European Journal of Cancer (2013) xxx, xxx–xxx

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Obesity increases the incidence of distant metastases in oestrogen receptor-negative human epidermal growth factor receptor 2-positive breast cancer patients

Luca Mazzarella [a,b,*], Davide Disalvatore [c], Vincenzo Bagnardi [c,d], Nicole Rotmensz [c], Donata Galbiati [e], Sara Caputo [b], Giuseppe Curigliano [a,*], Pier Giuseppe Pelicci [b,f,*]

[a] *Division of Medical Oncology, Istituto Europeo di Oncologia, Milan, Italy*
[b] *Department of Experimental Oncology, Istituto Europeo di Oncologia, Milan, Italy*
[c] *Division of Epidemiology and Biostatistics, Istituto Europeo di Oncologia, Milan, Italy*
[d] *Department of Statistics and Quantitative Methods, University of Milan-Bicocca, Milan, Italy*
[e] *The Falck Division of Medical Oncology, Ospedale Niguarda Ca' Granda, Milan, Italy*
[f] *Dipartimento di Medicina, Chirurgia e Odontoiatria, Università degli Studi di Milano, 20122 Milan, Italy*

KEYWORDS
Body mass index
Breast neoplasms
HER2
Obesity

Abstract ***Background:*** Obesity is a major negative determinant of breast cancer outcome. However, there are contrasting data on the differential impact of obesity on specific breast cancer subtypes. In particular, very little is known on human epidermal growth factor receptor 2-positive (HER2+) tumours.

Patients and methods: We assessed the prognostic role of increased body mass index (BMI) on a consecutive series of non-metastatic HER2+ patients treated at our institution before the introduction of adjuvant Trastuzumab. We separately analysed oestrogen receptor-positive (ER+) and -negative (ER−) HER2+ cases.

Results: In ER−/HER2+ tumours we observed a significantly worse overall survival (Hazard ratio (HR) 1.79, *p*-value 0.041) and cumulative incidence of distant metastases (HR 2.03, *p*-value 0.019) in obese (BMI > 30) versus normal/underweight (BMI < 25) patients. Local relapses appeared to be non-significantly reduced in obese patients, masking the overall effect on disease-free survival. Outcome in ER+ tumours, instead, was not significantly different between BMI groups.

Conclusions: Obesity significantly correlates with worse overall survival and cumulative incidence of distant metastases in ER−/HER2 positive breast cancer. Differences in the biology

* *Corresponding authors:* Address: Department of Experimental Oncology, IFOM-IEO Campus, Via Adamello 16, 20139 Milan, Italy. Tel.: +39 02 9437 5083; fax: +39 02 9437 5991 (L. Mazzarella), tel.: +39 02 9437 2056; fax: +39 02 9437 5991 (P.G. Pelicci). Address: Division of Medical Oncology, European Institute of Oncology, Via Ripamonti 435, 20141 Milano, Italy. Tel.: +39 02 57489 599; fax: +39 02 94379 224 (G. Curigliano).

E-mail addresses: luca.mazzarella@ieo.eu (L. Mazzarella), giuseppe.curigliano@ieo.it (G. Curigliano), piergiuseppe.pelicci@ieo.eu (P.G. Pelicci).

0959-8049/$ - see front matter
http://dx.doi.org/10.1016/j.ejca.2013.07.016

Please cite this article in press as: Mazzarella L. et al., Obesity increases the incidence of distant metastases in oestrogen receptor-negative human epidermal growth factor receptor 2-positive breast cancer patients, *Eur J Cancer* (2013), http://dx.doi.org/10.1016/j.ejca.2013.07.016

of breast tumours may determine individual susceptibility to obesity. The biology of the underlying tumour should be taken into account in the design of dietary intervention trials in breast cancer.

1. Introduction

Besides its established role as a risk factor, there is now widespread consensus on the importance of obesity as a negative prognostic factor for breast cancer.[1–3] This recognition has provided a strong rationale for past and on-going studies on the metabolic control of breast cancer patients through dietary or pharmacological interventions.[4–7]

Breast cancer is, however, a biologically heterogeneous disease in which treatment modalities are dictated by molecular features;[8] definitive evidence is still lacking on the impact of obesity on specific breast cancer types. Studies including information on oestrogen receptor (ER)-positive versus -negative tumours were meta-analysed by Niraula et al.[2] The authors concluded that the receptor status did not significantly alter the obesity effect on overall survival (OS) (obese/normal hazard ratio (HR): 1.31 and 1.18 in ER+ and ER−, respectively) or on breast cancer-specific survival (BCSS) (obese/normal HR: 1.36 and 1.46 in ER+ and ER−, respectively). However, there was substantial heterogeneity among the studies included in the analysis, due to differences in body mass index (BMI) categorisation and variability in the definition of the ER− disease, with early studies considering tumours with <10% ER expression as ER negative, contrarily to current guidelines.[8] Individual studies did in fact observe differences between ER+ and ER− groups.[9,10]

If differential effects according to hormone receptor status are still a matter of debate, even less is known on human epidermal growth factor receptor 2-positive (HER2+) tumours. In the present study, we assessed the prognostic role of increased BMI on a consecutive series of non-metastatic HER2+ patients treated at our institution. As the introduction of targeted therapy has radically altered the natural history of this disease, we decided to limit our analysis to patients treated before the introduction of Trastuzumab adjuvant therapy. ER+ and ER− HER2+ tumours were separately analysed, as they constitute clinically and biologically distinct groups.[8,11] Surprisingly, a role for obesity could be observed only in ER− tumours, with a significantly worse OS and an increased risk of distant metastases.

2. Patients and methods

We systematically collected information on all consecutive breast cancer patients operated at the European Institute of Oncology in a dedicated data base, thus we had access to the clinical data of interest (from 1995 to 2005, prior to Trastuzumab adjuvant therapy). We identified 1250 HER2+ early stage breast cancer patients operated during this period for whom data were available regarding weight and height, which we used to calculate the BMI [weight in kilograms/(height in metres)^2]. Data were also available regarding age, menopausal state, date of surgery, tumour characteristics (histological type, tumour size, nodal involvement, grade, perivascular infiltration, Ki-67 and ER/progesterone receptor (PgR) expression) and treatment modality (type of surgery, adjuvant radiotherapy, endocrine therapy and chemotherapy).

Patients' follow-up included: physical examination every 6 months, annual mammography and breast ultrasound, blood tests every 6–12 months and, in case of symptoms, further evaluation. When possible, the status of those women not attending the scheduled follow-up visits at the institute for more than one year was obtained by telephone contact. Forty patients (3.2%) were lost to follow-up. The median length of follow-up was 8.2 years. The study was approved by the Institutional Review Board.

2.1. Statistics

Patients were assigned to BMI groups, according to the standard World Health Organisation (WHO) categorisation,[12] as follows: underweight (BMI < 18.5), normal weight (BMI between 18.5 and 24.99), overweight (BMI between 25 and 29.99) and obese (BMI $\geqslant$ 30).

Differences in the distribution of subject characteristics between groups were evaluated by the Chi-square test.

End-points included disease-free survival (DFS), overall survival (OS), cumulative incidence of local or regional recurrence (CI-LR) and distant metastases (CI-DM). DFS was defined as the time from surgery to events such as relapse (including ipsilateral breast recurrence), appearance of a second primary cancer (including contralateral breast cancer), or death, whichever occurred first. OS was defined as the time from surgery until the date of death (from any cause). DFS and OS functions were estimated using the Kaplan–Meier method. The log-rank test was used to assess differences between groups. The CI-LR and CI-DM were defined as the time from surgery to the appearance of a local or regional recurrence and distant metastases, respectively.

CI-LR and CI-DM functions were estimated according to methods described by Kalbfleisch and Prentice,[13]

Please cite this article in press as: Mazzarella L. et al., Obesity increases the incidence of distant metastases in oestrogen receptor-negative human epidermal growth factor receptor 2-positive breast cancer patients, *Eur J Cancer* (2013), http://dx.doi.org/10.1016/j.ejca.2013.07.016