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ESMO Clinical Research Fellowship (March 2012 – February 2013)

Association between insulin resistance and pathologic response to neoadjuvant chemotherapy among women with localized infiltrating breast cancer.

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Final Report

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Introduction

Many retrospective studies have shown the link between insulin resistance and metabolic syndrome with breast cancer (1-5). Most of these studies on breast cancer were developed retrospectively and in the adjuvant setting.

The insulin resistance determined by biochemical parameters or anthropometric measures has been associated with increased risk of developing breast cancer in epidemiological studies (6-12). Its association has been described not only as a risk factor, but as a poor prognostic factor for overall survival and disease-free survival in patients where the diagnosis of breast cancer has been made (13-17).

Evidence of insulin resistance and its impact as a possible independent predictor of response to cancer treatment is lacking, specifically its role as a predictor of response to chemotherapy (18-19). Besides, from the therapeutic point of view, there are studies suggesting that metformin consumption in the context of neoadjuvant chemotherapy in breast cancer, decrease cancer cells proliferation and increase the likelihood of complete pathological response (20-24).

There is a lack of prospective studies that have reviewed the impact of insulin resistance and /or the metabolic syndrome across the neoadjuvant chemotherapy time and the likelihood of pathologic complete response on localized breast cancer.

The aim of our study was to determine the association between insulin resistance measured by HOMA2 IR and the pathological response to neoadjuvant chemotherapy among women with localized infiltrating breast cancer.

As a secondary goals, we described the change in fasting glucose, lipids and insulin resistance measured by HOMA2 IR (baseline, during and final cycles of neoadjuvant chemotherapy). We explained the type and number of components of metabolic syndrome and its relationship with the pathological response. We also linked serum glucose, insulin and HOMA2 IR with biological breast cancer subtypes.

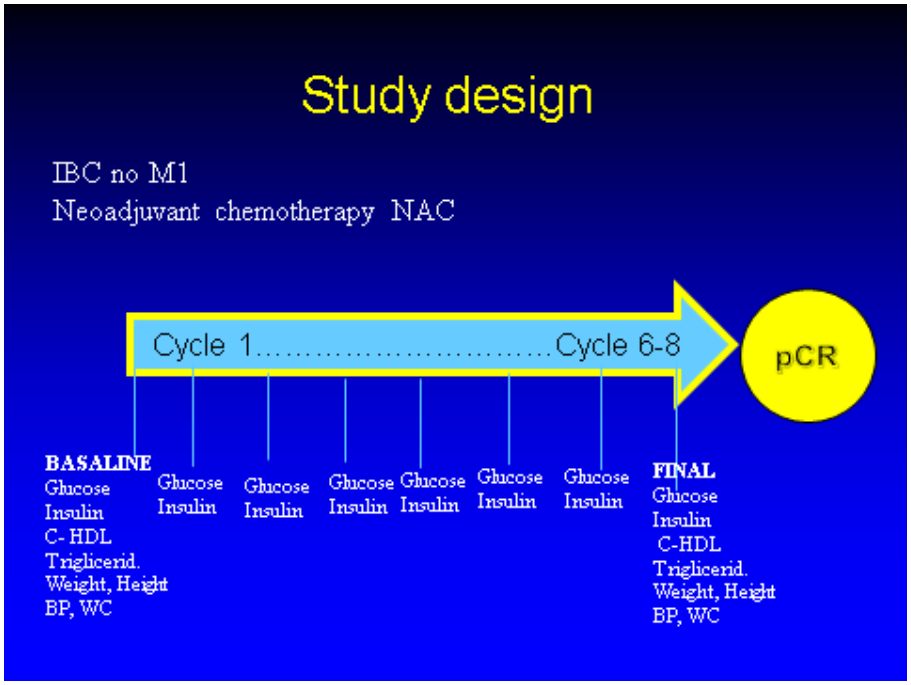
Patients and Methods

It was a prospective, multicenter and non-interventional cohort study. 64 patients were included with localized IBC (infiltrating breast cancer) who were treated with NAC (neoadjuvant chemotherapy).The patients were recruited in three Spanish oncology centers: Hospital del Mar, Parc Taulí Sabadell Hospital Universitari and Hospital Clinic I Provincial de Barcelona.

All the patients signed an agreement that was previously approved by the ethics committee of each center. The inclusion criteria were: female age 18 years or older, ECOG Performance Status of 0 or 1. Women with measurable localized invasive breast cancer diagnosed by core needle biopsy, T2, T3, or T4 tumors clinically staged as M0, patients with multi-focal breast cancer and synchronous contralateral breast were included. All the patients received as primary oncology treatment neoadjuvant chemotherapy (NAC), at least 6 cycles with one of two standards of care regimens that must consist of the following agents: epirrubicin (E), cyclophosphamide (C), and a taxane (T) such as docetaxel, paclitaxel, and trastuzumab in HER2 positive group, were our eligibility criteria. In the other hand, exclusion criteria were previous diagnosis of diabetes mellitus and/or hypoglycemiant treatment (oral hypoglycemiant or subcutaneous insulin), definitive or radiologic evidence of distant metastatic disease, excisional or incisional biopsy for primary breast tumor, any prior therapy for invasive breast cancer, surgical axillary dissection before study entry, synchronous or metachronous malignant disease other than in situ cervical cancer or non-melanoma skin cancer.

Histopathological diagnosis of IBC was made by core needle biopsy. All tumors had IHQ (immunohistochemistry) evaluation. Hormonal receptors (ER, PR) were positive with tumor staining ≥1% and negative with <1% tumor staining. HER2 status meeting 1 of the following criteria: HER2-positive disease was defined 3+ by immunohistochemistry (IHC) and/or positive by fluorescence in situ hybridization (FISH or CISH) or HER-2 negative disease 0 or 1+ by IHC or 2+ by IHC and negative by FISH or CISH. We defined four biological subtypes (luminal A, luminal B, HER2 positive and triple negative) according to the St. Gallen modified criteria. Due to the size of the luminal subgroups we fused it into a single category (luminal A/B). The pathological response was evaluated by an expert pathologist of each center and it was considered as complete if residual infiltrating tumor was not observed in breast and axilla (ypT0N0).

Clinical evaluations: At baseline visit, demographic characteristic were collected. Anthropometric measures, (current height (m), weight (kg), waist circumference) and blood pressure were taken at baseline and final visit. The biochemical determinations (glucose, insulin) were measured every three weeks as follows :



The body mass index (BMI) was calculated as weight (kg) divided by height (m^2). We used the WHO categories for BMI. Anthropometric measures (abdominal circumference, weight and height) and blood pressure were measured baseline and in final NAC cycle.

All biochemical measurements were centralized and obtained by automatized methods in the central laboratory of Hospital Clinic Barcelona. Serum glucose, insulin and lipids were measured every three weeks in venous blood samples taken in morning with 12 hours overnight fast.

The insulin resistance was calculated by computarized HOMA2 -IR® (homeostasis model assessment-insulin resistance) calculator with the following ecuation: [(fasting insulin (IU/mL) 3 fasting glucose (mg/dL)]/22.5.

The diagnosis of MS was made by the ATP III criteria with three or more of the following: abdominal circumference >88 cms, sistolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mm Hg, glucose ≥100 mg/dl, HD cholesterol <50 and triglicerids ≥150 mg/dl.

Statistics

Based on the fact that there are no studies that have assessed the relationship between changes over time in insulin resistance and the likelihood of pathological response to NAC, for this pilot study we used a non-probabilistic convenience sampling.

Continuous variables were expressed by measures of central tendency: mean, median and standard deviation. Dichotomous variables as frequencies and percentages. Primary endpoint pathologic response will be a dichotomous outcome variable with two levels: pCR (pathologic complete response) and no pCR (no pathologic complete response).

The cut-off value to define insulin resistance in the cohort was HOMA2-IR ≥1.9. To compare continuous variables (glucose, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, insulin, BMI, waist circumference), baseline and NAC cycles 2-8 visits, we performed a repeated measures analysis for interaction between time (visits) and pathologic response. Chi-squared test and logistic regression analysis (HR and 95% CI) were used to confirm the association between insulin resistance and pCR. Value of <0.05 two sided was set as a significant p value. All analyses were performed with SPPS software.(v. 21)

Results

There were 70 eligible patients, 6 were excluded (1 for endometrial cancer synchronous M1 disease, 1 in whom the surgery was not realized, 1 with local progression during NAC and three with M1 breast cancer disease). The median age of 49 years was set, rang between28-79 (min-max). The menopausal status was pre-menopausal in 31 patients (48.4%), peri-menopausal 2 (3.1%) and postmenopausal 31 (48.4%). All the patients had localized or locally advanced infiltrating breast cancer. Axillary nodes were involved in 37 patients (57.8%). cTNM stage was stage IIA 21 (32.9%), IIB 29 (45.3%), and stage IIIA 8 (12.5%) IIIB 4 (6.3%) and IIIC 2(3.1%). (TABLE 1)

TABLE 1- Patients characteristics

Clinical characteristics	Full cohort n=64 No. %
Median age, years	49.5 (28-79) min-max
Menopausal status	
Pre-menopausal	31 (48.4)
Peri-menopausal	31 (48.4)
Post-menopausal	2 (3.1)
ECOG	
0	59 (92.2)
1	5 (7.8)
Tumor stage	
T1	2 (3.1)
T2	41(64.1)
T3	17(26.6)
T4	4(6.3)
T(median) mm	34 (16-106) min-max
Nodal stage	
N0	27(42,1)
N1-3	37(57.8)
cTNM	
IIA	21 (32.9)
IIB	29(45.3)
IIIA	8 (12.5)
IIIB	4 (6.3)
IIIC	2 (3.1)

ER was positive in 41 (64.1%), PR was positive in 32 (50%), HER2 positive 18 (28%) and triple negative 14 (21.9%). The histological grade (g1,g2,g3) in the core biopsy was 6 (9.4%), 29 (45.3%) and 29 (45.3%) respectively. The most common histological type was invasive ductal carcinoma 59 (92.2%).

According to the modified St. Gallen scale we classified the type of tumour in three biological subtypes: 1) luminal A or B (ER and/or PR positive, HER2 negative), HER2 positive (HER2 positive, ER and/or PR positive or negative) and triple negative (ER, PR and HER2 negative). The frequency of pCR in the full cohort was 37.5% (24 patients). pCR frequency in the subgroups luminal A / B, HER2 and triple negative was 15.6%, 61.1% and 57.1% respectively. (TABLE 2 and 3)

TABLE 2 – Tumour histological characteristics

Histopathologic characteristics	No. %
Oestrogen receptor	
Positive	41 (64.1)
Negative	23 (35.9)
Progesterone receptor	
Positive	32 (50)
Negative	32 (50)
HER2	
Positive	18 (28.1)
Negative	46 (71.8)
Triple negative	14 (21.9)
Histological grade	
G1	6 (9.4)
G2	29 (45.3)
G3	29(45.3)

TABLE 3- Breast cancer biological subtype

Biological subtype (modified St.Gallen)	n 64 No. %	pCR (n 24) No. %	No pCR (n 40) No. %
Luminal A or B	32 (50)	5 (15.6)	27(84.4)
HER2 positive (HR+ or HR-)	18 (28.1)	11 (61.1)	7 (38.9)
Triple negative	14 (21.9)	8(57.1)	6 (42.9)

The basal median BMI in the entire cohort was 27.7 kg/m^2, 23.6-30.4 kg/m^2 (P25-P75) and median BMI in the final evaluation was 27.87 kg/m^2, 24.9-30.5 kg/m^2 (P25-P75). (p=.001) This change in BMI represents a median weight gain of 2 kg in 81,3% women of the full cohort, only twelve patients(18,7%) had a decrease in BMI with an average weight loss of 2.5 kg. According to WHO criteria for BMI classification, at baseline evaluation 24 patients (37.5%) had normal weight and 40 (62.5%) were overweight or obese. In the final evaluation only 16 patients (25%) maintained normal weight and 47 patients (73.4%) were overweight or obese. No significant differences in baseline BMI were observed in the full cohort or according to biological subtype. (TABLE 4).

TABLE 4 BASELINE BMI WHO classification

Biological subtype	Normal weight	Overweight	Grade I Obesity	Grade III Obesity	p
Full cohort (n 64)	24 (37.7%)	23(35.9%)	16(25%)	1(1,6%)	0.07
Luminal A/B (n 32)	16 (50.0%)	12 (37.5%)	4 (12.5%)	-	
Her 2 (n 14)	6 (33.3%)	6(33.3%)	6(33.3%)	-	
Triple negative (n 18)	2 (14.3%)	5(35.7%)	6(42.9%)	1 (7.9%)	

A quarter of the patients had a diagnosis of metabolic syndrome (≥ 3 criteria) at baseline evaluation and up to almost 40% at the end of the NAC. We observed statistically significant differences in baseline and final diagnosis of SM in the luminal and triple negative subgroups.
TABLE 5

TABLE 5. Biological subtype and metabolic syndrome

Biological subtype	MS baseline	MS final evaluation	p
Full cohort (n 64)	16 (25%)	25 (39.1%)	.001
Luminal A/B (n 32)	9 (28.1%)	12 (37.5%)	.003
Her2 (n 18)	5 (27.2%)	7 (38.9%)	.825
Triple negative (n 14)	2 (14.3%)	6 (42.9%)	.004

The criteria of MS most frequently altered in basal evaluation were: 76.6% waist circumference (> 88 cm), 39.1% high glucose (≥100 mg/dl) and 35.9% low cholesterol HDL. In the final evaluation were: 76% waist circumference, 54.7% low cholesterol HDL, and 43.8% high glucose.

In basal evaluation 29 patients (45.3%) had insulin resistance calculated by HOMA2 index and in the final evaluation 34 patients (53.1%). p=0.005 We observed a gradual and almost linear increase of insulin resistance during the time of NAC which was significant through cycles (p = 0.019) FIG 1

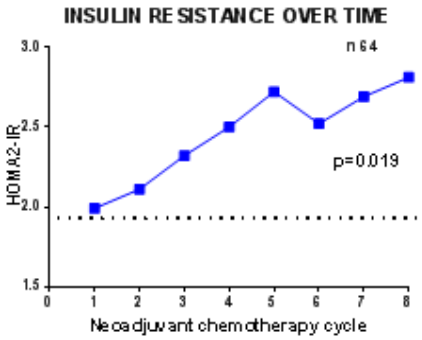


FIG 1 Insulin resistance over the time of neoadjuvant chemotherapy (full cohort)

+The dashed line on the Y axis marks the cutoff for cohort insulin resistance

When insulin resistance was considered as a categorical variable we divided the cohort in two groups: 1) IR group (HOMA ≥1.9) and 2) No IR group: (HOMA <1.9). The group with no IR had a higher likelihood of pCR at baseline (HR 3.1) and in final evaluation (HR 2.4). TABLE 6

TABLE 6 Likelihood of pCR and insulin resistance (categorical)

HOMA2- IR group	HR	95%CI	p
IR group basal evaluation	0.55	0.37 to 0.82	
No IR group basal "	3.41	1.34 to 7.39	.002
IR group final evaluation	0.54	0.34 to 0.89	
No IR group final "	2.43	1.26 to 4.70	.006

When insulin resistance was considered as a continuous variable over time of the NAC, we observed in the pCR group that the HOMA2 remained below or slightly above on the cut-off for definition IR and with no significant changes over the time. (p=0.225) Inversely to the above in the no pCR group the IR increase over time and almost with a linear trend. (p=0.013) FIG 2

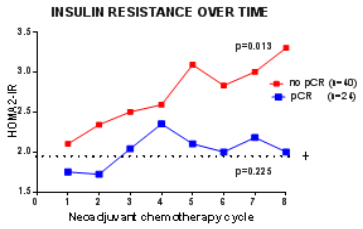


FIG 2 Association of Insulin resistance over the time of neoadjuvant chemotherapy pCR group versus no pCR group.
+The dashed line on the Y axis marks the cutoff for cohort insulin resistance

In the analysis of HOMA2-IR medians we found that in the pCR group versus no pCR group there were significant differences and these were more marked in the basal evaluation (p = 0.049) and final evaluation (p = 0.030) between the groups FIG 3

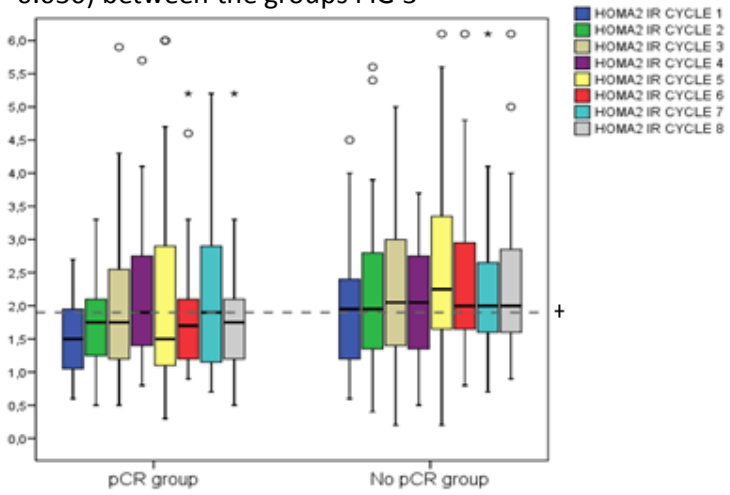


FIG 3 HOMA2-IR in pCR group versus no pCR group over time of NAC.
+The dashed line on the Y axis marks the cutoff for cohort insulin resistance

The insulin resistance was different between the three biological subtypes. The luminal group A / B showed more IR and the largest increase in insulin resistance over time with an almost linear trend (p = 0.002). FIG 4. The triple negative group presented no IR at baseline but it was increased after the third cycle of NAC and remained constant, these changes were not significant (p = 0.707). FIG 5. The HER2 positive group was less resistance to insulin and HOMA2-IR values remained close to the cut-off. There were no significant differences over time in the NAC. (p = 0.622) FIG 6

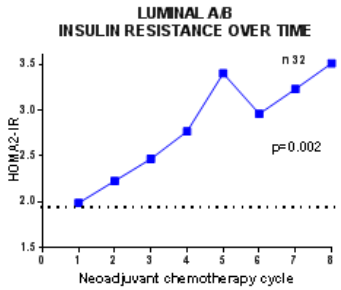


FIG 4 Insulin resistance over the time of neoadjuvant chemotherapy in Luminal A/B subgroup-
+The dashed line on the Y axis marks the cutoff for cohort insulin resistance

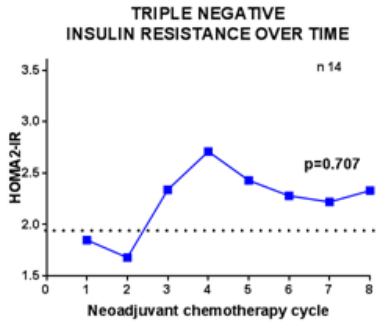


FIG 5 Insulin resistance over the time of neoadjuvant chemotherapy in triple negative subgroup
+The dashed line on the Y axis marks the cutoff for cohort insulin resistance

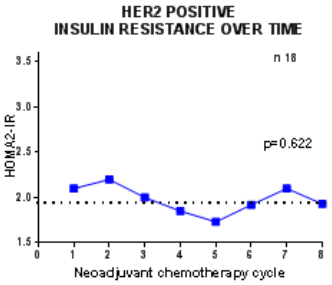


FIG 6 Insulin resistance over the time of neoadjuvant chemotherapy in triple negative subgroup
+The dashed line on the Y axis marks the cutoff for cohort insulin resistance

In the repeated measures analysis of HOMA2-IR over time of the NAC in the three biological subgroups, significant differences were observed only in the luminal group A (p = 0.044) and not in the triple negative (p =.241) and HER2 positive subgroups. (p = .767) FIG 7

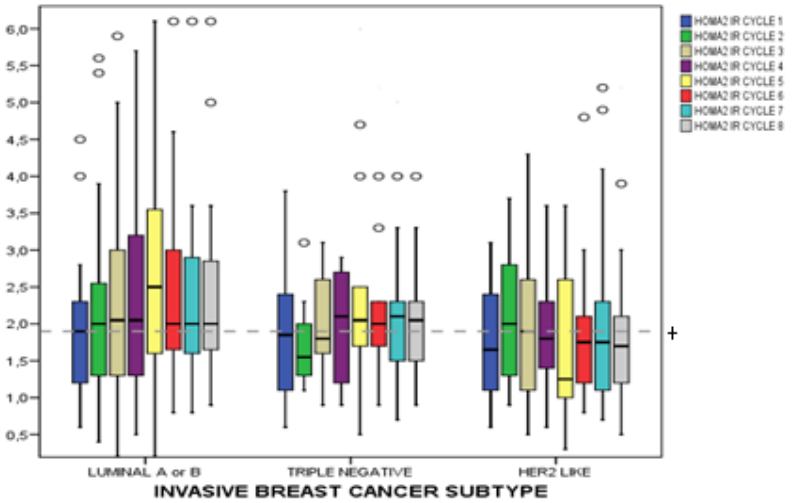


FIG 7 Insulin resistance over the time of neoadjuvant chemotherapy in biological breast cancer subtypes

+The dashed line on the Y axis marks the cutoff for cohort insulin resistance

We separated into quartiles biochemical variables (basal and final evaluation) glucose, insulin and HOMA2-IR. Comparing the Q1-2 versus Q3-4 and the probability of pCR, we note that the basal glucose (p = .018), the basal HOMA2-IR (p = 0.032) were significantly associated with pCR and the end HOMA2-IR had a trend. (p = 0.052)

TABLE 7. Likelihood of pCR by biochemical variables Q1-2 vs Q3-4

Insulin-related variables	Pathologic Complete Response		
	Univariable		
	HR	95% CI	P
Baseline Glucose, mmol/L			
4.5 (Q1: 3.8-4.7)			
5.1 (Q2:4.8-5.3)			
5.5 (Q3:5.3-5.7)			
6.1 (Q4:5.7-7.5)			
Q1-2 vs Q3-4	1.02	0.54 to 1.92	.98
Final Glucose, mmol/L			
4.8 (Q1: 4.2-5.1)			
5.1 (Q2:5.1-5.4)			
5.6 (Q3:5.4-6.2)			
6.9 (Q4:6.2-9.6)			
Q1-2 vs Q3-4	1.56	0.71 to 3.07	.18
Baseline Insulin, pmol/L			

40.9 (Q1: 5.5-50.7) **68.7 (Q2:50.8-87.7)** **97.2 (Q3:87.8-114.8)** **145.8 (Q4:114.9-364.6)** **Q1-2 vs Q3-4**	2.2	1.09 to 4.76	.018
Final Insulin, pmol/L **43.1 (Q1: 32.2-66.8)** **78.0 (Q2:66.9-84.8)** **94.8 (Q3:84.9-116.8)** **143.1 (Q4:116.9-621.9)** **Q1-2 vs Q3-4**	1.03	0.54 to 1.98	.912
Basal HOMA2 IR **0.80 (Q1: 0.60-1.0)** **1.30 (Q2:1.10-1.69)** **1.90 (Q3:1.70-2.29)** **2.65 (Q4:2.30-7.80)** **Q1-2 vs Q3-4**	3.0	1.08 to 8.85	.032
Final HOMA2 IR **1.10 (Q1: 0.50-1.39)** **1.70 (Q2: 1.40-1.99)** **2.10 (Q3: 2.00-2.69)** **4.00 (Q4: 2.70-27.0)** **Q1-2 vs Q3-4**	2.01	1.03 to 3.90	.052

In a multivariate logistic regression analysis for pathological complete response, adjusted for histological grade, biological subtype, hormone receptors, cTNM, the insulin resistance (HOMA2 IR) remained as an independent factor for pathological complete response (p = 0.018).

Conclusion

To our knowledge this is the first prospective study describing the natural history of IR before and during neoadjuvant chemotherapy and its association with pathological response. Our results indicate a strong association between the IR calculated by HOMA2 and the likelihood of pCR in neoadjuvant setting of breast cancer. The pCR likelihood inversely associated with insulin resistant.

Furthermore we describe a positive gradient, the IR increased over time of the NAC. IR is likely to be worse at baseline in the luminal subgroup and this increase over time of NAC. Interestingly it is a biological subgroup which is characterized by less pathological response to chemotherapy. In this way the IR could play a predominant role, however we know our study limitations (sample size, classification bias in the biological subtypes). This is a hypothesis generating study which suggests verify that the IR is an independent predictor of response to NAC having available DNA microarray profiles of the biological subtypes.

In our cohort, woman with breast cancer have baseline MS prevalence similar to the general population (25-30%). Unfortunately it is evident that during the cycles of NAC the diagnosis of MS increases by 40% and not only the diagnosis but components such as waist circumference, glucose and C-HDL that are markers of cardiovascular risk and central adiposity. Central adiposity is strongly correlated with IR; it is possible that these anthropometric and bio-chemicals markers that are non-invasive and inexpensive could be markers of response to chemotherapy.

The practical implications of this study suggest changes in clinical practice to be aware of the patient's metabolic environment especially during neoadjuvant chemotherapy. Because pCR has been accepted as a surrogate for disease-free survival in some molecular subtypes of breast cancer is clear that the control of metabolic factors during chemotherapy could lead to more successful treatment that impact patient survival. We believe that in the near future will be possible to speak of the metabolic phenotypes of breast cancer as prognostic or predictors of response to cancer treatment.

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List of oral/poster presentations resulting from the fellowship

- 37 European Multidisciplinary Cancer Congress, ESMO Congress. Vienna, Austria. Sep 28 to oct 2 2012. **Armengol Alonso Alejandra**, Arance Ana, Campayo Marc. Impact of body mass index (BMI) on disease free survival and likelihood of pathologic complete response in patients with locally advanced breast cancer treated with neoadjuvant chemotherapy.
- 2nd Symposium SEOM (Spanish Society Medical Oncology). Oct 24-26 2012. Madrid, Spain. **Armengol Alonso Alejandra,** Ana Arance, Marc Campayo, Xavier González-Farré, Luis Feliz, Veronica Pereira, Martin Velasco, Adriana Garcia, Pedro L. Fernández, Montserrat Muñoz. Impact of neoadjuvant chemotherapy dose Intensity over likelihood of pathologic complete response and free disease survival.
- 2nd Symposium SEOM (Spanish Society Medical Oncology). October 24-26 2012. Madrid, España. Veronica Pereira, Luis Feliz, **Armengol Alonso Alejandra,** Ivan Victoria, Ana Arance, Marc Campayo, Xavier González, Montserrat Muñoz. Progression to first-line treatment of metastatic breast cancer by tumor markers and imaging. Can they be used interchangeably?
- IX International Symposium of the Spanish Group for breast cancer research (GEICAM): Research and clinic: Looking to the future. Valencia, Spain. April 18 y 19 2013. **Armengol Alonso Alejandra,** Pereira Veronica, Velasco M, Santamaria G, Caparros X, Arance A, Bargalló X, Alonso I, Farrús B, González-Farre X, Campayo M, Fernández P, Muñoz M. What is the impact of the breast cancer biological subtype on radiological and pathological response to neoadjuvant chemotherapy (QTNA)?

Personal Statement

I am a Mexican medical oncologist devoted to breast cancer clinic research. I am also involved in health care activities and academic training for oncologists in formation.

The year in which I developed my research allowed me to improve my skills in clinical research, coordinate a multi-centre study and be patient with the rigor and time required in clinical research. For me it was important to present my original idea and convince other oncologic groups over their potential utility in the clinic, which resulted in a multi-centre study. The results proved that the hypothesis of my research was correct, this work has been so positive that I believe it contributes to the advance of science in the field of insulin resistance and breast cancer, and it is now being sent for publication. Given that the duration of the scholarship is one year, it was during the second year of my research that I also discovered the great potential to direct or coordinate studies at distance by electronic means such as the Internet. This has allowed me to develop joint clinical research projects between my hospital and the host hospital. Surely one of the most important contributions of this grant was to find a line of research that greatly interested me, I am very passionate about this research and I am currently dedicated to: metabolic phenotype and breast cancer. This research has generated new ideas and more questions on the importance of host in breast cancer and not only in the tumour. I am conducting one prospective cohort and one case-control study in my country to evaluate the impact of insulin resistance and metabolic syndrome in breast cancer.

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Acknowledgements

I am deeply grateful for the opportunity that ESMO-Novartis offered me for the development of my clinical research and development as a fellow in breast cancer.

A special acknowledgement To Montserrat Muñoz who has mentored me and gave me the opportunity to learn and work every day in the Breast Cancer Unit of Hospital Clinic.

I would like to acknowledgement all the people and patients that have contributed to my research.

Photograph: Breast Cancer Board Hospital Clinic Barcelona

Photograph: Forum Clinic Breast Cancer web page for breast cancer patients information and support.

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The ESMO Clinical Research Fellowship is supported by an Educational Grant From Novartis.