed

Last Edited
22/01/2025

Condition category
Cancer

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Breast cancer is the most common cancer in women and endometrial (womb) cancer is the fourth. Being overweight and not having a healthy lifestyle increases the risk of developing both of these cancers. Compared with a healthy weight woman, those who are three stone (20 kg) above a healthy weight have a 20% greater chance of developing breast cancer and three times the risk of developing endometrial cancer.
A maintained weight loss (in the region of 2 stone/15kg) can be achieved with a dietitian-supported weight loss programme. Programmes like this have been shown to manage weight-related Type-2 Diabetes. We now wish to see whether this programme could be used to lose weight and reduce cancer risk markers in women, ultimately helping prevent breast and endometrial cancers.
The study has two main aims. Firstly, to measure any changes in cancer risk markers within biopsies of the breast and endometrium (womb lining), blood and urine after three months of weight loss.
Secondly, since maintained weight loss is key for preventing cancer we will also see whether the weight loss achieved in the first three months is maintained up to twelve months, with a dietitian-supported diet and physical activity programme.

Who can participate?
We are looking to recruit women aged 30-50 years with a body mass index (BMI) of greater than 30 (or greater than 27.5 if Asian or South Asian ethnicity) and having regular periods.
We cannot accept women with a prior history of breast or endometrial cancer or preinvasive breast disease (Ductal Carcinoma in situ (DCiS), Lobular Carcinoma in situ (LCiS), Atypical Ductal Hyperplasia (ADH), Atypical Lobular Hyperplasia (ALH)); women using a hormonal contraceptive (including progestin releasing IUCD, such as Mirena®) in the 12 weeks prior to study entry; pregnant women; those suffering with severe anxiety, depression or binge eating.

What does the study involve?
This study will involve forty-seven women and has one group who receive the weight loss intervention at the start and another group who receive this three months later. The intervention is a 12-month weight loss programme including three months of diet replacement drinks (850 calories per day), one month of diet reintroduction (weekly increase up to 1500

calories per day) and eight months of weight maintenance following a Mediterranean diet, and including physical activity.
Thirty-one women will be placed in the immediate 850-calorie diet group, and sixteen will be placed in a delayed diet group. All participants will have breast and endometrial biopsies at the start and after three months. The delayed diet group will be asked to maintain their normal diet for the first three months until they have had their baseline and 3-month biopsies, before commencing the 12-month weight loss programme. This delayed group will act as a control, to allow us to see if the dietary intervention has any positive changes on the breast and womb biopsies.
Hospital visits will be mostly at Wythenshawe Hospital in Manchester, with the exception of the endometrial (womb) biopsies, which will be at St. Mary's Hospital, Manchester.

What are the possible benefits and risks of participating?
BENEFITS
Participants will receive personalised advice and support to undertake a weight loss programme which is not routinely available to women at risk of breast and endometrial cancer. Participants will be contributing to scientific knowledge about the benefits of weight loss for the prevention of breast and endometrial cancer.
Participants will receive regular support from a specialist dietitian using a novel app (Oviva UK Ltd). The support aims to motivate participants to get past previous barriers or difficulties that have stood in the way of successful weight loss. Weight loss achieved with this advice and adherence to the low-calorie diet may reduce the risk of developing breast and endometrial cancer. Weight loss is also likely to reduce the risk of ten other weight related cancers and conditions including diabetes, heart disease, stroke and dementia.

RISKS
Mammograms are used within this study and as a result, there is a very small risk of radiation-induced cancer developing later in life due to exposure to x-rays from mammograms.
The breast biopsies may cause bruising, bleeding from the wound site, infection of the wound site, scarring. The endometrial biopsies can be uncomfortable and patients sometimes find intimate examinations like this embarrassing. The breast and endometrial biopsies could potentially identify a very early breast or endometrial cancer that a participant was not aware of.
The blood samples taken could result in slight discomfort or bruising. There is a chance we could identify Type 2 Diabetes on the baseline blood tests that the participant was not aware of.
Participants may find the 850-calorie dietary replacement diet difficult to stick to. Our own work and that of others tell us that Optifast® meal replacements are unlikely to make participants feel unwell. Some people experience hunger, feeling a little colder, bad breath, headache, light headedness, fatigue, nausea, and constipation. Other rare side effects reported in studies using Optifast® include diarrhoea (in 3 out of 100 users), dry skin (in 3 out of 100 users), hair loss (< 1 out of 100 users) and gallstones (<1 out of 100 users).

Where is the study run from?
The study is run by the University of Manchester in conjunction with Manchester University NHS Foundation Trust.

When is the study starting and how long is it expected to run for?
October 2019 to April 2023

Who is funding the study?
1. Cancer Research UK
2. National Institute of Health Research, Biomedical Research Centre

Who is the main contact?
Dr Sacha Howell (Chief Investigator) mft.probe-tdr@nhs.net

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
274621

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
B00754, CPMS 44943, IRAS 274621

Study information

Scientific Title
Defining the feasibility and molecular impact of total diet replacement for the prevention of breast and endometrial cancer

Acronym
ProBE-TDR

Study objectives
To determine the effects of 12+/- 4 weeks of Total Diet Replacement (TDR) on cancer risk markers in the breast and endometrium of women at increased risk of breast and/or endometrial cancer as compared to a normal diet control group

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 22/04/2020, North West Preston Regional Ethics Committee (Barlow House, 3rd Floor, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 (0)207 104 8056; nrescommittee.northwest-preston@nhs.net), ref: 20/NW/0095

Study design
Interventional randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Community

Study type(s)
Prevention

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Cancer prevention

Interventions
Women will either be approached in clinics or by invitation through mailshot from the Nightingale Family History clinic. Posters will also be placed in clinics and staff invited to join if they fulfil eligibility criteria. Women will either be sent or handed the PIS and will have at least 24 hours to consider whether they wish to participate. If so they will sign informed consent form with an investigator and commence screening.

Screening will consist of measurement of height and weight to calculate BMI, the trial of an Optifast® drink in clinic, unless previously tried and exclusion of pregnancy through urine pregnancy test. Medical history will be taken and screening questionnaires completed: Alcohol Use Disorders Identification Test (AUDIT), Binge Eating Scale (BES), Patient Health Questionnaire-9 (PHQ-9) and Generalised Anxiety Disorder scale (GAD-7).

If eligibility is confirmed baseline breast biopsy and blood sampling will be undertaken in the luteal phase (one week before expected menstruation) of the menstrual cycle, endometrial sampling will then be undertaken in the follicular phase (week following menstruation) of the menstrual cycle.

This study will involve 47 women. Thirty-one will be placed in an immediate 850 calorie diet group (group 1), and 16 will be placed in a delayed 850 calorie diet group (group 2).

Randomisation:
Via minimisation routine software package. Stratified based upon:
1. Above or below a BMI of 35 kg/m²
2. Above or below projected median lifetime risk of breast cancer ≥17% remaining lifetime risk (Tyrer-Cuzick score)

The delayed diet group will be asked to maintain their normal diet for the first three months until they have had their baseline and 3-month biopsies, before commencing the 12-month weight loss programme. This is to act as a control, to show us if the dietary intervention does indeed have any positive change.

These will be repeated after at least 8 weeks of total diet replacement (TDR) in the same phase of the menstrual cycle as the baseline tests. The control group will provide vital analytical controls for the TDR arm of the study.

Participants will remain on the TDR until they have undergone their second breast and endometrial biopsies (with blood tests again at the time of second breast biopsy) which will be undertaken after 12 +/-4 weeks of TDR.

Once this is complete, the TDR group will move into diet reintroduction over a 4 week period, gradually increasing daily calorie intake to 1500 kcal/day. This will be maintained then for 8 months, following a Mediterranean style diet. A structured exercise programme will be introduced alongside.

The control arm will move onto 12 weeks of TDR after the initial 12 week control phase and then move into the 9 month diet reintroduction/weight maintenance/exercise programme.

Blood and urine tests will be repeated at 3, 6 and 9 months after the second biopsies. At the same time the women will be asked to complete PROMs to evaluate quality of life, levels of anxiety and depression and also self efficacy and self satisfaction.

The 12-month weight loss programme
This has three diet phases:
Phase 1: 3 months of an 850-calorie total diet replacement using Optifast® liquid meal replacements and 8 portions of vegetables each day. Optifast® ready to drink shakes are nutritionally complete and are delivered free to the participants' homes. They are available in a range of flavours but are not suitable for anyone with allergies to milk, shellfish and soya.

Phase 2: 4 weeks of a food reintroduction with a progressively increased calorie intake food-based diet (1000–1500 calories/day).

Phase 3: The remainder of the 12-month study period involves a food-based calorie-controlled healthy Mediterranean diet aimed at either further weight loss or weight maintenance if participants have reached participants weight loss goal. A Mediterranean diet includes low-fat meats, fish, fruit, vegetables, wholegrain starchy foods (e.g. wholegrain bread and cereals), beans, pulses, low-fat dairy products and healthy fats found in foods like nuts, seeds and olive /rapeseed oil. If participants gain weight in this time participants have the option to return to the 850-calorie total diet replacement for a short time to help participants lose the weight they have gained.

Physical Activity
Participants will be encouraged to do some simple specific muscle strengthening exercises 3 times a week during phase 1 of the diet. The remainder of the programme includes the 3 weekly muscle strengthening exercises as well as 150-300 minutes of moderate-intensity physical activity a week (i.e. 30-60 minutes 5 times per week).

Advice and support
All participants will receive personalised one to one advice and support from a specialist dietitian throughout the programme. This will be provided by a mixture of face to face and/or remote smartphone/tablet telephone/text reviews using a specialist health care smartphone /tablet app (Oviva app). The app also allows participants to record participants' weight, food intake and any physical activity participants have done and send messages to the dietitian. Participants may also be offered professional support with the emotional and behavioural aspects of weight loss from a clinical psychologist. Some medications may need to be adjusted when following these diets (i.e. blood pressure medications). Any changes to medicines will be advised from the doctors working on the study.

Intervention Type
Mixed

Primary outcome measure
Epithelial cell proliferation (Ki67) in the breast and endometrium at baseline and 12 +/- 4 weeks measured using biopsy

Secondary outcome measures
1. Cancer risk biomarkers; including fasting insulin, lipids, glucose, inflammatory markers inc. CRP, leptin, adiponectin, methylation, insulin like growth factor -1 (IGF-1) measured using blood tests at baseline, 3, 6, 9, and 12 months
2. Uptake, retention and adherence to TDR and 12-month weight loss programme measured using patient records at end of study
3. Weight (kg) measured at baseline, 3, 6, 9, and 12 months
4. Body fat measured using bioelectrical impedance at baseline, 3, 6, 9, and 12 months
5. Fat free mass (kg) measured using bioelectrical impedance at baseline, 3, 6, 9, and 12 months
6. Waist and hip circumference measured at baseline, 3, 6, 9, and 12 months
7. Blood and tissue markers of breast and endometrial cancer and cardiovascular disease measured using a blood test and biopsy at baseline, 3, 6, 9, and 12 months
8. Quality of life (anxiety, depression, quality of life, self-efficacy, self-satisfaction with weight loss during the programme measured using: Generalised Anxiety Disorder-7 [GAD-7] scale, Participant Health Questionnaire-9 [PHQ-9], EQ-5D-3L, Weight Efficacy Lifestyle Questionnaire Short Form [WEL-SF], Obesity and Weight Loss Quality of Life [OWL-QOL] baseline, 3 months, 6 months, 9 months, 12 months, 15 months (control group only)
9. Adverse effects measured using patient records at end of study
10. Diet measured using a 7 day food diary questionnaire at baseline, 3 months, 6 months, 9 months, 12 months, 15 months (control group only)
11. Physical activity behaviours measured using IPAQ at baseline, 3 months, 6 months, 9 months, 12 months, 15 months (control group only)
12. Fidelity of delivery of the 12-month TDR and weight loss programme measured using adherence (7 day food diary)/compliance (weight loss) /loss to follow-up - evaluated at close of trial

Exploratory outcome measures:
13. Markers of the cellular hierarchy in breast +/- endometrium measured using dual immunofluorescence/FACS sorting, using paired biopsy samples from months 0 and 3
14. Transcriptional and proteomic changes measured using RNAseq/qRT-PCR, using paired biopsy samples from months 0 and 3
15. Mammographic density of the breast assessed at baseline and trial exit, scored using Bi-RADS

Overall study start date
01/10/2019

Completion date
14/04/2023

Eligibility

Key inclusion criteria
1. Women aged 30-50 years
2. BMI ≥30 kg/m2 or ≥27.5 mg/m2 in Asian and South Asian women
3. Pre-menopausal, with regular menstrual cycles (cycle length 21 to 40 days)
4. Have access to and be able to use a smartphone or tablet running iOS or Android and be able to use the Oviva app OR access and ability to use a telephone
5. Willing to follow the TDR using Optifast® drinks and have previously sampled them
6. Agree to maintain non-hormonal contraception (barrier or abstinence) until both sets of biopsies are complete and must have a negative urine pregnancy test at screening.
7. Women with Type 2 Diabetes Mellitus on diet +/- Metformin control can be included.
8. Must be able to read, understand and communicate in English

Participant type(s)
Healthy volunteer

Age group
Adult

Sex
Female

Target number of participants
47

Total final enrolment
47

Key exclusion criteria
1. Prior history of breast or endometrial cancer or preinvasive breast disease (Ductal Carcinoma in situ (DCiS), Lobular Carcinoma in situ (LCiS), Atypical Ductal Hyperplasia (ADH), Atypical Lobular Hyperplasia (ALH))
2. Any hormonal contraceptive (including progestin releasing IUCD, such as Mirena®) in the 12 weeks prior to study entry
3. Preventative Tamoxifen therapy within the last 6 months

4. Prior anti-progestin therapy (e.g. Ulipristal Acetate) within the last 6 months
5. Carrier of the BRCA 1 or 2 gene
6. Confirmed pregnant via a pregnancy test at screening, planning pregnancy in the next 12 months, or currently breast feeding
7. Taking prohibited medications (see Appendix 1) including warfarin or novel anticoagulants (NOAC), low molecular weight heparin (LMWH) or equivalent anti-coagulants, anti-psychotic medication, anti-diabetic medication other than Metformin
8. Currently on treatment with Orlistat or other pharmacological treatments for weight loss
9. Chronic use of steroids (more than 20mg daily of prednisolone or its equivalent)
10. Previously had bariatric surgery for weight loss including gastric bypass and sleeve gastrectomy
11. Hypersensitivity to any of the ingredients of Optifast® e.g. lactose intolerance
12. Allergies to the ingredients of Optifast® e.g. fish, milk, soy
13. Substance abuse or harmful alcohol use as indicated by a score of 16 or above on the Alcohol Use Disorders Identification Test (AUDIT)
14. Diagnosed with an eating disorder, or patients with severe binge eating assessed by a score of 27 or more on the Binge Eating Scale (BES)
15. Severe depression assessed by a score of 15 or more on the Patient Health Questionnaire-9 (PHQ-9) questionnaire.
16. Severe anxiety assessed by a score of 15 or more on the General Anxiety Disorder (GAD-7) questionnaire.
17. Psychiatric or physical comorbidity or scheduled for major surgery, which in the opinion of the treating medical physician, or the Chief Investigator (CI), would compromise their safety or adherence to the study
18. Lack capacity or are unable to read or understand written or verbal instructions in English

Date of first enrolment
01/10/2020

Date of final enrolment
15/10/2021

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Manchester University NHS Foundation Trust
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Sponsor type
Hospital/treatment centre

Website
https://mft.nhs.uk/

ROR
https://ror.org/00he80998

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Cancer Research UK

Alternative Name(s)
CR_UK, Cancer Research UK - London, CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Trial protocol publication before end of recruitment. Planned publication in a high-impact peer-reviewed journal.

Intention to publish date
31/12/2025

Individual participant data (IPD) sharing plan
All data generated or analysed during this study will be included in the subsequent results publication

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		19/07/2022	05/04/2023	Yes	No
HRA research summary			20/09/2023	No	No