ISRCTN20130557 https://doi.org/10.1186/ISRCTN20130557

Patient nutrition before diagnosis and tumour response to chemotherapy

Submission date
12/10/2022

Recruitment status
No longer recruiting

Registration date
12/12/2022

Overall study status
Completed

Last Edited
07/10/2025

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
Survival of breast cancer patients has improved a lot in the last few decades, but this is not the case for triple-negative breast cancer (TNBC). Survival is lower if a patient's tumour is able to 'resist' the chemotherapy drugs that are being used to treat it. This is called chemoresistance. When drugs stop working patients need to have their treatment changed. This means that they lose valuable time in the fight against their cancer. The patient may also suffer from unnecessary side effects. It is unclear why a particular chemotherapy drug works better for one patient but not for other patients.

In this study, we want to identify chemotherapy pathways altered by nutrients in Triple Negative Breast Cancer, and if patients' nutritional behaviour and lifestyle are in line and demonstrate adherence to the World Cancer Prevention Fund cancer prevention recommendations or not. We will recruit new TNBC patients and try to predict how their tumours will respond to chemotherapy using this nutrition information. We will use data collected from measuring the activity of the nutrient and chemotherapy genes inside their tumours. We will also collect information about how close their diet is to the World Cancer Prevention Fund's cancer prevention guidelines.

Who can participate?
Adult men and women aged 18 years and over with a new diagnosis of uni- or bilateral TNBC not in an advanced stage, who had a clinical recommendation for chemotherapy before surgery

What does the study involve?
Patients will give permission to take part in the study, agree to provide information about themselves, their body measurements (height and weight/waist and hip), and their nutritional and physical activity habits, provide blood and tumour samples and give permission for us to use your samples and information in our research.

What are the possible benefits and risks of participating?
The study will not benefit patients directly, but participants may find the study to be a positive

experience and gain satisfaction from contributing to research which has the potential to impact the lives of breast cancer patients. There are no specific risks related to your participation in this study.

Where is the study run from?
The Leeds Teaching Hospitals NHS Trust and The University of Leeds (UK)

When is the study starting and how long is it expected to run for?
October 2021 to October 2025

Who is funding the study?
World Cancer Research Fund UK

Who is the main contact?
Dr James Thorne (UK)
j.l.thorne@leeds.ac.uk

Contact information

Type(s)
Scientific

Contact name
Dr Giorgia Cioccoloni

ORCID ID
https://orcid.org/0000-0003-0102-9182

Contact details
School of Food Science and Nutrition @ Parkinson (p2.24a)
Faculty of Environment
University of Leeds
Leeds
United Kingdom
LS2 9JT
+44 (0) 113 3437724
g.cioccoloni@leeds.ac.uk

Type(s)
Principal investigator

Contact name
Dr James Thorne

ORCID ID
https://orcid.org/0000-0002-3037-8528

Contact details
School of Food Science and Nutrition @ Parkinson (p2.32)
Faculty of Environment
University of Leeds

Leeds
United Kingdom
LS2 9JT
+44 (0) 113 343 0684
j.l.thorne@leeds.ac.uk

Type(s)
Scientific

Contact name
Mr Baek Kim

ORCID ID
https://orcid.org/0000-0001-9759-7533

Contact details
The Leeds Teaching Hospitals NHS Trust
St. James’s University Hospital
Beckett Street
Leeds
United Kingdom
LS9 7TF
+44 (0)113 2068724
b.kim@nhs.net

Type(s)
Public

Contact name
Dr Sue Hartup

ORCID ID
https://orcid.org/0000-0002-8852-7872

Contact details
Bexley Wing
St. James’s University Hospital
Beckett Street
Leeds
United Kingdom
LS9 7TF
+44 (0)113 2068628
s.hartup@nhs.net

Type(s)
Scientific

Contact name
Dr Nisha Sharma

Contact details

The Leeds Teaching Hospitals NHS Trust
St. James's University Hospital
Beckett Street
Leeds
United Kingdom
LS9 7TF
+44 (0)1132067398
nisha.sharma2@nhs.net

Type(s)
Scientific

Contact name
Dr Stephen Hursting

ORCID ID
https://orcid.org/0000-0003-3605-2833

Contact details
University of North Carolina at Chapel Hill
235 Dauer Drive
Chapel Hill
United States of America
27599
+1 9199667346
hursting@email.unc.edu

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
311845

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 52522, IRAS 311845

Study information

Scientific Title
Predicting REsponses to chemotherapy from NUTRition In Triple NegatIVE Breast Cancer: The PRE-NUTRITIVE Study.

Acronym
PRE-NUTRITIVE

Study objectives
This prospective, non-randomised, feasibility, cohort study will test the hypothesis that nutrient-metabolism parameters in triple-negative breast cancer (TNBC) and adherence to the World Cancer Research Fund (WCRF) cancer prevention recommendations can influence the expression of functional chemoresistance biomarkers.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 11/05/2022, West Midlands -Solihull Research Ethics Committee (Equinox House, City Link, Nottingham, NG2 4LA, United Kingdom; +44 (0)207 104 8191, (0)207 104 8269; solihull.rec@hra.nhs.uk), ref: 22/WM/0087

Study design
Observational prospective non-randomized feasibility cohort study

Primary study design
Observational

Study type(s)
Screening

Health condition(s) or problem(s) studied
Malignant neoplasm of breast

Interventions
Current interventions as of 21/08/024:
This prospective, non-randomised, feasibility, cohort study will test the hypothesis that nutrient-metabolism parameters in TNBC and adherence to the WCRF cancer prevention recommendations can influence the expression of functional chemoresistance biomarkers. A feasibility study is required given the current lack of information in the literature about sample size and the effect of adherence to the WCRF cancer prevention recommendations and how this impacts chemoresistance. Furthermore, further research is required to select candidate pathways and nutrient-dependent transcription factors responsible for chemoresistance.

In this study, the sample size was purely based on practical considerations regarding time (recruitment period of 18 months) and financial constraints. However, a minimum of 15 and a maximum of 20 TNBC patients undergoing neo-adjuvant chemotherapy (NACT) at Leeds Teaching Hospitals NHS Trust (LTHT) will be recruited in 18 months and the data collected will inform the design of a subsequent trial that will be sufficiently powered.

Study participants will be identified at the breast multidisciplinary (MDT) meeting, in breast surgery and breast oncology clinics by the clinical team directly involved in the patient's care at LTHT. Subsequently, the direct clinical team (consultant breast surgeons, oncologists, or radiologists) and appropriately trained members of the team (including i.e. research nurses or trial assistants) will discuss the option of study participation with the patient at the clinic and provide a patient information sheet (PIS) at the time of the clinic consultation. Patients who agree to participate in the study, will sign and date the latest approved version of the informed consent form (ICF). ICF will be taken by the direct clinical team and appropriately trained members of the team (as specified above). All research visits will take place at the same time as

routine clinical visits, including discussion about study participation and completion of the consent form, so patients will not incur additional hospital visits as a result of agreeing to participate in the study. The only exception will be for tumour biopsies collection for patients who already have the marking clip placed (a small device placed in the breast during the biopsy which is used to locate tumour tissue). In this scenario, we will ask the patients to come to LTHT and all the activities planned at baseline will be performed at that time. For these patients, undergoing the additional biopsy will not be mandatory for participating in the remaining components of the trial. "

Eligibility criteria will be assessed by LTHT team. At baseline (T0), the clinical team will collect pseudonymised information relevant to the study from the hospital electronic patient record (EPR) (i.e. demographic data, pathological data at diagnosis, type of NACT, MRI results) and will report the research data in the CRF. Other data to collect at baseline are breastfeeding and smoking habits. At baseline, one validated food frequency questionnaire (FFQ) (EPIC-Norfolk) for the UK population; 20 minutes for completion), one 24h dietary recall (24HR) (myfood24.org; 20 minutes for completion) and one physical activity questionnaire (10 minutes for completion) will be administrated at LTHT. At the same time blood (50 ml; fasting state) and tumour tissue collection (performed during routine marker clip placement) along with anthropometric measurements (weight, height, waist and hip) will be collected. At Baseline the research visit will require ~1.5 hours extra as a routine clinical visit. At T1 and T2, data about MRI results after the 2nd and 4th NACT cycle will be collected from the hospital EPR and recorded into the CRF. At T3, the clinical team will collect pseudonymised information relevant to the study from the hospital EPR (i.e. Surgery data, Pathological data from cancer resection and further treatments) and will record the research data in the CRF. At T3, another blood collection (50 ml; fasting state) and the second administration of one FFQ, one 24HR (20 minutes for completion/each) and one physical activity questionnaire (10 minutes for completion) will be performed before surgery at LTHT. Tumour tissue (two tumour core biopsies (14 gauge) of the surgical specimen) will also be collected during surgery once the cancer has been resected (T3) by the research team at the LTHT. The surgical team will perform two tumour core biopsies (14 gauge) of the surgical specimen once the cancer has been resected. At T3, the research visits will require ~1 hour extra compared with the routine clinical visits. All the activities mentioned are research specific, including height and weight.

Validated FFQ (EPIC-Norfolk) and physical activity questionnaire EPAQ2 could be completed electronically (University of Leeds online questionnaires https://www.survey.leeds.ac.uk on a tablet) or on paper. myfood24.org 24HR will be performed using myfood24 app pre-downloaded on tablet. We will offer tutorials for mobile app data collection. Once data are collected, they will be sent to the Sponsor for data analysis. Personal data will be NOT used for any survey. The LTHT team will provide the respective surveys (electronic or on paper) to the participants with the pseudonymized code already reported and they will be responsible for saving respective files /hard copies and transfers to the Sponsor. myfood24.org and the University of Leeds comply with the General Data Protection Regulation (GDPR) and are ISO27001 certified. myfood24.org also has NHS Data Security and Protection Toolkit (https://www.dsptoolkit.nhs.uk /OrganisationSearch/Q0Y5Q) accreditation.
For electronic surveys, only the administrator user (Chief Investigator) will provide his personal data and consent to let myfood24.org hold his personal information.
Patient recruitment, along with all the previously cited activities on study participants, will be performed at LTHT. The University of Leeds will be responsible to perform analytical methods including RNA extraction from tumour tissue, as well as analysis of micro- and macro-nutrients in blood samples.

No interim analyses/reports will be carried out during this trial. Blinding is not applicable to this study, however, to contain research bias, the research team who will collect any form of data in LTHT will not be informed of molecular results and vice versa, the research team who will collect any form of data at laboratory level at the University of Leeds will not be informed of the patient's clinical data.

Chemoresistance biomarker genes were identified during a systematic review performed previously (PROSPERO ID: CRD42021243047). Markers of metabolic and nutritional processing (nuclear receptors and target genes). Depending on the amount of RNA obtainable from the biopsies we will either analyse the genes indicated using Taqman Low-density array cards, or with RNA-Sequencing.

Previous Interventions:
This prospective, non-randomised, feasibility, cohort study will test the hypothesis that nutrient-metabolism parameters in TNBC and adherence to the WCRF cancer prevention recommendations can influence the expression of functional chemoresistance biomarkers. A feasibility study is required given the current lack of information in the literature about sample size and the effect of adherence to the WCRF cancer prevention recommendations and how this impacts chemoresistance. Furthermore, further research is required to select candidate pathways and nutrient-dependent transcription factors responsible for chemoresistance.

In this study, the sample size was purely based on practical considerations regarding time (recruitment period of 18 months) and financial constraints. However, a minimum of 15 and a maximum of 20 TNBC patients undergoing neo-adjuvant chemotherapy (NACT) at Leeds Teaching Hospitals NHS Trust (LTHT) will be recruited in 18 months and the data collected will inform the design of a subsequent trial that will be sufficiently powered.

Study participants will be identified at the breast multidisciplinary (MDT) meeting, in breast surgery and breast oncology clinics by the clinical team directly involved in the patient’s care at LTHT. Subsequently, the direct clinical team (consultant breast surgeons, oncologists, or radiologists) and appropriately trained members of the team (including research nurses or trial assistants) will discuss the option of study participation with the patient at the clinic and provide a patient information sheet (PIS) at the time of the clinic consultation. Patients who agree to participate in the study, will sign and date the latest approved version of the informed consent form (ICF). ICF will be taken by the direct clinical team and appropriately trained members of the team (as specified above). All research visits will take place at the same time as routine clinical visits, including discussion about study participation and completion of the consent form, so patients will not incur additional hospital visits as a result of agreeing to participate in the study. The only exception will be for tumour biopsies collection for patients who already have the marking clip placed (a small device placed in the breast during the biopsy which is used to locate tumour tissue). In this scenario, we will ask the patients to come to LTHT and all the activities planned at baseline will be performed at that time. For these patients, undergoing the additional biopsy will not be mandatory for participating in the remaining components of the trial. “

Eligibility criteria will be assessed by LTHT team. At baseline (T0), the clinical team will collect pseudonymised information relevant to the study from the hospital electronic patient record (EPR) (i.e. demographic data, pathological data at diagnosis, type of NACT, MRI results) and will report the research data in the CRF. Other data to collect at baseline are breastfeeding and smoking habits. At baseline, one validated food frequency questionnaire (FFQ) (EPIC-Norfolk) for the UK population; 20 minutes for completion), one 24h dietary recall (24HR) (myfood24.org; 20 minutes for completion) and one physical activity questionnaire (10 minutes for completion)

will be administrated at LTHT. At the same time blood (50 ml; fasting state) and tumour tissue collection (performed during routine marker clip placement) along with anthropometric measurements (weight, height, waist and hip) will be collected. At Baseline the research visit will require ~1.5 hours extra as a routine clinical visit. At T1 and T2, data about MRI results after the 2nd and 4th NACT cycle will be collected from the hospital EPR and recorded into the CRF. At T3, the clinical team will collect pseudonymised information relevant to the study from the hospital EPR (i.e. Surgery data, Pathological data from cancer resection and further treatments) and will record the research data in the CRF. At T3, another blood collection (50 ml; fasting state) and the second administration of one FFQ, one 24HR (20 minutes for completion/each) and one physical activity questionnaire (10 minutes for completion) will be performed before surgery at LTHT. At T3, the research visits will require ~1 hour extra compared with the routine clinical visits. All the activities mentioned are research specific, including height and weight.

Validated FFQ (EPIC-Norfolk) and physical activity questionnaire EPAQ2 could be completed electronically (University of Leeds online questionnaires https://www.survey.leeds.ac.uk on a tablet) or on paper. myfood24.org 24HR will be performed using myfood24 app pre-downloaded on tablet. We will offer tutorials for mobile app data collection. Once data are collected, they will be sent to the Sponsor for data analysis. Personal data will be NOT used for any survey. The LTHT team will provide the respective surveys (electronic or on paper) to the participants with the pseudonymized code already reported and they will be responsible for saving respective files /hard copies and transfers to the Sponsor. myfood24.org and the University of Leeds comply with the General Data Protection Regulation (GDPR) and are ISO27001 certified. myfood24.org also has NHS Data Security and Protection Toolkit (https://www.dsptoolkit.nhs.uk /OrganisationSearch/Q0Y5Q) accreditation.
For electronic surveys, only the administrator user (Chief Investigator) will provide his personal data and consent to let myfood24.org hold his personal information.
Patient recruitment, along with all the previously cited activities on study participants, will be performed at LTHT. The University of Leeds will be responsible to perform analytical methods including RNA extraction from tumour tissue, as well as analysis of micro- and macro-nutrients in blood samples.

No interim analyses/reports will be carried out during this trial. Blinding is not applicable to this study, however, to contain research bias, the research team who will collect any form of data in LTHT will not be informed of molecular results and vice versa, the research team who will collect any form of data at laboratory level at the University of Leeds will not be informed of the patient's clinical data.

Chemoresistance biomarker genes were identified during a systematic review performed previously (PROSPERO ID: CRD42021243047). Markers of metabolic and nutritional processing (nuclear receptors and target genes). Depending on the amount of RNA obtainable from the biopsies we will either analyse the genes indicated using Taqman Low-density array cards, or with RNA-Sequencing.

Intervention Type
Other

Primary outcome(s)
Current primary outcome measure as of 21/08/2024:
The patient’s nutritional status will be measured using the following surveys:
1. Validated food frequency questionnaire (FFQ) using EPIC-Norfolk at T0 and T3
2. 24 dietary recall using myfood24.org at T0 and T3

The patient's nutritional status will also be measured using nutritional profiling of:
3. Blood micro- and macro-nutrient levels (cholesterol and cholesterol precursor/derivatives (oxysterols), vitamins, unsaturated and saturated fatty acids, and eicosanoids) determination using LC-MS/MS and T0 and T3

4. Gene expression in tumour biopsies using RNA sequencing or TaqmanTM Low-Density Array at T0 and T3
5. Anthropomorphic measures (body weight will be measured using a technical balance, height with a stadiometer, and waist and hip circumferences using a tape measure) at T0
6. Tumour size will be measured using Magnetic resonance imaging (MRI) at T0, T1, T2 and T3
7. Physical activity will be measured using the EPAQ2 questionnaire at T0 and T3

T0: Corresponds to the day when patients attend Leeds Teaching Hospitals NHS Trust (LTHT) to have their marker clip placed. For those who already had the marker clip placement done, it is the day they return to LTHT for a second biopsy
T1: Corresponds to the end of 2nd neo-adjuvant chemotherapy (NACT) cycle (approximately 8 weeks after T0)
T2: Corresponds to the end of 4th or 6th cycle of treatment overall, depending on response seen on the MRI at the T1 timepoint.
T3: Corresponds to the day of surgery for tumour resection

Previous primary outcome measure:
The patient's nutritional status will be measured using the following surveys:
1. Validated food frequency questionnaire (FFQ) using EPIC-Norfolk at T0 and T3
2. 24 dietary recall using myfood24.org at T0 and T3

The patient's nutritional status will also be measured using nutritional profiling of:
3. Blood micro- and macro-nutrient levels (cholesterol and cholesterol precursor/derivatives (oxysterols), vitamins, unsaturated and saturated fatty acids, and eicosanoids) determination using LC-MS/MS and T0 and T3

4. Gene expression in tumour biopsies using RNA sequencing or TaqmanTM Low-Density Array at T3
5. Anthropomorphic measures (body weight will be measured using a technical balance, height with a stadiometer, and waist and hip circumferences using a tape measure) at T0
6. Tumour size will be measured using Magnetic resonance imaging (MRI) at T0, T1, T2 and T3
7. Physical activity will be measured using the EPAQ2 questionnaire at T0 and T3

T0: Corresponds to the day when patients attend Leeds Teaching Hospitals NHS Trust (LTHT) to have their marker clip placed. For those who already had the marker clip placement done, it is the day they return to LTHT for a second biopsy
T1: Corresponds to the end of 2nd neo-adjuvant chemotherapy (NACT) cycle (approximately 8 weeks after T0)
T2: Corresponds to the end of 4th NACT cycle (approximately 8 weeks after T1)
T3: Corresponds to the day of surgery for tumour resection

Key secondary outcome(s))

1. Patient uptake rate of blood and tumour tissue donation measured using the study Case report form (CRF) at the end of the study
2. Completion rate of the patient surveys measured using study records (CRF) at the end of the study
3. Determine potential variation in the nutritional status of the study participants measured

using data from molecular assays and the survey questionnaires at the end of the study
4. Accuracy and compliance of WCRF guideline adherence measured using FFQ and myfood24-based methods of data collection at the end of the study
5. RNA yield from tumour biopsies measured using a spectrometer-based microplate reader at the end of the study
6. Measurement of predictors of chemoresponse by gene expression analysis measured using RNA sequencing or TaqmanTM Low-Density Array at the end of the study

Completion date
31/10/2025

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 21/08/2024:
1. Patients aged 18 years or older
2. Uni or bilateral TNBC in the breast and/or axilla (including primary, second primary, locoregional recurrence, or inflammatory breast cancer)
3. Clinical recommendation for NACT
4. Ability to provide informed consent
5. Uni- or multi-focal invasive breast cancer of any histological subtype (if multifocal, dominant lesion that is triple negative to be biopsied) and any tumour (T) and clinical node (N) staging.

Previous participant inclusion criteria:
1. Patients aged 18 years or older
2. Newly diagnosed uni- or bilateral TNBC in the breast and/or axilla
3. Clinical recommendation for NACT
4. Ability to provide informed consent
5. Uni- or multi-focal invasive breast cancer of any histological subtype (if multifocal, dominant lesion that is triple negative to be biopsied)
6. Tumour staging T1, T2 or T3
7. Clinical node staging cN0 or cN1

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria

Current participant exclusion criteria as of 21/08/2024:
1. Patients diagnosed with pure non-invasive breast cancer (e.g. DCIS) or with non-TNBC invasive subtypes,
2. Patients diagnosed with distant metastatic disease at the time of primary breast cancer diagnosis
3. Inability to provide informed written consent

Previous participant exclusion criteria:
1. Patients diagnosed with pure non-invasive breast cancer (e.g. DCIS) or with non-TNBC invasive subtypes (e.g. luminal/HER2 positive)
2. Patients diagnosed with breast cancer locoregional recurrence (i.e. previous history of primary breast cancer)
3. Patients diagnosed with distant metastatic disease at the time of primary breast cancer diagnosis
4. Inability to provide informed written consent
5. Patients with inflammatory breast cancer
6. Tumour staging T4
7. Clinical node staging N2 and N3

Date of first enrolment
02/02/2023

Date of final enrolment
31/01/2025

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
St James University Hospital NHS Trust
St James's University Hospital
Gledow Wing
Beckett Street
Leeds
United Kingdom
LS9 7TF

Sponsor information

Organisation
University of Leeds

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Government

Funder Name
World Cancer Research Fund

Alternative Name(s)
World Cancer Research Fund UK, World Cancer Research Fund International, WCRF International, WCRF, WCRF UK

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in publicly available repositories.

Raw sequencing data will be stored by the LeedsOmics facility for 5 years and then in March 2030 will be deposited at the European Nucleotide Archive (https://www.ebi.ac.uk/ena/browser/home), with a unique DOI. Fully anonymized data containing statistical analyses will be available open-endedly

Fully anonymized research data will be deposited in the University of Leeds data repository as well as in the Leeds Data Repository (https://archive.researchdata.leeds.ac.uk/) with a unique DOI, approximately 6 months after the end of the study. Fully anonymized data containing statistical analyses will be available open-endedly. The full trial report, pseudonymised participant-level dataset, and statistical code for generating the results will not be publicly available.

IPD sharing plan summary
Stored in publicly available repository, Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Protocol (preprint)		21/03/2025	07/10/2025	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes