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High fasting blood glucose and obesity significantly and independently increase risk of breast cancer death in hormone receptor-positive disease

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KEYWORDS
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Abstract ***Purpose:*** We investigated the effect of fasting blood glucose and body mass index (BMI) at diagnosis on risk of breast cancer death for cases diagnosed in five Italian cancer registries in 2003–2005 and followed up to the end of 2008.
Methods: For 1607 Italian women (⩾15 years) with information on BMI or blood glucose or diabetes, we analysed the risk of breast cancer death in relation to glucose tertiles (⩽84.0, 84.1–94.0, >94.0 mg/dl) plus diabetic and unspecified categories; BMI tertiles (⩽23.4, 23.5–27.3, >27.3 kg/m^2, unspecified), stage (T1–3N0M0, T1–3N+M0 plus T4anyNM0, M1, unspecified), oestrogen (ER) and progesterone (PR) status (ER+PR+, ER−PR−, ER and

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PR unspecified, other), age, chemotherapy and endocrine therapy, using multiple regression models. Separate models for ER+PR+ and ER−PR− cases were also run.

Results: Patients often had T1–3N0M0, ER+PR+ cancers and received chemotherapy or endocrine therapy; only 6% were M1 and 17% ER−PR−. Diabetic patients were older and had more often high BMI (>27 kg/m^2), ER−PR−, M1 cancers than other patients. For ER+PR+ cases, with adjustment for other variables, breast cancer mortality was higher in women with high BMI than those with BMI 23.5–27.3 kg/m^2 (hazard ratio (HR) = 2.9, 95% confidence interval (CI) 1.2–6.9). Breast cancer mortality was also higher in women with high (>94 mg/dl) blood glucose compared to those with glucose 84.1–94.0 mg/dl (HR = 2.6, 95% CI 1.2–5.7).

Conclusion: Our results provide evidence that in ER+PR+ patients, high blood glucose and high BMI are independently associated with increased risk of breast cancer death. Detection and correction of these factors in such patients may improve prognosis.

1. Introduction

Diabetes, impaired glucose tolerance and hyperglycaemia are associated with increased risk of developing breast cancer [1,2]. There is also evidence that these conditions may worsen prognosis for the disease [3,4]. Obesity is associated with hyperglycaemia, and is also associated with increased breast cancer risk after menopause [5,6], as well as poor prognosis and unfavourable tumour characteristics in breast cancer patients of all ages [7,8]. However, the combined effects of adiposity and hyperglycaemia on the survival of breast cancer patients have been poorly investigated.

That lifestyle factors can influence breast cancer incidence and outcomes clearly has major implications for primary and secondary prevention. It is also possible that variable prevalence of dysmetabolic conditions across Europe may contribute to the variations in breast cancer survival across the continent that have been repeatedly documented by EUROCARE [9]. These survival differences are not completely explained by differences in stage at diagnosis or patient management [10]. For example, poorer breast cancer survival in Denmark, compared to other Nordic countries, has been suggested to be related to lifestyle and co-morbidity differences between Danish and other Nordic women [11]. However, reliable population-based information on lifestyle and co-morbidities is not easily available, and studies of their effect on cancer survival in populations require *ad hoc* data collection [12–14] or electronic linking of population-based cancer registry data on incidence and survival, to clinical data from other sources [15].

Hypothesising that high body mass index (BMI) and high fasting blood glucose adversely influence survival [18], we analysed survival in relation to BMI and fasting glucose in a random set of breast cancer cases diagnosed in 2003–2005.

2. Materials and methods

As specified by the Italian High Resolution study protocol [16], breast cancer cases were sampled from the Italian Association of Cancer Registries (CRs) database [17] by a randomised procedure balanced for each participating registry and year of diagnosis (2003–2005). Each participating CR had to access patients' clinical records to collect information on diagnostic investigations, disease stage, hormone receptor status, treatment, fasting blood glucose, BMI (or height and weight), and presence of diabetes (or treatment with oral hypoglycaemic drugs or insulin). Five Italian CRs (Modena, Napoli, Romagna, Sassari, Trapani) contributed 1607 cases to the present study: in all cases information on BMI and/or fasting blood glucose (or diabetes, including treatment with hypoglycaemic drugs or insulin) was available.

We analysed information on age (15–39, 40–49, 50–69 and 70–99 years), stage, coded according to the sixth edition of the tumour-node-metastasis (TNM) manual [18], (T1–3N0M0, T1–3N+M0 plus T4anyNM0, M1 and unspecified), oestrogen (ER) and progesterone (PR) status (both positive (ER+PR+), both negative (ER−PR−), both unknown (unspecified) and any other combination of categories (other)), chemotherapy and endocrine therapy (given, not given, unspecified). ER and PR were considered positive when at least 10% of cancer cells showed nuclear staining.

To minimise intra-patient measurement variation, we requested up to three measurements of fasting blood glucose and BMI, determined from three months before diagnosis up to hospital admission for breast cancer surgery. When more than one measurement was available, we used the mean of the two or three values determined nearest to diagnosis. If BMI was not reported but height and weight were available, BMI was calculated according to World Health Organization indications [19]. The BMI variable consisted of tertiles (⩽23.4,