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Geneeskunde & Farmacie

GF

PhD in Medical Sciences
2015-2016

INVITATION to the Public defence of

Sylvia DE BRAKELEER

To obtain the academic degree of **'DOCTOR IN MEDICAL SCIENCES'**

Towards a better understanding of genetic predisposition in breast cancer

Tuesday 28 June 2016
Auditorium **Brouwer**, 17:00
Faculty of Medicine and Pharmacy, Laarbeeklaan 103, 1090 Brussel

How to reach the campus Jette:
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Summary of the dissertation

Breast cancer (BC) is the most frequently diagnosed cancer in women (12%) in Western industrialized countries. Heterozygous mutation carriers for the two major BC predisposing genes, *BRCA1* and *BRCA2*, are at increased risk for developing breast and/or ovarian cancer. Germline mutations in *BRCA1/2* are found in only 20% of the BC families. What the underlying genetic cause could be in the remaining 80% of the BC families still needs to be elucidated. In this PhD thesis, we try to further identify the genetic factors responsible for breast cancer predisposition. The ultimate aim would be to identify any person at risk for BC.

Firstly, we present the proof of principle for a Next Generation Sequencing based mutation screening procedure that allows the systematic detection of inherited Alu element insertions at any sequence position in the coding regions of *BRCA1/2*, and by extension in any gene. This approach was successfully implemented in the diagnostic procedure. Secondly, we try to discover new genetic factors (= pathogenic mutations in "new" genes) responsible for the occurrence of BC cases in families where no *BRCA1/2* mutation was found. We investigated the role of BARD1 (a BRCA1 interacting protein) in BC predisposition by analysing a set of patients belonging to high risk non-*BRCA1/2* BC families and a set of patients selected for a specific type of BC (Triple Negative BC or TNBC). Our data indicated a contribution of *BARD1* to the development of BC, especially in TNBC patients.

In a third part, we investigate the nuclear BRCA1 expression pattern obtained in freshly collected leucocytes (normal cells) from *BRCA1/2* mutation carriers. We show that the number of leucocytes presenting a BRCA1 nuclear staining is significantly decreased in *BRCA1/2* mutation carriers when compared to leucocytes from sporadic BC cases and healthy controls. Therefore, we hypothesize that normal cells from heterozygous *BRCA1/2* mutation carriers already present a slightly enhanced genomic instability.

Finally, we present an alternative cancer predisposition model built on the assumption that efficiencies of DNA maintenance mechanisms in normal cells are similar but not identical for each person. The relative level of genomic instability in a normal cell would correlate with the probability of the cell to transform into a cancer cell. When validated, this model may provide a more accurate estimation of individual cancer risks, even in persons without familial antecedents.

Curriculum Vitae

Sylvia De Brakeleer (°Geraardsbergen, 16-01-1980) graduated with great distinction in Biomedical Sciences at the Vrije Universiteit Brussel. She started her PhD work at the Lab of Medical and Molecular Oncology (LMMO) under the promotorship of Erik Teugels (PhD) and Jacques De Grève (MD, PhD). Her work focused on the identification of genetic factors responsible for breast cancer predisposition. In parallel with her PhD work, she was in charge for the setup of several mutation detection techniques (including Next Generation Sequencing) that she afterwards implemented in the molecular cancer diagnostics. Since 2009, she carried out (under supervision of Erik Teugels) the diagnostic *BRCA1/2* germline mutation screens (till December 2014) as well as the diagnostic somatic mutation screens in tumor tissue (till July 2015) at the UZ Brussel (including interpretation, management and reporting to the clinic). Sylvia De Brakeleer is (co)author of eleven articles published in international peer-reviewed journals, of which five as first author. The results obtained during her PhD were presented at several national and international conferences.