Hereditary breast cancer and the clinical significance of variants in the BRCA1 and BRCA2 genes.

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1. Developing novel approaches to determine the clinical significance of UVs. 2. Developing new clinical guidelines and implement them into clinical practice.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Observational invasive

Summary

ID

NL-OMON37491

Source
ToetsingOnline

Brief title
Hereditary breast cancer and DNA Unclassified Variants.

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
hereditary breast cancer, mamma carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: NWO Mozaïek (projectnummer 017.008.022) en Van de Kampfonds LUMC (projectnummer 30925)

Intervention

Keyword: BRCA1, BRCA2, Hereditary breast cancer, Unclassified Variant

Outcome measures

Primary outcome

Following the KGCL protocol (Klinisch Genetisch Centrum Leiden), all the affected family members of the patient will be tested on the presence of the Unclassified Variant. Furthermore, also at least one older not affected family member should be tested. This information helps to understand more about the association between carrying a variant and developing cancer.

Secondary outcome

Niet applicable.

Study description

Background summary

The BRCA1 and BRCA2 genes together make the largest contribution to the predisposition to hereditary breast and ovarian cancer. The identification of a disease causing mutation initiates intensive surveillance or risk reducing surgery in carriers. However, in about 10-20% of the DNA tests gene variants with an uncertain clinical significance (unclassified variants or UVs) are identified. The uncertainty of the effect of these variants on protein function and thus on the estimated cancer risk in UV carriers makes both clinical surveillance and genetic counseling of patients and their families very problematic.

Study objective

1. Developing novel approaches to determine the clinical significance of UVs.
2. Developing new clinical guidelines and implement them into clinical practice.

Study design

1) Although individual UV-related characteristics can be informative, they rarely provide sufficient information for a definitive classification. Information will be collected about co-segregation of the UV with cancer in the family, extent of personal and family history, in-silico analysis, effects on RNA splicing, morphological and pathological characteristics of tumors, LOH and array CGH. Subsequently, a multifactorial likelihood-ratio model will be developed that integrates all available information that is collected regarding a specific UV. The model will provide an overall odds of causality.
2) The DNA diagnostic laboratories currently use in silico analysis to categorize UVs into a four-class system with increasing probability of pathogenicity, and uses this categorization to make clinical recommendations. This classification system has a subjective element and performs poorly in assigning a UV to a specific class. Guidelines and a decision aid will be developed to assist DNA laboratories and genetic counselors in improving and objectivising the classification and communication of UVs to counselees.

Study burden and risks

The burden of this research project consists of:
-Bruises after vena puncture.
We have already experience with this typr of research, see P02.050.
The participants experience it as not extemly painful or stressful.

Families in which an unclassified variant is identified experience considerable psychological distress, not only due to the possibility that they may face a cancer risk as high as that for known pathogenic mutations, but also due to the uncertainty of this cancer risk. Reliable classification of UVs will considerably increase the clinical utility and cost-effectiveness of DNA testing and alleviate the psychological burden on these families.

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

1) UV-cohort: patients who are carrier of an unclassified variant.
2) Affected relatives of the UV-cohort patients will be invited for this study.
3) At least one non-affected family member of the UV-cohort patients will be invited to take part in this study. ;The UV-cohort consists of patients diagnosed with a primary breast tumor before the age of 60 years and are unrelated.
The patient can be included if only one unclassified variant is found in the BRCA1 or BRCA2 gene.
All the participants should be older than 18 years, competent and independent of the researcher.
They should all be informed about the study, its goal and its duration.
They know about the possibility of interim quitting the study.

Exclusion criteria

Exclusion criteria:
- Younger than 18 years old and older than 60 years old. Not affected family members may however, be older than 60 years old.
-The participants should be competent to be able to make decision about participation.

Study design

Design

Study type: Observational invasive

Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Health services research

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-12-2012
Enrollment:	270
Type:	Actual

Ethics review

Approved WMO

Date:	16-10-2012
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	29-11-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	NL39318.058.12