European Journal of Cancer 75 (2017) 5–13

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

An association study of established breast cancer reproductive and lifestyle risk factors with tumour subtype defined by the prognostic 70-gene expression signature (MammaPrint®)

M. Makama [a,b], C.A. Drukker [c,d], E.J.Th. Rutgers [c], L. Slaets [e], F. Cardoso [f], M.A. Rookus [a], K. Tryfonidis [g], L.J. Van't Veer [b], M.K. Schmidt [a,b,*]

[a] *Division of Psychosocial Research and Epidemiology, Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands*
[b] *Division of Molecular Pathology, Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands*
[c] *Department of Surgery, Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands*
[d] *Albert Schweitzer Hospital, Department of Surgery, Dordrecht, The Netherlands*
[e] *Department of Statistics, European Organization for Research and Treatment of Cancer, Brussels, Belgium*
[f] *Breast Unit, Champalimaud Clinical Center, Lisbon, Portugal*
[g] *Medical Department, European Organization for Research and Treatment of Cancer, Brussels, Belgium*

Received 3 July 2016; received in revised form 1 December 2016; accepted 20 December 2016
Available online 16 February 2017

KEYWORDS
70-Gene signature;
MammaPrint;
Breast cancer prognosis;
Subtypes;
Breast cancer risk factors

Abstract ***Background:*** Reproductive and lifestyle factors influence both breast cancer risk and prognosis; this might be through breast cancer subtype. Subtypes defined by immunohistochemical hormone receptor markers and gene expression signatures are used to predict prognosis of breast cancer patients based on their tumour biology. We investigated the association between established breast cancer risk factors and the 70-gene prognostication signature in breast cancer patients.
Patients and methods: Standardised questionnaires were used to obtain information on established risk factors of breast cancer from the Dutch patients of the MINDACT trial. Clinical-pathological and genomic information were obtained from the trial database. Logistic regression analyses were used to estimate the associations between lifestyle risk factors and tumour prognostic subtypes, measured by the 70-gene MammaPrint® signature (i.e. low-risk or high-risk tumours).

* *Corresponding author*: Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066CX, Amsterdam, The Netherlands.
E-mail address: mk.schmidt@nki.nl (M.K. Schmidt).

http://dx.doi.org/10.1016/j.ejca.2016.12.024

Results: Of the 1555 breast cancer patients included, 910 had low-risk and 645 had high-risk tumours. Current body mass index (BMI), age at menarche, age at first birth, age at menopause, hormonal contraceptive use and hormone replacement therapy use were not associated with MammaPrint®. In parous women, higher parity was associated with a lower risk (OR: 0.75, [95% confidence interval {CI}: 0.59–0.95] $P = 0.018$) and longer breastfeeding duration with a higher risk (OR: 1.03, [95% CI: 1.01–1.05] $P = 0.005$) of developing high-risk tumours; risk estimates were similar within oestrogen receptor–positive disease. After stratifying by menopausal status, the associations remained present in post-menopausal women.

Conclusion: Using prognostic gene expression profiles, we have indications that specific reproductive factors may be associated with prognostic tumour subtypes beyond hormone receptor status.

1. Introduction

Breast cancer is the most frequently diagnosed cancer among women worldwide [1]. The implementation of organised breast cancer screening and increased awareness in many European countries has resulted in early detection thereby, contributing to an increase in the incidence rate [2]. Incidence rates for women aged below 40 and 40–49 years has increased by 2.1% and 2.4%, respectively, annually since 1995 [3]. Survival of breast cancer has also increased, relative 10-year survival rates for women aged 50–69 years (period analysis) increased from 53–75% between 1975 and 2004 [3].

Well-established risk factors for breast cancer include both genetic and lifestyle/environmental factors; such as obesity, lack of physical activity, hormone replacement therapy, late maternal age at first childbirth, low parity and alcohol use [4]. Advances in early detection and adjuvant therapies have resulted in an increase in breast cancer survival [5]. Moreover, specific breast cancer subtypes, e.g. oestrogen receptor (ER) positive and ER negative, are associated with subsequent relatively better or worse survival [6]. In view of this, it is important to investigate how these established lifestyle risk factors are associated with the development of different breast cancer subtypes.

Several studies have investigated associations of breast cancer risk lifestyle factors with development of specific breast cancer molecular subtypes [7–10], and with survival after breast cancer diagnosis [11–15], measured by immunohistochemistry. However, whether molecular subtypes by gene expression profiling, representing a more complex tumour biology, are associated with breast cancer lifestyle risk factors has not yet been investigated.

Gene expression signatures like MammaPrint® [16] are already being used in daily clinical practice, in combination with clinical-pathological factors such as tumour size, stage, nodal status and hormone receptor status, to predict the prognosis of breast cancer patients [17]. In this study, we aim to investigate the association between established risk factors and MammaPrint® (low-risk or high-risk) in breast cancer patients. This will provide more insight into the impact of these lifestyle/environmental risk factors on the development of specific molecular tumour subtypes.

2. Methods

2.1. Study design and population

The Microarray In Node negative and 1–3-positive Disease may Avoid ChemoTherapy (MINDACT) trial is an international prospective, randomised phase III trial evaluating the clinical utility of MammaPrint® when added to commonly used clinical-pathologic criteria, for the selection of breast cancer patients with node-negative disease or a maximum of 3 positive lymph nodes for adjuvant chemotherapy. During the trial, risk assessment based on clinical-pathological factors (by using a modified version of Adjuvant!Online) and based on MammaPrint® was obtained from all enrolled patients. The details of the MINDACT trial have been previously published [18,19]. In short, patients included in the study were women aged between 18 and 70 years at the time of randomisation, with early invasive breast cancer.

The MINDACT lifestyle study is a study that was designed to assess lifestyle and environmental factors that act (together with genetic susceptibility) in the aetiology and prognosis of breast cancer. Here, we present cross-sectional analyses between these risk factors and breast cancer subtype. Patients were asked about lifestyle and reproductive factors before breast cancer diagnosis.

2.2. Data collection

Standardised self-administered questionnaires were used to obtain information on established risk factors for breast cancer. An invitation to complete an online