Dear Editor,

It is generally accepted that women with breast cancer (BC) have an increased risk of venous thromboembolism (VTE) compared with age-matched women without cancer. Metastatic disease, chemotherapy (Chavez-MacGregor et al. 2011) and tamoxifen treatment (Pritchard et al. 1996) are all risk factors for increased VTE risk. Particularly, a 6% annual VTE incidence while undergoing chemotherapy, and up to 1 month after, has been recently reported in a cohort study, showing that VTE risk was markedly higher in the 3 months after initiation of tamoxifen, but not aromatase inhibitors (Walker et al. 2016).

As BC is the most common female cancer, treatment-related VTE poses serious concerns in terms of both patient care and health costs, while thromboprophylaxis could provide an opportunity to substantially improve BC management. Nonetheless, consensus guidelines do not recommend routine prophylaxis for the primary prevention of VTE in cancer outpatients receiving chemotherapy, except for selected high-risk patients (Khorana et al. 2014). To guide the oncologist community in VTE risk assessment, the International Society for Thrombosis and Haemostasis has recently proposed the adoption of the Khorana score (Khorana et al. 2008). In this context, the PTV Bio.Ca.Re. (Policlinico Tor Vergata Biospecimen Cancer Repository) and the Interinstitutional Multidisciplinary Biobank of the IRCCS San Raffaele Pisana (SR-BioBIM) are actively involved in the recruitment of BC outpatients undergoing chemotherapy, who are prospectively followed under appropriate Institutional ethics approvals, as part of a clinical database and biobanking project. Among them, 390 patients with primary (84%) or relapsing (16%) BC completed the clinical assessment for VTE. As expected, VTE incidence was lower in BC compared with other cancer types, with only 9 (2.3%) events recorded during treatment, mostly in advanced/metastatic stages. Nonetheless, since BC is considered a low-risk tumour in the Khorana score (Khorana et al. 2008), risk stratification assigned 81.5% (n=318) and 18% (n=70) of patients to the low- and intermediate-risk category, whereas only 2 (0.5%) obese patients fell into the high-risk category and would have been, therefore, eligible for thromboprophylaxis.

Obesity has been linked to VTE risk in cancer outpatients at a point that BMI has been included in the Khorana score (Khorana et al. 2008). Actually, obese (body mass index (BMI) >30) patients undergoing mastectomy had an approximately two-fold increased risk of VTE (Tran et al. 2013), but only weak interaction was reported between BC and the Charlson co-morbidity index (including obesity and diabetes) on the rate of VTE (Ording et al. 2014).

In this scenario, a possible explanation for the relationship between obesity and VTE may come from the central role played by insulin resistance (IR). It is, thus, legitimate to ask whether IR itself is a risk factor for VTE. Unfortunately, little information is available and only one large prospective population-based cohort study specifically addressed this issue, showing that individuals with higher IR scores had an increased risk of unprovoked VTE, which was independent of several related risk factors, but not BMI (Van Schouwenburg et al. 2012).

Both obesity and IR are well-recognized co-morbid conditions of BC, and general consensus exists on the possibility that they may also contribute to BC risk and/or prognosis (Ferroni et al. 2015). However, no study has investigated, so far, the role of IR as a VTE risk factor in BC. Thus, based on the hypothesis that IR might play a role in BC-associated VTE, we investigated the performance of HOMA (homeostasis model assessment) index in VTE risk prediction in the cohort of BC women (n=390, mean age 56±13 years) enrolled in the PTV Bio.Ca.Re and SR-BioBIM. All patients entered the study...
after providing written informed consent and before the start of chemotherapy (17% neoadjuvant, 55% adjuvant, 15% metastatic regimens) or adjuvant endocrine therapy (13%, tamoxifen or aromatase inhibitor) for luminal-like A (LLA, 28%), LLB (54%), HER2-enriched (5%) or triple-negative (13%) BC, with an Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0 (96%) or 1 (4%). All patients were prospectively followed for the entire duration of treatment or until VTE occurrence. No patient received thromboprophylaxis.

HOMA index was calculated for each participating subject from fasting blood glucose and insulin levels according to the formula: glucose (mg/dL) × insulin (μIU/mL)/405. All measurements were performed blinded to patient’s outcome.

Cox-proportional hazard analysis was performed to evaluate the association between clinical variables and VTE (either DVT or PE). Time-to-event (TTE) was calculated from the date of enrollment until VTE occurrence or end of chemotherapy. For patients receiving neoadjuvant chemotherapy, TTE was calculated at the completion of an entire antiblastic treatment and before surgery. Survival curves were calculated by Kaplan–Meier and log-rank methods. Sample size of the study was based on the willingness to provide informed consent rather than on sample size calculations. However, subsequent calculation showed that the recruited population was capable of yielding a power >90%, at a two-sided 5% significance level. This was based on the assumption of a true hazard ratio (HR) of at least 2, an accrual period of no less than 2 years, an elapsed time between cycles within 30 days and a median TTE of 2.5 months.

A condition of overweight/obesity was observed in 54% of BC women, while impaired glucose tolerance (IGT) or type 2 diabetes (T2D) was diagnosed in 18% of cases. It is well recognized that overweight/obesity increases the chances of developing T2D; accordingly, the rate of T2D rose from 9% in normoweight to 17% and 36% in overweight and obese BC patients, respectively. Median pre-chemotherapy HOMA index was 2.4 in the overall BC cohort (interquartile range (IQR): 1.5–5.2). As expected, median HOMA index was associated with BMI and increased steadily going from 1.9 in normoweight (n=179) to 2.5 and 4.1 in overweight and obese BC patients, respectively. Median pre-chemotherapy HOMA index was 2.4 in the overall BC cohort (interquartile range (IQR): 1.5–5.2). As expected, median HOMA index was associated with BMI and increased steadily going from 1.9 in normoweight (n=179) to 2.5 and 4.1 in overweight (n=151) and obese (n=60) BC women, respectively (Kruskal–Wallis H = 17.9, P = 0.0001). Similarly, IR was associated with the presence of IGT (median HOMA index 6.6) or T2D (median HOMA index 5.3).

As stated above, VTE occurred in 9 (2.3%) BC patients (median TTE: 2.1 months), in agreement with
previous findings (Chavez-MacGregor et al. 2011). No patient had asymptomatic VTE on onset as confirmed by restaging procedures at the end of chemotherapy. Clinical characteristics of all 9 patients with VTE are given in Table 1. As reported, 8 out of 9 women had advanced/metastatic BC, and a BMI ranging from 17.5 to 35.9. No patient had overt T2D, with the exception of one patient who developed iatrogenic diabetes while on treatment. All patients were negative for HER2/NEU. This is surprising, as an independent association between HER2 and IR has been reported (Ferroni et al. 2015). However, we could speculate that aggressive combination chemotherapies could have triggered VTE development in this subset of patients. No event was recorded in endocrine-treated patients, in agreement with previous observations (Walker et al. 2016). No patient was classified at high risk for VTE, as per current guidelines (Khorana et al. 2014).

On the other hand, all patients who developed VTE had a condition of IR, as demonstrated by HOMA indexes above the 2.5 cutoff for normality (Table 1). Furthermore, median HOMA index in VTE patients was higher (6.82) than those without VTE (2.28, Mann–Whitney test: \( P = 0.0034 \)). Survival analyses were then performed after dichotomizing patients into two groups according to the 2.5 cutoff. Univariate Cox proportional analysis showed that HOMA index was able to significantly predict the occurrence of a first VTE episode with an HR of 12.2 (95% CI: 1.52–97.4). These results were substantially unmodified after adjusting for other variables known to interfere with VTE risk (stage, overweight/obesity, type of treatment or tamoxifen use). Indeed, both metastatic disease (HR 11.0 (95% CI: 1.73–70.3)) and HOMA index (HR 8.26 (95% CI: 1.00–68.5)) acted as independent VTE predictors in a multivariate Cox analysis (overall model fit: \( \chi^2 = 20.0 \), \( P = 0.0013 \)). Accordingly, patients with a HOMA index above the 2.5 cutoff \( (n = 165) \) had a worst 1-year event-free survival (94%) compared with those with a HOMA index within the normal range \( (n = 225) \), who were all VTE-free at the end of the treatment (log-rank test: 2.5, \( P = 0.0005 \)) (Fig. 1).

Our results are in partial agreement with the findings by Van Schouwenburg and coworker and those of a recently published meta-analysis demonstrating that the increased risk of diabetes-associated VTE might result from confounders (i.e., obesity) rather than an intrinsic effect of diabetes (Gariani et al. 2015). However, the predictive value of IR in our analysis was independent of a condition of overweight/obesity, suggesting that other factors associated to IR might play a role in VTE occurrence. An intriguing hypothesis that, however, deserves further investigation is that the low-grade inflammatory status that accompanies IR may play a role in VTE development, as suggested by the association of HOMA index with platelet \( (P < 0.0001) \) and neutrophil/lymphocyte ratio \( (P < 0.0001) \).

In conclusion, the results here reported demonstrate that IR appraisal may allow for VTE risk stratification, helping in identifying chemotherapy-treated BC patients who could benefit from thromboprophylaxis. Further multicenter prospective studies involving a larger number of patients are presently needed.

Patrizia Ferroni1,2
Mario Roselli3
Silvia Riondino2,3
Francesco Cavaliere4
Fiorella Guadagni1,2

1San Raffaele Roma Open University, Rome, Italy
2IRCCS San Raffaele Pisana, Interinstitutional Multidisciplinary Biobank, Rome, Italy
3Department of Systems Medicine, Medical Oncology, PTV Bio.Ca.Re., University of Rome “Tor Vergata”, Rome, Italy
4Department of Surgery, San Giovanni Hospital-Addolorata, Rome, Italy

(Correspondence should be addressed to P Ferroni; email: patrizia.ferroni@sanraffaele.it)
Declaration of interest
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Author contributions
P F, M R and F G designed the study, analyzed and interpreted the data and wrote the manuscript; S R and F C analyzed and interpreted the data, performed statistical analysis and wrote the manuscript; all authors revised and approved the final version of the manuscript.

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