Improving risk estimates for familial breast cancer

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Main and long-term goal of this project is to gain more knowledge of the relationship between genome-wide genetic variation and the risk of breast cancer, in the context of a positive family history. This knowledge will improve individual risk...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Reproductive tract and breast disorders congenital
Study type	Observational non invasive

Summary

ID

NL-OMON33487

Source
ToetsingOnline

Brief title
Improving risk estimates for familial breast cancer

Condition

- Reproductive tract and breast disorders congenital
- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Breast cancer; mammary carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Nederlandse Kanker Bestrijding;verschillende projecten

Intervention

Keyword: Breast cancer, Genetic causes, Risk estimation

Outcome measures

Primary outcome

1. A rare high-risk mutation in a gene that is associated with breast cancer,

of relevance to the individual.

2. A common low-risk SNP-variation in a gene that is associated with breast

cancer, of relevance to the familial breast cancer group as a whole.

3. A genetic profile that occurs more often among affected family members than

among controls (sporadic patients or healthy subjects).

4. An association between the result of a functional assay on cell material of

study participants and disease status, at the individual or familial level.

5. A gene expression profile in cell material of study participants that is

associated with disease status, at the individual or familial level.

6. A proteomics profile in cell or serum material of study participants that is

associated with disease status, at the individual or familial level.

Secondary outcome

not applicable

Study description

Background summary

Genetic factors contribute signficantly to susceptibility to breast cancer, but only a minority of them have been identified. Mutations and genetic variation in about 20 genes are currently known to influence breast cancer risk; together they explain almost 30% of the familial risk. The clinical geneticist can

counsel women with a positive family history for breast cancer. In 10-15% of the families a pathogenic mutation in the BRCA1 or BRCA2 gene is detected. In another 15% a variation is detected of which the clinical relevance is unclear. This implies that in over 70% of the patients seeking counseling, risk estimation is based solely on family anamnesis. Other known genes are presently not incorporated in the risk assessment models, mainly because it is presently unclear how the various genes interact with each other to determine individual breast cancer risk.

Study objective

Main and long-term goal of this project is to gain more knowledge of the relationship between genome-wide genetic variation and the risk of breast cancer, in the context of a positive family history. This knowledge will improve individual risk assessment for the development of breast cancer within these families.
New, unknown genes could complement the genetic multifactorial model, while an in-depth characterization of known genes in a large set of families will enable the analysis of genetic interactions that may underlie familial clustering of breast cancer. Ultimately, this will lead to a refinement of gene diagnostics and an improvement of personal risk assessment for individuals from these families.

Study design

We will collect DNA, serum, and fibroblasts of at least 100 probands from eligible breast cancer families and 300-400 relatives. We will use the DNA for the characterization of genetic variation associated with breast cancer. The serum will be used for proteomic analyses if the technology will allow the discovery of protein biomarkers from these samples. Fibroblast cultures can be subjected to a variety of functional analyses, such as gene expression profiling, or cellular response to genotoxic stress.
The detected genetic variation, gene expression and other biological parameters will be analyzed within the framework of the family history of breast cancer. This allows the detection of co-segregation of breast cancer and gene variant in the family, but also, through a *genetical genomics* approach whether various parameters co-segregate and thus have a genetic basis. This approach could lead to the discovery of new genetic determinants for breast cancer, even in the relatively small research population proposed here.

Study burden and risks

The following biomaterials will be collected from study participants:
1. DNA from blood lymphocytes
2. Blood serum
3. Skin biopsy (short term fibroblast cultures will be stored frozen)

The medical side-effects associated with sample collection are negligible. Participants will be invited to visit the Department of Clinical Genetics. For the proband, this means one extra visit (after 2 weeks respite for reflection); for family members it will be a one-time visit. There will be no physical examinations during these visits.
In addition, we will ask permission to request medical data regarding the tumor diagnosis and the formalin-fixed paraffin-embedded tumor tissue. After sample collection, there will be no contact with the proband and the family, except in the case when research has led to insights into the personal breast cancer risk that would be clinically relevant to the individual.

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

- Patient has an elevated risk to develop breast cancer on the basis of her family history for the disease
- Patient has been tested for DNA mutations in BRCA1 and BRCA2
- If patient is known with breast cancer, she has at least two first- or second degree relatives with breast cancer
- If patient has no personal history of breast cancer, she has at least three first- or second-degree relatives with breast cancer
- Families are elible for inclusion if at least two breast cancer patients are alive at the time of ascertainment to donate blood and/or a skin biopsy

Exclusion criteria

1. Individuals younger than 18
2. Individuals with mental illnesses

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-01-2011
Enrollment:	600
Type:	Actual

Ethics review

Approved WMO Date:	22-02-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	NL27093.058.09