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## Health Behaviors and Breast Cancer Survivorship

Antonio Di Meglio

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# Health Behaviors And Breast Cancer Survivorship

Thèse de doctorat de l'université Paris-Saclay

École doctorale n° 582 : Cancérologie : biologie - médecine - santé (CBMS)  
Spécialité de doctorat : Aspects moléculaires et cellulaires de la biologie  
Unité de recherche : Prédicteurs moléculaires et nouvelles cibles en oncologie,  
Inserm 981, Institut Gustave Roussy, Villejuif, France  
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**Titre : Les comportements de santé dans l'après cancer du sein**

**Mots clés :** Cancer du sein, Après cancer, Toxicités liées aux traitements, Comportements de santé, CANTO

**Résumé :** Les survivantes du cancer du sein (CS) de stade précoce ont souvent un impact considérable et persistant des symptômes liés aux traitements.

Cette thèse rassemble plusieurs projets exploitant les données de l'étude CANcer TOxicity (CANTO; NCT01993498) pour comprendre le potentiel des comportements de santé (CSAN), notamment le maintien d'un indice de masse corporelle (IMC) sain, le respect des recommandations en matière d'activité physique (AP), l'arrêt du tabac et la limitation de la consommation d'alcool, pour préserver la qualité de vie (QV) chez les survivantes du CS. CANTO est une cohorte multicentrique et prospective de CS de stade I-II-III. La cohorte recueille des informations clinico-comportementales (IMC, consommation de tabac et d'alcool, AP [GPAQ-16]), psychologiques (HADS), sociodémographiques, et liées au traitement. Les toxicités sont évaluées par les « patient-reported outcomes (PROs) » (EORTC QLQ-C30, -BR23 et -FA12) et par CTCAE. Les patientes font l'objet d'un suivi longitudinal annuel à compter du moment du diagnostic.

Un certain nombre de méthodes statistiques ont été utilisées pour l'analyse des données, notamment la régression linéaire et logistique multivariable, la régression multinomiale, les modèles mixtes à effets aléatoires et les analyses de classe latente.

Dans une première partie, cette thèse vise à (1) décrire les CSAN dans l'après CS, en se concentrant sur les facteurs de risque (FR) de persistance des comportements malsains. Ensuite, ce travail vise (2) à caractériser les toxicités et à définir leur interaction avec les CSAN. Des groupes de patientes spécifiques à priori risque élevés des toxicités ont été évalués, notamment: (2a) les patientes recevant une chimiothérapie (CT) adjuvante, afin de décrire la QV et sa relation avec les CSAN, et (2b) les patientes obèses, afin d'explorer l'association des PROs avec les changements de poids, l'impact social du CS et sa relation avec l'IMC.

Les principales conclusions sont les suivantes : (1) certaines femmes ont amélioré leur CSAN après CS, bien que la plupart des comportements malsains de base aient persisté, avec des déterminants cliniques, sociodémographiques et psychologiques fluctuant selon le CSAN ; (2a) il y a une grande variabilité dans les trajectoires de la QV après la CT, un groupe de patientes ayant une forte détérioration des PROs, et étant également particulièrement enclin à des comportements malsains ; (2b) parmi les patientes obèses, la perte de poids était associée à de meilleurs PROs après traitement et à des taux plus élevés de retour au travail.

Dans une deuxième partie, cette thèse a exploré une étude de cas spécifique, en se concentrant sur la fatigue liée au cancer (FAT). Dans un premier temps, (3) la prévalence et les FR de la FAT sévère (globale, physique, émotionnelle et cognitive) ont été évalués. Nous avons ensuite (4) caractérisé la mise en œuvre des stratégies de gestion recommandées pour améliorer la FAT, y compris l'AP.

Les résultats ont révélé que : (3) il existe une forte prévalence et persistance de la FAT sévère après CS, avec une multitude de FR comprenant la détresse psychologique, les symptômes concomitants et les comportements malsains, en particulier surpoids et tabagisme (des équations prédictives préliminaires ont également été générées) ; et que (4) l'application des recommandations pour améliorer la FAT, ainsi qu'en matière d'AP, semblait sous-optimale.

L'objectif principal de cette thèse était d'éclairer les interventions comportementales ciblées pour les patientes à risque de toxicité persistante. Ce travail a donc abouti (5) à la génération d'un protocole d'étude pour un essai randomisé de phase III : « Motivating to Exercise and Diet, and Educating to healthy behaviors After breast cancer - MEDEA ». Cette étude, visant à évaluer l'impact d'une intervention personnalisée de perte de poids sur la FAT liée au cancer chez les survivantes de CS en surpoids et obèses, est actuellement en cours (NCT04304924).

**Title : Health Behaviors And Breast Cancer Survivorship**

**Keywords :** Breast Cancer, Survivorship, Treatment-related toxicities, Health Behaviors, CANTO

**Abstract:** Survivors of early-stage breast cancer (BC) often face relevant late and long-term health-related *sequelae*, downstream functional impact of treatments and persistent symptoms.

This thesis gathers several projects exploiting data of the CANcer TOxicity study (CANTO; NCT01993498), to understand the potential of health behaviors (HB), including maintenance of a healthy body mass index (BMI), adherence to physical activity (PA) recommendations, tobacco abstinence and limitation of alcohol consumption, to improve overall health and preserve quality of life (QOL) of BC survivors. CANTO is a nationwide, prospective cohort of patients with stage I-II-III BC. Longitudinal clinico-behavioral (e.g., nurse-reported BMI, tobacco and alcohol use, PA [GPAQ-16]), psychological (HADS), socio-demographic, and treatment data are available at diagnosis and yearly afterwards. Treatment-related toxicities are extensively assessed by patient-reported outcomes (PROs; EORTC QLQ-C30, -BR23, and -FA12) and by provider's evaluation (CTCAE).

A number of statistical analytic methods were involved in this thesis, including multivariable linear and logistic regression, multinomial regression, random-effects mixed-models, and latent-class analyses (i.e., group-based trajectory models).

In the first part, this thesis aimed at (1) describing HB over the survivorship period, focusing on risk factors for persistent unhealthy behaviors, and at (2) characterizing the evolution of treatment-related toxicities and defining their interplay with HB. We assessed QOL in two specific and frail populations, at risk of severe downstream treatment impact: (2a) among patients receiving adjuvant chemotherapy (CT) and (2b) among obese BC survivors, where we also specifically studied the social impact of BC and its relationship with BMI.

Key findings include the following: (1) most women pursue a healthy lifestyle and some are prone to improvements after diagnosis, although unhealthy behaviors tend to persist, with varying clinico-demographic and psychological determinants by HB (Manuscript [MS]1); (2a) there is great variability in

trajectories of post-CT QOL, with a clinically relevant cluster of patients reporting severely deteriorating QOL, never recovering to pre-treatment levels for over 4 years, and being also particularly prone to unhealthy behaviors (MS2); (2b) among obese survivors, those that lose weight report less of a decline in PROs, without evidence of worsened functionality or symptomatology in any QOL domain (MS3). Moreover, excess weight seems to represent a barrier to occupational reintegration, and weight loss is associated with higher rates of return to work after BC (MS4).

In its second part, the thesis explored a core case-study, cancer-related fatigue (CRF). First, (3) prevalence and risk factors for severe CRF were evaluated, analyzing global CRF and its physical, emotional, and cognitive dimensions. We then (4) characterized the uptake of recommended management strategies to improve CRF, including PA.

Findings revealed that: (3) there is a high prevalence of post-treatment severe CRF, which stays persistently elevated over time, with a multitude of risk factors including psychological distress, concomitant symptoms, and unhealthy behaviors, particularly excess weight and tobacco use (preliminary predictive equations were also generated) (MS5); (4) recommendations uptake, including PA adherence, seems suboptimal and in need of implementation in clinical practice (MS6).

The overarching goal of this thesis was to inform targeted behavioral interventions for patients at risk of persistent toxicities. This work resulted therefore in (5) the generation of a study protocol for a phase III randomized trial: "Motivating to Exercise and Diet, and Educating to healthy behaviors After breast cancer - MEDEA". This study, aimed to evaluate the impact of a personalized telephone-based weight loss intervention on CRF in overweight and obese BC survivors, is currently ongoing (NCT04304924) (MS7).

Further interventional studies informed by this thesis work are planned.

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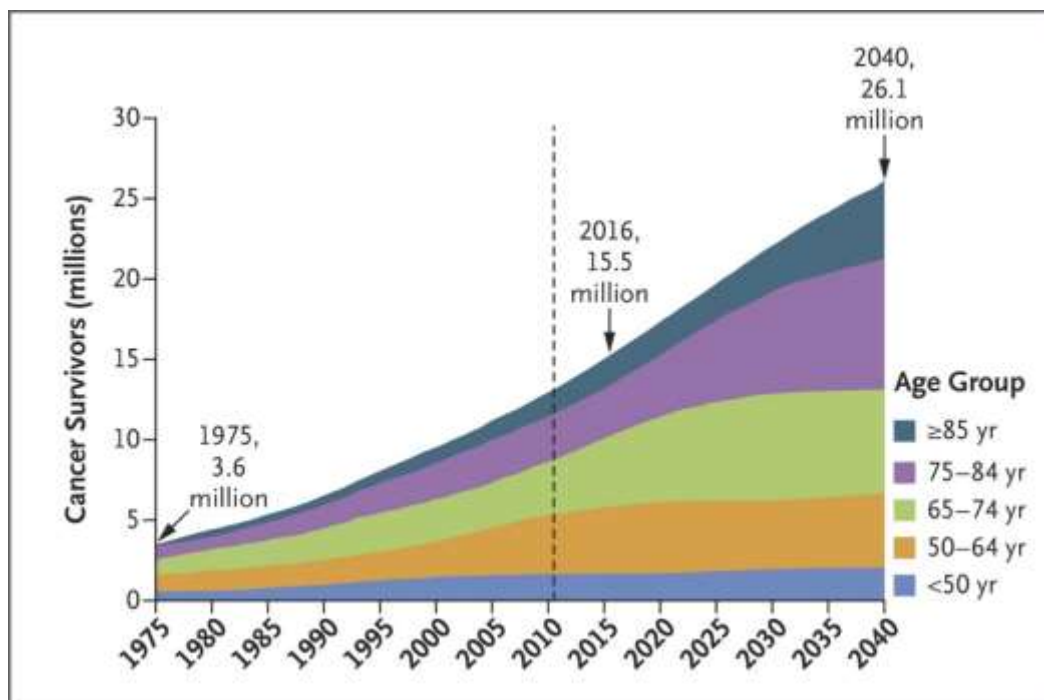
# INTRODUCTION

## Epidemiology of breast cancer

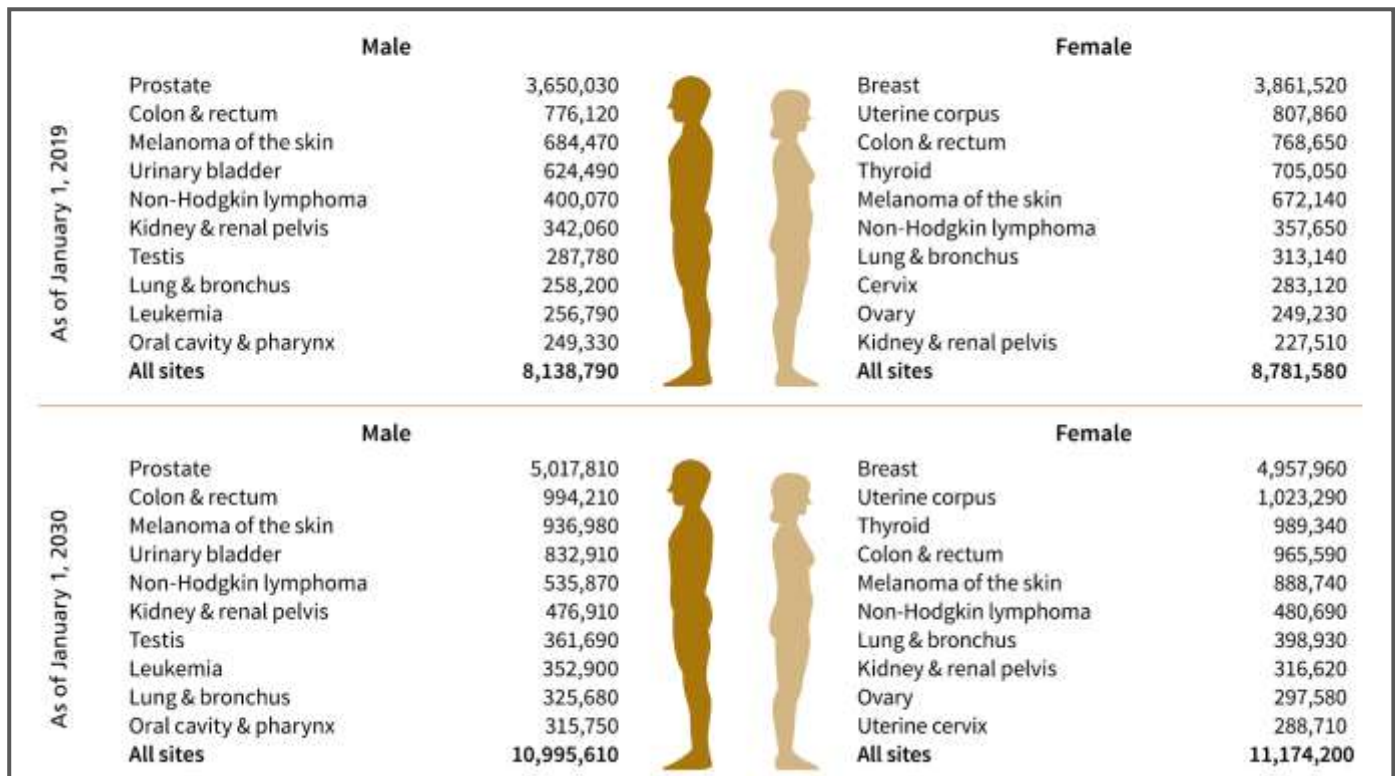
Female breast cancer is the most frequently diagnosed cancer in women worldwide, with around 2.1 million diagnosis in 2018.<sup>1</sup> Globally, approximately every 1 in 8 women from those reaching the age of 85 years are affected by breast cancer.<sup>1</sup> In the European Union, breast cancer is also the main cause of female cancer and cancer-related death, with an estimated absolute number of diagnosis, incidence and mortality of 364,450 cases, and 108.8 and 22.4 cases per 100,000 women/year (age-standardized rates), respectively.<sup>2</sup> Of all cases of breast cancer, between 90 and 95% are diagnosed in stage I-III and are thus eligible for curative treatments.<sup>3</sup>

## Breast Cancer Survivorship

There are currently over 18 million individuals living with a history of cancer worldwide, and this number is expected to increase to over 26 million by 2040 (**Figure 1**).<sup>4</sup> In 2006, Rowland defined a “cancer survivor” as “anyone with history of cancer, from the time of diagnosis and for the remainder of life”.<sup>5</sup> In its holistic definition, survivorship starts therefore at the time of diagnosis, lasting throughout the lifespan, encouraging clinicians to think about the care of survivors as an integral part of the cancer care continuum. Family members, friends, and caregivers are included in this definition, primarily because “in most cases cancer is not experienced alone”.<sup>4</sup>



**Figure 1. Cancer Survivors worldwide, by age group 1975-2040.** Changing demographic characteristics of the cancer population, with an estimated 26 million survivors in 2040, the majority of whom will be in their 60s, 70s, or 80s (Adapted from Shapiro CL, *NEJM* 2018).



**Figure 2. Estimated number of cancer survivors in the United States by site.** (Adapted from Miller KD, *CA Cancer J Clin*, 2019)

Women diagnosed with **breast cancer** encompass over 3 million in the United States (**Figure 2**) and approximately 2 million in the European Union.<sup>6-8</sup> The wide implementation of screening contributed to the identification of tumors in earlier stages.<sup>9</sup> Earlier diagnosis and several advances in adjuvant treatments were responsible for significant improvements in cure rates and survival for breast cancer over the past decades.<sup>10-13</sup> Among major treatment advances, adjuvant chemotherapy decreases breast cancer recurrence risk of 30%-50% and reduces mortality in women with early-stage breast cancer.<sup>14-16</sup> In addition, endocrine therapy determines a 50% reduction in breast cancer recurrence and 10% improvement in survival among women with estrogen-receptor positive breast cancer. As a result, current multimodal risk-reduction strategies, including chemotherapy, endocrine therapies and targeted agents, led to survival rates exceeding 80% ten years after diagnosis.<sup>17</sup>

The increasingly longer lifespan of breast cancer survivors led to the emergence of **new research priorities and needs**. Corresponding with improved survival, an awareness of **survivorship care challenges** has indeed also increased. Besides continuing to find therapies that will prevent or arrest the disease, we now need to also focus on minimizing the physical, psychological and social burden of surviving breast cancer.<sup>18-20</sup> Particularly, rather than dying from breast cancer, many women will become part of a new community of cancer survivors, living with or beyond their disease, yet having to cope with long-term and late effects of ongoing or previous treatments. Despite many breast cancer survivors will fully recover to their pre-diagnosis health status or experience a health trajectory that is overall comparable to individuals without breast cancer, a substantial number of them will have to endure a variety of treatment-related *sequelae* and is at risk of seeing their quality

of life severely impacted and progressively deteriorate. Common effects of breast cancer treatment include fatigue, emotional disorders such as anxiety and depression, cognitive impairment, obesity and metabolic alterations, cardiotoxicity, bone loss, lymphedema, sexuality and fertility issues. The downstream impact of these conditions on psychological, functional and social dimensions of quality of life can be dramatic and persistent.<sup>21-26</sup>

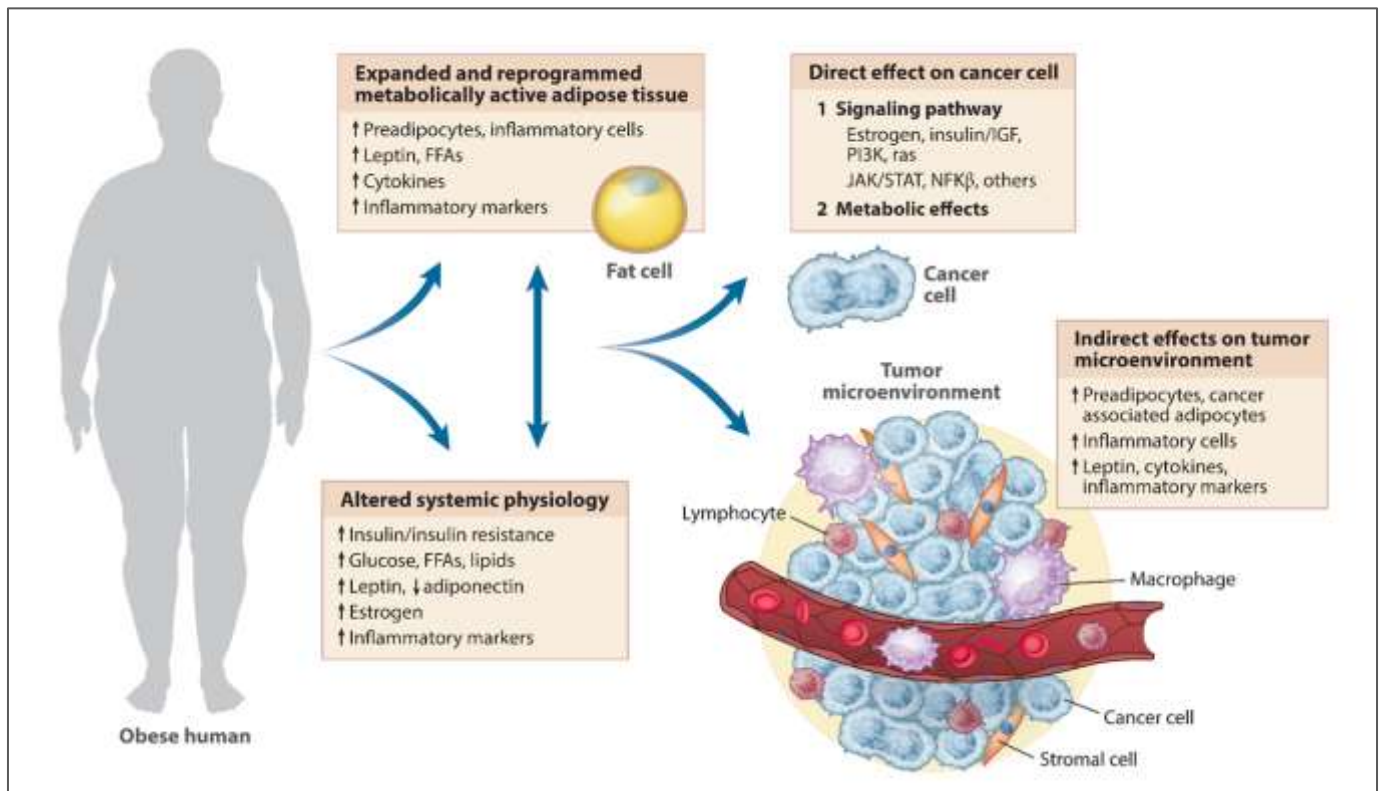
**There is evidence calling into question substantial under-diagnosis and inadequate management of treatment-related sequelae among breast cancer survivors.<sup>27</sup> Recognition of the adverse health effects and emotional toll of surviving breast cancer is part of the main goals of cancer survivorship.<sup>4</sup>**

### **Health behaviors**

The National Institute of Health (NIH) defines a health behavior as “an action taken by a person to maintain, attain, or regain good health and to prevent illness.” Weight management, increased physical activity, smoking cessation, and limited alcohol consumption are the foundation for improved health and wellness for the general population, and especially for cancer survivors.

*Obesity and weight management.* The epidemic of excess weight and obesity is a public health issue in general, and particularly among breast cancer survivors, with up to 70% of them being overweight or obese in the United States, and with concerning figures also in the European Union, where around 50% have a body mass index (BMI) of 25 Kg/m<sup>2</sup> or higher. Particularly, obesity represents a risk factor for the development of several cancers, including breast cancer. A recent meta-analysis of 82 studies looking at obesity and survival in breast cancer reported a hazard ratio (HR) for overall survival of 1.41 (95% Confidence Interval [CI] 1.29-1.53) among obese vs. lean patients with breast cancer.<sup>28</sup> Among women with breast cancer enrolled in the Women's Healthy Eating and Living (WHEL) study, obesity was also associated with significantly worse physical function and with worse physical health, vitality, pain and overall health-related quality of life.<sup>29</sup> A significantly higher prevalence of treatment-related symptoms, such as cancer-related fatigue, was observed among heavier as compared to leaner breast cancer survivors and was described in several reports.<sup>30-32</sup>

Our understanding of the biologic nature of the link between excess adiposity, obesity, and cancer suggests the presence of a complex interplay between the adipose tissue, its fat-containing microenvironment, and the whole patient. Adipose tissue is expanded and reprogrammed in obese individuals, with specific metabolic activations leading to localized inflammation and altered cytokine/adipokine secretion. Additional interactions occur between local changes and alterations in systemic physiology. This complex interplay can be responsible of direct and indirect effects that trigger worse cancer treatment-related symptomatology in obese individuals, effects that are substantially mediated by the activity of the cancer-associated inflammatory *milieu* (**Figure 3**).<sup>33</sup>



**Figure 3. The complex association of obesity and cancer and its biologic substrate.** (Adapted from Goodwin PJ, *Annu Rev Med*, 2015).

Randomized trials are testing whether obese survivors of breast cancer who lose weight (and increase their physical activity) have improved survival outcomes and can maintain better quality of life after treatment.<sup>34</sup>

*Physical activity.* The American College of Sports Medicine (ACSM) published physical activity guidelines for cancer survivors.<sup>35</sup> Their systematic review and findings from other meta-analyses<sup>36,37</sup> demonstrate that physical activity is safe and effective in improving overall quality of life, specifically cancer-related fatigue and physical function. While overall effect sizes are small, there is consistent empirical evidence to support physical activity promotion as part of cancer care.

There is preliminary but promising evidence linking increased physical activity to improved cancer outcomes. A recent systematic review and pooled analysis of 26 observational studies found that cancer survivors who engaged in higher levels of activity had a 37% lower risk of dying from cancer, compared with those who engaged in lower levels of activity (HR, 0.63; 95% CI, 0.54-0.73).<sup>38</sup> This risk reduction is remarkably consistent across breast (but also colorectal, and prostate cancer survivors).

The graphic below summarizes recommendations of the ACSM (**Figure 4**). **In general, 150 or 75 minutes of moderate or vigorous intensity physical activity per week, respectively, or an equivalent combination, are recommended among cancer survivors.**









# Effects of Exercise on Health-Related Outcomes in Those with Cancer

## What can exercise do?

- **Prevention of 7 common cancers\***  
Dose: 2018 Physical Activity Guidelines for Americans: 150-300 min/week moderate or 75-150 min/week vigorous aerobic exercise
- **Survival of 3 common cancers\*\***  
Dose: Exact dose of physical activity needed to reduce cancer-specific or all-cause mortality is not yet known; Overall more activity appears to lead to better risk reduction

\*bladder, breast, colon, endometrial, esophageal, kidney and stomach cancers  
\*\*breast, colon and prostate cancers

Overall, avoid inactivity, and to improve general health, aim to achieve the current physical activity guidelines for health (150 min/week aerobic exercise and 2x/week strength training).

Outcome	Aerobic Only	Resistance Only	Combination (Aerobic + Resistance)
<b>Strong Evidence</b>	Dose	Dose	Dose
 <b>Cancer-related fatigue</b>	3x/week for 30 min per session of moderate intensity	2x/week of 2 sets of 12-15 reps for major muscle groups at moderate intensity	3x/week for 30 min per session of moderate aerobic exercise, plus 2x/week of resistance training 2 sets of 12-15 reps for major muscle groups at moderate intensity
 <b>Health-related quality of life</b>	2-3x/week for 30-60 min per session of moderate to vigorous	2x/week of 2 sets of 8-15 reps for major muscle groups at a moderate to vigorous intensity	2-3x/week for 20-30 min per session of moderate aerobic exercise plus 2x/week of resistance training 2 sets of 8-15 reps for major muscle groups at moderate to vigorous intensity
 <b>Physical Function</b>	3x/week for 30-60 min per session of moderate to vigorous	2-3x/week of 2 sets of 8-12 reps for major muscle groups at moderate to vigorous intensity	3x/week for 20-40 min per session of moderate to vigorous aerobic exercise, plus 2-3x/week of resistance training 2 sets of 8-12 reps for major muscle group at moderate to vigorous intensity
 <b>Anxiety</b>	3x/week for 30-60 min per session of moderate to vigorous	Insufficient evidence	2-3x/week for 20-40 min of moderate to vigorous aerobic exercise plus 2x/week of resistance training of 2 sets, 8-12 reps for major muscle groups at moderate to vigorous intensity
 <b>Depression</b>	3x/week for 30-60 min per session of moderate to vigorous	Insufficient evidence	2-3x/week for 20-40 min of moderate to vigorous aerobic exercise plus 2x/week of resistance training of 2 sets, 8-12 reps for major muscle groups at moderate to vigorous intensity
 <b>Lymphedema</b>	Insufficient evidence	2-3x/week of progressive, supervised, program for major muscle groups does not exacerbate lymphedema	Insufficient evidence
<b>Moderate Evidence</b>			
 <b>Bone health</b>	Insufficient evidence	2-3x/week of moderate to vigorous resistance training plus high impact training (sufficient to generate ground reaction force of 3-4 time body weight) for at least 12 months	Insufficient evidence
 <b>Sleep</b>	3-4x/week for 30-40 min per session of moderate intensity	Insufficient evidence	Insufficient evidence

Citation: [bit.ly/cancer\\_exercise\\_guidelines](https://bit.ly/cancer_exercise_guidelines)

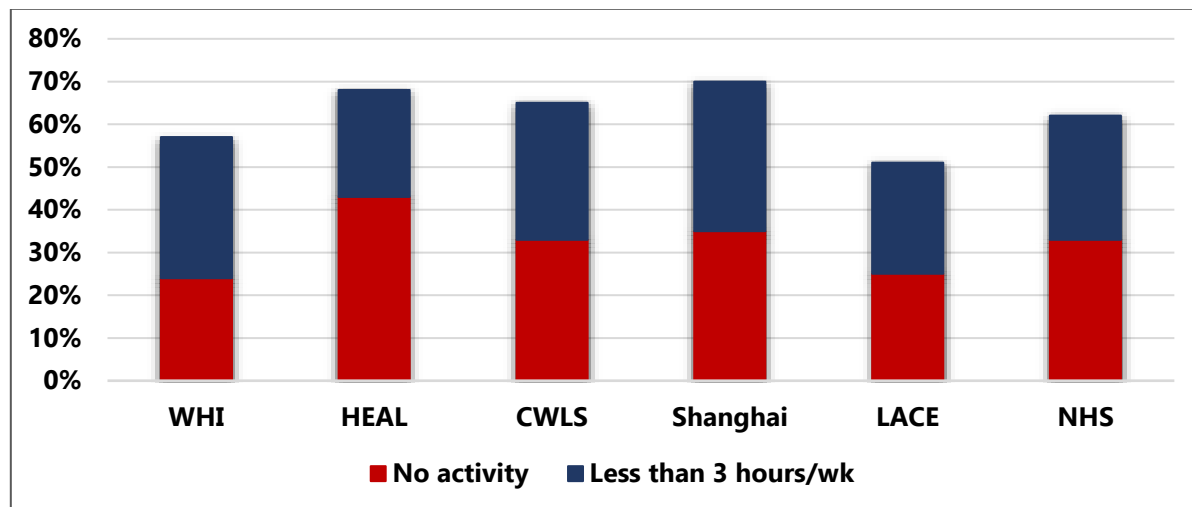
Moderate intensity (40%-59% heart rate reserve or VO<sub>2</sub>R) to vigorous intensity (60%-89% heart rate reserve or VO<sub>2</sub>R) is recommended.

Exercise is Medicine

AMERICAN COLLEGE of SPORTS MEDICINE

Figure 4. Effects of exercise on Health-Related outcomes in Those with Cancer. Adapted from ACSM, 2018.

Nevertheless, there are repeated suggestions that inactivity or insufficient physical activity is extremely prevalent among survivors of breast cancer enrolled in a number of different clinical trials or observational studies (**Figure 5**).



**Figure 5. Physical activity patterns in breast cancer survivors.** WHI: Women’s Health Initiative study Irwin, *Canc Prev Res* 2011; HEAL: Health, Eating, Activity, and Lifestyle Study Irwin, *JCO* 2008; CWLS: Collaborative Women’s Longevity Study Holick, *CEBP* 2008; Population-based Shanghai Cancer Registry Chen, *Canc Prev Res* 2011; LACE: Life After Cancer Epidemiology study Sternfeld, *CEBP* 2009; NHS: Nurses’ Health Study Holmes, *JAMA* 2005.

Analogously to the link obesity-cancer, the link between physical activity and cancer outcomes has strong biologic plausibility related to a number of described mediators. These include sex hormones, cell growth regulators, DNA damage repair, inflammatory markers, immune function, and antioxidant pathways. Particularly, physical activity interventions are capable of inducing significant modulation of chronic inflammation. For example, in the context of biologic changes related to cancer-related fatigue, pro-inflammatory cytokines, including IL-1 $\beta$ , TNF- $\alpha$ , and IL-6, are released by immune cells may also be released by the tumor itself or as a result of tissue damage from surgery, radiation, or chemotherapy. These cytokines can signal to the central nervous system, leading to symptoms of fatigue. Inflammatory processes may also be influenced by neuroendocrine dysregulation. Individuals who are more physically active show lower inflammatory activity; thus, interventions that increase physical activity (and potentially reduce BMI) can influence the onset and persistence of several symptoms that are related to presence of inflammation or neuroendocrine dysregulation.<sup>39,40</sup>

*Smoking behavior.* Smoking has been implicated in a variety of different cancers, including breast. It has been associated with increased postoperative complications, decreased wound healing and pulmonary complications. It also has been shown to worsen the side effects of radiation and chemotherapy and to decrease their efficacy.<sup>41</sup>

In addition to decreasing the risk of malignancy, smoking cessation is considered an important step

toward a reduction in the risk of stroke and myocardial infarction, chronic obstructive pulmonary disease and a host of other ailments among survivors of cancer. Tobacco cessation and referral to smoking-cessation programs are essential components of care for survivors. All individuals diagnosed with malignancies that are current smokers should be encouraged and supported to quit smoking. Nevertheless, about half of them do not receive smoking-cessation counseling.<sup>4,41</sup>

Inflammatory alterations, worsened by tissue hypoxia and disruptions in hormone levels and circadian rhythm were observed in current smokers, which may account for part of the associations with treatment-related adverse effects in cancer survivors.<sup>101,139,148–150</sup> Reduction in inflammatory *stimuli* and re-equilibration of triggers and immunologic response to vascular injury induced by smoking were observed among successful quitters. This was also associated with decreased levels of inflammatory markers, such as C-reactive protein and white blood cell count, which can in turn modulate the evolution of inflammation-associated effects.<sup>42</sup>

*Alcohol consumption.* Alcohol is also dose-dependent risk factor for the development of multiple cancers, and continued consumption of alcohol appears to increase cause-specific mortality among survivors with various cancers. However, compared with the wealth of evidence about the associations between alcohol drinking and the risk of developing cancer, research on the impact of alcohol drinking on outcomes in patients with cancer is still in its nascent stages.<sup>43</sup>

In breast cancer survivors, several studies suggest that alcohol drinking is not associated with decreased overall survival,<sup>44</sup> whereas other studies indicate that breast cancer-specific mortality may be increased in at least some subgroups of the patient population.<sup>45,46</sup> An increase in breast cancer-specific mortality or risk of recurrence has been observed with moderate to heavy levels of alcohol drinking. Alcohol abuse was associated with treatment complications contributing to longer hospitalizations, increased surgical procedures and prolonged recovery and contribute to low quality of life outcomes. Less consistent evidence is available about lighter alcohol use among breast cancer survivors and its implication with treatment-related effects and health-related quality of life.<sup>43</sup>

### **Mitigating the impact of cancer and its treatments: promotion of healthy behaviors among breast cancer survivors.**

Major cancer societies, including the American Society of Clinical Oncology (ASCO), endorse the integration of health promotion strategies, such as management of a healthy weight, exposure to recommended levels of physical activity, smoke cessation and alcohol use limitation, as a priority in survivorship care.<sup>39,43,47,48</sup> These health behaviors are modifiable factors that may represent a potential tool to combat functional health impairment and symptoms exacerbation, mitigating the detrimental impact of breast cancer treatment. The increasing population of breast cancer survivors presents several challenges and opportunities

in this process of integration of such tools in the care pathway.

The first need is therefore the identification of patients that are at higher risk of treatment-related *sequelae*. A major barrier to identifying factors associated with the development and persistence of long-term toxicities - and potential targets for impactful behavioral interventions - has been the scarcity of longitudinal and well-powered datasets assessing toxicities and including detailed demographic, lifestyle, social, medical, psychological, treatment-related data and that are complemented by patient-reported outcomes. Particularly, most of the available data are focused on the acute effects of cancer treatments, assess cross-sectional data, and do not capture the long-term complexity and variability of symptoms over time. Symptoms can indeed be intermittent and fluctuate from years to decades, while having a major impact on patients' day-to-day function.<sup>49</sup>

In an effort to optimize resource utilization, research should be now focused on healthy lifestyle promotion interventions among specific target subpopulations, and on how to best deliver patient-specific behavioral support.<sup>50-52</sup>

## AIMS OF THE THESIS

Specific Aims	
<b>PART I</b>	<p><b>Specific Aim 1:</b> To describe Health Behaviors (HB) over the course of breast cancer (BC) survivorship and to define their relationship with patient-reported outcomes (PROs) and quality of life (QOL). Particularly, we aimed:</p> <p>(1) To focus on risk factors for persistent unhealthy behaviors (<b>Manuscript 1</b>)</p> <p>(2) To assess QOL in two specific populations, at risk of severe downstream treatment impact:</p> <p style="padding-left: 20px;">(2a) among patients receiving adjuvant chemotherapy (<b>Manuscript 2</b>)</p> <p style="padding-left: 20px;">(2b) among obese BC survivors during primary treatment (<b>Manuscripts 3 and 4</b>)</p>
<b>PART II</b>	<p><b>Specific Aim 2:</b> To explore a specific core case-study in BC survivorship: cancer-related fatigue (CRF). Particularly, we aimed:</p> <p>(1) To evaluate prevalence and risk factors for severe CRF (<b>Manuscript 5</b>)</p> <p>(2) To characterize the uptake of recommended management strategies to improve CRF, including HB such as physical activity (<b>Manuscript 6</b>)</p>
<b>PART III</b>	<p><b>Specific Aim 3:</b> To inform and design a targeted behavioral intervention to improve treatment-related <i>sequelae</i> (CRF) among patients at risk (overweight and obese BC survivors) (<b>Manuscript 7</b>)</p>

## OVERALL METHODOLOGY

**DATA SOURCE.** In Part I and II, This thesis exploited data from the **CANcer TOxicities (CANTO)** cohort (NCT01993498, ["Study of chronic toxicity of treatment in patients with localized breast cancer"]).

CANTO is a project led by a consortium including UNICANCER (National French Cooperative Breast Cancer InterGroup), Gustave Roussy (Villejuif, FR), Centre Léon Bérard (Lyon, FR), Centre François Baclesse (Caen, FR), and Centre Georges Leclercq (Dijon, FR), partly funded by Agence Nationale de la Recherche (ANR; "Programmes Investissement d'avenir, Cohorte programme"). CANTO aims at investigating the main survivorship issues in patients with early-stage breast cancer, in order to advance the care of this population. Particularly, the goal of CANTO is to identify toxicities, to quantify their impact on quality of life and to predict them.

CANTO is a French longitudinal, prospective, multicentre cohort study of women with localised, stage I–IIIA breast cancer receiving their primary breast cancer care at one of the 26 participating French cancer centres. CANTO recruiting centres include 20 comprehensive cancer centres, two university hospitals in the greater Paris area, two public non-teaching hospitals and two private hospitals. Enrolment started in March 2012; by October 2018, 12,012 patients were enrolled.

Patients with the following characteristics are eligible for inclusion: **(1)** have a proven invasive breast cancer, **(2)** cT0–cT3, cN0–3 tumor by American Joint Committee on Cancer (AJCC) seventh edition, **(3)** 18 years old or older at diagnosis, **(4)** untreated at the time of inclusion (including surgery), **(5)** fluent in French and **(6)** able to provide written, informed consent. Patients with the following characteristics are excluded: **(1)** T4 and stage IV breast cancer by AJCC seventh edition, **(2)** evidence of local or distant recurrence, **(3)** history of other cancer within 5 years prior to entry into the study, with the exception of basal cell carcinoma of the skin or carcinoma in situ of the cervix and **(4)** receipt of any breast cancer treatment prior to study entry.

All patients are followed for a minimum of 5 years. Data are collected at the time of diagnosis before any treatment, and then 1 year, 3 years and 5 years after primary treatment. This is defined as completion of surgery, chemotherapy or radiotherapy, whichever comes last. Adjuvant trastuzumab, adjuvant endocrine therapy or participation in clinical trials can be ongoing during follow-up, as well as any reconstructive or prophylactic surgery. Data collection is interrupted in case of metastatic recurrence or second cancer.

Data collection includes demographics, detailed clinical and treatment data, nurse collected toxicity data (using Common Terminology Criteria for Adverse Events [CTCAE] v.4 criteria) social and economic ad hoc questionnaires, and validated patient-reported data including, quality of life, psychological, mental health,

physical activity and nutrition questionnaires (including European Organisation for Research and Treatment of Cancer [EORTC] QLQ-C30, -BR23, Fatigue [FA]-12, Hospital Anxiety and Depression Scale [HADS], and Global Physical Activity Questionnaire [GPAQ16]).<sup>19,53–60</sup>

**CANTO is currently the largest prospective study in the world dedicated to cancer survivorship, with the ability to answer the open research questions in this field that ultimately will impact clinical care.**<sup>61</sup>

*Outcomes research as a tool to study survivorship issues.* Real-world data, i.e. observational data collected from routine clinical practice (e.g. through electronic medical records, registries and billing data) or directly from patients (e.g. through wearables and health applications) and not from clinical trials, allows the generation of real-world evidence.<sup>62</sup> As the overall group of patients seen in daily-life clinics compose the real-world data, real-world evidence maximizes the external validity of study findings. However, while external validity is maximized, other methodological issues may arise, namely the risk for confounding and bias. To deal with the methodological challenges of such research, the field of real-world research matured to apply methodological tools of epidemiology to reach solid and sound conclusions. This dynamic field of clinical research is commonly referred to as **outcomes research**. Outcomes research deals with the study of the end results, i.e. the outcomes, of different clinical interventions. In the United States national library of medicine medical subject heading (MeSH), outcomes research is considered a synonym of “outcome assessment (health care)” and defined as “research aimed at assessing the quality and effectiveness of health care, as measured by the attainment of a specified end result or outcome. Measures include parameters such as improved health, lowered morbidity or mortality, and improvement of abnormal states.”<sup>63</sup> The outcomes that are measured can be collected both through the lens of health-professionals (e.g. CTCAE) or through the lens of patients (patient reported outcomes [PROs]). While health-professional and PROs should report a similar perception of a clinical phenomenon, it is becoming clearer that the characterization of clinical phenomena from both perspectives can tell complementary stories, thus making the case for the systematic collection of PROs in clinical research studies.<sup>64</sup>

One of the aims of epidemiology is to estimate unbiased associations. To attain this, several methodological optimizations were implemented to prevent, reduce and quantify bias and confounding.<sup>65</sup> While bias derives from inadequate study design and/or conduct, confounding reflects the rich interrelationships between factors and outcomes. Several design and analytic techniques are available to handle bias and confounding. Given the non-interventional nature of outcomes research, strategies to overcome bias should come from thoughtful study design and careful patient selection. While impossible to exclude, bias needs to be proactively handled and be taken into consideration when interpreting results. Design strategies to reduce confounding include stratification and adjustment. In the body of work presented here we took advantage of thoughtful study design and patient selection, and we further adjusted analyses using standard statistical methods, including multivariable modelling.

**Throughout the present body of work, we made use of real-world evidence derived from a big national data source such as CANTO to answer several clinical questions.**

## **OVERVIEW OF STATISTICAL METHODS USED**

A number of statistical analytic methods were involved during the preparation of this thesis, including

- (1) Descriptive analyses
- (2) Association studies
  - a. Linear and logistic regression models
  - b. Multinomial regression models
  - c. Techniques for longitudinal data analysis
    - i. Generalized Estimating Equations
    - ii. Random-effects mixed model
    - iii. Latent-class analysis, particularly Group-Based Trajectory Modeling

Statistical analyses were performed using SAS statistical software Version 9.4 (SAS Institute Inc.) and R Studio.

## **ROLE AND CONTRIBUTION OF THE CANDIDATE**

All the following tasks were primarily performed by Antonio DI MEGLIO:

- Projects conceptualization
- Data curation
- Investigation and methodology curation
- Formal analysis of data (SAS + R Studio)
- Projects administration
- Funding acquisition
- Submission and presentation of findings in scientific meetings
- Manuscript writing, review and editing
- Submission of findings for publication

Formal coursework to complement specific skills of the candidate in patient-reported data analysis and software utilization included:

- 2019 INSERM Workshop: "Recent development in the analysis of patient-reported outcomes and psychometric data in health"
- 2020 RITME Formation: "Formation R"

## **RESULTS - PART I**

## MANUSCRIPT 1 (MS1):

### Unhealthy behaviors after breast cancer: capitalizing on a teachable moment to promote lifestyle improvements

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**Previous Presentations:** Findings of this study were partly presented in poster form at the 2019 San Antonio Breast Cancer Symposium, San Antonio, TX, US. Ref: "Lifestyle changes after breast cancer: A prospective study among 8580 women" [abstract]. In: Proceedings of the 2019 San Antonio Breast Cancer Symposium; 2019 Dec 10-14; San Antonio, TX. Philadelphia (PA): AACR; Cancer Res 2020;80(4 Suppl):Abstract nr P2-13-03.

**Publication:** Submitted for publication in November 2020.

## **Abstract**

**Background:** Unhealthy lifestyle behaviors such as physical inactivity, smoking and regular alcohol consumption can lead to poorer overall health and cancer-related outcomes. We sought to determine prevalence and risk factors of unhealthy behaviors among women with early-stage breast cancer.

**Methods:** We analyzed 9556 patients from the prospective, multicentric CANTO cohort (NCT01993498). Physical activity (PA), smoke, and alcohol use were longitudinally assessed at diagnosis (baseline), year-1 and year-2 post-diagnosis. Behavior was defined as unhealthy if patients failed to maintain their PA above recommendations ( $\geq 10$  MET-hours/week), to reduce or quit smoking, or to decrease frequency of alcohol consumption (to at least less-than-daily). Multivariable-adjusted Generalized Estimating Equations explored associations between baseline characteristics and unhealthy behaviors at any time post-diagnosis.

**Results:** At diagnosis, 41.7% patients were inactive, 18.2% currently smoked, and 14.6% consumed alcohol daily. At year-1 and year-2 respectively, unhealthy PA behavior was prevalent among 37.0% and 35.6% patients, unhealthy smoke behavior among 11.3% and 9.5% patients, and unhealthy alcohol behavior among 13.0% and 12.6% patients overall. Smoking and alcohol reduction or abstinence concerned approximately 1/3 and 1/10 of current smokers and daily alcohol users, respectively. Older women were more prone to inactivity (5-year increment, adjusted odds ratio 1.03 [95%CI 1.01-1.05]) and alcohol use (1.28 [1.22-1.34]), but less likely to engage in unhealthy smoking behavior (0.81 [0.78-0.85]). Depression cases were associated with reduced odds of unhealthy smoking behavior (vs. non-case, 0.67 [0.46-0.97]), and with higher likelihood of unhealthy alcohol behavior (1.59 [1.19-2.19]). College education was linked with reduced unhealthy PA behavior (vs. primary, 0.61 [0.51-0.73]) and more likely alcohol use (1.85 [1.14-2.19]).

**Conclusions:** The majority of women in this cohort pursued a healthy lifestyle. Behavioral improvements were observed, although unhealthy baseline behaviors mostly persisted. There was a complex interplay among multiple clinical, socio-demographic, and psychological risk factors, with varying determinants according to behavior. This large study will inform targeted behavioral interventions for health promotion.

## **Introduction**

Breast cancer is the most common cancer in women worldwide<sup>66</sup>, with a progressively increasing number of survivors of early-stage cancers each year.<sup>67</sup> There is a strong link between lifestyle-related factors, breast cancer risk, and prognosis, and evidence shows that pursuing a healthy lifestyle is associated with multiple benefits, including improved cancer-specific outcomes.<sup>68</sup> However, unhealthy lifestyle habits are still very common. Physical inactivity is highly prevalent among women newly diagnosed with breast cancer, and a substantial portion of them are current smokers or consume alcohol regularly.<sup>69,70</sup>

Being diagnosed with breast cancer may have a substantial psychological impact and can be a catalyzer to adopt health-improving strategies, with some women spontaneously starting to seek information about lifestyle modifications and positively changing certain behaviors,<sup>71</sup> or pursuing techniques to manage stress, improve wellbeing, and maintain good quality of life.<sup>72,73</sup>

Nevertheless, for many of them, additional support through lifestyle interventions is required to facilitate change and maintain it on the long term. In addition, some studies showed that many survivors seem to fail in improving their lifestyle and that they do not seem particularly more prone to healthy behaviors compared to individuals without a history of cancer.<sup>74-76</sup>

Previous research tried to identify vulnerable patient populations that do not uptake unhealthy lifestyle after breast cancer diagnosis,<sup>77</sup> since characterizing their profiles is essential to build successful interventions for health promotion.<sup>77,78</sup> Limitations included small sample size, non-detailed characterizations, and limited generalizability. We sought to describe patterns of lifestyle after breast cancer and their associated factors in the CANcer TOxicity (CANTO) cohort. This large longitudinal clinical study has availability of granular and comprehensive clinical, tumor-related, treatment, and behavioral data.<sup>61</sup> Specifically, we aimed at describing factors associated with unhealthy behaviors and at identifying women at higher risk of adverse lifestyle changes.

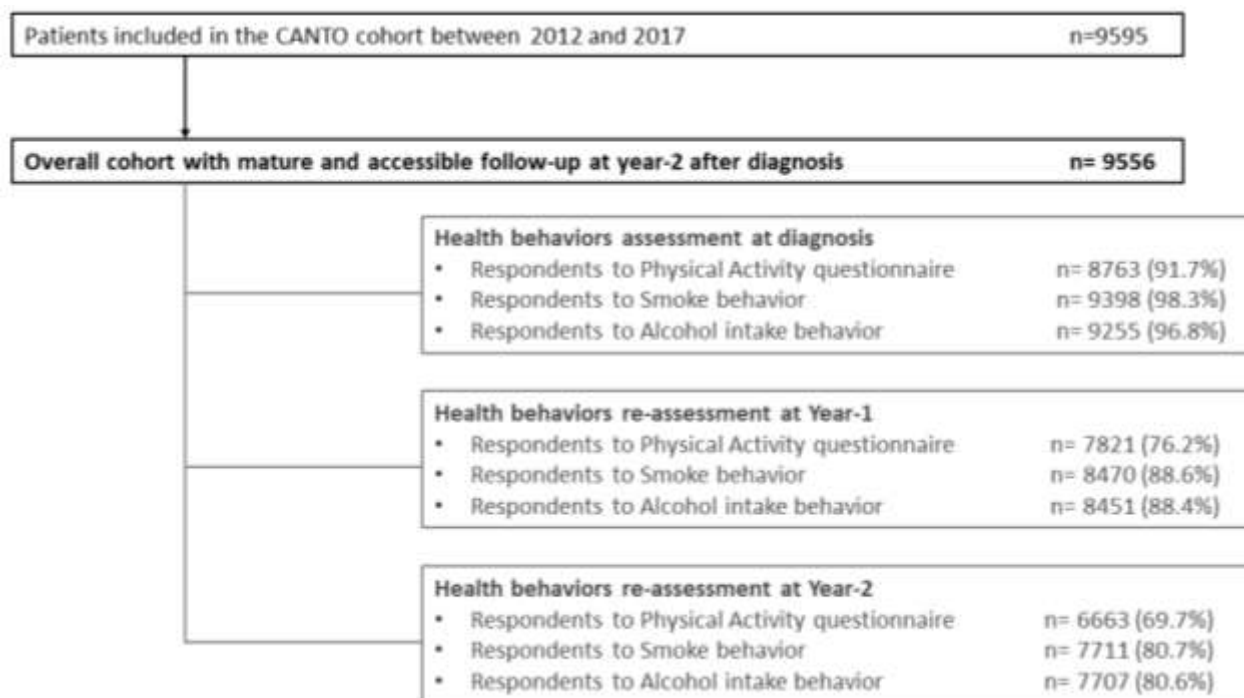
## **Methods**

### Data source

CANTO (NCT01993498) is a prospective, multicentric cohort that enrolled patients with stage I-II-III breast cancer.<sup>61</sup> Patients exited the CANTO study at the time of any breast cancer recurrence (other than local) or second cancers. For the present sub-study, named TEachable MomentS in CANTO (TEAMS), we used patient information that were longitudinally assessed at breast cancer diagnosis (baseline) and at year-1 and year-2 post-diagnosis. Objective anthropometric measures (including body mass index [BMI]), tobacco smoke, and alcohol intake were assessed during evaluations with trained study nurses. Physical activity was self-reported. All participants provided informed consent. The study was approved by national regulatory authorities and ethics committee (ID-RCB:2011-A01095-36, 11-039).

### Study cohort

We included 9556 women diagnosed with breast cancer from 2012-2017 with accessible follow-up data until year-2 after diagnosis. The number of respondents to behavior assessments at each time point is reported in **MS1-Figure 1**. Respondents to physical activity questionnaires were slightly younger, leaner, with lower depression scores, and higher socioeconomic status (SES). No major differences were present between responders and non-responders to smoking and alcohol questionnaires (**MS1-Supplementary Table 1**).



**MS1-Figure 1. CONSORT diagram of patient population.** Note: CANTO enrolled a total of 12,012 patients overall. This analyses included 9556 patients for whom mature follow-up until year-2 after diagnosis was available.

#### Variables of interest

##### *Outcome variables: definitions of lifestyle behaviors*

**Physical Activity.** The Global Physical Activity Questionnaire (GPAQ)-16 (World Health Organization [WHO])<sup>60</sup> was used to assess duration and intensity of work, transportation, and leisure-time physical activity in metabolic equivalents of task [MET]-hours/week, as well as sedentary behavior (hours/day). Ten or more MET-hours/week defined patients as “sufficiently active” (vs. “insufficiently active”; i.e., according to WHO recommendations [150 minutes/week of moderate-intensity or 75 minutes/week of vigorous intensity or an equivalent combination]).<sup>60</sup> Categories for change were “maintained” (i.e., sufficiently active before and after), “increased” (i.e., insufficiently active before and sufficiently active after), “decreased” (i.e., sufficiently active before and insufficiently active after), or “persistently-insufficient” activity (i.e., insufficiently active before and after) compared to the previous assessment.

**Smoking and Alcohol behavior.** At diagnosis, patients were defined as “current” or “former or never”

tobacco smokers. Frequency of alcohol consumption was defined as “daily” or “less than daily”. At year-1 and year-2 post-diagnosis, patients were asked whether their behavior had “remained unchanged”, “increased” or “decreased” compared to the previous assessment. Number of packets/year and smoking duration were also collected.

To identify patients that were more prone to negative changes, we focused on (i) unhealthy physical activity behavior (“decreased” or “persistently insufficient” activity”), and (ii) unhealthy smoke or (iii) alcohol behavior (“unchanged” behavior in case of previously “current” smoker or “daily” alcohol consumption vs. “increased”, compared to the previous assessment).

### *Covariates*

Clinical, socioeconomic, tumor and treatment characteristics were categorized as per **MS1-Table 1**. Anxiety and depression at diagnosis were explored using the Hospital Anxiety and Depression Scale (subscales categorized into “non-case” [points 0-7], “doubtful” [8-10], and “case” [11-21]).<sup>53</sup> Quality of life was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30.<sup>57,79</sup>

### Statistical analysis

First, descriptive statistics were used to summarize baseline cohort characteristics, nature (healthy vs. unhealthy) and evolution of behaviors from diagnosis to year-1 and year-2.

Then, we evaluated baseline exposure variables in relation to changes in lifestyle behaviors. The GENMOD procedure was used to fit models to correlated responses by Generalized Estimating Equations, to explore the association between baseline exposure variables and the outcome of engaging in an unhealthy physical activity, smoke, or alcohol behavior at year-1 and year-2 post-diagnosis. Separate models were constructed for each outcome. An exchangeable working correlation matrix structure was specified to account for within-subject correlations. The variance function for the binomial distribution and the logit link function were used since the response data were binary. In order to assess relative differences between levels of explanatory variables, model-based multivariable-adjusted Odds Ratios (aORs) and respective 95% Confidence Intervals (CI) were obtained. Explanatory variables included in the models are listed in **MS2-Table 2**.

Changes in sedentary behavior were evaluated as a continuous variable using a multivariable random effect mixed model, adjusting for baseline covariates, time, and baseline-by-time interactions, as appropriate, obtaining model-based means and respective 95% CI (an interval not crossing 0 represents a significant change).

In sensitivity analyses, smoking was defined by number of packets/year (continuous).

Statistical analysis was performed using SAS statistical software Version 9.4 (SAS Institute Inc.). Statistical significance was defined with a 2-sided p-value < 0.05.

## Results

### Cohort characteristics

A complete baseline characterization of CANTO patients is displayed in **MS1-Table 1** (N=9556). The mean age at inclusion was 56.3 years.

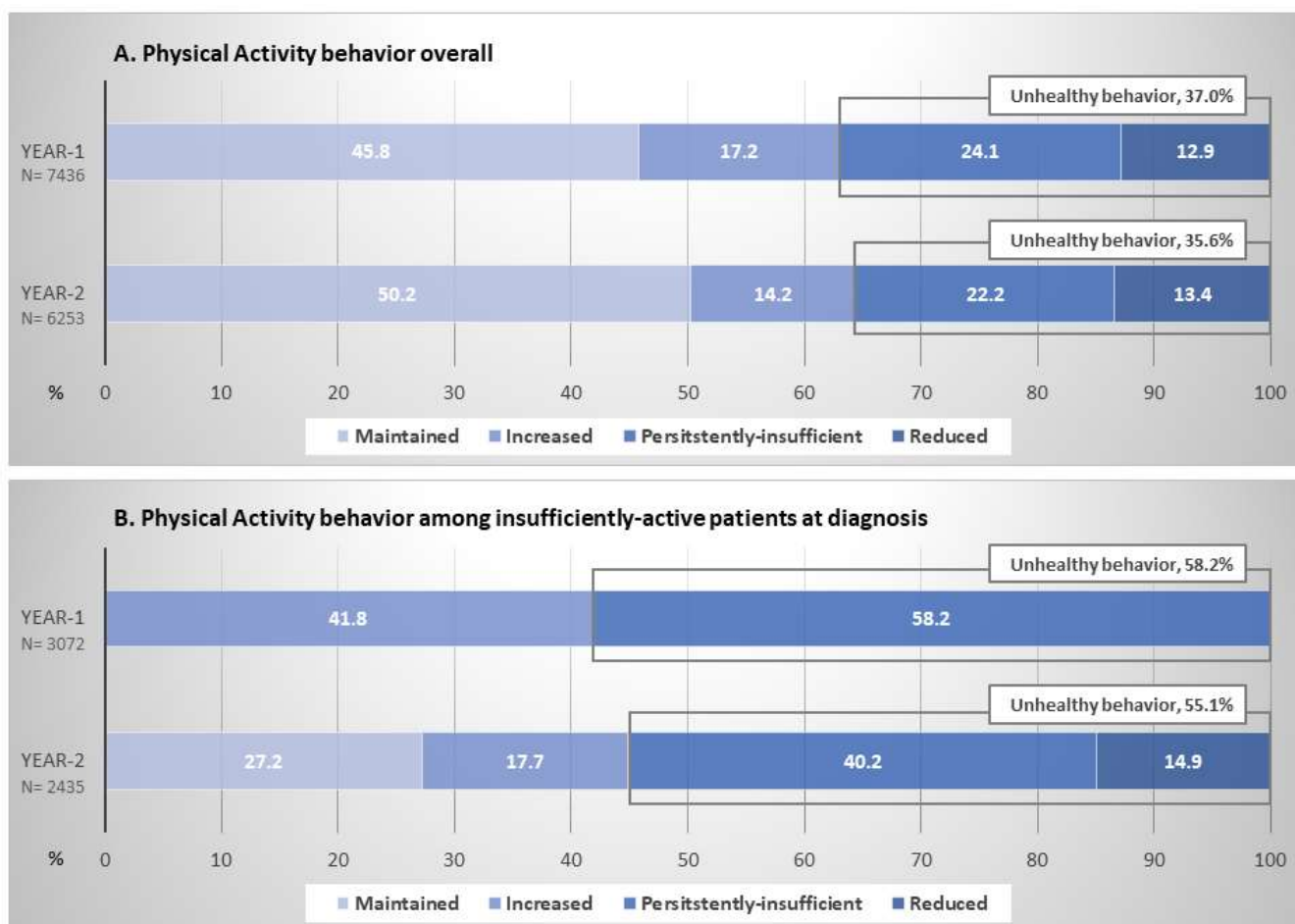
<b>MS1-Table 1. Baseline cohort characteristics (N= 9556), N (%)</b>	
<b>Age, years</b>	
Mean (SD)	56.3 (11.4)
<b>Body Mass Index, Kg/m<sup>2</sup></b>	
Mean (SD)	25.9 (5.4)
Missing	57
<b>Body Mass Index, Kg/m<sup>2</sup></b>	
<18.5, Underweight	225 (2.4)
18.5-24.9, Normal weight	4633 (48.8)
25.0-29.9, Overweight	2773 (29.2)
≥30.0, Obese	1868 (19.7)
Missing	57
<b>Menopausal status</b>	
Premenopausal	3486 (37.2)
Postmenopausal	5891 (62.8)
Missing	179
<b>Charlson comorbidity score</b>	
0	7077 (80.8)
≥1	1684 (19.2)
Missing	795
<b>Anxiety</b>	
Non-case	3446 (39.5)
Doubtful	2340 (26.8)
Case	2929 (33.6)
Missing	841
<b>Depression</b>	
Non-case	7107 (81.5)
Doubtful	996 (11.4)
Case	617 (7.1)
Missing	836
<b>Patient-reported Quality of Life Summary Score, EORTC QLQ-C30*</b>	
Mean (SD)	82.7 (12.8)
Missing	1139
<b>Highest education level</b>	
Primary school	1298 (15.0)
High School	4045 (46.6)
College degree or higher	3332 (38.4)
Missing	881
<b>Marital status</b>	
Partnered	6169 (72.0)
Not partnered	2398 (28.0)
Missing	989
<b>Monthly household income</b>	
<3,000 Euro	4503 (56.2)
≥3,000 Euro	3513 (43.8)
Missing	1540

<b>Center volume</b>	
High (>1000 patients)	2314 (24.2)
Low-Intermediate (≤1000 patients)	7242 (75.8)
<b>Stage</b>	
I	4706 (49.5)
II	3868 (40.7)
III	923 (9.7)
Missing	59
<b>Breast cancer surgery</b>	
Mastectomy	2516 (26.4)
Partial breast surgery**	6997 (73.6)
Missing	43
<b>Axillary surgery</b>	
Axillary dissection	3589 (37.7)
Sentinel node or none	5924 (62.3)
Missing	43
<b>Chemotherapy</b>	
Yes	5037 (53.0)
No	4471 (47.0)
Missing	48
<b>Radiation therapy</b>	
Yes	8665 (91.3)
No	827 (8.7)
Missing	64
<b>Endocrine therapy</b>	
Yes	7677 (81.1)
No	1788 (18.9)
Missing	91
<b>Anti-HER2 therapy</b>	
Yes	1152 (12.1)
No	8343 (87.9)
Missing	61
<b>Physical activity, WHO recommendations</b>	
Insufficiently active	3658 (41.7)
Sufficiently active	5105 (58.3)
Missing	793
<b>Tobacco smoke</b>	
Current smoker	1709 (18.2)
Former or never smoker	7689 (81.8)
Missing	158
<b>Alcohol consumption</b>	
Daily	1351 (14.6)
Less than daily	7904 (85.4)
Missing	301
SD= Standard deviation; WHO= World Health Organization; HER2= Human Epidermal Growth Factor Receptor 2; MET= Metabolic Equivalent of task.	
*Summary Score is a composite score that includes 13/15 domains of EORTC QLQ-C30, namely Physical Function, Emotional Function, Social Function, Cognitive Function, Role Function, Fatigue, Pain, Insomnia, Nausea/Vomit, Dyspnea, Appetite Loss, Constipation, and Diarrhea **Includes 30 patients who did not undergo breast surgery.	

## Physical activity behavior

Over time, there was a slight reduction in patients not meeting recommendations on physical activity (41.7% at diagnosis [N=3658], 37.1% at year-1 [N=2901], and 36.0% at year-2 [N=2400]; Cochran-Armitage  $p_{\text{trend}} < 0.0001$ ) and fewer patients reported not to engage in any (i.e., 0 MET-hours/week) physical activity (26.8% [N=2345], 21.9% [N=1716], and 21.0% [N=1398] at each time point, respectively;  $p_{\text{trend}} < 0.0001$ ).

At year-1 and year-2, 37.0% and 35.6% patients overall reported decreased or persistently-insufficient physical activity compared to the previous assessment, respectively (**MS1-Figure 2A**). Among insufficiently-active patients at diagnosis, 41.8% had increased their activity at year-1, then 27.2% maintained and 17.7% increased their activity at year-2 compared to year-1 (**MS1-Figure 2B**).



**MS2-Figure 2. Physical Activity change over time.** Patients were “sufficiently-active” if they reported  $\geq 10$  MET-hours/week and “insufficiently-active” if  $< 10$ . Categories for change in activity were as follows: “maintained” (ie, sufficiently-active before and after), “increased” (ie, insufficiently-active before and sufficiently-active after), “decreased” (ie, sufficiently-active before and insufficiently-active after), or “persistently-insufficient” activity (ie, insufficiently-active before and after) compared to the previous assessment (ie, year-1 compared to baseline and year-2 compared to year-1).

Mean sedentary time at diagnosis was 6.40 hours/day (95% CI 6.13-6.65). There was a global tendency towards reducing sedentary time after diagnosis, with larger reductions reported over the first year (mean change [95%CI]: year-1 -0.27 [-0.37 to -0.17] hours/day, adjusted  $p < 0.0001$ ; year-2 -0.14 hours/day [-0.25 to -0.03], adjusted  $p = 0.0124$ ).

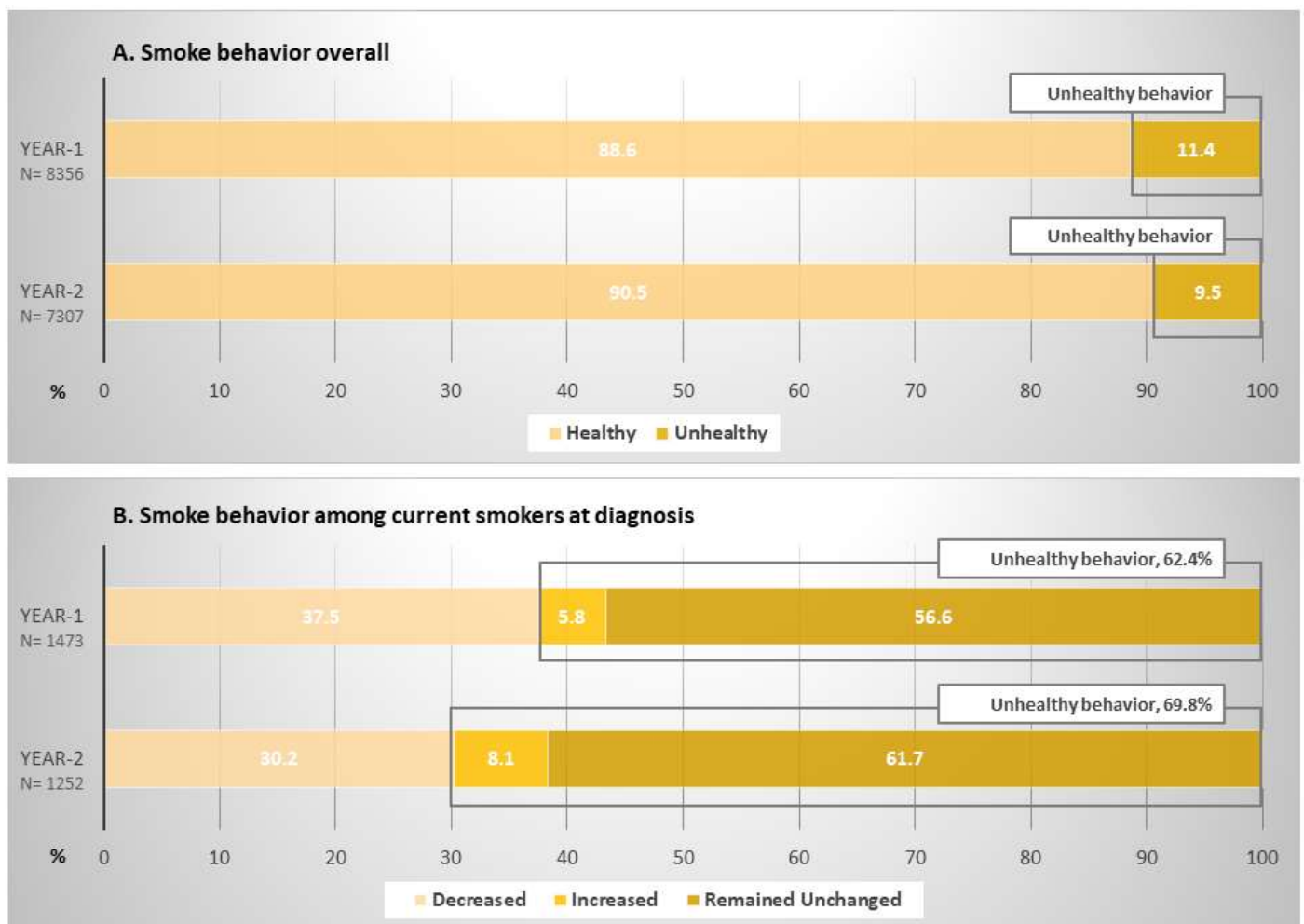
Older age (for a 5-year increment, aOR 1.03 [95% CI 1.01-1.05]), higher BMI (for 1-unit increment, 1.06 [1.05-1.07]), partnered status (vs. not, 1.29 [1.14-1.47]), and current smoker status (vs. former/never, 1.43 [1.25-1.63]) were risk factors for an unhealthy physical activity behavior. Conversely, women qualifying as anxiety cases (vs non-case, 0.85 [0.74-0.97]) and those with higher education (college vs. primary school, 0.61 [0.51-0.73]) were less likely to engage in an unhealthy physical activity behavior (**MS1-Table 2**).

### Smoking behavior

Current smoking was prevalent among 18.2% (N= 1709) of patients at diagnosis, who reported a median of 19 packets (Quartile [Q]1-Q3, 10-30) smoked per year and of 32 years (Q1-Q3, 25-39) since smoke initiation.

An unhealthy smoke behavior was reported by 11.4% patients at year-1 and 9.5% patients at year-2, who either resumed or increased smoking, or maintained a status of current smoker (**MS1-Figure 3A**).

For those who were current smokers at diagnosis, reduction or quit was prevalent among 37.5% patients at year-1 and 30.2% patients at year-2 (**MS1-Figure 3B**).

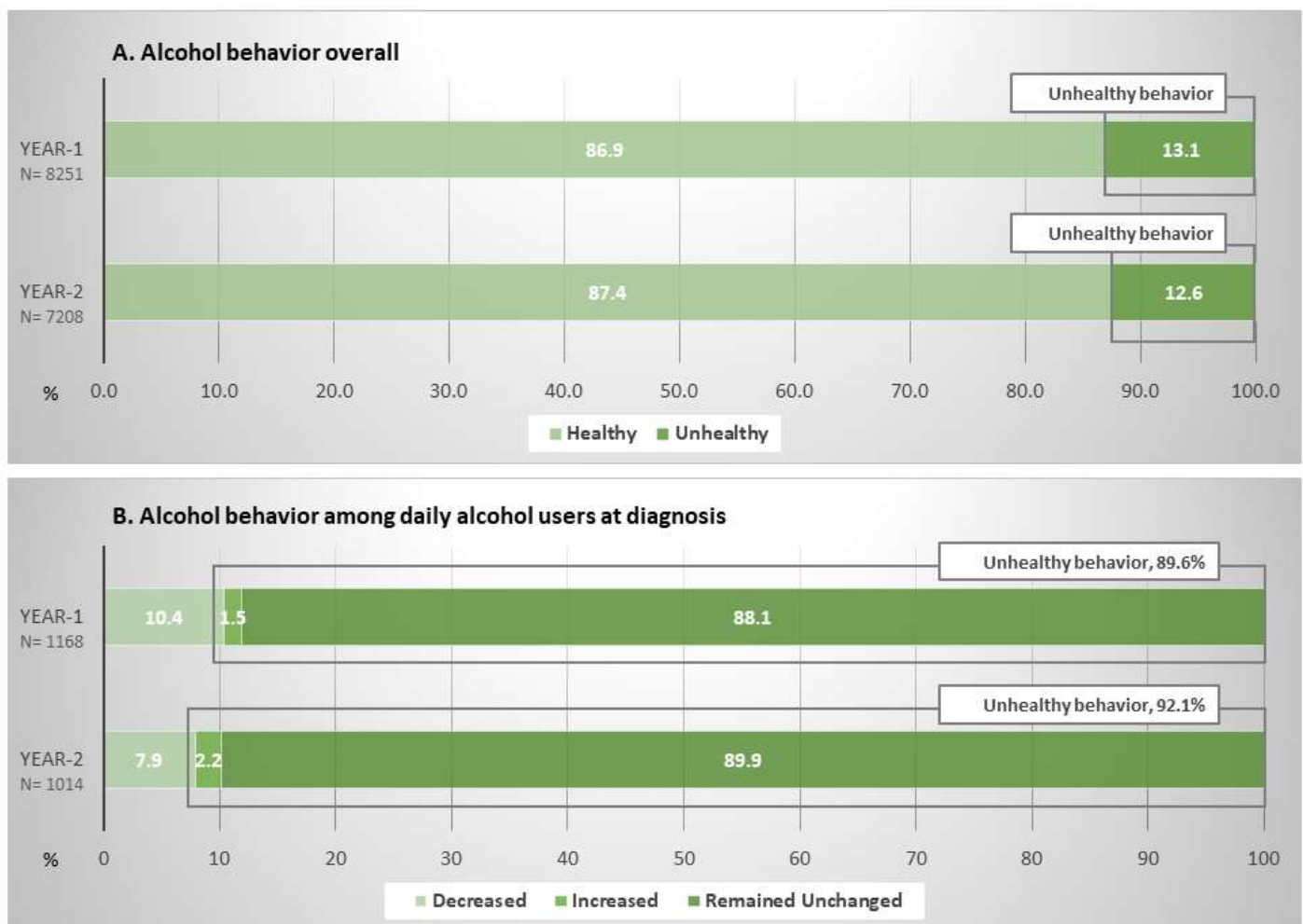


**MS1-Figure 3. Changes in smoking behavior over time.** Behavior was classified as: “remained unchanged”, “increased” or “decreased” compared to the previous assessment (ie, year-1 compared to baseline and year-2 compared to year-1).

Odds of unhealthy smoke behavior were lower among women who were older (for a 5-year increment, 0.81 [0.78-0.85]), heavier (for a 1-unit BMI increment, 0.96 [0.94-0.98]), partnered (vs. not, 0.71 [0.58-0.88]), those who received chemotherapy (vs. not 0.76, [0.61-0.94]), and those who were sufficiently physically active (vs. insufficiently active, 0.73 [0.62-0.87]) (**MS1-Table 2**).

### Alcohol behavior

Daily alcohol use was prevalent among 14.6% (N= 1351) participants at diagnosis. An unhealthy alcohol behavior was present among 13.1% patients at year-1 and 12.6% patients at year-2. The vast majority of patients did not change their alcohol behavior, although a minority of daily alcohol users at diagnosis reported reductions in use over time, namely 10.4% at year-1 and 7.9% at year-2 (**MS1-Figure 4A, B**).



**MS1-Figure 4. Changes in alcohol behavior over time.** Behavior was classified as: “remained unchanged”, “increased” or “decreased” compared to the previous assessment (ie, year-1 compared to baseline and year-2 compared to year-1).

Older age (for a 5-year increment, aOR 1.28 [95% CI 1.23-1.33]), depression cases (vs. non-cases, 1.58 [1.14-2.19]), higher education (college vs. primary school, 1.85 [1.37-2.49]), and partnered status (vs. not, 1.34 [1.09-1.64]) were significantly associated with risk of unhealthy alcohol behavior. Women with higher BMI were

less prone to an unhealthy alcohol behavior (for 1-unit increment, 0.96 [0.95-0.98]) (**MS1-Table 2**).

### *Sensitivity analyses*

Sensitivity analyses yielded consistent results. In addition, heavier smoking was a significant risk factor for unhealthy physical activity (for each 10-unit increment in packets of cigarettes/year, aOR 1.15 [95%CI 1.10-1.21]) and alcohol behavior (aOR 1.27 [95%CI 1.19-1.35]).

**MS1-Table 2. Multivariable models of baseline factors associated with unhealthy behaviors.**

	Model 1 Unhealthy Physical Activity behavior				Model 2 Unhealthy Smoke behavior				Model 3 Unhealthy Alcohol behavior			
Prevalence - Event rate	Year-1, <b>37.0%</b> / Year-2, <b>35.6%</b>				Year-1, <b>11.4%</b> / Year-2, <b>9.5%</b>				Year-1, <b>13.1%</b> / Year-2, <b>12.6%</b>			
Variable	OR*	95%CI		p	OR*	95%CI		p	OR*	95%CI		p
		Low	High			Low	High			Low	High	
Age, Continuous (5-year increase)	1.03	1.01	1.05	0.045	0.81	0.78	0.85	<.0001	1.28	1.23	1.33	<.0001
BMI, Continuous (1-unit increase)	1.06	1.05	1.07	<.0001	0.96	0.94	0.98	<.0001	0.96	0.95	0.98	<.0001
Comorbidities, Charlson $\geq 1$ vs 0	1.03	0.91	1.17	0.611	1.11	0.89	1.38	0.350	1.14	0.94	1.39	0.187
Anxiety, Doubtful vs Non-case	0.90	0.79	1.02	0.094	1.04	0.84	1.29	0.703	0.89	0.73	1.08	0.245
Anxiety, Case vs Non-case	0.85	0.74	0.97	0.016	1.09	0.87	1.35	0.464	0.81	0.65	1.00	0.055
Depression, Doubtful vs Non-case	1.21	1.03	1.43	0.023	1.02	0.78	1.33	0.907	1.08	0.82	1.44	0.570
Depression, Case vs Non-case	1.14	0.91	1.42	0.248	0.67	0.46	0.97	0.035	1.58	1.14	2.19	0.006
Overall QOL, C30-Summary Score, Continuous (10-unit increase)	0.95	0.91	0.99	0.033	0.87	0.81	0.94	0.001	0.97	0.91	1.05	0.500
Education, High school Primary school	0.81	0.69	0.95	0.010	1.14	0.84	1.54	0.400	1.33	1.01	1.74	0.043
Education, College vs Primary school	0.61	0.51	0.73	<.0001	0.80	0.57	1.13	0.206	1.85	1.37	2.49	<.0001
Marital status, Partnered vs Not Partnered	1.29	1.14	1.47	<.0001	0.71	0.58	0.88	0.001	1.34	1.09	1.64	0.005
Household income, $\geq 3000$ vs $< 3000$ Euro/month	0.93	0.83	1.05	0.230	0.89	0.72	1.09	0.261	0.97	0.80	1.17	0.741
Centre Volume, Low-intermediate volume vs High	1.01	0.90	1.14	0.854	0.99	0.81	1.20	0.918	1.13	0.93	1.37	0.212
Stage, II vs I	1.11	0.98	1.26	0.102	1.10	0.89	1.35	0.384	1.16	0.95	1.42	0.134

<b>Stage III vs I</b>	0.98	0.79	1.21	0.829	1.16	0.80	1.67	0.437	1.24	0.87	1.76	0.234
<b>Breast surgery, Partial vs Mastectomy</b>	0.95	0.82	1.08	0.422	1.08	0.86	1.36	0.515	0.96	0.76	1.20	0.715
<b>Axillary surgery, Dissection vs None or Sentinel</b>	1.03	0.90	1.18	0.658	0.92	0.74	1.14	0.446	0.97	0.79	1.20	0.786
<b>Chemotherapy, Yes vs No</b>	0.98	0.86	1.12	0.776	0.76	0.61	0.94	0.012	1.16	0.94	1.42	0.171
<b>Radiotherapy, Yes vs No</b>	0.89	0.72	1.09	0.263	1.54	1.07	2.20	0.019	0.80	0.58	1.10	0.174
<b>Endocrine therapy, Yes vs No</b>	0.99	0.87	1.12	0.844	0.93	0.75	1.15	0.502	1.11	0.89	1.37	0.352
<b>Anti HER-2 therapy, Yes vs No</b>	0.99	0.85	1.16	0.934	1.02	0.79	1.33	0.865	0.83	0.64	1.09	0.184
<b>Physical Activity, Sufficiently vs Insufficiently active</b>	-	-	-	-	0.73	0.62	0.87	0.0001	0.99	0.84	1.16	0.898
<b>Smoking behavior, Current vs. Former/Never</b>	1.43	1.25	1.63	<.0001	-	-	-	-	2.19	1.81	2.64	<.0001
<b>Alcohol behavior, Daily vs Less than daily</b>	0.99	0.86	1.14	0.901	2.24	1.82	2.75	<.0001	-	-	-	-

CI= Confidence Interval. BMI=Body Mass Index; QOL= Quality of life; HER2= Human Epidermal Growth Factor Receptor 2; MET= Metabolic Equivalent of task. \*Adjusted for all variables in the table. Estimates are obtained by a multivariable-adjusted generalized estimating equation model correcting for all factors included in the Table. Probability modeled Is "unhealthy" behavior at any time point (year-1 or year-2).

## Discussion

In this large study of women with non-metastatic breast cancer, the majority seemed to pursue a healthy lifestyle at the moment of diagnosis. Over the first two years after diagnosis, a sizable proportion of them also seemed to improve unhealthy behaviors. However, unhealthy behaviors mostly tended to persist, with a complex interplay among multiple risk factors.

Awareness about the importance of pursuing healthy behaviors has recently increased among cancer survivors, and multiple lifestyle recommendations for patients living with and beyond breast cancer now exist.<sup>31,35,80</sup> However, changing behavior is complex and highly dependent on individual and community resources.<sup>81,82</sup> Our study points at distinct patterns and risk factors for unhealthy behaviors depending on the specific behavior analyzed.

First, despite a general trend showing increasingly higher adherence to recommendations, physical inactivity was still very common after diagnosis. There was also a relevant proportion of initially physically active patients who reduced their activity afterwards, while reductions in sedentary time happened mostly in the early segment of follow-up. Similarly to our study, an analysis from the American Cancer Society Study of Cancer Survivors-II found that only 30%-47% met physical activity guidelines and that 31% of patients were completely inactive,<sup>83</sup> while the HEAL study reported significant downward trends in time spent exercising after a diagnosis of breast carcinoma.<sup>84</sup>

Second, compared to data from the general population, indicating that up to 26.4% individuals in the United States<sup>85</sup> and 29.9% in France are current cigarette smokers, prevalence of current smoking among women with breast cancer in CANTO was slightly lower (18.2%), and only one in ten women engaged in an unhealthy smoking behavior after diagnosis. In addition, readiness to pursue smoking reduction was evident in approximately one-third of patients, who limited or quit smoke. This proportion is smaller than cessation rates that were found for smoke-related cancers, including among lung or head and neck cancer survivors (ranging 53%-81%), although similar to previous studies of breast cancer survivors<sup>83,86-92</sup>. Taken together, these data suggest that current smokers may be successfully encouraged to quit after breast cancer diagnosis<sup>77,91</sup>, but also that the vast majority of current smokers (approximately 70%) do not seem to correct this unhealthy behavior over time.

Third, most of CANTO patients reported less than daily alcohol consumption, with little overtime variation during follow-up. Alcohol abstinence usually ranged 8%-16% in other reports of breast cancer survivors, but could reach up to 57% in some studies.<sup>73,77</sup> This substantial variability across studies may derive from the way alcohol behavior is assessed. From CANTO data, we could only know whether consumption was daily or less frequent, without information about number of servings per day, and consumption was nurse-assessed (as opposed to patient-reported), which may influence patients' propensity to overtly declare their behavior.<sup>93</sup>

This analysis informs also about multiple risk factors that are associated with the uptake of unhealthy lifestyle after breast cancer diagnosis. Age, initial BMI, psychological distress, SES, and treatment-related factors

were significantly associated with unhealthy lifestyle changes, but the direction of associations greatly varied by behavior.

The period after diagnosis and the beginning of treatments is thought to be critical for psychosocial adaptation. Attitudinal and behavioral changes were often mentioned as possible strategies when patients were asked whether they felt if they could have any influence on breast cancer course.<sup>72</sup> Maunsell et al. had suggested that women facing a stressful experience such as cancer may adopt healthy behaviors as strategies to face distress.<sup>73</sup> Particularly, women with worse anxiety or depression were thought to be more concerned about recurrence or impact on quality of life, therefore the uptake of a healthy behavior may give them a greater sense of control.<sup>73</sup> This assumption has not been consistently confirmed, as psychological distress may not always act as a motivating factor towards a generally healthier lifestyle. For example, Ligibel et al. found that women with anxiety were more likely to decrease physical activity<sup>94</sup>, whereas anxiety was linked with reduced odds of decreasing activity in CANTO. Conversely, we found that depression was associated to increased alcohol consumption after diagnosis, suggesting that the uptake of an unhealthy drinking behavior may serve as a coping mechanism for women diagnosed with breast cancer and faced with more severe psychological burden. Finally, theoretical models of behavioral changes also highlighted powerful determinants of behavior improvements other than cancer-related psychological distress that need to be considered, including stage of readiness to change, intentions, and self-efficacy.<sup>95</sup>

Research assessing living situation and SES as determinants of adverse lifestyle changes after cancer has been sparse, despite its important clinical implications. Socioeconomic disparities that correlate with modifiable behavioral factors may be responsible of variations in disease outcomes and mediate part of the social inequalities related to breast cancer.<sup>96,97</sup> There is evidence that women with lower social support and lower SES are at higher risk of adverse health behavior change and that they may particularly benefit from interventions.<sup>98</sup> Khadanga et al. suggested that women with higher SES may have better opportunity and flexibility to modulate their behaviors, while less education and financial discomfort have the potential to negatively influence behavior change.<sup>70</sup> CANTO data show, on the other hand, that there are differences in propensity to unhealthy behaviors also among women with better SES and familiar support.

Based on the notion that a worse cancer-related prognosis may motivate to the adoption of healthier behaviors, an inverse relationship between higher tumor stage and odds of unhealthy behaviors had been suggested.<sup>78,89,99</sup> However, evidence from literature is not compelling, and breast cancer stage did not represent a significant determinant of behavior in our data. Nevertheless, we found an interesting association between receipt of chemotherapy and improved smoke behavior. This may suggest greater awareness of smoking-related health risks and willingness to pursue good behaviors among women receiving chemotherapy. In the same lines, we recently reported a similar relationship between receipt of chemotherapy and lower risk of non-adherence to adjuvant endocrine treatment.<sup>100</sup> We may speculate that women who are cognizant of a higher disease severity, therefore requiring more aggressive treatments, may also be more receptive and sensitive to the potential impact of positive behavioral changes, including, for example, that of smoking cessation on

reduced treatment-related toxicities.<sup>101</sup>

Early education and physician emphasis on health promoting initiatives are at the core of behavioral improvements among cancer survivors.<sup>77,86,102</sup> To facilitate change, lifestyle interventions should be made readily available very early after diagnosis, when patients may be more open to change<sup>91,103</sup>, as also suggested by our data, and likely to have more frequent interactions with healthcare professionals.<sup>104</sup> In this context, oncologists were described as optimally positioned to capitalize on cancer as a teachable moment, as they can act as a key determinant of change.<sup>77,105,106</sup> However, as suggested by Adams et al., the expectation to rely solely on the oncologists' role is overburdening and unrealistic.<sup>82</sup> Evidence shows that only around 20% of oncology care physicians provide assistance in this area, while patients would strongly want their caregivers to advise and refer more when it comes to healthy lifestyle after a cancer diagnosis.<sup>107-109</sup> According to previous research, including an ASCO survey, the majority of oncology providers are conscious to be responsible for recommending increased activity, cessation of smoke and alcohol abstinence, but many also believe that more consultation time and specific training are needed to adequately address these behavioral issues.<sup>77,91,110-113</sup> We may also hypothesize that bigger cancer centers have better availability of resources to offer lifestyle programs, however in our analysis there was no suggestion of an impact of volume of CANTO center on behavioral change.

Several strengths of our study include that our cohort is representative of a routinely treated clinical population, cancer-free at the time of study, and composed of consecutive patients, longitudinally assessed, with few exclusion criteria applied for this analysis. We could control for a number of patient-, context-, and tumor-related factors to reduce bias, using a large sample with adequate power. Limitations include the absence of a non-cancer control group and presence of some attrition. Baseline characteristics were homogenous, although respondents to behavior assessments may also have *per se* healthier lifestyles or differ in other ways from non-responders. However, it is unlikely that our findings are solely explained by a healthy screen effect or by social desirability bias, in light of their consistency with previous data.<sup>70,114</sup>

Healthy behavioral changes have potential to decrease breast cancer risk and improve prognosis, ameliorate a wide array of health parameters and modulate side-effects of treatments. Unfortunately, unhealthy behaviors tend to persist and the implementation of behavioral interventions in cancer survivor populations has been limited to date.<sup>47,52</sup> At this time, limited to no specific efforts are generally made to support patients' choices to maintain or initiate a healthy behavior after a cancer diagnosis, and referral to behavior improving programs is not usual standard of care. An integrated effort is strongly needed to urgently develop tailored, patient-centered, and easily accessible programs for health promotion, which have the greatest impact if targeted at women who are most inclined to unhealthy lifestyle choices.

Data Supplement

<b>MS1-Supplementary table 1. Cohort characteristics among respondents and non-respondents to health behavior assessments at baseline (N= 9556).</b>									
	<b>Physical Activity behavior</b>			<b>Smoke behavior</b>			<b>Alcohol behavior</b>		
<b>% patients</b>	<b>Respondents</b>	<b>Non-respondents</b>	<b>p*</b>	<b>Respondents</b>	<b>Non-respondents</b>	<b>p*</b>	<b>Respondents</b>	<b>Non-respondents</b>	<b>p*</b>
	N= 8763 (91.7%)	N= 793 (8.3%)		N= 9398 (98.3%)	N= 158 (1.6%)		N= 9257 (96.9%)	N= 302 (3.1%)	
<b>Age, years</b> Mean (SD)	56.1 (11.3)	58.2 (12.2)	<.0001	56.3 (11.4)	57.3 (12.2)	0.320	56.3 (11.4)	56.2 (11.6)	0.565
<b>Body Mass Index, Kg/m<sup>2</sup></b> Mean (SD)	25.9 (5.4)	26.3 (5.4)	0.021	25.9 (5.4)	25.1 (5.0)	0.010	25.9 (5.4)	25.5 (4.9)	0.320
<b>Body Mass Index</b>			0.125			0.746			0.966
Underweight	2.4	2.4		2.4	2.6		2.4	2.4	
Normal weight	49.1	45.0		48.7	52.3		48.7	50.0	
Overweight	29.1	30.4		29.2	28.5		29.2	29.0	
Obese	19.4	22.2		19.7	16.6		19.7	18.6	
<b>Menopausal status</b>			0.003			0.934			0.428
Premenopausal	37.6	32.2		37.2	37.5		37.1	39.4	
Postmenopausal	62.4	67.8		62.8	62.5		62.9	60.6	
<b>Charlson comorbidity score</b>			0.701			0.792			0.463
0	19.2	19.8		80.8	81.7		80.7	82.6	
≥1	80.8	80.2		19.2	18.3		19.3	17.4	
<b>Anxiety</b>			0.096			0.965			0.999
Non-case	39.6	29.2		39.6	38.6		39.5	39.7	
Doubtful	26.9	28.1		26.8	26.8		26.8	26.7	
Case	33.5	42.7		33.6	34.6		33.6	33.6	
<b>Depression</b>			<.0001			0.320			0.764
Non-case	81.7	61.8		81.4	86.6		81.5	80.2	
Doubtful	11.3	21.3		11.5	8.7		11.4	12.9	
Case	7.0	16.8		7.1	4.7		7.1	6.9	
<b>Summary Score, EORTC QLQ-C30**</b> Mean (SD)	82.8 (12.8)	80.7 (13.8)	0.121	82.7 (12.9)	84.3 (10.9)	0.348	82.7 (12.8)	82.3 (12.7)	0.517

<b>Highest education level</b>			<.0001			0.991			0.889
Primary school	14.6	35.9		15.0	15.1		14.9	15.6	
High School	46.7	41.9		46.6	46.0		46.6	47.6	
College degree	38.7	22.2		38.4	38.9		38.4	36.9	
<b>Marital status</b>			0.076			0.859			0.573
Partnered	72.1	65.8		72.0	72.7		72.1	70.3	
Not partnered	27.9	34.1		28.0	27.3		27.9	29.7	
<b>Monthly household income</b>			0.0014			0.894			0.225
<3,000 Euro	55.9	69.2		56.2	56.8		56.1	60.3	
≥3,000 Euro	44.1	30.8		43.8	43.2		43.9	39.7	
<b>Center volume***</b>			0.009			<.0001			<.0001
High (>1000 patients)	23.9	28.0		24.5	4.4		24.9	2.7	
Low-Intermediate (≤1000 patients)	76.1	72.0		75.4	95.6		75.1	97.3	
<b>Stage</b>			0.210			0.975			0.037
I	49.8	46.5		49.5	49.7		49.8	42.3	
II	40.5	43.3		40.7	40.1		40.6	46.0	
III	9.7	10.1		9.7	10.2		9.6	11.7	
<b>Breast cancer surgery</b>			0.922			0.581			0.275
Mastectomy	26.4	26.6		26.4	28.4		26.4	29.2	
Partial surgery	73.6	73.4		73.6	71.6		73.6	70.8	
<b>Axillary surgery</b>			0.899			0.154			0.004
Axillary dissection	37.7	37.9		37.6	43.2		37.5	45.6	
Sentinel node	62.3	62.1		62.4	56.8		62.5	54.4	
<b>Chemotherapy</b>			0.995			0.283			0.086
Yes	53.0	53.0		53.0	48.7		52.8	57.9	
No	47.0	47.0		47.0	51.3		47.2	42.1	
<b>Radiation therapy</b>			0.009			0.457			0.682
Yes	91.5	88.7		91.3	89.6		91.3	91.9	
No	8.5	11.3		8.7	10.4		8.7	8.0	
<b>Endocrine therapy</b>			0.343			0.040			0.246
Yes	81.2	79.8		81.2	74.7		81.2	78.5	
No	18.8	20.2		18.8	25.3		18.8	21.5	

<b>Anti-HER2 therapy</b>			0.484			0.198			0.164
Yes	12.1	12.9		12.1	15.5		12.0	14.7	
No	87.9	87.1		87.9	84.5		88.0	85.3	
<b>Physical activity, WHO recommendations</b>			-			0.606			0.005
Insufficiently active	NA	NA		41.7	44.0		41.5	50.9	
Sufficiently active				58.3	56.0		58.5	49.1	
<b>Tobacco smoke</b>			<.0001			-			0.005
Current smoker	17.7	23.7					18.0	26.3	
Former or never	82.3	76.3		NA	NA		82.0	73.7	
<b>Alcohol consumption</b>			0.385			0.625			-
Daily	14.5	15.7		14.6	17.9				
Less than daily	85.5	84.3		85.4	82.1		NA	NA	

SD= Standard deviation; WHO= World Health Organization; HER2= Human Epidermal Growth Factor Receptor 2. NA= not applicable.

\*chi-square test for categorical variables and Wilcoxon/Kruskal-Wallis test for continuous variables

\*\* Summary Score is a composite score that includes 13/15 domains of EORTC QLQ-C30, namely Physical Function, Emotional Function, Social Function, Cognitive Function, Role Function, Fatigue, Pain, Insomnia, Nausea/Vomit, Dyspnea, Appetite Loss, Constipation, and Diarrhea

\*\*\*Patients recruited in CANTO 2012-2017.

## MANUSCRIPT 2 (MS2):

# Dynamic portrait of long-term patient-reported quality of life following adjuvant chemotherapy for breast cancer: a group-based trajectory analysis focused on behavioral factors

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**Previous Presentations:** Findings of this study were partly presented with a 2-year follow-up update at the European Society for Medical Oncology (ESMO) Congress, October 20, 2018: Abstract 1684PD\_PR 'Physical activity (PA) and patterns of quality of life (QOL) after adjuvant chemotherapy (CT) for breast cancer (BC)' presented by Antonio Di Meglio during the Poster Discussion Session on Saturday, 20 October, 09:30-10:30 (Annals of Oncology, Volume 29 Supplement 8 October 2018). Portions of this work were also highlighted in the official ESMO Press Release (<https://www.esmo.org/newsroom/press-office/physical-exercise-qol-chemo-therapy-sports-cancer-dimeglio-vanlemmens>). Antonio Di Meglio received an **ESMO Merit Award** for the present work during the ESMO Congress 2018.

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## **Abstract**

**Purpose:** Behavioral factors such as healthy Body Mass Index (BMI), recommended levels of physical activity (PA), and tobacco abstinence have the potential to positively impact quality of life (QOL). We aimed to characterize post-chemotherapy trajectories of QOL among breast cancer (BC) survivors, focusing on behavioral factors.

**Methods:** Women in CANTO (NCT01993498) with early-stage BC treated with (neo)adjuvant chemotherapy were included. Outcome variable, the EORTC QLQ-C30 Summary-Score (C30-SumScore), and behavior variables (BMI, PA, and tobacco use behavior) were assessed at diagnosis (baseline), year-1, -2, and -4 post-diagnosis. Baseline clinical, socio-demographic, tumor- and treatment-related characteristics were also available. Trajectories of C30-SumScore and associations with trajectory-group membership were identified by iterative estimations of group-based trajectory models and multivariable multinomial logistic regression.

**Results:** Four trajectory-groups were identified (N=2313), with "Excellent" (47.7%), "Very good" (34.7%), "Deteriorating" (11.2%), and "Poor" (6.4%) QOL. Women in the "Deteriorating" trajectory-group reported fairly good baseline QOL (mean [95%CI]: 77.2/100 [74.8-79.5]), significantly worsening at year-1 (58.5/100 [56.2-60.8]) and never recovering to pre-treatment values through year-4 (62.6/100 [60.0-65.2]). Factors associated with group-membership included younger age (adjusted Odds Ratio per additional year, 0.98 [95%CI 0.96-0.99]), Charlson  $\geq 1$  (vs. 0, 2.22 [1.58-3.13]), axillary dissection (vs. sentinel, 1.57 [1.12-2.21]) and endocrine-therapy (vs. no, 1.48 [1.04-2.12]). Healthy behaviors were positively and consistently associated with better performing trajectory-groups. In contrast, excess weight, post-diagnosis inactivity, and current smoking were highly prevalent in the "Deteriorating" group: at year-4, 59.0% women were overweight or obese, 37.2% were insufficiently active (<10 MET-hours/week) and tobacco behavior persisted among half of current smokers.

**Conclusions:** There is great variability in post-chemotherapy QOL trajectories. Although the majority of patients will do well, we identified a clinically relevant group of patients at high-risk of severe, persistent QOL deterioration, where unhealthy behaviors were particularly common. Behavior-improving interventions may help mitigate the detrimental impact of chemotherapy, targeting patients with similar deteriorating long-term trajectory and unremitting decline of QOL.

## Introduction

Breast cancer ranks first for incidence among female malignancies in developed countries.<sup>6</sup> There has been a dramatic increase in breast cancer survival over the last decades, due to earlier diagnosis and many advances in treatments.<sup>10-13</sup> Among these, adjuvant chemotherapy decreases breast cancer recurrence risk of 30%-50% and reduces mortality in women with early-stage breast cancer.<sup>14-16</sup> In addition, endocrine therapy determines a 50% reduction in breast cancer recurrence and 10% improvement in survival among women with estrogen-receptor positive breast cancer. As a result, current multimodal risk-reduction strategies, including chemotherapy, endocrine therapies and targeted agents, led to survival rates exceeding 80% ten years after diagnosis.<sup>17</sup>

Nevertheless, this survival benefit often comes with relevant late and long-term health-related costs for patients. Downstream effects of adjuvant chemotherapy and other systemic breast cancer treatments include substantial impact on general well-being, physical functioning and vitality, and alterations in cognition, metabolism, and sexuality.<sup>21-23</sup> Chemotherapy was also associated with poorer emotional and social functioning, body image issues, with increased likelihood of unemployment after cancer, and with the onset of persisting conditions including fatigue, neuropathy, and menopausal symptoms.<sup>25-27,115</sup>

Although previous data indicate that overall the negative impact of chemotherapy on QOL is transient, there may be considerable inter-individual variability in the longitudinal trajectory of patient-reported outcomes (PROs).<sup>30</sup> This variability may be obscured by focusing on a description of the average population level, an approach that was usually adopted in previous studies aimed to identify individual differences in the evolution of treatment-related symptoms.<sup>116</sup> In addition, few studies have comprehensively evaluated PROs beyond the first year after treatment, an important limitation of previous literature, considering a high prevalence of some symptoms up until 10 years after treatment completion.<sup>24</sup>

Some subgroups of patients may follow trajectories at high-risk of long-term deterioration in functional health and symptom burden. The early identification of such groups is crucial to offer timely and patient-specific supportive care interventions, including those facilitating the uptake of a healthy lifestyle.<sup>117</sup> Non-pharmacological approaches tested to mitigate side effects of adjuvant chemotherapy and preserve QOL include indeed interventions to improve health behaviors, combining healthy weight management, improved diet, promotion of exercise and active lifestyles, and smoking cessation support. These interventions proved safe, feasible, and effective among cancer survivors on a number of outcomes, including in women with breast cancer before, during, and after chemotherapy.<sup>39,118-121</sup>

We performed the present study, among women that received (neo)adjuvant chemotherapy for early-stage breast cancer, with the following aims: (1) to describe patterns of patient-reported QOL over four years from diagnosis of breast cancer; (2) to identify patients at high-risk of QOL deterioration; (3) to assess factors associated with long-term QOL deterioration; and (4) to focus on how modifiable health behaviors are associated with distinct trajectory-groups over time.

## Methods

### Data source

CANcer TOxicity (CANTO) cohort data were used (NCT01993498).<sup>61</sup> Briefly, CANTO is a prospective, multicentric cohort of patients with stage I-II-III breast cancer (breast cancer recurrences [other than local] or second cancers determine study termination). We used longitudinal information collected at breast cancer diagnosis (baseline) and approximately at year-1, -2, and -4 after diagnosis (primary surgery, chemotherapy, and/or radiation-therapy were completed 3-6 months before year-1 visit). Endocrine and anti-human epidermal growth factor receptor (HER)-2 treatment could be ongoing during follow-up.

All participants provided informed consent and the study was approved by the national regulatory and ethics committee (ID-RCB:2011-A01095-36,11-039).

### Study cohort

We accessed data from 6619 women diagnosed with breast cancer from 2012-2015, with mature follow-up until year-4 post-diagnosis. Patients not returning a valid response at baseline assessment and at least one follow-up for the outcome variable (i.e., European Organization for Research and Treatment of Cancer [EORTC] QOL Questionnaire [QLQ]-C30 Summary Score [C30-SumScore]) were excluded from the analysis. To assess potential selection bias, we compared respondents with patients with missing outcome evaluations (N=428). The latter tended to be older, to have more comorbidities, lower income, and higher stage cancers, although no major differences were present (data not shown). The final analytic cohort included 2787 patients. Flowchart of patient inclusion is available in **MS2-Supplementary Figure 1**.

### Variables of interest

#### *Outcome variables*

Our outcome of interest was the C30-SumScore. The EORTC QLQ-C30 is a 30-item questionnaire including functional and symptom domains, providing 4-point Likert scale responses for each item: 'not at all', 'a little', 'quite a bit, and 'very much' (with exception of Global Health Status, which has a seven-point response format).<sup>117,122,123</sup> All items are converted to a 0-100 scale using a standard scoring algorithm, where higher scores reflect better functionality or greater symptom severity. C30-SumScore is calculated from the mean of 13 of 15 QLQ-C30 scales (27 items, Global Health Status and Financial Difficulties excluded). Symptom scales scores are reversed to obtain a uniform direction with functional scales.<sup>124</sup> Higher scores for C30-SumScore indicate better QOL. A validated French version of EORTC QLQ-C30 is available.<sup>57,122,124,125</sup>

#### *Exposure variables*

Baseline clinical, socioeconomic, tumor and treatment characteristics were collected at diagnosis. We focused on behavior-related variables, available at baseline and at each follow-up time point: (1) Body Mass

Index (BMI), objectively assessed by study nurses, categorized as follows: "Underweight", <math><18.5 \text{ Kg/m}^2</math>, "Normal", 18.5-24.9  $\text{Kg/m}^2$ , "Overweight", 25.0-29.9  $\text{Kg/m}^2$ , "Obese",  $\geq 30.0 \text{ Kg/m}^2$  (for analyses accommodating only binary variables, categories were "lean", <math><25.0 \text{ Kg/m}^2</math> vs. "overweight or obese",  $\geq 25.0 \text{ Kg/m}^2$ )<sup>126</sup>; (2) physical activity, self-reported using the Global physical activity Questionnaire (GPAQ)-16<sup>60</sup>, assessing duration and intensity of activity (work, transportation [travel to/from places] and leisure [e.g., sports and fitness]), with  $\geq 10$  metabolic equivalents of task [MET]-hours/week defining "sufficiently active" (i.e., adhering to WHO recommendations) vs. "insufficiently active" patients [ $<10$ ]<sup>33</sup>; and (3) smoking behavior at baseline, assessed by study nurses and categorized as "current" vs. "former/never" smoker, and smoking persistence during follow-up, defined as "increased or unchanged" vs. "reduced" behavior compared to the previous assessment.

## Statistical analysis

### *Cohort description*

Patient characteristics were descriptively summarized for the whole cohort.

### *Definition of trajectory-groups*

Longitudinal variations in repeated measures of C30-SumScore were assessed by multivariable latent-class models using Group-Based Trajectory Modeling (GBTM). This procedure has been extensively described.<sup>127-131</sup> Briefly, GBTM describes the course of an outcome over time, segmenting the data into trajectory-groups and identifying longitudinal unobserved (latent) clusters of individuals following similar courses of the defined outcome. GBTM is a semi-parametric procedure. Model selection involves the iterative estimation of (1) the number of trajectory groups and (2) the best shape/order of each trajectory group, tested using maximum likelihood methods. The best-fitting number of trajectory-groups with best-fitting shape (i.e., zero-order vs. intercept vs. quadratic vs. cubic) is selected. Latent trajectory-groups are based on multivariable-adjusted models correcting for baseline characteristics, listed in **MS2-Table 1**. A detailed description of model selection procedure is provided in the **MS2-Supplementary methods**.

A label name was assigned to each identified trajectory-group, to provide a brief descriptive representation for the associated outcome pattern. After identification of latent groups, we described participant characteristics in each group. Fisher's exact tests and Wilcoxon rank sum tests were used to compare distributions across trajectory-groups for categorical and continuous variables, as appropriate.

Mean scores for all the 15 scales included in the EORTC QLQ-C30 were also descriptively summarized by trajectory-group, in order to (i) complement the information provided by C30-SumScore, and (ii) provide additional granular details on the dynamics of distinct QLQ-C30 scales.

### *Trajectory-group membership*

After definition of the best-fitting model, we estimated the association of potential predictors (“factors associated with group membership”) with trajectory-groups. Associations were identified using weighted multinomial logistic regression (Odds Ratios [OR] and respective 95% Confidence Interval [CI] for each predictor were adjusted for aforementioned baseline characteristics. Multi-level categorical variables were dichotomized, as GBTM can only accommodate binary factors. Membership to the trajectory-group with best pattern of C30-SumScore was chosen as reference, to focus on risk factors for clustering into groups with worse patterns. The procedure automatically dropped observations with missing data in the risk factor variables (N=474).

### *Behavioral factors and trajectory-groups*

Longitudinal measures of BMI, physical activity, and smoking behavior were tabulated and evaluated by trajectory-group, including testing for significant time-trends.

Statistical analysis was performed using SAS statistical software Version 9.4 (SAS Institute Inc.) and the PROC Traj Procedure developed for SAS. Statistical significance was defined with a 2-sided p-value<0.05.

## **Results**

### Cohort characteristics

Among the whole cohort (N=2787), mean age was 52.5 years (Standard Deviation [SD] 10.9), mean baseline BMI was 25.7 Kg/m<sup>2</sup> (SD 5.4) and 1282 patients (46.0%) were overweight or obese. There were 1196 (42.9%) insufficiently active patients and 506 (18.12%) current smokers at diagnosis. The vast majority of patients received a chemotherapy regimen containing anthracyclines and taxanes (>85%). Complete cohort characterization is provided in **MS2-Supplementary Table 1**.

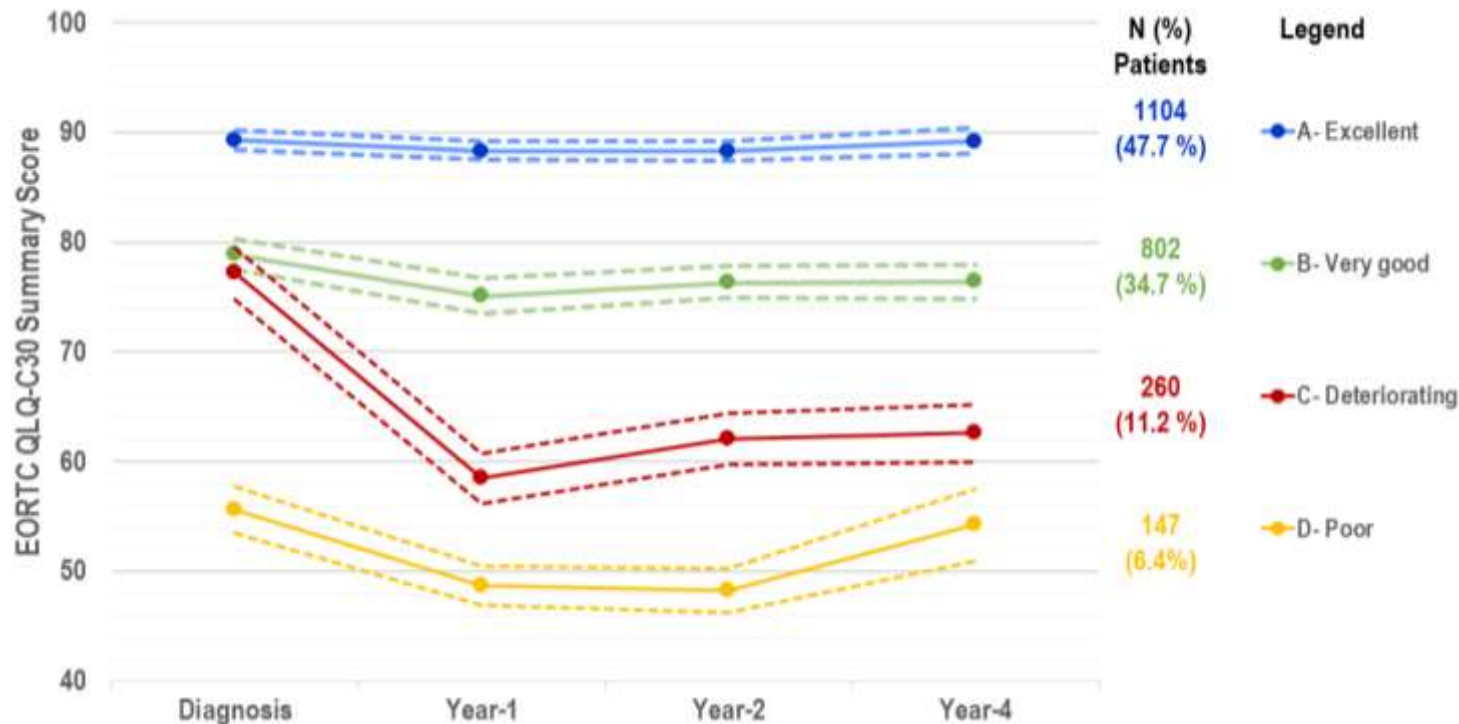
### Definition of trajectory-groups

Metrics used for model selection are available in **MS2-Supplementary Table 2**. Based on an average Posterior Probability of group membership close to or greater than 0.80, there was a high degree of certainty in group assignment.<sup>127,129,131</sup>

Our final model (N= 2313) identified four trajectory-groups of C30-SumScore, graphically represented in **MS2-Figure 1**. The best trajectory-group included the majority of patients in this analysis (47.7%; “Excellent”), reporting an excellent overtime pattern for C30-SumScore. The second trajectory-group (34.7%; “Very good”) also fared overall very well, scoring at its lowest 75.1/100 at a single time-point. QOL in the third trajectory-group (11.2%; “Deteriorating”) started-off with a fairly good mean score at diagnosis (77.2/100, 95% CI for the mean 74.8-79.5), similar to the second group, but then declined significantly at year-1, and recovered only partially by year-4. The fourth group (6.4% of patients; “Poor”) reported overall low/very low scores, with a best mean score of 55.6/100 (53.5-57.7) at diagnosis and some additional downward inflections, returning to

baseline values only at year-4. The Maximum Likelihood Estimates of the model parameters and the estimates for baseline characteristic included in the model are provided in **MS2-Supplementary Table 3** and **4**.

Mean scores and respective 95% CI for all QLQ-C30 scales are available in **MS2-Supplementary Table 5** by trajectory-group and time-point. Women in the "Deteriorating" trajectory-group reported mean values crossing the threshold for clinically important functional impairment or symptom severity<sup>132</sup> across multiple domains (**MS2-Figure 2A, B**, red-shaded bars) and experienced the largest mean score changes from diagnosis to year-1 (i.e., segment including the active chemotherapy portion), showing the greatest impairment across the four trajectory-groups (**MS2-Figure 3**, red-shaded bars).



**MS2-Figure 1. Trajectory-groups according to best-fitting prediction model.**

Solid lines represent the predicted trajectories and dashed lines represent the respective 95% Confidence Intervals. EORTC QLQ-C30= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C-C30. Table below the figure displays predicted C30-SumScore values and respective 95% Confidence Intervals by trajectory-group.

**C30-SumScore values and respective 95% Confidence Intervals by trajectory-group (N= 2313).**

Trajectory-group	Assigned Patients	Mean value	95% CI		Mean value	95% CI		Mean value	95% CI		Mean value	95% CI	
			Low	High		Low	High		Low	High		Low	High
	N (%)	Diagnosis		Year-1		Year-2		Year-4					
“Excellent”	1104 (47.7%)	89.3	88.4	90.2	88.3	87.5	89.2	88.3	87.4	89.2	89.2	88.1	90.4
“Very good”	802 (34.7%)	78.9	77.5	80.3	75.1	73.5	76.7	76.3	74.9	77.8	76.4	74.8	78.0
“Deteriorating”	260 (11.2%)	77.2	74.8	79.5	58.5	56.2	60.8	62.1	59.8	64.4	62.6	60.0	65.2
“Poor”	147 (6.4%)	55.6	53.5	57.7	48.7	46.9	50.5	48.3	46.3	50.3	54.3	51.0	57.5

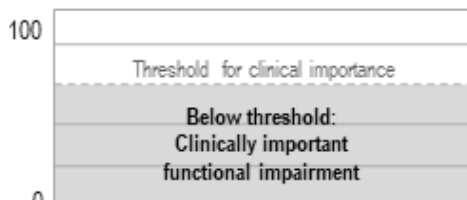
C30-SumScores were available for all patients at diagnosis, then among 2589 (92.9%), 2287(82.0%), and 1464 (52.5%) patients at year-1, -2, and -4 follow-up, respectively. Higher scores reflect better functionality or greater symptom severity. C30-SumScore= European Organization for Research and Treatment of Cancer (EORTC) QOL Questionnaire (QLQ)-C30 Summary Score; CI= Confidence Interval.

**MS2-Figure 2. Mean QOL scores by trajectory-group and by time-point.** Thresholds for clinical importance are defined by dashed grey lines. Scores below and above threshold indicate clinically important functional impairment and symptomatology, respectively (Giesinger JM et al., *Journal of Clinical Epidemiology* 2020).

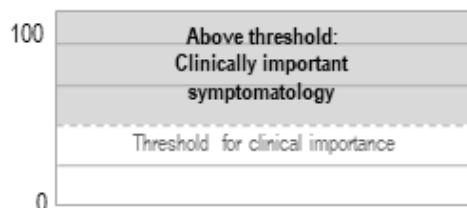
**Trajectory-group legend:**

- ■ ■ ■ ■ Excellent
- ■ ■ ■ ■ Very Good
- ■ ■ ■ ■ Deteriorating
- ■ ■ ■ ■ Poor

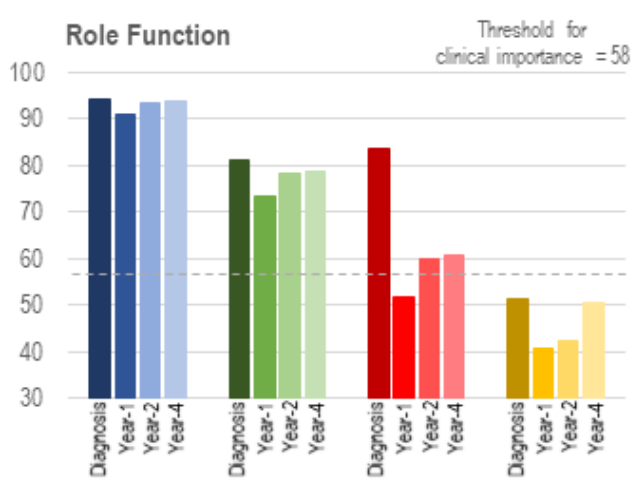
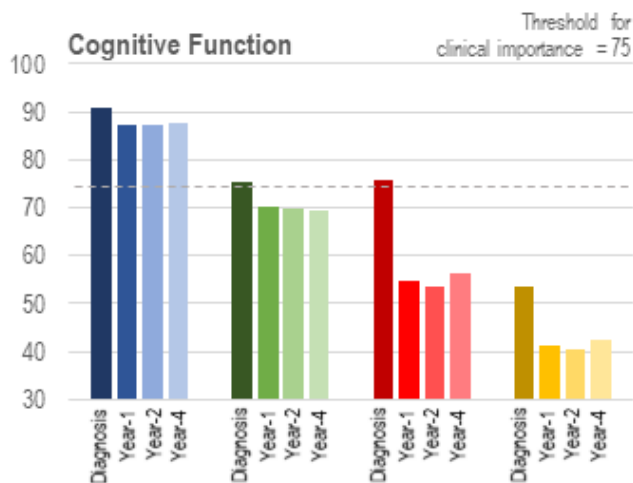
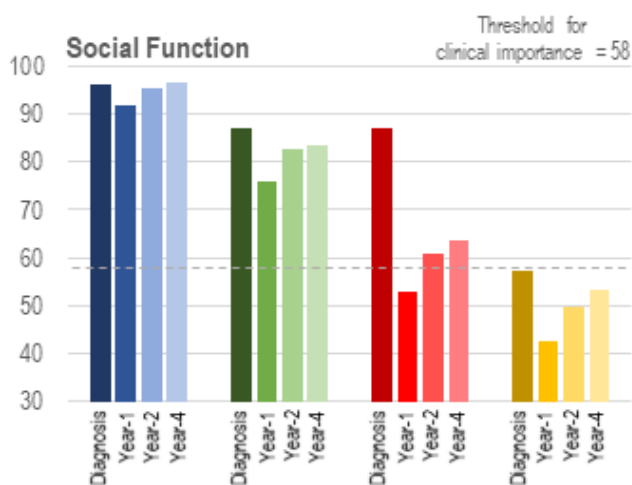
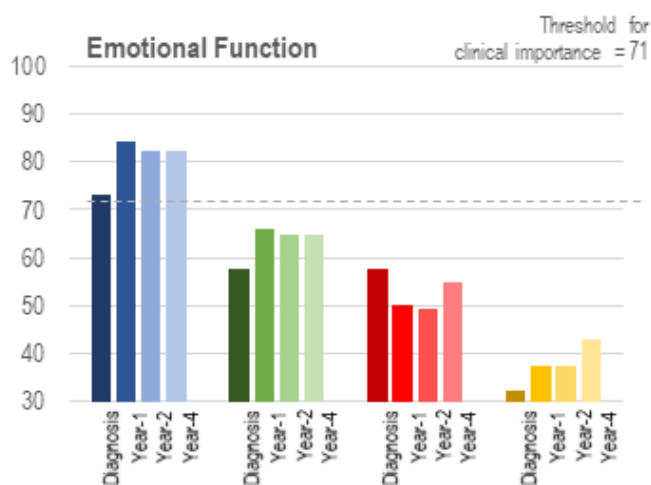
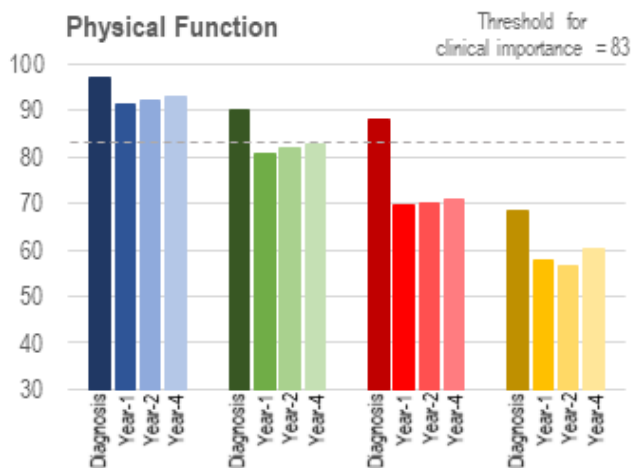
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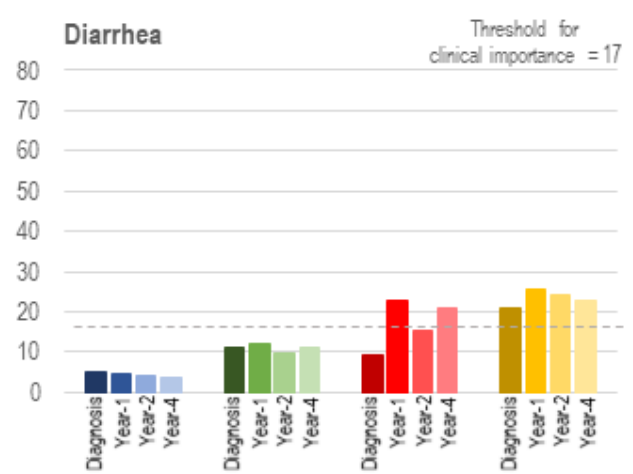
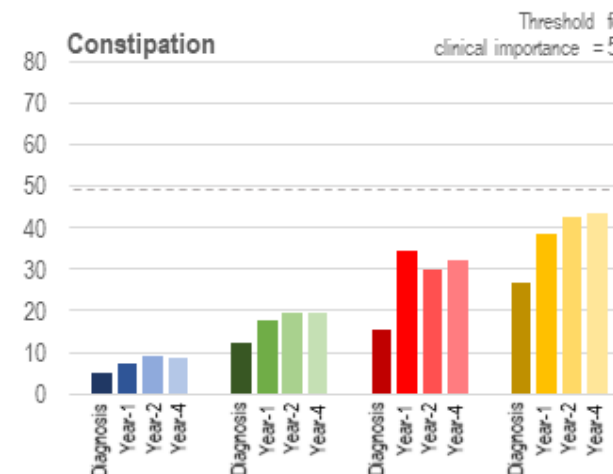
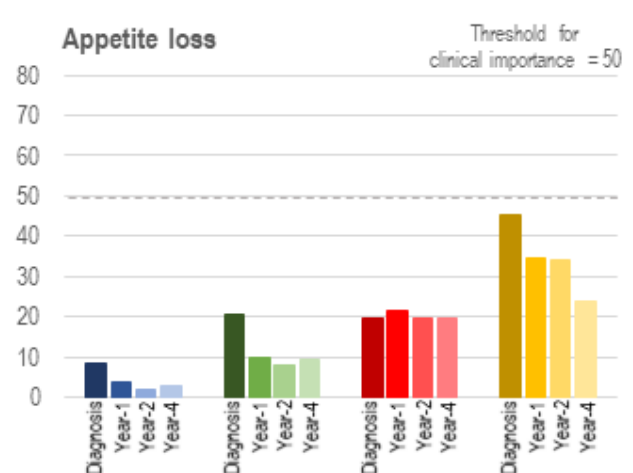
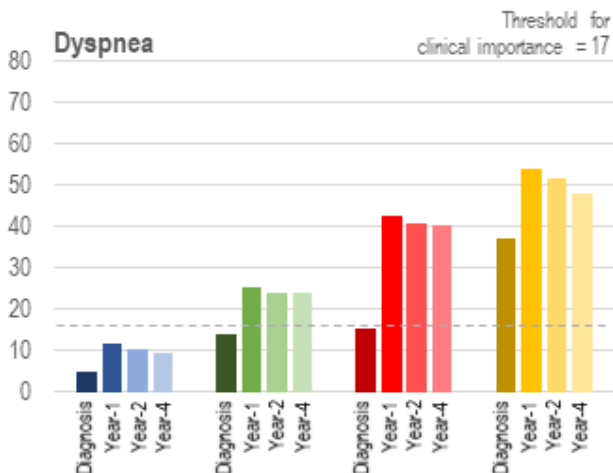
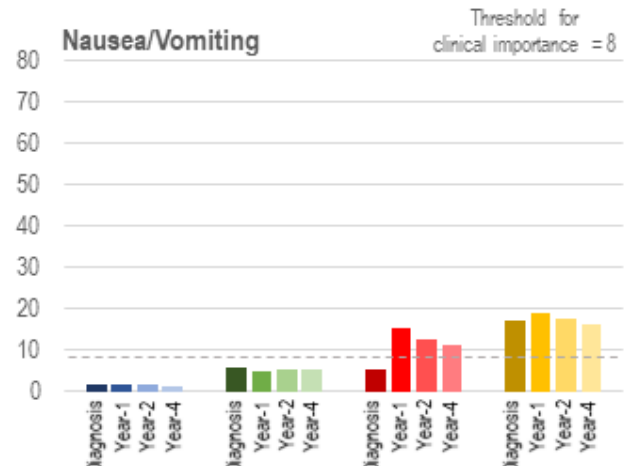
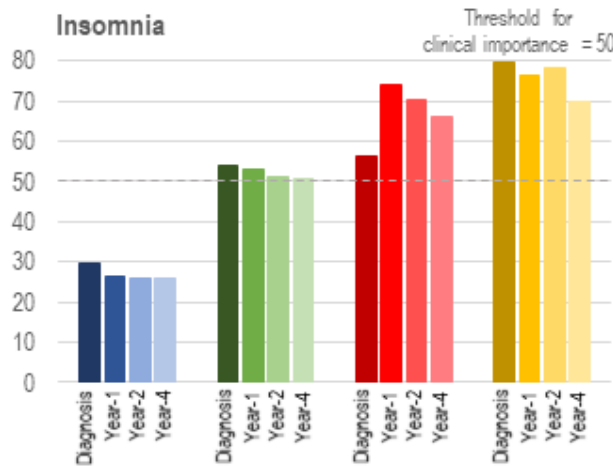
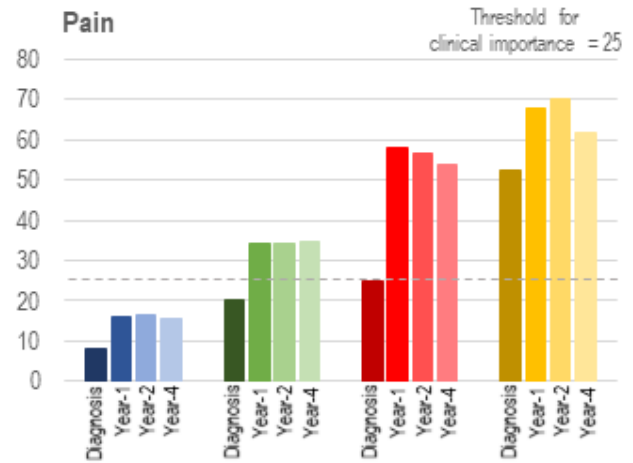
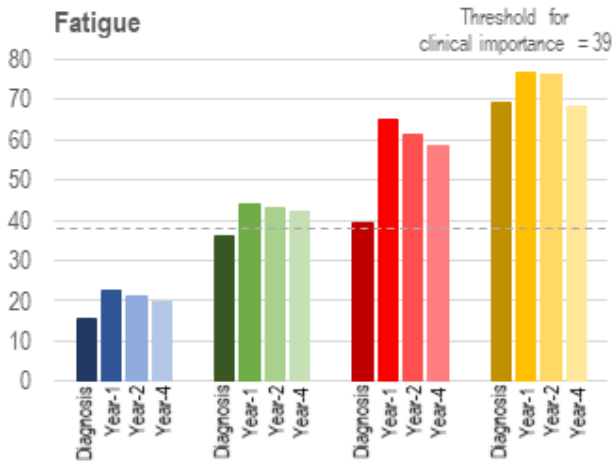
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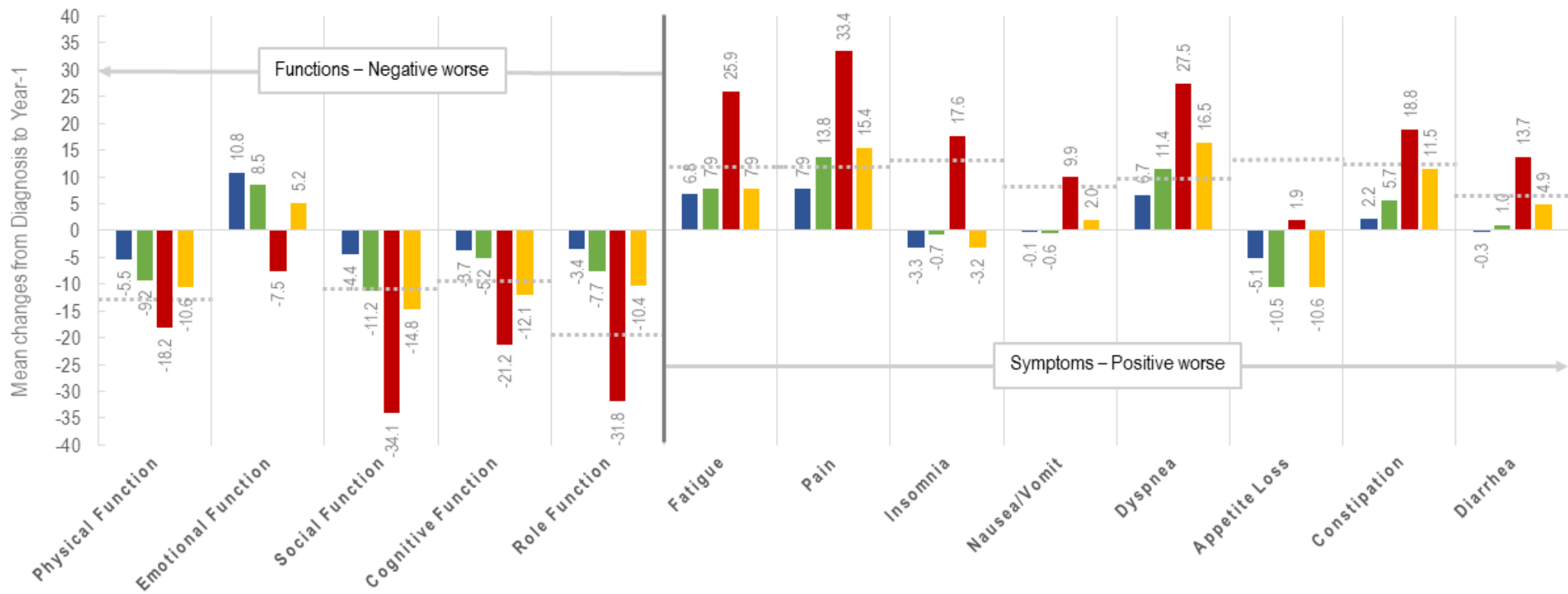


**2A. EORTC QLQ-C30 Functions**



## 2B. EORTC QLQ-C30 Symptoms





**Trajectory-group legend:**

- Excellent
- Very Good
- Deteriorating
- Poor
- ..... Lower boundaries for medium-size mean change

Ranges for medium-size mean differences between time points. Lower boundaries are indicated by horizontal dotted lines in the plot area. Emotional function subscale was omitted due to medium estimate being lower than estimate for small-size difference. (Adapted from Cocks K. et al, J Clin Onc 2011).

Physical Function	14-22	Role Function	13-19	Insomnia	13-24	Appetite Loss	14-23
Social Function	11-15	Fatigue	13-19	Nausea/Vomit	8-15	Constipation	13-19
Cognitive Function	9-14	Pain	13-19	Dyspnea	9-15	Diarrhea	>7

**MS2-Figure 3. Mean changes in EORTC QLQ-C30 functional and symptom domains during the chemotherapy segment (Diagnosis to Year-1) by trajectory-group.** Negative and positive changes indicate functional impairment and worse symptomatology, respectively. Lower boundaries for medium-size mean change are defined by dashed grey lines (Cocks K, J Clin Onc 2011).

## Trajectory-group membership

The distribution of patient characteristics at diagnosis by trajectory-group is displayed in **Table 1**. Results of the multinomial logistic regression for group membership are presented in **Table 2**. There were consistent associations with membership to worse trajectory groups for overweight or obese vs. lean women (ORs [95% CI] 1.36 [1.11-1.65], 1.69 [1.26-2.26], and 1.72 [1.18-2.49] for groups "Very good", "Deteriorating", and "Poor", respectively). Compared to being insufficiently active, adherence to physical activity recommendations at diagnosis was associated with lower odds of membership to the "Very good" (OR 0.63 [0.52-0.76]) and "Poor" (OR 0.54 [0.38-0.77]) groups than to the "Excellent" group, and with higher likelihood of membership to the "Deteriorating" group (OR 1.64 [1.21-2.22]). Current smoker status was as well a consistent risk factor for group-membership (ORs [95% CI] 1.27 [0.98-1.63], 1.88 [1.33-2.67], and 2.66 [1.77-3.99] for groups "Very good", "Deteriorating", and "Poor", respectively). Other significant associations included clinical (comorbidities), and contextual (lower socioeconomic status) characteristics. Treatment-related factors were significantly associated with increased likelihood of membership to the "Deteriorating" group (receipt of axillary dissection vs. sentinel node biopsy, OR 1.57 [1.12-2.21] and endocrine therapy vs. no, OR 1.48 [1.04-2.12]).

<b>MS2-Table 1. Distribution of patient characteristics at diagnosis by trajectory-group (N= 2313).</b>					
	<b>Trajectory-group</b>				<b>p</b>
	<b>"Excellent" N= 1104 (47.7%)</b>	<b>"Very good" N= 802 (34.7%)</b>	<b>"Deteriorating" N= 260 (11.2%)</b>	<b>"Poor" N= 147 (6.4%)</b>	
<b>Age, years</b> Mean (SD)	52.8 (11.0)	50.9 (11.0)	51.0 (9.7)	51.7 (10.0)	<b>0.0001</b>
<b>Body Mass Index, continuous (Kg/m<sup>2</sup>)</b> Mean (SD)	25.0 (5.0)	25.8 (5.5)	26.3 (5.7)	26.6 (6.0)	<b>&lt;.0001</b>
<b>Body Mass Index, WHO definition</b> Lean (<25 Kg/m <sup>2</sup> ) Overweight or obese (≥25 Kg/m <sup>2</sup> )	669 (60.6) 435 (39.40)	428 (53.4) 374 (46.6)	124 (47.7) 136 (52.3)	67 (45.6) 80 (54.4)	<b>&lt;.0001</b>
<b>Level of physical activity, continuous (MET-h/week)</b> Total activity, median (Q1-Q3) Tansport and leisure-time activity, median (Q1-Q3)	16.0 (4.0-40.0) 12.0(0.0-26.2)	10.7 (0.0-30.0) 6.7(0.0-17.0)	20.0 (4.0-67.0) 10.0 (0.0-24.0)	8.0 (0.0-50.0) 2.7(0.0-20.0)	<b>&lt;.0001</b>
<b>Level of physical activity, who definition</b> Sufficiently active (≥10 MET-h/week) Insufficiently active (<10 MET-h/week)	688 (62.3) 416 (37.7)	405 (50.5) 397 (49.5)	185 (71.1) 75 (28.8)	68 (46.3) 79 (53.7)	<b>&lt;.0001</b>
<b>Smoking behavior</b> Former or never smoker Current smoker	944 (85.5) 160 (14.5)	653 (81.4) 149 (18.6)	198 (76.1) 62 (23.8)	99 (67.3) 48 (32.7)	<b>&lt;.0001</b>
<b>Charlson comorbidity score</b> 0 ≥1	954 (86.4) 150 (13.6)	653 (81.4) 149 (18.6)	192 (73.8) 68 (26.1)	112 (76.2) 35 (23.8)	<b>&lt;.0001</b>
<b>Marital status</b> Not partnered Partnered	271 (24.5) 833 (75.4)	212 (26.4) 590 (73.6)	62 (23.8) 198 (76.1)	55 (37.4) 92 (62.6)	<b>0.0078</b>
<b>Monthly household income</b> <3,000 Euro ≥3,000 Euro	520 (47.1) 584 (52.9)	447 (55.7) 355 (44.3)	162 (62.3) 98 (37.7)	110 (74.8) 37 (25.2)	<b>&lt;.0001</b>
<b>Stage</b> I II/III	308 (27.9) 796 (72.1)	229 (28.5) 573 (71.4)	54 (20.8) 206 (79.2)	33 (22.4) 114 (77.5)	<b>0.0439</b>

<b>Breast cancer surgery</b>					
Mastectomy	378 (34.2)	313 (39.0)	94 (36.1)	55 (37.4)	0.1961
Partial breast surgery	726 (65.8)	489 (61.0)	166 (63.8)	92 (62.6)	
<b>Axillary surgery</b>					<b>0.0029</b>
Axillary dissection	632 (57.2)	468 (58.3)	178 (68.5)	97 (66.0)	
Sentinel node	472 (42.7)	334 (41.6)	82 (31.5)	50 (34.0)	
<b>Radiation therapy</b>					<b>0.022</b>
Yes	1042 (94.4)	745 (92.9)	235 (90.4)	143 (97.3)	
No	62 (5.6)	57 (7.1)	25 (9.6)	4 (2.7)	
<b>Endocrine therapy</b>					0.0697
Yes	831 (75.3)	603 (75.2)	214 (82.3)	107 (72.8)	
No	273 (24.7)	199 (24.8)	46 (17.7)	40 (27.2)	
<b>Anti-HER2 therapy</b>					0.6321
Yes	244 (22.1)	188 (23.4)	52 (20.0)	30 (20.4)	
No	860 (77.9)	614 (76.6)	208 (80.0)	117 (79.6)	
SD= Standard Deviation; MET= Metabolic-equivalent of task; Q1= Quartile 1; Q3= Quartile 3; HR= Hormone Receptor; HER2= Human Epidermal Growth Factor Receptor 2.					

**Table 2. Multinomial logistic regression of factors associated with C30-SumScore trajectory-group membership (vs. reference “Excellent”, N= 1104 [47.7%]).**

Predictor of group membership (Risk Factor)	Trajectory-group					
	“Very good” (N= 802 [34.7%])		“Deteriorating” (N= 260 [11.2%])		“Poor” (N= 147 [6.4%])	
	aOR* (95% CI)	p	aOR* (95% CI)	p	aOR* (95% CI)	p
<b>Age</b> , continuous (1-year increase)	0.98 (0.97-0.99)	<.0001	0.98 (0.96-0.99)	0.0011	0.98 (0.97-1.00)	0.0571
<b>BMI</b> , Overweight or obese vs. lean	1.36 (1.11-1.65)	0.0024	1.69 (1.26-2.26)	0.0005	1.72 (1.18-2.49)	0.0043
<b>Physical Activity</b> , Sufficiently vs. insufficiently active	0.63 (0.52-0.76)	<.0001	1.64 (1.21-2.22)	0.0014	0.54 (0.38-0.77)	0.0008
<b>Smoking behavior</b> , Current vs. former or never smoker	1.27 (0.98-1.63)	0.0675	1.88 (1.33-2.67)	0.0004	2.66 (1.77-3.99)	<.0001
<b>Charlson</b> , ≥1 vs. 0	1.49 (1.16-1.93)	0.0021	2.22 (1.58-3.13)	<.0001	1.91 (1.24-2.95)	0.0036
<b>Marital status</b> , Partnered vs. not	1.01 (0.79-1.28)	0.9566	1.49 (1.05-2.13)	0.0268	0.87 (0.58-1.31)	0.5158
<b>Income</b> , ≥3000 vs. <3000 Euro/month	0.72 (0.58-0.89)	0.0020	0.52 (0.38-0.71)	<.0001	0.36 (0.23-0.56)	<.0001
<b>Breast cancer stage</b> , II/III vs. I	0.87 (0.69-1.10)	0.2498	1.19 (0.82-1.74)	0.3639	0.951 (0.59-1.54)	0.8402
<b>Breast cancer surgery</b> , Mastectomy vs. Partial breast surgery	1.21 (0.97-1.51)	0.0836	0.78 (0.57-1.08)	0.1391	1.09 (0.73-1.64)	0.6721
<b>Axillary surgery</b> , Axillary dissection vs. Sentinel node	0.98 (0.78-1.23)	0.8707	1.57 (1.12-2.21)	0.0095	1.33 (0.85-2.08)	0.2067
<b>Radiation therapy</b> , yes vs. no	0.88 (0.59-1.31)	0.5276	0.43 (0.25-0.74)	0.0023	2.02 (0.70-5.88)	0.1957
<b>Endocrine therapy</b> , yes vs. no	0.99 (0.79-1.23)	0.9293	1.48 (1.04-2.12)	0.0302	0.83 (0.56-1.25)	0.3789
<b>Anti-HER2 therapy</b> , yes vs. no	1.04 (0.83-1.30)	0.7347	0.95 (0.67-1.34)	0.758	0.91 (0.59-1.42)	0.6799

\*models are adjusted for all the factors in the table. aOR= adjusted Odds Ratio; CI= Confidence Interval; BMI= Body Mass Index; HER2= Human Epidermal Growth Factor Receptor 2.

## Behavioral factors and trajectory-groups

**Table 3** displays the distribution of behavioral factors across trajectory-groups over time. Overall, there were increments in the proportion of overweight and obese patients in this cohort, which was highest among groups "Deteriorating" and "Poor" at year-4 (59.0% and 58.7%, respectively). There were also differential patterns in physical activity participation across groups. Particularly, Group "Excellent" and Group "Very good" were characterized by significant reductions in the proportion of patients being insufficiently active (32.7% to 32.0% [Cochrane-Armitage  $p_{\text{trend}}=0.0044$ ] and 49.5% to 36.1% [ $p_{\text{trend}} <.0001$ ], respectively), whereas inactivity rates significantly increased from diagnosis through year-4 in Group "Deteriorating" (28.9% to 37.2%, [ $p_{\text{trend}}=0.043$ ]) and were high and stable in Group "Poor" (53.7% to 56.0% [ $p_{\text{trend}}=0.855$ ]). Prevalence of current smokers at diagnosis was highest in groups "Deteriorating" and "Poor" (23.8% and 32.7%, respectively). Smoking persistence was most frequent (50.0%) in group "Deteriorating" at year-4, with no evident time-trend ( $p_{\text{trend}} 0.247$ ).

<b>MS2-Table 3. Distribution and time trends of Behavioral Factors by trajectory-group (N= 2313).</b>				
	<b>Trajectory-group</b>			
	<b>“Excellent” N= 1104 (47.7%)</b>	<b>“Very good” N= 802 (34.7%)</b>	<b>“Deteriorating” N= 260 (11.2%)</b>	<b>“Poor” N= 147 (6.4%)</b>
<b>Body Mass Index, continuous (Mean [SD], Kg/m<sup>2</sup>)</b>				
Diagnosis	25.0 (5.0)	25.8 (5.5)	26.3 (5.7)	26.6 (6.0)
Year-1	25.1 (5.0)	25.8 (5.4)	26.7 (5.9)	26.6 (6.5)
Year-2	25.4 (5.0)	26.2 (5.4)	27.1 (5.8)	27.3 (6.7)
Year-4	25.4 (4.8)	26.2 (5.4)	27.0 (6.0)	26.9 (5.8)
	$p_{\text{trend}}^* = 0.0068$	$p_{\text{trend}}^* = 0.0267$	$p_{\text{trend}}^* = 0.1036$	$p_{\text{trend}}^* = 0.3680$
<b>Overweight or obese, %</b>				
Diagnosis	39.4	46.6	52.3	54.4
Year-1	41.4	48.3	53.9	51.8
Year-2	43.0	50.3	58.3	55.6
Year-4	44.2	51.3	59.0	58.7
	$p_{\text{trend}}^{**} = 0.024$	$p_{\text{trend}}^{**} = 0.059$	$p_{\text{trend}}^{**} = 0.107$	$p_{\text{trend}}^{**} = 0.495$
<b>Level of physical activity, continuous (MET-h/week)</b>				
<b>Total activity, median (Q1-Q3)</b>				
Diagnosis	16.0 (4.0-40.0) ↑	10.0 (0.0-30.0) ↑	20.0 (4.0-67.0)	8.0 (0.0-50.0)
Year-1	18.0 (6.0-40.0) ↑	16.0 (4.0-36.0) ↑	18.0 (4.0-56.0)	12.0 (0.0-39.0)
Year-2	19.0 (7.2-41.7) ↑	16.0 (4.0-37.3) ↑	16.0 (3.3-48.0) ↔	8.0 (0.0-27.0) ↔
Year-4	18.0 (5.3-44.0)	16.0 (5.3-37.7)	16.0 (1.5-44.0)	4.0 (0.0-32.0)
	$p_{\text{trend}}^* = 0.0238$	$p_{\text{trend}}^* < .0001$	$p_{\text{trend}}^* = 0.0670$	$p_{\text{trend}}^* = 0.2355$
<b>Transport and leisure-time activity, median (Q1-Q3)</b>				
Diagnosis	12.0 (0.0-26.2) ↑	6.7 (0.0-17.0) ↑	10.0 (0.0-24.0)	2.7 (0.0-20.0)
Year-1	15.0 (4.0-28.7) ↑	12.0 (1.3-26.7) ↑	12.0 (0.0-28.0)	8.0 (0.0-21.0)
Year-2	14.7 (4.0-32.0) ↑	12.0 (2.7-26.0) ↑	8.0 (0.0-21.0) ↔	5.0 (0.0-16.0) ↔
Year-4	14.7 (4.0-32.0)	12.0 (2.7-24.0)	10.3 (0.0-24.0)	0.0 (0.0-20.0)
	$p_{\text{trend}}^* < .0001$	$p_{\text{trend}}^* < .0001$	$p_{\text{trend}}^* = 0.5715$	$p_{\text{trend}}^* = 0.7705$
<b>Insufficiently active (&lt;10 MET-h/week), %</b>				
Diagnosis	37.7 ↓	49.5 ↓	28.9 ↑	53.7 ↔
Year-1	32.7 ↓	35.5 ↓	36.0 ↑	45.7 ↔
Year-2	31.4 ↓	36.0 ↓	38.4 ↑	51.4
Year-4	32.0	36.1	37.2	56.0
	$p_{\text{trend}}^{**} = 0.0044$	$p_{\text{trend}}^{**} < .0001$	$p_{\text{trend}}^{**} = 0.043$	$p_{\text{trend}}^{**} = 0.855$

<b>Smoke behavior persistence compared to previous visit, among current smokers at diagnosis, %</b> (Diagnosis, N [%] smokers) <sup>§</sup>				
Year-1	52.0	61.4	62.1	68.8
Year-2	49.3	48.4	50.0	53.7
Year-4	44.2	43.6	50.0	33.3
	$p_{\text{trend}}^{**}=0.234$	$p_{\text{trend}}^{**}=0.0065$	$p_{\text{trend}}^{**}=0.247$	$p_{\text{trend}}^{**}=0.004$

Time trends were teste using either (\*) the Jonckheere-Terpstra Test (continuous variables) or (\*\*) the Cochran-Armitage Trend Test (categorical variables). <sup>§</sup>% not included in the trend tests. SD= Standard Deviation; MET= Metabolic-equivalent of task; Q1= Quartile 1; Q3= Quartile 3. Green arrows highlight a positive change or a healthier behavior compared to the previous assesment, red arrows highlight the persistence of an unhealthy behavior or a unhealthy change compared to the previous assesment.

## Discussion

We found four different patterns of patient-reported post-chemotherapy QOL trajectories among breast cancer patients by longitudinally analyzing C30-SumScore from diagnosis to year-4 post-diagnosis, respectively characterized by “Excellent” (47.7%), “Very good” (34.7%), “Deteriorating” (11.2%), and “Poor” (6.4%) QOL. Women clustering in the “Deteriorating” group reported fairly good QOL at diagnosis that significantly worsened in the aftermath of chemotherapy and never recovered to pre-treatment values. Factors associated with membership to this group included younger age, comorbidities, extensive axillary surgery and endocrine therapy. Healthy behaviors were positively and consistently associated with better performing trajectory-groups. In contrast, excess body weight, inactivity, and smoking persistence were particularly prevalent among the “Deteriorating” trajectory-group.

Quite reassuringly, the majority of patients in our cohort (~80%) followed fairly good QOL trajectories, scoring either very good or excellent on C30-SumScore. However, for two cluster of patients, the dynamics of QOL were worryingly worse. Particularly, the group with “Deteriorating” QOL seemed the most impacted by primary treatment, experiencing a dramatic drop of approximately 20 points in mean C30-SumScore from diagnosis to Year-1, which never resolved. A sharp deterioration of clinically relevant magnitude was observed for multiple functions in this segment, particularly physical, social, cognitive, and role function, and symptoms including fatigue, pain, and dyspnea. These changes can be dramatic from a patient’s perspective, qualifying overall as “moderately-to-very-much worse” than before treatment<sup>133</sup>, and are considered of “medium-to-large” as proposed by Cocks et al<sup>134</sup>. Almost all mean scores in the “Deteriorating” trajectory-group met the thresholds of clinical importance recently validated by Giesinger and colleagues<sup>132</sup>, red-flagging functional impairment and severe symptoms that should trigger specific clinician’s attention and urge dedicated supportive care.

Our findings also highlight the complexity of risk factors for membership to the identified trajectory-groups. Younger age, higher comorbidity burden, and lower income were all associated with higher risk of clustering into one of the two groups at worse profile of QOL over time. More aggressive breast cancer treatment including extensive axillary surgery and receipt of adjuvant endocrine therapy specifically discriminated membership to the “Deteriorating” QOL group from other trajectory-groups. These results are in keeping with our previous CANTO analysis, where we had reported that endocrine therapy acts a major player determining a persistent detrimental impact on C30-SumScore.<sup>135</sup>

We had a specific interest in behavioral factors as correlates of trajectory-group membership, hypothesizing that a leaner body type, higher levels of activity, and smoke abstinence would be associated with better trajectories of QOL.<sup>39</sup> Overweight or obese women were approximately 1.7 times more likely to cluster into the “Deteriorating” QOL group, where the prevalence of overweight increased to approximately 60% at year-4 post-diagnosis. Although women with “Deteriorating” QOL pattern had high levels of physical activity at diagnosis, (71.1% adherent to recommendations), these substantially and significantly declined through year-4. In addition, current smokers at diagnosis were almost two-fold more likely to belong to the “Deteriorating” group,

where smoke persistence was also most prevalent post-diagnosis. These data suggest that QOL deterioration could be partly mediated by these observed unhealthy behaviors.

Previous research has largely described marked and deleterious consequences of excess adiposity and sedentary lifestyle after breast cancer diagnosis. Not only weight gain and deconditioning were associated with reduced QOL in post-treatment breast cancer survivors<sup>36,37,118,136</sup>, but also with worse survival.<sup>137,138</sup> Furthermore, research showed that current smokers have higher odds of experiencing severe levels of treatment-related physical or cognitive side effects and persistent sleep or mood disturbances.<sup>101,139</sup> Smoking habit was also associated to increased side effects of endocrine therapy among breast cancer patients.<sup>140,141</sup> Conversely, smokers who quit are more likely to endure cancer treatments and speed up symptom recovery-time<sup>101</sup>, and have reduced all-cause mortality.<sup>142,143</sup>

From a biological standpoint, a strong interplay was described between higher BMI and reduced exercise exposure with alterations in circulating biomarkers such as inflammation axis effectors, immunomodulatory cytokines, metabolic-steroid hormones and growth factors, which can contribute to symptom deterioration and worse treatment-related side-effects among women with breast cancer.<sup>118,144–147</sup> Similar inflammatory alterations, worsened by tissue hypoxia and disruptions in hormone levels and circadian rhythm were observed in current smokers, which may account for part of the associations with treatment-related adverse effects.<sup>101,139,148–150</sup>

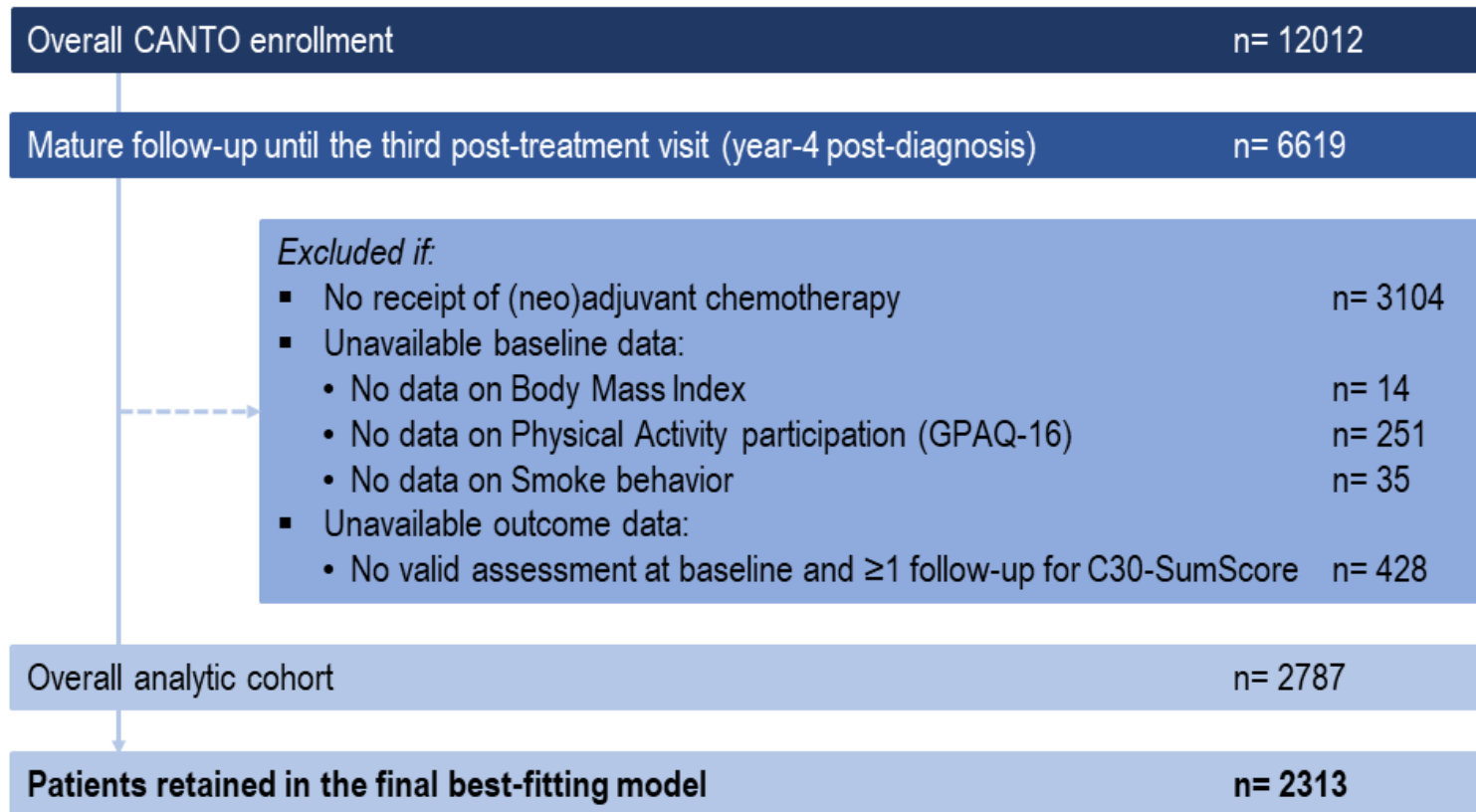
Whether behavioral changes can influence cancer recurrence and other cancer-related outcomes including QOL is still the subject of a vivid research debate.<sup>50</sup> A number of studies investigated the effects of exercise training during cancer treatments and documented improvements in physiologic variables and psychosocial status.<sup>151</sup> In addition, physical activity interventions delivered after completion of adjuvant chemotherapy among women with early-stage breast cancer proved to have beneficial effects on QOL.<sup>37</sup> Ongoing randomized trials will further expand this knowledge, including testing whether combined interventions of weight loss (with multiple components of diet, physical activity, and personalized behavioral coaching)<sup>152–154</sup>, and smoke cessation programs<sup>50,51</sup> can reduce treatment-related symptoms, improve QOL, and impact recurrence rates and survival of breast cancer survivors.

Strengths of this analysis include the use of a single, higher-order QOL outcome measure that summarizes multiple scales into a multidimensional response profile, avoiding multiple comparisons and containing the type 1 error.<sup>117,123</sup> Specific psychometric properties include that C30-SumScore is more robust against inherent limitations of PROs such as “dispositional optimism” and “response shift”.<sup>155–157</sup> Secondly, a novelty in the present analysis is the use of GBTM, which provides an overall dynamic portrait and avoids to summarize QOL data by fitting a simplistic population mean. For example, our previous analyses using a mixed-model methodology showed no detrimental effect of chemotherapy on C30-SumScore in the overall population<sup>135</sup>, whereas GBTM “unmasked” latent patient groups that are clinically very relevant. Finally, we examined a large and heterogeneous sample of women enrolled in a prospective, multicenter, contemporary cohort, with a wealth of longitudinal data and PROs.

A limitation of this study was the presence of some attrition at year-4, therefore our results may be driven by mid- rather than long-term changes. However, GBTM is particularly robust accommodating missing outcome data. Trajectory-groups are also not fixed and may change, as GBTM performs a dynamic grouping that is susceptible to additional follow-up.<sup>128</sup> We could not granularly describe QOL evolution over the active chemotherapy period, as only a baseline and a year-1 assessment were available. However, we believe that our findings are novel and offer a long-term landscape view revealing variability that may become evident only after several years post-diagnosis.

In this dynamic portrait of post-chemotherapy QOL, we identified and characterized patients at risk of steep and clinically meaningful decline. Most of the identified associated factors were non-modifiable, including socio-demographics and receipt of more extensive treatment. Behavioral factors were consistently associated with QOL trajectory-groups. Weight modulation, physical activity uptake, and smoke abstinence are modifiable factors that may represent a potential tool to combat functional health impairment and symptoms exacerbation, mitigating the detrimental impact of chemotherapy. However, personalized behavioral interventions supporting lifestyle changes may be difficult to implement.<sup>158,159</sup> Personalization is all the more important in the current scenario where lifestyle change programs are not standard of care and cancer is not a qualifying diagnosis for third-party reimbursement of behavioral interventions.<sup>39,51,52</sup> In an effort to optimize resource utilization, research is now increasingly focused on healthy lifestyle promotion interventions among specific target subpopulations, and on how to best deliver patient-specific behavioral support.<sup>50-52</sup> Our study offers further insight on how to screen relevant patient-level factors and identify clusters of at-risk patients that are suitable for tailored interventions aimed at preservation of QOL, including healthy lifestyle support programs.

Data Supplement



**MS2-Supplementary Figure 1.** Consort diagram of patient population. GPAQ-16= Global physical activity Questionnaire-16; C30-SumScore= European Organization for Research and Treatment of Cancer (EORTC) QOL Questionnaire (QLQ)-C30 Summary Score.

## MS2-Supplementary Methods description. Definition of trajectory-groups

Definition of trajectory-groups. Longitudinal variations in repeated measures of C30-SumScore were assessed by multivariable latent-class models using Group-Based Trajectory Modeling (GBTM). Briefly, GBTM describes the course of an outcome over time, segmenting the data into trajectory-groups and identifying longitudinal unobserved (latent) clusters of individuals following similar courses of the defined outcome. GBTM is a semi-parametric procedure.

Model selection involves the iterative estimation of (1) the number of trajectory groups and (2) the best shape/order of each trajectory group, tested using maximum likelihood methods. Non-significant polynomial terms are iteratively eliminated by a stepwise procedure to achieve the simplest final model where each trajectory-group is significant at  $\alpha=0.05$ .

Model selection typically begins with a model consisting of one group with a quadratic degree polynomial, then the order is increased or decreased according to the significance of the parameter estimates. Groups are then increased until the number that best fit the data is identified. Statistical criteria for ascertaining the best fitting model include: Akaike's Information Criterion (AIC), Bayesian Information Criterion (BIC), the sample-size adjusted BIC (ssBIC), and the consistent AIC (CAIC), where smaller values (smallest negative number) of AIC, BIC, ssBIC, and CAIC indicate better fitting models. In addition, posterior probability (PP) is a post-estimation calculation that assigns a numeric likelihood that an individual belongs to each group. The average posterior probabilities (AvePP) should be superior to 0.70, with higher values denoting better classification accuracy. Finally, the odds of correct classification (OCC), based on the PP of group membership, have to exceed a minimum threshold of 5.

For each trajectory-group, a close correspondence is required between estimated probability of group membership and proportion assigned based on avePP. Non-statistical criteria include reasonable sample size in each identified trajectory-group and non-overlapping and reasonably tight confidence intervals. These subjective judgments are important in the selection of the best trajectory model because the aim is to identify a final model that is not only mathematically sound, but also parsimonious and clinically useful.

### References to the procedure:

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<b>MS2-Supplementary Table 1. Baseline patient characteristics in the overall analytic cohort (N= 2787).</b>	
	<b>Whole cohort</b>
<b>N (%)</b>	
<b>Age, years</b>	
Mean (SD)	52.5 (10.9)
Missing	-
<b>Body Mass Index, continuous (Kg/m<sup>2</sup>)</b>	
Mean (SD)	25.7 (5.4)
Missing	-
<b>Body Mass Index, WHO definition</b>	
Underweight, <18.5 Kg/m <sup>2</sup>	70 (2.5)
Normal weight, 18.5-24.9 Kg/m <sup>2</sup>	1435 (51.5)
Overweight, 25.0-29.9 Kg/m <sup>2</sup>	754 (27.0)
Obese, ≥30.0 Kg/m <sup>2</sup>	528 (19.0)
Missing	-
<b>Level of physical activity, continuous (MET-h/week)</b>	
Total activity, median (Q1-Q3)	13.3 (0.0-40.0)
Transport and leisure-time activity, median (Q1-Q3)	8.0 (0.0-23.3)
Missing	-
<b>Level of physical activity, WHO definition</b>	
Sufficiently active (≥10 MET-h/week)	1591 (56.1)
Insufficiently active (<10 MET-h/week)	1196 (42.9)
Missing	-
<b>Smoking behavior</b>	
Former or never smoker	2281 (81.8)
Current smoker	506 (18.2)
Missing	-
<b>Menopausal status</b>	
Premenopausal	1340 (49.0)
Postmenopausal	1397 (51.0)
Missing	50

<b>Charlson comorbidity score</b>	
0	2103 (81.7)
≥1	470 (18.3)
Missing	214
<b>Marital status</b>	
Not partnered	677 (25.1)
Partnered	2020 (74.9)
Missing	90
<b>Monthly household income</b>	
<3,000 Euro	1380 (53.8)
≥3,000 Euro	1185 (46.2)
Missing	222
<b>Stage</b>	
I	756 (27.2)
II	1543 (55.4)
III	485 (17.4)
Missing	3
<b>Subtype</b>	
HR+/HER2-	1669 (60.0)
HR±/HER2+	687 (24.7)
HR-/HER2-	425(15.3)
Missing	6
<b>Breast cancer surgery</b>	
Mastectomy	1032 (37.0)
Partial breast surgery	1755 (63.0)
Missing	-
<b>Axillary surgery</b>	
Axillary dissection	1658 (59.5)
Sentinel node	1129 (40.5)
Missing	-
<b>Type of chemotherapy</b>	
Anthracyclines +taxanes	2419 (86.8)
Anthracyclines	109 (3.9)
Taxanes	259 (9.3)

<b>Radiation therapy</b>	
Yes	2596 (93.3)
No	187 (6.7)
Missing	4
<b>Endocrine therapy</b>	
Yes	2115 (75.9)
No	671 (24.1)
Missing	1
<b>Type of Endocrine therapy, if applicable</b>	
Tamoxifen ± LHRH analog	834 (39.6)
Aromatase Inhibitor ± LHRH analog	978 (46.4)
Tamoxifen + Aromatase Inhibitor ± LHRH analog	295 (14.0)
Missing	8
<b>Anti-HER2 therapy</b>	
Yes	610 (21.9)
No	2177 (78.1)
Missing	-
SD= Standard Deviation; MET= Metabolic-equivalent of task; Q1= Quartile 1; Q3= Quartile 3; HR= Hormone Receptor; LHRH= Luteinizing hormone-releasing hormone; HER2= Human Epidermal Growth Factor Receptor 2.	

**MS2-Supplementary Table 2. Metrics used for comparison across tested trajectory-group models.**

<b>N. groups (order of each group)</b>	<b>BIC (total number of observations)</b>	<b>BIC (actual number of subjects)</b>	<b>AIC</b>	<b>Bayes Factor</b>	<b>Interpretation*</b>	<b>Estimated probability of group membership</b>	<b>AvePP</b>	<b>OCC</b>	<b>Proportion assigned to group based on AvePP</b>
<b>2 groups (3, 3)</b>	-29664.14 (N= 7620)	-29650.43 (N= 2313)	-29584.34	2.1127 <sup>-123</sup>	Strong evidence for model 3 better than 2	27.8	0.91	26.86	27.3
						72.2	0.96	9.26	72.7
<b>3 groups (3, 3, 2)</b>	-29391.81 (N= 7620)	-29367.96 (N= 2313)	-29253.04	3-groups vs. 2-groups model	Strong evidence for model 3 better than 2	9.7	0.91	99.39	09.3
						35.4	0.86	11.48	35.2
						54.9	0.92	9.90	55.5
<b>4 groups (2, 3, 3, 2)</b>	-29363.52 (N= 7620)	-29329.54 (N= 2313)	-29165.77	2.062557 <sup>-17</sup>	Strong evidence for model 4 better than 3	6.3	0.88	111.75	<b>6.4</b>
						12.4	0.80	28.52	<b>11.2</b>
						34.3	0.79	7.51	<b>34.7</b>
						47.0	0.89	9.64	<b>47.7</b>

The final model is a four-group model (highlighted in grey). Order: 0= zero-order (intercept), 1=linear; 2= quadratic; 3=cubic.

BIC= Bayesian Information Criterion; AIC= Akaike's Information Criterion; AvePP= Average Posterior Probability; OCC= Odds of Correct Classification.

\*Level of strength is based on Bayes Factor (tested model vs. reference [null] model): <1/10, Strong evidence for tested model; 1/10 to <1/3, Moderate evidence for tested model;

1/3 to <1, Weak evidence for tested model; 1 to <3 Weak evidence for reference model; 3 to <10 Moderate evidence for reference model; ≥10 Strong evidence for reference model (Adapted from Arrandale V et al. 2006).

<b>MS3-Supplementary Table 3. Maximum Likelihood Estimates of the model parameters.</b>					
<b>Trajectory-group</b>	<b>Parameter order</b>	<b>Estimate</b>	<b>Standard Error</b>	<b>T value</b>	<b>Prob &gt;  T </b>
<b>“Excellent”</b>	Intercept	68.89519	3.20577	21.491	<0.00001
	Linear	-16.53924	3.03314	-5.453	<0.00001
	<b>Quadratic</b>	3.22198	5.177	0.62241	<0.00001
<b>“Very good”</b>	Intercept	143.69875	7.83779	18.334	<0.00001
	Linear	-98.88033	11.62894	-8.503	<0.00001
	Quadratic	36.63444	4.98856	7.344	<0.00001
	<b>Cubic</b>	-4.24560	0.65181	-6.514	<0.00001
<b>“Deteriorating”</b>	Intercept	94.11615	3.60942	26.075	<0.00001
	Linear	-22.90060	5.59509	-4.093	<0.00001
	Quadratic	8.77212	2.44857	3.583	0.0003
	<b>Cubic</b>	-1.03808	0.32401	-3.204	0.0014
<b>“Poor”</b>	Intercept	92.12646	0.89628	102.787	<0.00001
	Linear	-2.72353	0.84826	-3.211	0.0013
	<b>Quadratic</b>	0.53628	0.17095	3.137	0.0017
Trajectories of C30-SumScore for groups A and D are described with an intercept plus a linear and a quadratic ( $p < 0.00001$ and $p = 0.0017$ , respectively) time parameter. Groups B and C are further described with a cubic time parameter ( $p < 0.00001$ and $p = 0.0014$ , respectively).					

**MS2-Supplementary Table 4. Estimates for trajectory-group membership (vs. reference “Excellent”, N= 1104 [47.7%]).**

Baseline characteristics	Trajectory-group											
	“Very good” N= 802 (34.7%)				“Deteriorating” N= 260 (11.2%)				“Poor” N= 147 (6.4%)			
	Estimate	SE	T value	Prob >  T	Estimate	SE	T value	Prob >  T	Estimate	SE	T value	Prob >  T
<b>Age</b> , continuous (1-year increase)	-0.02205	0.00629	-3.506	0.0005	-0.01958	0.00813	-2.407	0.0161	-0.01533	0.00982	-1.562	0.1183
<b>BMI</b> , Overweight or obese vs. lean	0.2681	0.1360	1.917	0.0553	0.50332	0.17950	2.804	0.0051	0.45316	0.21578	2.100	0.0358
<b>Physical Activity</b> , Sufficiently vs. insufficiently active	-0.35074	0.1279	-2.740	0.0062	0.39660	0.19806	2.002	0.0453	-0.54829	0.20516	-2.672	0.0075
<b>Smoking behavior</b> , Current vs. former or never smoker	0.19953	0.17303	1.153	0.2489	0.49209	0.21599	2.278	0.0227	1.00810	0.23344	4.318	<.0001
<b>Charlson</b> , ≥1 vs. 0	0.33867	0.17422	1.944	0.0519	0.69575	0.20270	3.432	0.0006	0.69875	0.24683	2.831	0.0047
<b>Marital status</b> , Partnered vs. not	0.02732	0.16082	0.170	0.8651	0.24139	0.21156	1.141	0.2539	-0.18175	0.23277	-0.781	0.4349
<b>Income</b> , ≥3000 vs. <3000 Euro/month	-0.33505	0.14074	-2.381	0.0173	-0.66815	0.18885	-3.538	0.0004	-1.00923	0.24642	-4.095	<.0001
<b>Breast cancer stage</b> , II/III vs. I	-0.02926	0.15958	-0.183	0.8545	0.11653	0.23086	0.505	0.6137	0.02470	0.28757	0.086	0.9315
<b>Breast cancer surgery</b> , Mastectomy vs. Partial breast surgery	0.17884	0.14946	1.197	0.2315	-0.18617	0.20121	-0.925	0.3549	0.08702	0.23750	0.366	0.7141
<b>Axillary surgery</b> , Axillary dissection vs. Sentinel node	-0.03868	0.15231	-0.254	0.7995	0.37722	0.21511	1.754	0.0795	0.28496	0.26812	1.063	0.2879
<b>Radiation therapy</b> , yes vs. no	-0.06252	0.27687	-0.226	0.8213	-0.56571	0.33681	-1.680	0.0931	0.48801	0.66357	0.735	0.4621
<b>Endocrine therapy</b> , yes vs. no	0.02298	0.14548	0.158	0.8745	0.37105	0.22609	1.641	0.1008	-0.17398	0.23111	-0.753	0.4516
<b>Anti-HER2 therapy</b> , yes vs. no	0.04160	0.15117	0.275	0.7832	-0.03640	0.21196	-0.172	0.8636	-0.05048	0.24930	-0.202	0.8395

SE= Standard Error; BMI= Body Mass Index; HER2= Human Epidermal Growth Factor Receptor 2.

**MS2-Supplementary Table 5. Mean scores and respective 95% CI for all scales included in the EORTC QLQ-C30**

**“Excellent” (N= 1104 [47.7%])**

Domain	Diagnosis			Year-1			Year-2			Year-4		
	Mean	95% CI		Mean	95% CI		Mean	95% CI		Mean	95% CI	
		Low	High		Low	High		Low	High		Low	High
Global Health*	76.4	75.5	77.4	77.3	76.5	78.2	75.8	75.0	76.7	76.6	75.5	77.7
Physical Function	96.8	96.4	97.2	91.3	90.7	91.8	91.9	91.4	92.5	92.9	92.2	93.6
Emotional Function	73.3	72.2	74.5	84.1	83.1	85.1	82.1	81.0	83.2	82.3	80.9	83.7
Social Function	96.3	95.7	96.9	91.9	91.0	92.8	95.4	94.7	96.1	96.6	95.8	97.3
Cognitive Function	91.0	90.2	91.7	87.3	86.4	88.3	87.2	86.2	88.2	87.5	86.3	88.7
Role Function	94.2	93.4	95.0	90.8	89.9	91.8	93.2	92.3	94.0	93.8	92.7	94.9
Fatigue	15.5	14.5	16.5	22.3	21.2	23.3	21.2	20.2	22.2	19.8	18.6	21.0
Pain	8.2	7.5	9.0	16.1	15.0	17.2	16.5	15.3	17.7	15.5	14.1	16.9
Insomnia	29.6	28.0	31.2	26.3	24.7	28.0	26.1	24.4	27.9	26.1	24.0	28.3
Nausea/Vomit	1.8	1.4	2.2	1.7	1.3	2.1	1.6	1.2	2.0	1.2	0.8	1.6
Dyspnea	4.7	4.0	5.4	11.4	10.3	12.5	10.3	9.2	11.4	9.5	8.2	10.8
Appetite Loss	8.6	7.6	9.7	3.5	2.8	4.3	1.6	1.1	2.1	2.6	1.8	3.5
Constipation	5.2	4.3	6.1	7.4	6.4	8.4	9.1	7.9	10.3	8.6	7.1	10.0
Diarrhea	5.0	4.2	5.9	4.7	4.0	5.5	3.9	3.1	4.6	3.6	2.8	4.5
Financial difficulties*	3.1	2.4	3.7	7.3	6.2	8.4	3.2	2.4	3.9	1.6	0.8	2.4

**“Very good” (N= 802 [34.7%])**

Domain	Diagnosis			Year-1			Year-2			Year-4		
	Mean	95% CI		Mean	95% CI		Mean	95% CI		Mean	95% CI	
		Low	High		Low	High		Low	High		Low	High
Global Health*	63.2	62.0	64.5	63.0	61.9	64.1	61.8	60.7	62.9	61.4	59.9	62.8
Physical Function	90.0	89.1	90.8	80.8	79.8	81.7	81.7	80.6	82.7	82.6	81.4	83.9
Emotional Function	57.6	56.0	59.3	66.1	64.6	67.7	64.8	63.2	66.5	64.7	62.6	66.7
Social Function	87.0	85.6	88.3	75.8	74.2	77.4	82.5	81.0	84.0	83.4	81.6	85.3
Cognitive Function	75.5	73.9	77.1	70.3	68.7	71.9	69.8	68.1	71.5	69.5	67.4	71.7
Role Function	80.9	79.2	82.5	73.2	71.6	74.7	78.1	76.5	79.7	78.6	76.7	80.5
Fatigue	36.0	34.5	37.5	43.9	42.5	45.3	42.9	41.4	44.3	42.0	40.1	43.8
Pain	20.3	18.8	21.8	34.1	32.5	35.7	34.2	32.5	36.0	34.7	32.5	37.0
Insomnia	53.7	51.4	56.0	53.0	50.7	55.3	51.2	48.8	53.6	50.7	47.7	53.7
Nausea/Vomit	5.5	4.6	6.4	4.9	4.0	5.7	5.0	4.1	5.9	5.4	4.0	6.7
Dyspnea	13.9	12.4	15.5	25.3	23.5	27.1	24.0	22.2	25.8	24.0	21.8	26.2
Appetite Loss	20.5	18.6	22.4	10.0	8.6	11.4	7.8	6.6	9.1	9.2	7.3	11.0
Constipation	12.2	10.6	13.8	17.9	16.0	19.7	19.5	17.5	21.6	19.6	17.0	22.1
Diarrhea	11.1	9.7	12.4	12.1	10.5	13.6	9.8	8.3	11.3	11.0	9.0	13.0
Financial difficulties*	8.6	7.3	10.0	17.4	15.5	19.3	9.1	7.5	10.7	5.5	4.0	7.1

<b>"Deteriorating" (N= 260 [11.2%])</b>												
<b>Domain</b>	<b>Diagnosis</b>			<b>Year-1</b>			<b>Year-2</b>			<b>Year-4</b>		
	<b>Mean</b>	<b>95% CI</b>		<b>Mean</b>	<b>95% CI</b>		<b>Mean</b>	<b>95% CI</b>		<b>Mean</b>	<b>95% CI</b>	
		<b>Low</b>	<b>High</b>		<b>Low</b>	<b>High</b>		<b>Low</b>	<b>High</b>		<b>Low</b>	<b>High</b>
Global Health*	62.4	60.3	64.6	51.3	49.3	53.2	52.2	50.2	54.1	50.6	47.8	53.3
Physical Function	87.9	86.3	89.6	69.7	67.8	71.7	70.1	68.0	72.2	70.9	68.1	73.6
Emotional Function	57.5	54.5	60.6	50.0	46.9	53.2	49.5	46.2	52.8	54.8	51.0	58.7
Social Function	87.1	84.9	89.3	53.0	49.4	56.6	60.8	57.2	64.3	63.8	59.5	68.2
Cognitive Function	75.8	73.3	78.3	54.6	51.4	57.8	53.6	50.2	56.9	56.5	52.3	60.7
Role Function	83.5	81.0	85.9	51.7	48.5	55.0	59.8	56.8	62.7	60.8	57.1	64.4
Fatigue	39.3	36.7	41.8	65.2	62.5	67.9	61.5	58.6	64.3	58.7	55.1	62.2
Pain	24.7	21.7	27.7	58.1	54.7	61.5	56.5	53.3	59.7	53.6	49.6	57.6
Insomnia	56.5	52.3	60.8	74.1	70.3	77.8	70.1	66.0	74.1	66.2	61.0	71.4
Nausea/Vomit	5.1	3.8	6.3	15.0	12.2	17.7	12.3	9.8	14.8	11.0	8.0	14.0
Dyspnea	15.1	12.5	17.8	42.6	38.9	46.4	40.6	36.4	44.8	40.3	35.1	45.4
Appetite Loss	19.7	16.6	22.9	21.6	18.1	25.0	19.7	16.4	23.0	19.5	14.9	24.1
Constipation	15.5	12.5	18.5	34.3	30.1	38.4	29.9	25.4	34.5	32.4	26.8	38.1
Diarrhea	9.2	6.9	11.6	22.9	19.4	26.5	15.5	12.2	18.9	20.8	15.9	25.7
Financial difficulties*	13.8	10.6	17.1	34.5	30.2	38.9	26.0	21.6	30.4	20.9	15.6	26.1
<b>"Poor" (N= 147 [6.4%])</b>												
<b>Domain</b>	<b>Diagnosis</b>			<b>Year-1</b>			<b>Year-2</b>			<b>Year-4</b>		
	<b>Mean</b>	<b>95% CI</b>		<b>Mean</b>	<b>95% CI</b>		<b>Mean</b>	<b>95% CI</b>		<b>Mean</b>	<b>95% CI</b>	
		<b>Low</b>	<b>High</b>		<b>Low</b>	<b>High</b>		<b>Low</b>	<b>High</b>		<b>Low</b>	<b>High</b>
Global Health*	41.9	38.9	44.8	44.1	41.0	47.2	41.4	37.7	45.0	46.8	41.9	51.8
Physical Function	68.4	64.8	72.0	57.8	54.7	60.8	56.7	53.0	60.5	60.4	54.3	66.5
Emotional Function	32.3	28.1	36.5	37.5	33.1	41.8	37.5	32.8	42.3	42.8	35.5	50.2
Social Function	57.4	52.3	62.5	42.6	37.8	47.4	49.8	44.3	55.4	53.4	45.2	61.6
Cognitive Function	53.4	48.6	58.2	41.3	36.7	45.8	40.4	35.4	45.3	42.4	35.1	49.7
Role Function	51.1	46.3	56.0	40.7	36.2	45.1	42.1	36.8	47.5	50.3	42.0	58.6
Fatigue	69.0	65.0	73.0	76.9	73.2	80.7	76.1	71.6	80.6	68.4	61.8	74.9
Pain	52.2	47.5	56.9	67.6	63.3	71.9	70.2	65.3	75.1	61.9	54.3	69.4
Insomnia	79.6	74.6	84.6	76.4	71.1	81.8	78.3	72.5	84.1	69.6	61.0	78.2
Nausea/Vomit	16.8	13.1	20.4	18.8	14.5	23.1	17.6	12.6	22.6	16.1	9.6	22.6
Dyspnea	37.2	31.9	42.5	53.7	48.6	58.7	51.4	45.6	57.1	48.0	40.6	55.5
Appetite Loss	45.1	39.6	50.7	34.5	28.6	40.5	33.9	27.0	40.9	23.6	15.2	31.9
Constipation	27.0	21.6	32.4	38.5	32.0	45.1	42.8	35.4	50.3	43.7	34.5	52.8
Diarrhea	20.9	16.3	25.5	25.8	20.3	31.2	24.1	17.7	30.5	22.8	14.3	31.4
Financial difficulties*	31.7	25.6	37.8	46.7	40.0	53.4	34.3	26.8	41.8	32.2	22.5	41.9

\*Global Health and Financial difficulties are not part of the C-30 SumScore, but are included in the Table for completeness. Higher scores reflect better functionality or greater symptom severity. EORTC QLQ-C30= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C-C30; QOL= Quality of life.

## MANUSCRIPT 3 (MS3):

### Changes in weight, physical and psychosocial patient-reported outcomes among obese women receiving treatment for early-stage breast cancer: a nationwide clinical study

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## **Abstract**

**Background:** Evidence on how weight loss correlates to health-related quality-of-life (HRQOL) among obese breast cancer (BC) patients is limited. We aimed to evaluate associations between weight changes and HRQOL.

**Methods:** We included 993 obese women with stage I-II-III BC from CANTO, a multicenter, prospective cohort collecting longitudinal, objectively-assessed anthropometric measures and HRQOL data (NCT01993498). Associations between weight changes ( $\pm 5\%$  between diagnosis and post-treatment [shortly after completion of surgery, adjuvant chemo- or radiation-therapy]) and patient-reported HRQOL (EORTC QLQ-C30/B23) were comprehensively evaluated. Changes in HRQOL and odds of severely impaired HRQOL were assessed using multivariable generalized estimating equations and logistic regression, respectively.

**Results:** 14.1% women gained weight, 67.3% remained stable and 18.6% lost weight. Significant decreases in functional status and exacerbation of symptoms were observed overall post-treatment. Compared to gaining weight or remaining stable, obese women who lost weight experienced less of a decline in HRQOL, reporting better physical function (mean change [95%CI] for gain, stability and loss: -12.9 [-16.5,-9.3], -6.9 [-8.2,-5.5] and -6.2 [-8.7,-3.7];  $p_{\text{interaction[weight-change-by-time]}}=0.006$ ), less dyspnea (+18.9 [+12.3,+25.6], +9.2 [+6.5,+11.9] and +3.2 [-1.0,+7.3];  $p_{\text{interaction}}=0.0003$ ), and fewer breast symptoms (+22.1 [+16.8,+27.3], +18.0 [+15.7,+20.3] and +13.4 [+9.0,+17.2];  $p_{\text{interaction}}=0.044$ ). Weight loss was also significantly associated with reduced odds of severe pain compared with weight gain (OR [95%CI]=0.51 [0.31-0.86],  $p=0.011$ ) or stability (OR [95%CI]=0.62 [0.41-0.95],  $p=0.029$ ). No associations between weight loss and worsening of other physical or psychosocial parameters were found.

**Conclusions:** This large contemporary study suggests that weight loss among obese BC patients during early survivorship was associated with better patient-reported outcomes, without evidence of worsened functionality or symptomatology in any domain of HRQOL.

## Introduction

Obesity is a risk factor for a number of chronic diseases, including diabetes and cardiovascular disease, as well as for early mortality.<sup>160</sup> Several physical, psychological, and social dimensions of health that contribute to the self-perception of quality of life (QOL), referred to as health-related (HR)-QOL, are also negatively impacted by obesity.<sup>161</sup>

Obesity has increasingly become recognized as a risk factor also for cancer and as a prognostic factor for individuals diagnosed with early-stage malignancies. Compelling evidence points at the strong link between obesity and breast cancer: excess weight represents a risk factor for postmenopausal breast cancer<sup>162</sup>, increases the risk of recurrent and second primary breast cancer<sup>163</sup> and that of overall and breast cancer-specific mortality.<sup>28</sup> Obesity may also interfere with adequate breast cancer treatment delivery<sup>164</sup>, exacerbating toxicities and burdening healthcare costs.<sup>165</sup> As the prevalence of obese has risen around the world, the number of obese patients with breast cancer has dramatically increased.<sup>33</sup>

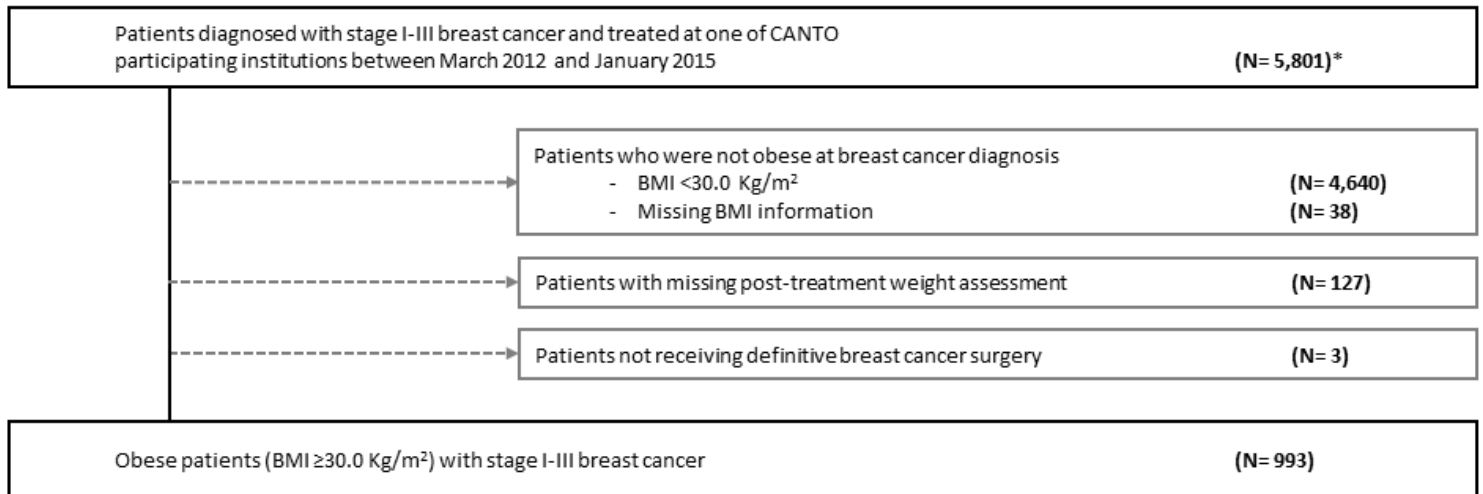
Weight changes occurring after diagnosis of early breast cancer are common and post-treatment weight gain is associated with poor HRQOL, body image issues and psychological distress, further aggravating the deterioration of HRQOL that is frequently caused by cancer treatment.<sup>166</sup> Randomized clinical trials reported on some benefits of weight loss on physical function and fitness level of obese individuals.<sup>167,168</sup> Nevertheless, such trials did not address the impact of weight loss on overall HRQOL during or shortly after cancer treatment, and often focused on selected patient groups (e.g. postmenopausal women). In addition, recent large systematic reviews among the general population remarked that studies on obesity, weight loss, and HRQOL have been very heterogeneous in terms of design, study population, and HRQOL assessment<sup>169,170</sup>, recommending that research should focus on prospective studies with high retention rates and carefully-chosen HRQOL measures.<sup>171</sup>

Because only limited evidence suggests that weight loss in obese breast cancer patients consistently improves HRQOL<sup>171</sup>, we aimed to evaluate if weight changes occurring between breast cancer diagnosis and shortly after primary treatment completion are associated with HRQOL using CANTO, a large, contemporary, prospective clinical study of breast cancer survivors that accesses extensive and longitudinal information, including comprehensive serial assessments of patient-reported outcomes (PROs).<sup>61</sup>

## Methods

CANTO (CANcer Toxicities, ClinicalTrials.gov/NCT01993498) enrolled patients with stage I-II-III breast cancer<sup>172</sup> across 26 French centers. For this sub study, we used data collected at diagnosis (baseline) and during the first visit after primary treatment completion, defined as completion of definitive breast surgery, adjuvant chemotherapy or radiotherapy, as appropriate (adjuvant endocrine therapy and anti-human epidermal growth-factor receptor (HER)-2 therapy were allowed to be ongoing). Study protocol was approved by a central ethical committee for human subjects. Informed consent was obtained at patient inclusion. Details about the CANTO study procedures were previously published.<sup>61</sup>

We accessed information from 5,801 women diagnosed from 2012-2015. We excluded patients who were not obese at diagnosis (Body Mass Index [BMI] <30.0 Kg/m<sup>2</sup> [N=4,640] or missing [N=38]), 127 patients with missing post-treatment weight reassessment, and three patients not treated with curative intent (**MS3-Figure 1**).



**Figure 1. CONSORT diagram of patient population.** \*Note: total accrual in CANTO 12,012 patients. We accessed information from 5,801 women who were enrolled from March 2012 to January 2015.

#### Variables of interest

##### *Outcome variables*

We assessed PROs using the European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life-questionnaires QLQ-C30 and QLQ-BR23. The EORTC QLQ-C30 is a 30-item questionnaire that includes a) a global health status subscale, b) five multi-item functional subscales for physical, emotional, social, cognitive, and role functioning, c) three multi-item symptom scales for fatigue, pain, and nausea/vomiting, and d) six single-item symptom scales assessing other cancer-related symptoms including sleep disturbance, dyspnea, appetite loss, constipation, diarrhea, and financial difficulties. The EORTC QLQ-BR23 is the breast cancer-specific companion module to the EORTC QLQ-C30 and consists of 23 items that include a) four functional scales for body image, sexual functioning, sexual enjoyment, and future perspective, and b) four symptom scales for systemic side-effects, breast symptoms, arm symptoms, and upset by hair loss. Questionnaires include two 7-point Likert scale items with response ranging from 'very poor' to 'excellent' for global health, and 4-point Likert scale items with possible responses of 'not at all', 'a little', 'quite a bit, and 'very much' for functioning and symptoms. A standard scoring algorithm was used to convert responses to all items to a 0-100 scale. For global health and functional scales, higher scores reflect a better level of QOL and function, whereas for symptom scales higher scores reflect greater symptom severity compared with lower scores. A validated French version of EORTC QLQ-C30 and QLQ-B23 was used in CANTO.<sup>57,61,122,124,125</sup> PROs were comprehensively

modeled: (1) as continuous; and dichotomizing HRQOL scores by clinical severity, namely (2) HRQOL deterioration from baseline to post-treatment (change  $\geq 10$  points on global/functional or symptoms scales); (3) prevalence of patients scoring  $<60$  on global/functional or  $\geq 40$  on symptoms scales, which defined 'poor functions' and 'severe symptoms', respectively; and (4) prevalence of patients transitioning from non-poor function or non-severe symptoms at baseline to reporting so post-treatment. All cut-offs were based on previously validated thresholds defining a change as at least "moderate" <sup>133</sup> or considered to define problems of substantial clinical relevance <sup>173</sup> from the patient's perspective.

### *Independent variables*

Weight change between baseline and post-treatment was defined as weight gain  $\geq 5\%$ , stable weight within  $\pm 5\%$ , and weight loss  $\geq 5\%$ . These cut-offs were based on evidence that a weight change as low as 5% of baseline can be clinically meaningful, including being associated with cardiovascular and metabolic disease risk factors and outcomes. <sup>174-177</sup>

### *Covariates*

These included clinical variables, socioeconomic status, psychological variables (as per the Hospital Anxiety and Depression Scale <sup>53</sup>), health behaviors (including physical activity as per Global Physical Activity Questionnaire-16 <sup>60</sup>), and type of breast cancer treatment received. Variables were categorized as per **MS3-Table 1**.

### Statistical analysis

Baseline characteristics were tabulated and compared by category of weight change using descriptive statistics.

Associations between outcomes and the independent variable were then examined using different sets of multivariable-adjusted models, which also accounted for baseline HRQOL score (details in respective table footnotes and figure legends).

First, we explored the association between weight change category and HRQOL scores as continuous outcomes. Repeated measurements of HRQOL scores collected from diagnosis to the post-treatment visit were analyzed using the GENMOD procedure and fitting multivariate generalized estimating equations (GEE) with independent correlation structure. We obtained: a) Model-derived least square mean values for HRQOL scores at baseline and post-treatment and b) respective mean least square differences between baseline and post-treatment, according to weight change category (as independent variable). Standard errors and respective 95% Confidence Intervals (CIs) were also calculated. All models accounted for weight change, time, interaction weight-change-by-time, and covariates (ie, age, menopausal status, baseline Body Mass Index, comorbidities, marital status, education, anxiety and depression, smoking status, physical activity, breast and axillary surgery, receipt of chemotherapy, radiation therapy, endocrine therapy, anti-HER2 therapy). To test the hypothesis that

the population-averaged HRQOL domain scores differ by weight change category, p-values for the effect of weight change ( $p_{\text{group}}$ ), time ( $p_{\text{time}}$ ) and weight-change-by-time interaction ( $p_{\text{interaction}}$ ) were obtained.

Then, we fit distinct multivariable logistic regression models for each dichotomous outcome to assess odds of HRQOL deterioration and of reporting poor functions or severe symptoms, which returned adjusted odds ratios (aORs) and respective 95% CIs. Logistic regression models were also adjusted for all covariates detailed above.

In sensitivity analyses, we repeated the models by categorizing weight change as  $\pm 10\%$  of baseline and as continuous percent-unit change of baseline.

P values  $< 0.05$  were considered significant. All tests were two-sided. Analyses were conducted with SAS v9.4.

## Results

Our analytic cohort included 993 obese patients. Excluded patients did not differ from those included in the analytic cohort (data not shown). Median time from diagnosis to post-treatment was 10.5 months (interquartile range [IQR] 7.8-12.5). Mean age at diagnosis was 59.1 years (Standard Deviation=10.5). All patients in this cohort received breast cancer surgery, 91.6% received radiation therapy, and 53.6% received adjuvant chemotherapy. Complete cohort characteristics are displayed in **MS3-Table 1**.

Mean baseline BMI was  $34.5 \text{ Kg/m}^2$  (range, 30.0-59.0), mean baseline weight was 89.4 Kg (range, 61.0-153.0). The majority of women, 67.3%, remained stable, 14.1% gained  $\geq 5\%$ , and 18.6% lost  $\geq 5\%$  of baseline weight. Women who lost weight were more likely to be older, postmenopausal, and never smokers (**MS3-Table 1**). Physical activity was associated with weight changes: 59.1%, 63.7% and 73.6% of patients among those who gained, remained stable, or lost weight reported at least same or higher amounts of physical activity post-treatment compared to baseline, respectively (Cochran-Armitage trend test  $p=0.009$ ; **MS3-Table 2**).

<b>MS3-Table 1. Baseline cohort characteristics.</b>					
<b>Characteristic, N (%)</b>	<b>Overall</b>	<b>By weight change</b>			<b>p-value<sup>^</sup></b>
		<b>Gain ≥5%</b>	<b>Stable ±5%</b>	<b>Loss ≥5%</b>	
	<b>993 (100)</b>	<b>140 (14.1)</b>	<b>668 (67.3)</b>	<b>185 (18.6)</b>	
<b>Baseline BMI, kg/m<sup>2</sup></b>					0.185
Mean (SD)	34.5 (4.1)	34.4 (3.8)	34.4 (3.9)	35.2 (4.7)	
Missing	-	-	-	-	
<b>Baseline BMI, WHO categories<sup>178</sup></b>					0.2140
Obese class I	640 (64.4)	92 (65.7)	439 (65.7)	109 (58.9)	
Obese class II	248 (25.0)	34 (24.3)	169 (25.3)	45 (24.3)	
Obese class III	105 (10.6)	14 (10.0)	60 (9.0)	31 (16.8)	
Missing	-	-	-	-	
<b>Baseline weight, continuous, Kg</b>					0.099
Mean (SD)	89.4 (12.8)	89.0 (12.1)	88.9 (12.7)	91.5 (13.2)	
Missing	-	-	-	-	
<b>Age at diagnosis, years</b>					<.0001
Mean (SD)	59.1 (10.5)	54.2 (10.8)	60.1 (10.5)	59.3 (9.2)	
Missing	-	-	-	-	
<b>Age at diagnosis, years</b>					<.0001
< 50	194 (19.5)	44 (31.4)	118 (17.7)	32 (17.3)	
50-64	471 (47.4)	72 (51.4)	302 (45.2)	97 (52.4)	
≥65	328 (33.1)	24 (17.2)	248 (37.1)	56 (30.3)	
Missing	-	-	-	-	
<b>Marital status</b>					0.325
In a relationship	687 (74.9)	107 (83.6)	463 (74.4)	117 (70.1)	
Not in a relationship*	230 (25.1)	21 (16.4)	159 (25.6)	50 (29.9)	
Missing	76	12	46	18	
<b>Highest education level achieved</b>					0.176
Primary or lower	256 (27.9)	34 (25.6)	180 (29.0)	42 (24.8)	
High school	451 (49.1)	67 (52.3)	308 (49.6)	76 (45.0)	
College graduate or higher	211 (23.0)	27 (21.1)	133 (21.4)	51 (30.2)	
Missing	75	12	47	16	
<b>Employment status</b>					0.019
Professionally active	379 (40.3)	72 (55.4)	245 (38.4)	62 (36.1)	
Professionally inactive	561 (59.7)	58 (44.6)	393 (61.6)	110 (63.9)	
Missing	53	10	30	13	
<b>Monthly total household Income</b>					0.579
<1500 Euro	185 (21.0)	27 (22.5)	124 (20.8)	34 (20.7)	
1500-3000 Euro	421 (47.8)	55 (45.8)	294 (49.3)	72 (43.9)	
≥3000 Euro	274 (31.1)	38 (31.7)	178 (29.9)	58 (35.4)	
Missing	113	20	72	21	
<b>Menopausal status</b>					0.001
Premenopausal	249 (25.6)	55 (40.4)	151 (23.1)	43 (23.6)	
Postmenopausal	724 (74.4)	81 (59.6)	504 (76.9)	139 (76.4)	
Missing	20	4	13	3	
<b>Charlson Comorbidity Index</b>					0.594
0	614 (68.9)	91 (71.6)	410 (68.4)	113 (68.5)	
1+	277 (31.1)	36 (28.4)	189 (31.5)	52 (31.5)	
Missing	102	13	69	20	
<b>Anxiety, score**</b>					0.644
Mean (SD)	8.8 (4.2)	8.6 (4.1)	8.9 (4.4)	8.6 (3.9)	
Missing	62	11	40	11	

<b>Anxiety, categorical**</b>					0.769
Non-case	387 (41.6)	50 (38.8)	269 (42.8)	68 (39.1)	
Doubtful case	246 (26.4)	41 (31.8)	153 (24.4)	52 (29.9)	
Case	298 (32.0)	38 (29.4)	206 (32.8)	54 (31.0)	
Missing	62	11	40	11	
<b>Depression, score**</b>					0.775
Mean (SD)	4.5 (3.7)	4.4 (3.6)	4.4 (3.6)	4.7 (3.9)	
Missing	62	11	40	11	
<b>Depression, categorical**</b>					0.202
Non-case	736 (79.0)	97 (75.2)	504 (80.2)	135 (77.6)	
Doubtful case	131 (14.1)	25 (19.4)	82 (13.1)	24 (13.8)	
Case	64 (6.9)	7 (5.4)	42 (6.7)	15 (8.6)	
Missing	62	11	40	11	
<b>Smoking behavior</b>					0.017
Active smoker	106 (10.8)	28 (20.4)	63 (9.6)	15 (8.2)	
Former smoker	200 (20.5)	32 (23.4)	132 (20.1)	36 (19.7)	
Never smoker	671 (68.7)	77 (56.2)	462 (70.3)	132 (72.1)	
Missing	16	3	11	2	
<b>Baseline alcohol consumption</b>					0.256
Daily consumption	859 (89.9)	17 (12.7)	60 (9.3)	19 (10.6)	
Less than daily consumption	96 (10.1)	117 (87.3)	582 (90.6)	160 (89.4)	
Missing	38	6	26	6	
<b>Physical Activity, MET-hours/week</b>					0.215
Median (IQR)	8.0 (0.0-26.7)	12.0 (0.0-48.0)	8.0 (0.0-26.0)	8.0 (0.0-19.0)	
Missing	70	13	45	12	
<b>Tumor stage</b>					0.007
I	438 (44.1)	56 (40.0)	317 (47.5)	65 (35.1)	
II	431 (43.4)	64 (45.7)	272 (40.8)	95 (51.4)	
III	123 (12.4)	20 (14.3)	78 (11.7)	25 (13.5)	
Missing	1	-	1	-	
<b>Tumor subtype</b>					<.0001
HR+/HER-	786 (79.6)	97 (69.3)	557 (83.8)	132 (72.1)	
HR±/HER2+	127 (12.8)	22 (15.7)	71 (10.7)	34 (18.6)	
HR-/HER2-	75 (7.6)	21 (15.0)	37 (5.6)	17 (9.3)	
Missing	5	-	3	2	
<b>Breast surgery</b>					0.471
Partial surgery	746 (75.1)	107 (76.4)	508 (76.0)	131 (70.8)	
Mastectomy	247 (24.9)	33 (23.6)	160 (24.0)	54 (29.2)	
Missing	-	-	-	-	
<b>Axillary surgery</b>					0.386
Axillary dissection	436 (43.9)	70 (50.0)	289 (42.3)	77 (41.6)	
Sentinel lymph node**	557 (56.1)	70 (50.0)	379 (56.7)	108 (58.4)	
Missing	-	-	-	-	
<b>Adjuvant radiation therapy</b>					0.354
Yes	908 (91.6)	129 (92.1)	615 (92.3)	164 (88.6)	
No	83 (8.4)	11 (7.9)	51 (7.6)	21 (11.3)	
Missing	2	-	2	-	
<b>(Neo) adjuvant chemotherapy</b>					<.0001
Yes***	532 (53.6)	84 (60.0)	314 (47.0)	134 (72.4)	
No	461 (46.4)	56 (40.0)	354 (53.0)	51 (27.5)	
Missing	-	-	-	-	

<b>Adjuvant endocrine therapy</b>					0.0008
Yes****	829 (83.5)	105 (75.0)	575 (86.1)	149 (80.5)	
No	164 (16.5)	35 (25.0)	93 (13.9)	36 (19.5)	
Missing	-	-	-	-	
<b>Adjuvant anti-HER2 therapy</b>					0.0006
Yes	97 (9.8)	18 (12.9)	49 (7.3)	30 (16.2)	
No	896 (90.2)	122 (87.1)	619 (92.7)	155 (83.8)	
Missing	-	-	-	-	

BMI= Body Mass Index; WHO= World Health Organization; SD= Standard Deviation; IQR= interquartile range; HR= Hormone-receptor; HER2= Human Epidermal Growth Factor receptor 2; MET= Metabolic Equivalent of Task.  
^Jonckheere-Terpstra test statistics \*Includes separated, divorced, widowed, unmarried \*\*Includes 7 patients who did not receive any axillary lymph node surgical procedure; \*\*\*Includes approximately 90% women receiving an anthracycline+taxane chemotherapy combination; \*\*\*\*Patients receiving endocrine therapy were at a median of 3.9 months (IQR 3.0-5.5 months) since treatment initiation at this time.

<b>MS3-Table 2. Metrics of change in weight and physical activity from baseline to post-treatment</b>				
<b>Characteristic</b>	<b>Overall</b>	<b>By weight change category</b>		
		<b>Gain ≥5%</b>	<b>Stable ±5%</b>	<b>Loss ≥5%</b>
<b>Total</b>	<b>993 (100)</b>	<b>140 (14.1)</b>	<b>668 (67.3)</b>	<b>185 (18.6)</b>
<b>Post-treatment BMI, kg/m<sup>2</sup></b>				
Mean (SD)	34.3 (4.4)	37.3 (4.3)	34.4 (3.9)	31.8 (4.7)
Missing	-	-	-	-
<b>Post-treatment weight, Kg</b>				
Mean (SD)	88.9 (13.4)	96.5 (13.3)	89.1 (12.7)	82.4 (12.7)
Missing	-	-	-	-
<b>Change in weight, Kg</b>				
Absolute change, mean (95% CI)	-0.5 (-0.9,-0.2)	+7.5 (+6.9,+8.0)	+0.1 (-0.1,+0.3)	-9.0 (-9.7,-8.3)
Percent change, mean (95% CI)	-0.5 (-0.9,-0.1)	+8.4 (+7.8,+9.1)	+0.2 (-0.01,+0.4)	-9.9 (-10.6,-9.2)
Missing	-	-	-	-
<b>Total Physical Activity behavior, N (%)</b>				
Maintained/Increased	559 (65.0)	68 (59.1)	371 (63.7)	120 (73.6)
Reduced	301 (35.0)	47 (40.9)	211 (36.2)	43 (26.4)
Missing	133	25	86	22

BMI= Body Mass Index; SD= Standard Deviation; CI= Confidence Interval; IQR= interquartile range; MET= Metabolic Equivalent of Task.

Median completion rate of EORTC-QLQs was 93.6% (IQR 91.0%-94.5%) at baseline and 91.7% (91.1%-92.1%) post-treatment (**MS3-Supplementary Table 1**).

We observed a significant reduction in functional scores and increased symptom scores across the majority of HRQOL domains overall ( $p_{\text{time}} < .0001$ ; **MS3-Supplementary Table 1**) and by weight change (**MS3-Table 3**). Compared to those who gained weight or remained stable, women who lost weight reported less of a decline in HRQOL, including scoring better in physical function (mean change for weight gain, stability and loss [95% Confidence Interval]: -12.9 [-16.5,-9.3], -6.9 [-8.2,-5.5] and -6.2 [-8.7,-3.7], respectively;  $p_{\text{interaction}} = 0.006$ ), dyspnea (+18.9 [+12.3,+25.6], +9.2 [+6.5,+11.9] and +3.2 [-1.0,+7.3], respectively;  $p_{\text{interaction}} = 0.0003$ ), and breast symptoms (+22.1 [+16.8,+27.3], +18.0 [+15.7,+20.3] and +13.4 [+9.0,+17.2], respectively;  $p_{\text{interaction}} = 0.044$ ). Similar patterns suggesting a smaller decrement in HRQOL among those who lost weight were

found for other domains (**MS3-Table 3**). Finally, in order to evaluate whether the relationship between weight change and changes in HRQOL differed by receipt of chemotherapy, we introduced weight-change-by-chemotherapy interaction terms in the models, which were not significant ( $p_{\text{interaction}}=0.256$  for physical function,  $p_{\text{interaction}}=0.690$  for dyspnea, and  $p_{\text{interaction}}=0.544$  for breast symptoms).

A substantial proportion of patients (range 15.6-56.5%) experienced at least moderate HRQOL-deterioration (**MS3-Supplementary Figure 1A**). In several domains, including dyspnea and body image, weight loss was associated with a smaller prevalence of patients experiencing such deterioration. Women who lost weight seemed also more likely to report reduced appetite over time (**MS3-Supplementary Figure 1B**).

Women tended to report poor function and severe symptoms more often post-treatment (**MS3-Figure 2A**), although this happened less frequently among women who lost weight (**MS3-Figure 2B**). Particularly, weight loss was associated with a significant reduction in the odds of reporting poor physical function (aOR [95% CI]=0.51 [0.27-0.95],  $p=0.033$ ), poor social function (aOR [95% CI]=0.45 [0.22-0.93],  $p=0.031$ ), poor role function (aOR [95% CI]=0.52 [0.28-0.98],  $p=0.046$ ), severe pain (aOR [95% CI]=0.51 [0.31-0.86],  $p=0.011$ ), and severe dyspnea (aOR [95% CI]=0.32 [0.17-0.61],  $p=0.0006$ ) compared to weight gain, and with those of reporting severe pain (aOR [95% CI]=0.62 [0.41-0.95],  $p=0.029$ ) and severe dyspnea (aOR [95% CI]=0.55 [0.31-0.97],  $p=0.039$ ) compared to stable weight (**MS3-Figure 2B**). Consistent results were found in sensitivity analyses (data not shown).

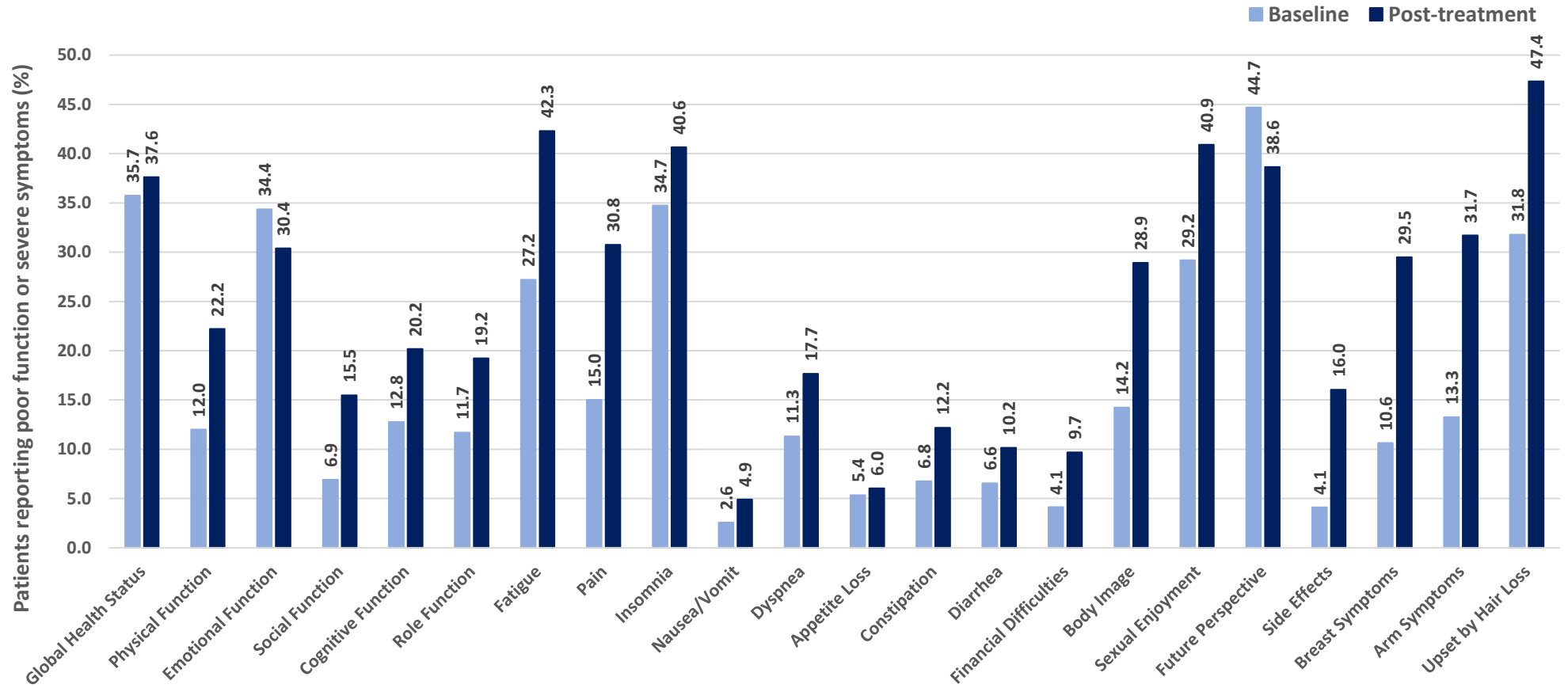
Among the patients who had not reported severe dyspnea at baseline, 13.1% started to report so post-treatment (**MS3-Supplementary Figure 2A**). Odds of onset of severe post-treatment dyspnea were elevated among women who gained weight (aOR [95% CI] = 1.84 [1.02-3.33],  $p=0.044$ ) and reduced among women who lost weight (aOR [95% CI] = 0.39 [0.17-0.86],  $p=0.019$ ) compared to those whose weight remained stable (**MS3-Supplementary Figure 2B**).

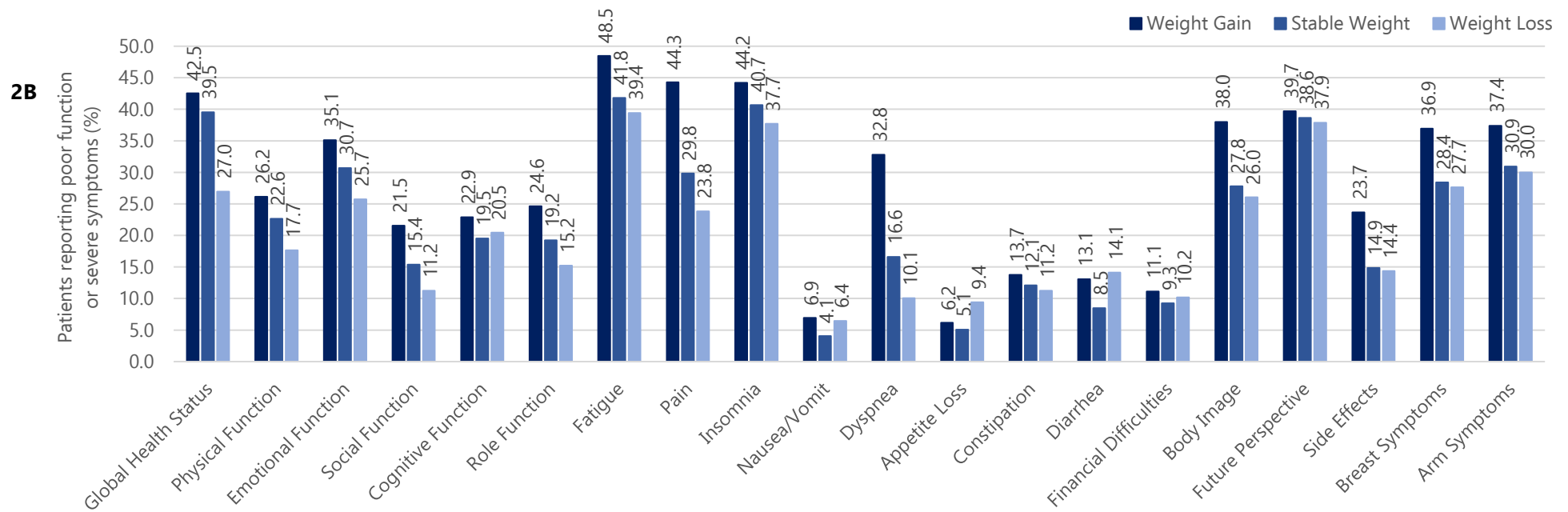
**MS3-Table 3. Post-treatment health-related quality of life and changes from baseline by category of weight change.**

HRQOL domain	Gain ≥5% N (%)= 140 (14.1)					Stable ±5% N (%)= 668 (67.3)					Loss ≥5% N (%)= 185 (18.6)					p <sub>group</sub>	P <sub>interac- tion</sub>
	Mean°	SE	Mean change°°	95% CI for the change		Mean°	SE	Mean change°°	95% CI for the change		Mean°	SE	Mean change°°	95% CI for the change			
				Lower	Upper				Lower	Upper				Lower	Upper		
<b>EORTC QLQ-C30</b>																	
Global Health	64.8	2.2	-3.3	-7.3	+0.6	62.2	1.6	-2.5	-4.3	-0.6	66.1	2.1	-0.1	-3.3	+3.2	0.048	0.346
Physical Function	67.9	2.3	-12.9	-16.5	-9.3	72.6	1.6	-6.9	-8.2	-5.5	75.6	2.0	-6.2	-8.7	-3.7	0.043	0.006
Emotional Function	73.3	2.5	+1.9	-2.0	+5.8	73.9	2.0	+4.0	+1.5	+6.3	75.6	2.4	+5.6	+1.7	+9.5	0.876	0.425
Social Function	78.4	3.1	-12.1	-17.5	-6.7	80.7	2.0	-10.8	-13.1	-8.6	84.6	2.4	-9.7	-13.6	-5.8	0.035	0.770
Cognitive Function	71.8	3.5	-6.4	-11.2	-1.5	74.3	2.2	-4.6	-6.8	-2.5	74.7	2.7	-5.4	-9.2	-1.5	0.674	0.799
Role Function	68.3	3.2	-13.4	-19.0	-7.9	71.4	2.1	-9.7	-12.1	-7.2	76.2	2.8	-8.0	-12.9	-3.1	0.058	0.335
<b>EORTC QLQ-BR23</b>																	
Fatigue	46.8	3.4	+16.7	+11.2	+22.3	43.5	2.2	+10.9	+8.6	+13.1	42.6	3.0	+10.3	+5.6	+15.0	0.930	0.138
Pain	36.1	3.4	+17.0	+11.7	+22.3	36.0	2.4	+14.4	+11.9	+16.9	31.2	3.1	+12.4	+7.5	+17.4	0.162	0.466
Insomnia	45.6	4.6	+8.2	+0.7	+15.7	44.7	3.3	+2.3	-0.9	+5.5	41.7	4.2	+1.6	-4.0	+7.3	0.535	0.321
Nausea/Vomit	11.3	2.2	+4.3	+0.7	+7.9	8.4	1.3	+3.2	+1.7	+4.7	9.4	1.8	+1.1	-2.1	+4.4	0.103	0.398
Dyspnea	44.6	3.9	+18.9	+12.3	+25.6	31.9	2.6	+9.2	+6.5	+11.9	24.5	3.1	+3.2	-1.0	+7.3	0.0003	0.0003
Appetite Loss	12.3	3.0	-1.7	-6.8	+3.4	12.7	1.9	-0.6	-2.8	+1.6	16.8	2.5	+2.3	-2.6	+7.2	0.329	0.492
Constipation	17.3	3.4	+8.4	+2.7	+14.1	15.9	2.2	+5.7	+3.4	+8.0	16.6	3.2	+10.3	+5.6	+15.1	0.693	0.199
Diarrhea	15.8	3.4	+5.1	-0.3	+10.6	17.0	2.1	+3.4	+0.9	+5.8	18.6	3.1	+3.9	-0.7	+8.6	0.472	0.854
Financial difficulties	15.7	3.3	+0.9	-5.4	+7.1	15.3	2.2	+4.2	+2.1	+6.3	16.8	2.8	+8.7	+4.2	+13.2	0.555	0.101
<b>EORTC QLQ-B23</b>																	
Body Image	68.0	3.3	-17.6	-23.4	-11.9	71.0	2.3	-12.9	-15.6	-10.3	74.8	2.8	-11.4	-15.9	-6.8	0.236	0.228
Sexual Function	18.6	3.1	+1.0	-3.6	+5.7	17.4	2.2	-2.0	-3.9	-0.2	18.9	2.8	+0.6	-3.9	+5.1	0.980	0.329
Sexual Enjoyment^	52.5	4.8	-6.3	-14.2	+1.6	51.5	4.1	-8.2	-12.1	-4.4	51.7	4.1	-5.3	-15.0	+4.4	0.915	0.805
Future Perspective	56.2	3.8	+3.4	-3.23	+10.1	53.4	2.7	+2.5	-0.5	+5.6	53.5	3.2	+7.1	+1.7	+12.4	0.308	0.345
<b>EORTC QLQ-B23</b>																	
Side Effects	24.1	2.3	+10.9	+6.9	+14.8	22.3	1.4	+10.3	+8.8	+11.8	21.4	1.9	+10.8	+8.0	+13.6	0.353	0.922
Breast Symptoms	33.1	3.2	+22.1	+16.8	+27.3	28.2	1.7	+18.0	+15.7	+20.3	28.1	2.4	+13.4	+9.0	+17.2	0.215	0.044
Arm Symptoms	34.8	3.8	+20.4	+13.6	+27.2	31.0	2.3	+14.2	+11.6	+16.8	29.5	3.0	+14.4	+9.5	+19.3	0.650	0.243
Upset by Hair Loss^^	39.2	8.3	-8.4	-31.6	+14.8	42.8	6.3	+16.0	+4.7	+27.3	9.3	3.0	+0.2	-22.6	+23.0	0.313	0.123

HRQOL= Health-related Quality of life; EORTC QLQ= European Organisation for Research and Treatment of Cancer Quality-of-Life questionnaire; SE= Standard Error; CI= Confidence Interval; °Model-based least square means for HRQOL scores post-treatment by category of weight change; °°Model-based differences in least squares means from baseline to post-treatment by category of weight change. Estimates were obtained using generalized estimating equations, adjusted for weight change category (group), time, interaction weight change category by time, age, menopausal status, Body Mass Index, comorbidities, marital status, education, smoking status, physical activity, breast and axillary surgery, receipt of chemotherapy, radiation therapy, endocrine therapy, anti-HER2 therapy, anxiety, and depression. P-values for the effect of weight change category (p<sub>group</sub>) and of interaction weight change category by time (p<sub>interaction</sub>) on differences in least squares means are reported.

2A





**Compared to weight gain**

	Physical Function		Social Function		Role Function		Pain		Dyspnea		Financial Difficulties	
	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p
<b>Stable</b>	0.76 (0.46-1.24)	0.269	0.75 (0.44-1.28)	0.294	0.83 (0.52-1.32)	0.429	0.83 (0.56-1.24)	0.355	0.58 (0.37-0.93)	0.024	0.62 (0.32-1.18)	0.147
<b>Loss</b>	0.51 (0.27-0.95)	0.033	0.45 (0.22-0.93)	0.031	0.52 (0.28-0.98)	0.046	0.51 (0.31-0.86)	0.011	0.32 (0.17-0.61)	0.0006	0.49 (0.22-1.09)	0.081

**Compared to stable weight**

	Physical Function		Social Function		Role Function		Pain		Dyspnea		Financial Difficulties	
	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p
<b>Gain</b>	1.32 (0.81-2.17)	0.269	1.33 (0.78-2.29)	0.294	1.21 (0.75-1.93)	0.429	1.21 (0.81-1.80)	0.355	1.71 (1.07-2.73)	0.024	1.61 (0.84-3.09)	0.147
<b>Loss</b>	0.67 (0.41-1.10)	0.117	0.60 (0.33-1.09)	0.095	0.63 (0.38-1.06)	0.081	0.62 (0.41-0.95)	0.029	0.55 (0.31-0.97)	0.039	0.80 (0.41-1.58)	0.524

**MS3-Figure 2. Prevalence (%) of patients reporting poor function or severe symptoms at baseline and post-treatment in the whole cohort (2A). Prevalence (%) of patients reporting poor function or severe symptoms post-treatment by category of weight change (2B).** Poor function is defined by a score < 60, poor symptoms by a score ≥ 40 on the respective EORTC QLQ-C30 and QLQ-B23 scales. Prevalence of severe sexual function is not displayed because of scaling of the y-axis (prevalence > 80% in all subgroups). Adjusted odds ratios (aOR) and respective 95% Confidence Intervals (CI) were obtained from multivariate generalized estimating equations and are reported for selected domains. All models were adjusted for time, age, menopausal status, Body Mass Index, comorbidities, marital status, education, smoking status, physical activity, breast and axillary surgery, receipt of chemotherapy, radiation therapy, endocrine therapy, anti-HER2 therapy, anxiety, and depression.

## Discussion

In this large study, we report on the relationship between weight changes and HRQOL in a cohort of obese women with early breast cancer. Overall, patients tended to report reduced HRQOL after breast cancer treatment compared to assessments obtained at diagnosis. Nevertheless, women who gained weight seemed to score the worst in several HRQOL domains, whereas weight loss was associated with more favorable variations in HRQOL. Importantly, there was no association between weight loss and worsened HRQOL after treatment.

Consistently with recent World Health Organization-Europe data, and reflecting the prevalence of obesity in the general French population, obese patients account for almost 20% of the CANTO cohort.<sup>126</sup> Avoiding functional decline and preventing symptom exacerbation among obese women with breast cancer are therefore priorities that concern many providers and patients. In line with past reports, we describe worsening of numerous physical symptoms including fatigue, pain, breast discomfort, and body image issues following breast cancer treatment.<sup>24</sup> Weight gain was previously shown to contribute to deterioration of objective physical and cardio-metabolic parameters,<sup>179</sup> and here we report that it is also linked with more bothersome, subjective, patient-reported HRQOL-changes. Beyond impaired well-being, post-treatment functional decline leads to loss of independence<sup>180</sup>, worse social and cost-related outcomes<sup>181</sup>, and possibly impairs cancer-specific outcomes<sup>182</sup>, while increased symptom burden is associated with higher rates of non-adherence to adjuvant treatment and worse social rehabilitation in breast cancer survivors.<sup>183,184</sup> Our results inform further studies aimed at testing whether weight control can modulate some of these negative consequences.

In our primary analysis, we reported negative changes in HRQOL after early breast cancer treatment overall, although among women who lost weight we found smaller or negligible changes. According to guidelines provided by Cocks et al.<sup>185</sup>, differences in mean HRQOL-changes among women that lost weight were at most trivial-to-small for domains such as physical function and dyspnea (-6.2 and +3.2 points, respectively), whereas differences in those that gained weight were significantly greater, reaching the range of medium-to-large size (-12.9 and +18.9 points, respectively). In additional analyses, we adopted particularly conservative cut-offs to categorize PROs (lower than median reference value for functions and higher than median for symptoms)<sup>186</sup>, and found that weight loss was also associated with smaller proportions of patients reporting severely impaired HRQOL.

Obesity is now defined as a disease state, and the American Society of Clinical Oncology endorses weight gain prevention and weight loss facilitation for all obese cancer patients.<sup>187</sup> Expert consensus suggests that, for obese women, moderate weight loss of up to one Kg/week can be pursued at any time post breast cancer diagnosis, also during active adjuvant treatment if under appropriate monitoring.<sup>188</sup> However, robust evidence supporting this statement is still lacking. A novel aspect of the present study is that our results did not show that weight loss during or shortly after completion of adjuvant treatment was linked to worsening in HRQOL. Women in our study had a diagnosis of early-stage breast cancer, and this specific setting is partly responsible for our findings. Prior studies have reported that weight loss during treatment correlates with

higher levels of toxicity and poorer outcomes, including cancer-specific survival,<sup>189,190</sup> but these studies mostly evaluated disease groups other than breast cancer or patients with more advanced disease. In addition, our study included exclusively obese women at diagnosis, for whom a beneficial effect of weight loss on health outcomes could be expected, particularly in physical parameters.<sup>68</sup>

Lifestyle interventions conducted in overweight or obese breast cancer survivors and that looked at HRQOL include the ENERGY and the LISA studies. ENERGY recruited patients with early-stage breast cancer diagnosed within the previous five years,<sup>167</sup> and LISA reported data in women who completed chemotherapy at least four weeks before inclusion.<sup>168</sup> Findings of these studies are consistent with ours, in that a mean weight loss of 6% of baseline in the interventional arm of ENERGY was linked to a more likely preservation of physical function, while participants in the LISA intervention experienced a mean weight loss of 4-5 Kg and reported a greater increase in physical condition, compared to respective control arms.<sup>167,168</sup> Our results expand on this prior work for obese breast cancer patients, highlighting how weight changes occurring during and shortly after adjuvant therapy are related to longer-term HRQOL. There is indeed scarce data from studies that follow up patients with breast cancer from initial diagnosis to post-primary treatment. CANTO offered an unparalleled opportunity to explore the relationship between obesity, weight changes, and HRQOL in early breast cancer survivors in one of the largest contemporary, prospective, longitudinal studies with comprehensive HRQOL assessments. By longitudinally collecting data at several time points after diagnosis, CANTO will also be informative about future questions on the relationship between weight changes and HRQOL occurring later on during the survivorship trajectory<sup>61</sup>.

Nevertheless, we acknowledge some limitations. First, it was not possible to assess whether weight loss was purposeful and to establish intentionality of weight changes. However, despite the possibility that some percentages of the observed weight loss were actually unintentional, our comprehensive PRO analyses showed that weight loss was not associated with worsened patient-reported condition in any of the explored outcomes. To improve our understanding of patients' behavioral characteristics, we also assessed other metrics, and found increased physical activity levels among patients who lost weight, an important mediator of successful attempts of weight management.<sup>68</sup> Although it is possible that we could not account for some unmeasured confounders, all our models were also adjusted for change in physical activity behavior, as well as for several important clinical and treatment-related factors. Second, we used a cut-off of 5% to define weight change, based on previously observed clinically meaningful benefits of a weight loss of such magnitude.<sup>174</sup> There has also been substantial variability in values previously used to establish thresholds for HRQOL<sup>191</sup>, and universal definitions for EORTC QLQ-C30 and QLQ-BR23 domains are still lacking. However, we provided rationale to support the notion that the chosen cut-offs were clinically meaningful. Third, we used self-reported instruments, subject to some recall and reporting biases, but CANTO adopted questionnaires that had already been consistently proven to be reliable and valid instruments for observational studies.<sup>192</sup> Finally, French law does not allow collection of race/ethnicity data, which could have provided relevant information in this context.

In conclusion, we have reported several significant associations between weight changes and differential variations in HRQOL of obese women undergoing breast cancer treatment. Our findings were consistent across several domains of general and breast cancer-specific HRQOL, particularly suggesting that weight loss was not associated with worse HRQOL. Weight loss among obese individuals is a complex process, which includes substantial behavioral changes based primarily on modification of dietary habits and increased energy expenditure. Weight loss interventions are now deemed feasible and also safe in obese breast cancer survivors<sup>168</sup> and randomized trials of weight loss are underway, holding the promise to improve breast cancer outcomes and PROs over the first years following diagnosis.<sup>152</sup> Our study suggests that prevention of weight gain and purposeful weight loss during the early survivorship period should be tested in dedicated studies as strategies to mitigate many downstream *sequelae* of primary breast cancer treatment. Answering this question has important implications, as it would help reduce the burden that secondary effects of breast cancer treatment pose on the care of obese survivors. Finally, from a patient's perspective, the cancer journey contains many "teachable moments" to improve health behaviors, including engaging in weight loss programs. If approached not only as a way to improve one's general well-being and reduce excess weight-related morbidity, but also to pursue functional preservation and symptom management during and after cancer treatment<sup>179</sup>, the goal of weight loss may be more favorably embraced, making attempts more likely successful.

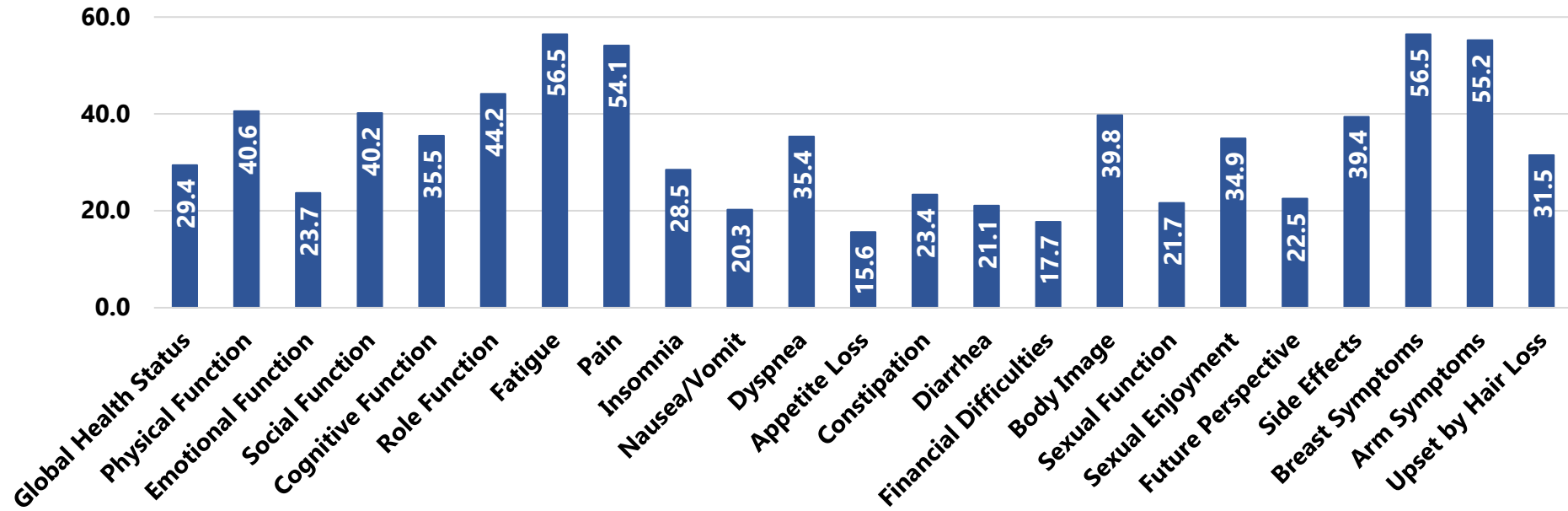
Data Supplement

MS3-Supplementary Table 1. Baseline and post-treatment health-related quality of life in the whole cohort.

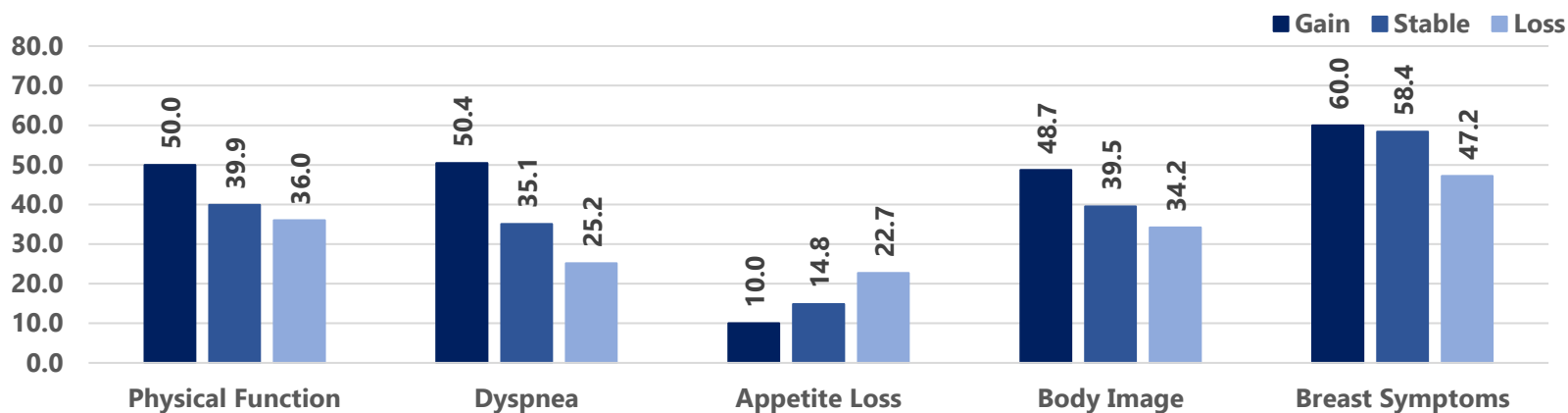
HRQOL domain	Baseline			Post-treatment						
	Completion rate (%)	Mean <sup>o</sup>	SE	Completion rate (%)	Mean <sup>o</sup>	SE	Mean change <sup>oo</sup>	95% CI for the change		p <sub>time</sub>
								Lower	Upper	
<b>EORTC QLQ-C30 Functional Scales</b>										
Global Health	93.6	66.4	1.5	90.2	64.3	1.5	-2.1	-3.6	-0.6	0.005
Physical Function	94.8	80.1	1.6	92.0	72.6	1.6	-7.5	-8.7	-6.4	<.0001
Emotional Function	94.7	70.4	1.8	92.4	74.3	1.9	+3.9	+2.1	+5.8	<.0001
Social Function	93.5	92.1	1.8	91.7	81.3	1.9	-10.8	-12.6	-8.9	<.0001
Cognitive Function	94.6	78.9	2.1	92.3	73.8	2.2	-5.0	-6.8	-3.2	<.0001
Role Function	94.8	82.1	2.1	92.1	72.2	2.1	-9.9	-11.9	-7.8	<.0001
<b>EORTC QLQ-C30 Symptom Scales</b>										
Fatigue	94.4	32.2	2.2	91.6	43.7	2.3	+11.5	+9.6	+13.5	<.0001
Pain	94.7	19.9	2.3	92.6	34.3	2.4	+14.4	+12.3	+16.4	<.0001
Insomnia	94.0	40.5	3.2	90.9	43.5	3.3	+3.0	+0.35	+5.6	0.026
Nausea/Vomit	94.5	6.7	1.3	92.2	9.7	1.4	+3.0	+1.7	+4.2	<.0001
Dyspnea	93.5	23.8	2.7	91.2	33.1	2.6	+9.4	+7.2	+11.6	<.0001
Appetite Loss	94.2	14.1	1.8	91.6	13.9	1.9	-0.2	-2.1	+1.7	0.830
Constipation	94.0	9.0	2.0	91.7	15.9	2.2	+6.9	+5.0	+8.9	<.0001
Diarrhea	93.8	13.2	2.2	92.1	16.9	2.2	+3.7	+1.7	+5.7	0.0003
Financial difficulties	92.6	11.3	2.1	90.4	16.0	2.2	+4.6	+2.8	+6.5	<.0001
<b>EORTC QLQ-B23 Functional Scales</b>										
Body Image	91.2	84.9	2.1	91.2	71.6	2.2	-13.3	-15.4	-11.1	<.0001
Sexual Function	85.3	18.9	2.1	85.9	17.8	2.1	-1.1	-2.8	+0.5	0.182
Sexual Enjoyment	36.3*	59.0	4.0	37.7	51.6	3.8	-7.4	-10.7	-4.1	<.0001
Future Perspective	90.8	50.5	2.5	91.7	54.0	2.6	+3.5	+1.0	+5.9	0.006
<b>EORTC QLQ-B23 Symptom Scales</b>										
Side Effects	93.1	12.1	1.3	91.7	22.5	1.4	+10.4	+9.2	+11.7	<.0001
Breast Symptoms	81.5	12.1	1.7	92.2	29.8	1.8	+17.7	+15.8	+19.6	<.0001
Arm Symptoms	90.4	16.0	2.2	92.1	31.1	2.3	+15.1	+12.9	+17.3	<.0001
Upset by Hair Loss	10.8*	29.0	7.6	26.6	38.6	6.5	+9.5	+0.2	+18.9	0.046

HRQOL= Health-related Quality of life; EORTC QLQ= European Organisation for Research and Treatment of Cancer Quality-of-Life questionnaire; SE= Standard Error; CI= Confidence Interval; \*Sexual enjoyment and upset by hair loss questions were only to be answered if patients stated to have been sexually active or if they had actually experienced hair loss, respectively, resulting in fewer patients responding and in lower-than-average completion rates compared to other domains; <sup>o</sup>Model-based least square means for HRQOL scores at baseline and post-treatment; <sup>oo</sup>Model-based differences in least squares means from baseline to post-treatment. Estimates were obtained using generalized estimating equations, adjusted for weight change category (group), time, age, menopausal status, Body Mass Index, comorbidities, marital status, education, smoking status, physical activity, breast and axillary surgery, receipt of chemotherapy, radiation therapy, endocrine therapy, anti-HER2 therapy, anxiety, and depression. P-values for the effect of time (p<sub>time</sub>) on differences in least squares means are reported.

S1A



S1B



**Compared to weight gain**

	Physical Function		Dyspnea		Appetite loss		Body Image		Breast Symptoms	
	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p
Stable	0.62 (0.39-1.00)	0.050	0.64 (0.39-1.03)	0.065	1.36 (0.67-2.77)	0.394	0.82 (0.50-1.36)	0.448	0.81 (0.48-1.36)	0.429
Loss	0.56 (0.31-0.99)	0.047	0.33 (0.18-0.61)	0.0004	2.14 (0.96-4.77)	0.063	0.53 (0.29-0.98)	0.042	0.59 (0.32-1.10)	0.097

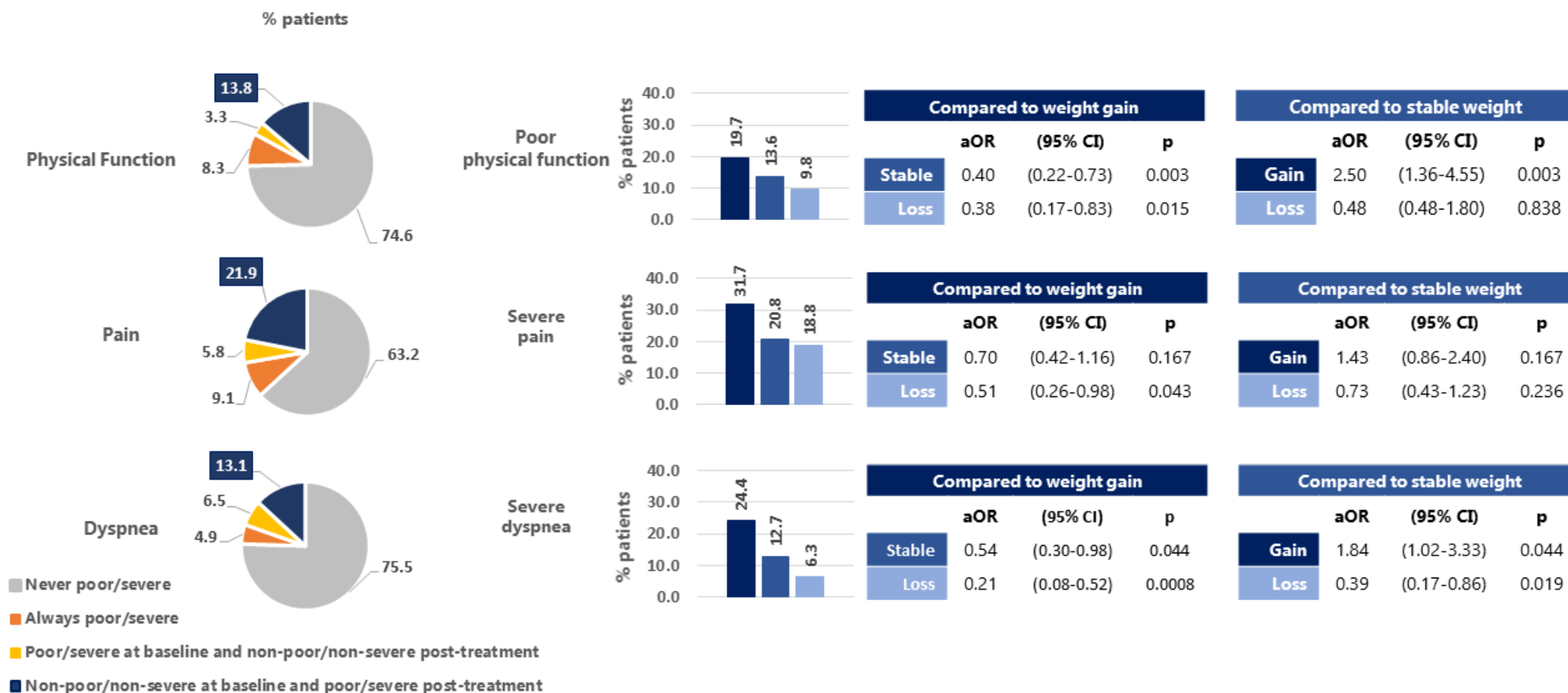
**Compared to stable weight**

	Physical Function		Dyspnea		Appetite loss		Body Image		Breast Symptoms	
	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p
Gain	1.60 (1.00-2.56)	0.050	1.57 (0.97-2.53)	0.065	0.73 (0.36-1.49)	0.394	1.21 (0.73-2.01)	0.448	1.23 (0.73-2.07)	0.429
Loss	0.89 (0.58-1.37)	0.610	0.52 (0.32-0.83)	0.006	1.57 (0.92-2.67)	0.095	0.64 (0.41-1.01)	0.058	0.73 (0.46-1.14)	0.168

**MS3-Supplementary Figure 1. Prevalence of deteriorated HRQOL in the overall cohort (1A). Distribution of patients reporting selected deteriorated HRQOL domains by weight change (1B).** Deterioration was defined as a decrease or an increase of at least 10 points from baseline on functional and symptom scales, respectively. Adjusted Odds ratios (aORs) and respective 95% Confidence Intervals (CI) were derived from multivariable logistic regression modeling the odds of HRQOL deterioration. Models are adjusted by age, menopausal status, Body Mass Index, comorbidities, marital status, education, smoking status, physical activity, breast and axillary surgery, receipt of chemotherapy, radiation therapy, endocrine therapy, anti-HER2 therapy, anxiety, and depression.

S2A. Overall cohort

S2B. By post-treatment weight change



**MS3-Supplementary Figure 2. Distribution of changes in HRQOL status from baseline to post-treatment in the overall cohort (2A).** % patients reporting non-poor/non-severe HRQOL at baseline that started reporting so post-treatment is highlighted in dark blue. **Distribution of patients reporting non-poor/non-severe HRQOL at baseline that started reporting so post-treatment, according to weight change (2B).** Adjusted Odds Ratios (aORs) and respective 95% Confidence Intervals (CI) derived from multivariable logistic regression models are reported, adjusted for age, menopausal status, Body Mass Index, comorbidities, marital status, education, smoking status, physical activity, breast and axillary surgery, receipt of chemotherapy, radiation therapy, endocrine therapy, radiation therapy, anti-HER2 therapy, anxiety, and depression.

## MANUSCRIPT 4 (MS4):

### Body weight and return to work among survivors of early-stage breast cancer

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**Previous Presentations:** This manuscript contains original material. Portions of the work described herein were presented in poster form at the 2019 ASCO Annual Meeting, May 31-June 4, Chicago, IL. Ref: “Impact of overweight, obesity, and post-treatment weight changes on occupational reintegration of breast cancer (BC) survivors.” DOI: 10.1200/JCO.2019.37.15\_suppl.11562 Journal of Clinical Oncology 37, no. 15\_suppl (May 20, 2019) 11562-11562. This work was awarded with a **Conquer Cancer Foundation Merit Award** to Antonio Di Meglio.

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## **Abstract**

**Background:** Many breast cancer (BC) survivors are employed at diagnosis and are expected to return to work after treatment. Among them, around 50% are overweight or obese. There is limited data about the impact of body weight on their ability to return-to-work.

**Methods:** We used data from CANcer TOxicity (NCT01993498), a prospective, multicenter cohort of women with stage I-III BC. Professionally active women that were  $\geq 5$  years younger than retirement age were identified. Multivariate logistic regression models examined associations of body mass index (BMI) at diagnosis and subsequent weight changes with non-return to work two years after diagnosis, adjusting for psycho-social, treatment and behavioral characteristics.

**Results:** Among 1869 women, 689 were overweight or obese. Overall, 398 patients (21.3%) had not returned-to-work two years after diagnosis. Non-return to work was more likely for overweight or obese than underweight or normal weight patients (adjusted odds ratio [aOR], 1.32; 95%CI, 1.01-1.75;  $p=0.045$ ). Weight loss ( $\geq 5\%$ ) was observed in 15.7% overweight or obese and 8.7% underweight or normal weight patients and was associated with significant increases in physical activity among overweight or obese patients (mean change, +4.7 MET-h/week; 95%CI, +1.9 to +7.5). Overweight or obese patients who lost weight were more likely to return to work compared to those who did not lose weight (aOR of non-return-to-work, 0.48; 95%CI, 0.24-0.97,  $p=0.0418$ ), whereas weight loss was associated with increased odds of non-return to work among underweight or normal weight women (aOR, 2.07; 95%CI, 1.20-3.56,  $p=0.0086$ ) ( $p_{\text{interaction BMI*weight changes}}=0.0002$ ). The continuous trend of weight gain on non-return to work was significant for overweight or obese patients (aOR for one-percent-unit difference, 1.03; 95% CI, 1.01-1.06,  $p=0.030$ ).

**Conclusions:** Excess weight may be a barrier to return-to-work. Among overweight or obese BC survivors, weight loss was associated with higher rates of return-to-work, whereas further weight gain with lower likelihood of return-to-work. Employment outcomes should be evaluated in randomized studies of weight management.

## Introduction

Due to early diagnosis and advances in multimodal treatments, survival rates of breast cancer patients have markedly improved in the last decades, with a 5-year relative survival estimated at 80-90% in women diagnosed with breast cancer in developed countries.<sup>6,193</sup> However, cancer survivors may face long-term and late physical and psychosocial effects of breast cancer treatment that could affect their ability to recover pre-cancer social relations and work capacity or productivity.<sup>194</sup> Unemployment has been shown to be higher in cancer survivors in general and particularly in breast cancer survivors.<sup>195</sup> Employment concerns can in turn lead to financial difficulties, depression, anxiety, and relationship changes, and can negatively affect breast cancer survivors' quality of life (QOL). Conversely, return to work has been shown to be associated with better QOL and feelings of full-recovery from cancer.<sup>196,197</sup> Considering the growing number of breast cancer survivors, of whom 25% are under the age of 60,<sup>198,199</sup> and the importance of return to work for both survivors and society, strategies to facilitate their return to work should be further explored.

Overweight and obesity are a substantial public health problem in developed countries and higher body mass index (BMI) has been shown to be consistently associated with lower overall and breast cancer survival.<sup>28</sup> Randomized controlled trials have been conducted or are underway to evaluate the impact of weight loss interventions on breast cancer recurrence and patients' QOL.<sup>152,168</sup> Although several factors have been previously identified that may negatively affect return to work after breast cancer, including socio-demographic features, such as lower education level and income<sup>200,201</sup>, presence of concomitant medical problems<sup>202</sup>, psychological factors such as anxiety and depression<sup>203-205</sup>, higher disease burden<sup>201</sup>, more aggressive breast cancer treatment modalities<sup>206,207</sup>, treatment-related side effects that lead to loss of functionality and reduced work capacity<sup>203-205</sup>, as well as disadvantageous working conditions<sup>208</sup>, limited data is currently available on whether BMI at BC diagnosis and subsequent weight changes correlate with return to work among BC survivors.

We aimed to answer this question using the CANcer TOxicity (CANTO) cohort, a prospective, longitudinal dataset of survivors of early-stage breast cancer that includes extensive clinical, social and work-related information, purposefully designed to characterize long-term breast cancer toxicities.

## Methods

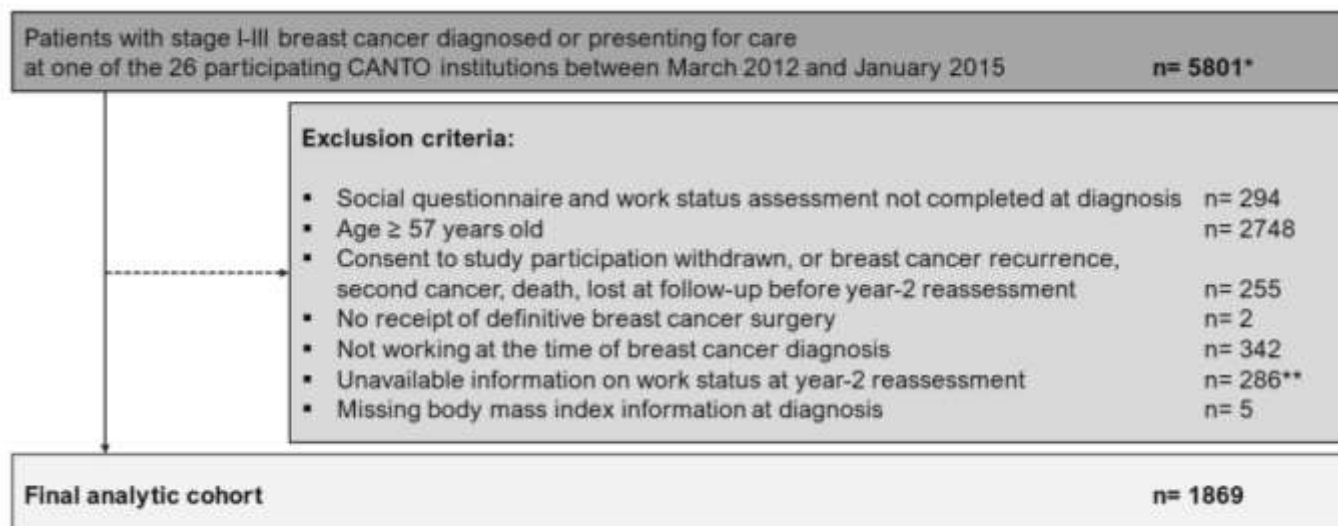
### Data source

We used data from a prospective multicenter cohort of women with stage I-III breast cancer enrolled in 26 French cancer centers since 2012 (CANcer TOxicities [CANTO], NCT01993498).

Patients exit CANTO at any breast cancer recurrence (other than local) or second cancers. Extensive sociodemographic, clinical, tumor and treatment information were assessed. All participants provided informed consent and the study was approved by the national regulatory and ethics committee (ID-RCB:2011-A01095-36,11-039). Study procedures were previously described.<sup>61</sup>

### Study cohort

Updated information from 5801 patients enrolled between March 2012 and January 2015 was accessed. We included women who were professionally active, age 57 years or younger at the time of breast cancer diagnosis (at least five years younger than legal retirement age in France) and who had updated work status two years after breast cancer diagnosis (**MS4-Figure 1**).



**Figure 1.** CONSORT diagram of patient inclusion. \*Note: total accrual in CANTO 12012 patients. We accessed information from 5801 women who were enrolled from March 2012 to January 2015.

\*\* Response rate to work status reassessment questions was associated with age and receipt of endocrine therapy, without major differences in terms of tumor stage, comorbidities, type of breast or axillary surgery, receipt of chemotherapy and radiation therapy.

#### Variables of interest

Our outcome of interest was non-return to work two years after breast cancer diagnosis. Exposure variables were objectively-assessed BMI at diagnosis (baseline) and weight changes between diagnosis and two years afterwards. Covariates previously identified as associated with the outcome of interest were explored and these included baseline socioeconomic and clinical variables, treatment-related covariates, behavioral characteristics, including physical activity (we considered physical activity as a mean of transportation [travel to/from places] and leisure-related domains [e.g., sports and fitness], assessed using the Global Physical Activity Questionnaire-16, and measured as metabolic-equivalent-of-task[MET]-hours[h]/week<sup>60</sup>; work-related domains were not included), psychosocial factors, including anxiety and depression (Hospital Anxiety and Depression Scale<sup>53</sup>), and baseline working conditions. Patient-reported measures of QOL were obtained using the European Organisation for Research and Treatment of Cancer QOL questionnaires (EORTC QLQ-C30 and QLQ-BR23).<sup>57,122</sup> Objectively-documented toxicities (Common Terminology Criteria for Adverse Events [CTCAE] V4.0) were obtained by trained clinical research nurses during health examinations. Variables were categorized as per **MS4-Table 1** and **MS4-Supplementary Table 1**.

## Statistical analyses

Patient characteristics were tabulated for the overall cohort. Then, distribution of variables by baseline BMI was described using chi-square tests for categorical variables and Wilcoxon rank sum tests for continuous variables, as appropriate. BMI was categorized according to the World Health Organization international classification, as follows:  $<25.0 \text{ Kg/m}^2$ =under or normal weight;  $\geq 25.0 \text{ Kg/m}^2$ =overweight or obese. Multivariable logistic regression models were used to examine associations between baseline BMI with non-return to work two years afterwards, and returned adjusted odds ratios (OR) with respective 95% Confidence Intervals (CIs). Using multivariable logistic regression, we also assessed the association between weight changes occurring after breast cancer diagnosis with non-return-to-work. Weight change was modeled both as categorical variable (weight loss [at least 5% of baseline weight], no weight loss [stable weight, within 5%, or weight gain, of at least 5%]) and as continuous (percent-unit weight difference compared to baseline weight). Covariates were selected for inclusion in the models in order to account for significant differences between BMI groups at baseline (with a univariate  $p$  value  $< 0.05$ ) and for variables that had been previously identified to affect employment after breast cancer. Analyses that assessed the association between weight changes occurring after breast cancer diagnosis with non-return to work were further stratified by baseline BMI ( $<25$  vs.  $\geq 25.0 \text{ Kg/m}^2$ ), after testing for significant interactions between baseline BMI and weight changes.

As sensitivity analyses, we entered in the models also patient-reported outcomes (fatigue [EORTC QLQ-C30] and arm symptoms [QLQ-BR23]) and late toxicities (arthralgia and myalgia [CTCAE v. 4.0]) evaluated at return to work assessment<sup>209</sup>. All tests were two-sided.  $P$  values  $< 0.05$  were considered significant. Analyses were conducted using SAS software (version 9.4; SAS Institute Inc., Cary, NC).

## Results

### Cohort characteristics

A total of 1869 patients were included. Baseline characteristics for the overall cohort population and according to BMI at diagnosis are shown in **MS4-Table 1**. Mean age at diagnosis for the overall cohort was 46.8 years ( $SD$  6.4), with a mean weight of 66.4 Kg ( $SD$  13.3) and a mean BMI of  $24.7 \text{ Kg/m}^2$  ( $SD$  4.9). At breast cancer diagnosis, 1180 (63.1%) were under or normal weight, and 689 (36.9%) were overweight or obese. Overweight or obese women tended to be slightly older, postmenopausal, non-smokers, less physically active, and to have lower education, lower income, and higher tumor stage. Finally, 16.9% overweight or obese vs. 12.3% under or normal weight women had at least one comorbidity ( $p=0.0073$ ) (**MS4-Table 1**). Working conditions were similar between under or normal weight and overweight or obese patients respective to work sector (private/public), type of contract (permanent/fixed-term position), workload (full/part-time) and length of daily home-work commuting (more/less than one hour) (all  $p>0.05$ ). However, compared to under or normal weight patients, overweight or obese patients were more likely to have lower-rank job positions (43.6% vs. 36.8% were employees and 18.1% vs. 28.4% were professionals or managers;  $p<0.0001$ ) (**MS4-Supplementary Table 1**).

**MS4-Table 1. Cohort characteristics.**

N (%)	Whole cohort	By body mass index at breast cancer diagnosis		<i>p</i> *
		Under/Normal weight <25 Kg/m <sup>2</sup>	Overweight/Obese ≥25 Kg/m <sup>2</sup>	
<b>Total</b>	1869 (100)	1180 (63.1)	689 (36.9)	
<b>Age at diagnosis, years</b>				
Mean (SD)	46.8 (6.4)	46.3 (6.3)	47.8 (6.3)	<.0001
Missing	-	-	-	
<b>Weight, Kg</b>				
Mean (SD)	66.4 (13.3)	59.0 (6.5)	79.1 (12.3)	NA
Missing	-	-	-	
<b>BMI, Kg/m<sup>2</sup></b>				
Mean (SD)	24.7 (4.9)	21.8 (1.9)	29.7 (4.4)	NA
Missing	-	-	-	
<b>BMI, categorical</b>				
Underweight	54 (2.9)			
Normal weight	1126 (60.2)	NA	NA	NA
Overweight	434 (23.2)			
Obese	255 (13.6)			
Missing	-			
<b>Marital status</b>				
In a relationship	1560 (84.2)	983 (83.8)	577 (84.9)	0.5035
Not in a relationship	292 (15.8)	190 (16.2)	102 (15.0)	
Missing	17	7	10	
<b>Highest education level</b>				
Primary or lower	76 (4.1)	29 (2.5)	47 (6.9)	<.0001
High school	852 (46.2)	475 (40.7)	377 (55.8)	
College graduate or higher	914 (49.6)	662 (56.8)	252 (37.3)	
Missing	27	14	13	
<b>Household Income</b>				
<3000 Euro/month	800 (44.2)	462 (40.2)	339 (51.3)	<.0001
≥3000 Euro/month	1008 (55.7)	686 (59.8)	322 (48.7)	
Missing	61	33	28	
<b>Menopausal status</b>				
Premenopausal	1369 (76.0)	906 (78.8)	463 (71.1)	0.0003
Postmenopausal	432 (24.0)	244 (21.2)	188 (28.9)	
Missing	68	30	38	
<b>Charlson Comorbidity Index</b>				
0	1502 (86.0)	977 (87.7)	525 (83.1)	0.0073
1+	244 (14.0)	137 (12.3)	107 (16.9)	
Missing	123	66	57	
<b>Anxiety, categorical</b>				
Non-case	667 (36.1)	419 (36.0)	248 (36.3)	0.953
Doubtful	474 (25.7)	297 (25.5)	177 (25.9)	
Case	706 (38.2)	448 (38.5)	258 (37.8)	
Missing	22	16	6	
<b>Depression, categorical</b>				
Non-case	1514 (82.0)	954 (82.0)	560 (82.0)	0.0684
Doubtful	202 (11.1)	120 (10.3)	86 (12.6)	
Case	127 (6.9)	90 (7.7)	37 (5.4)	
Missing	22	16	6	
<b>Smoking behavior</b>				
Current smoker	396 (21.5)	274 (23.5)	122 (18.0)	0.0055

Former/Never smoker	1448 (78.5)	892 (76.5)	556 (82.0)	
Missing	25	14	11	
<b>Alcohol consumption</b>				
≥ 1 drink/daily	178 (9.8)	122 (10.6)	56 (8.5)	0.1434
< 1 drink/daily	1637 (90.2)	1031 (89.4)	606 (91.5)	
Missing	54	27	27	
<b>Physical Activity, MET-hours/week, median (IQR)</b>				
Work, travel, leisure	16.0 (1.0-43.7)	16.0 (3.3-42.0)	12.0 (0.0-45.0)	0.0706
Travel, leisure	8.0 (0.0-22.0)	10.0 (0.0-26.0)	5.3 (0.0-17.3)	<.0001
Leisure only	0.0 (0.0-12.0)	2.0 (0.0-14.0)	0.0 (0.0-8.0)	<.0001
Missing max	11	5	6	
<b>Tumor stage</b>				
I	837 (44.8)	567 (48.0)	270 (39.2)	0.0005
II	823 (44.0)	496 (42.0)	327 (47.5)	
III	209 (11.2)	117 (9.9)	92 (13.3)	
Missing	-	-	-	
<b>Tumor subtype</b>				
HR+/HER-	1366 (73.5)	866 (73.9)	500 (72.8)	0.1401
HR+/HER2+	254 (13.7)	169 (14.4)	85 (12.4)	
HR-/HER2+	82 (4.4)	50 (4.3)	32 (4.7)	
HR-/HER2-	157 (8.4)	87 (7.4)	70 (10.2)	
Missing	10	8	2	
<b>Breast surgery</b>				
Partial surgery	1307 (69.9)	817 (69.2)	490 (71.1)	0.3924
Mastectomy	562 (30.1)	363 (30.8)	199 (28.9)	
Missing	-	-	-	
<b>Axillary surgery</b>				
Sentinel lymph node	1008 (53.9)	658 (55.8)	350 (50.8)	0.0378
Axillary dissection	861 (46.1)	522 (44.2)	339 (49.2)	
Missing	-	-	-	
<b>Adjuvant radiation therapy</b>				
No	158 (8.4)	106 (9.0)	52 (7.5)	0.2817
Yes	1711 (91.5)	1074 (91.0)	637 (92.4)	
Missing	-	-	-	
<b>(Neo)adjuvant chemotherapy</b>				
No	642 (34.3)	414 (35.1)	228 (25.5)	0.3813
Yes	1227 (65.6)	766 (64.9)	461 (66.9)	
Missing	-	-	-	
<b>Adjuvant endocrine therapy</b>				
No	328 (17.5)	198 (16.8)	130 (18.9)	0.2522
Yes	1541 (82.4)	982 (83.2)	559 (81.1)	
Missing	-	-	-	
<b>Adjuvant anti-HER2 therapy</b>				
No	1586 (84.9)	997 (84.5)	589 (85.5)	0.5628
Yes	283 (15.1)	183 (15.5)	100 (14.5)	
Missing	-	-	-	

\*Chi square for categorical variables, Wilcoxon rank sum test for continuous variables.

SD= standard deviation; BMI= body mass index; NA= non-applicable; MET= metabolic-equivalent-of-task; IQR= interquartile range; HR=hormone-receptor; HER2=human-epidermal-growth-factor-receptor-2

## Work status at 2 years after breast cancer diagnosis

At two years after breast cancer diagnosis (median time from diagnosis to work status reassessment=23.3 months [interquartile range, 21.2-25.3], no differences between under or normal weight patients and overweight or obese patients [ $p=0.5276$ ]), 398 patients (21.3%) had not returned to work. The rate of non-return to work was 17.7% among under or normal weight patients vs. 27.4% among overweight or obese patients ( $p <.0001$ ). The distribution of women that had not returned to work among those that were overweight or obese was as follows: 121/434 (27.9%) in patients with BMI of 25.0-29.9 Kg/m<sup>2</sup>; 49/169 (29.0%) in patients with BMI of 30.0-34.9 Kg/m<sup>2</sup>; and 19/86 (22.1%) in patients with BMI  $\geq 35.0$  Kg/m<sup>2</sup>. Overall, among women that had not returned to work, the majority ( $n= 294$ , 73.9%) were still on sick leave two years after breast cancer diagnosis. However, compared to under or normal weight women, overweight or obese survivors were less likely to declare that they were on sick leave (69.8% vs. 77.5%) or actively looking for a job (7.9% vs. 9.1%), and more likely to have received a long-term disability benefit (7.9% vs. 3.4%) or to have permanently retired (9.5% vs. 3.8%) ( $p=0.0398$ ). In addition, compared to under or normal weight women, overweight or obese survivors scored worse on fatigue (mean [SD] 38.8 [24.7] vs. 37.1 [25.4]) and arm symptoms (26.9 [26.1] vs. 23.3 [16.2]) scales, and reported more frequently late symptoms including arthralgia (56.5% vs. 46.4%) and myalgia (33.9% vs. 28.8%) at return to work assessment.

After multivariable adjustment, the OR of non-return to work for overweight or obese vs. under or normal weight was 1.32 (95% CI, 1.01-1.75),  $p=0.045$ . In addition, adjusted odds of non-return to work were also significantly increased in patients who had lower household income (<3000 vs.  $\geq 3000$  Euro/month, OR 1.37 [95% CI 1.03-1.80]), lower education level (primary school vs. college or higher, 2.96 [1.56-5.60]), more comorbidities (Charlson score 1+ vs. 0, 1.55 [1.08-2.18]), higher anxiety (case vs. non-case, 1.42 [1.01-2.00]), those who were smokers (vs. former/never, 1.56 [1.14-2.12]), and those who had higher tumor stage (III vs. I, 2.03 [1.23-3.36]), those who had undergone mastectomy (vs. partial surgery, 1.46 [1.07-1.99]), and those receiving anti-Human Epidermal growth factor Receptor-2 therapy (vs. no, 1.71 [1.21-2.42]) (**MS4-Table 2**). Being overweight or obese remained independently associated with non-return to work also after adjustment for imbalances in working conditions at baseline (adjusted OR of non-return to work vs. under or normal weight, 1.33 [95% CI, 1.01-1.76],  $p=0.043$ ; no significant associations were found between prior job position and return to work status). Consistent results were obtained from sensitivity analyses that accounted for late toxicity symptoms. Odds of non-return to work remained elevated among overweight or obese compared to under or normal weight patients (adjusted OR 1.40 [95% CI 1.05-1.88]). There were also significant associations of fatigue (continuous, adjusted OR 1.011 [95% CI 1.005-1.017]), arm symptoms (continuous, 1.013 [1.008-1.019]), and myalgia (any grade vs. no, 1.36 [95% CI 1.02-1.83]) with non-return to work (**MS4-Supplementary Table 2**).

**MS4-Table 2. Multivariable logistic regression of factors associated with non-return to work (N=1869)**

	<b>Adjusted*</b> <b>Odds Ratio</b>	<b>95%</b> <b>Confidence</b> <b>Interval</b>	<b>p</b>
<b>BMI at diagnosis (vs. Underweight/Normal)</b>			
Overweight/Obese	1.32	1.01 - 1.75	0.045
<b>Age (continuous, 1-year increase)</b>			
	1.01	0.98 - 1.04	0.391
<b>Highest education level (vs. College graduate or higher)</b>			
Primary or lower	2.96	1.56 - 5.60	0.0008
High school	1.58	1.18 - 2.10	0.002
<b>Household Income (vs. ≥3000 Euro/month)</b>			
<3000 Euro/month	1.37	1.03 - 1.80	0.0271
<b>Menopausal status (vs. premenopausal)</b>			
Postmenopausal	1.38	0.96 - 1.98	0.083
<b>Comorbidities (vs. Charlson 0)</b>			
Charlson 1+	1.55	1.08 - 2.18	0.016
<b>Anxiety (vs. Non-case)</b>			
Doubtful	1.41	1.01 - 1.99	0.0481
Case	1.42	1.01 - 2.00	0.0438
<b>Depression (vs. Non-case)</b>			
Doubtful	1.31	0.88 - 1.95	0.1888
Case	1.32	0.79 - 2.20	0.2905
<b>Smoking behavior (vs. Former/Never smoker)</b>			
Current smoker	1.56	1.14 - 2.12	0.0049
<b>Physical activity (Travel, leisure) (continuous, 1-MET-hour/week increase)</b>			
	0.99	0.99 - 1.00	0.296
<b>Tumor stage (vs. I)</b>			
II	1.20	0.85 - 1.70	0.290
III	2.03	1.23 - 3.36	0.0058
<b>Breast surgery (vs. Partial surgery)</b>			
Mastectomy	1.46	1.07 - 1.99	0.0179
<b>Axillary surgery (vs. Sentinel lymph node)</b>			
Axillary dissection	1.27	0.89 - 1.80	0.1845
<b>(Neo)adjuvant chemotherapy (vs. No)</b>			
Yes	1.01	0.69 - 1.45	0.9847
<b>Adjuvant endocrine therapy (vs. No)</b>			
Yes	0.77	0.55 - 1.09	0.1398
<b>Adjuvant anti-HER2 therapy (vs. No)</b>			
Yes	1.71	1.21 - 2.42	0.0024

BMI= Body Mass Index; MET= metabolic-equivalent-of-task; HER2= human-epidermal-growth-factor-receptor-2

\*for all factors in the Table.

## Post-treatment weight changes

In the overall cohort, 1010 patients (55.7%) reported stable weight, whereas 599 (33.0%) reported  $\geq 5\%$  weight gain and 205 (11.3%) reported  $\geq 5\%$  weight loss. Respectively, among under or normal weight patients and overweight or obese patients, 677 (59.1%) and 333 (49.8%) reported stable weight, 369 (32.2%) and 230 (34.4%) reported  $\geq 5\%$  weight gain, whereas 100 (8.7%) and 105 (15.7%) reported  $\geq 5\%$  weight loss.

There seemed to be no significant association between weight change and change in physical activity among under or normal weight patients (mean change: -6.3 vs. +1.4 MET-h/week among whose weight decreased vs was stable or increased, respectively,  $p=0.539$ ). Conversely, changes in physical activity were significantly associated with weight change in patients who were overweight or obese, with those who lost weight being also more likely to have reported an increase in physical activity compared to those whose weight was stable or increased (mean change: +4.7 vs. +1.0 MET-h/week, respectively,  $p=0.010$ ) (**MS4-Table 3**).

**MS4-Table 3. Associations between changes in physical activity and weight.**

	Weight stability/gain	Weight loss	$p^*$
<b>Physical activity (Travel, leisure), mean change (95%CI)</b>			
Whole cohort	+1.3 (+0.2 to +2.3)	-0.7 (-9.3 to +7.9)	0.046
Under/Normal weight	+1.4 (-0.1 to +2.9)	-6.3 (-23.7 to +11.1)	0.539
Overweight/Obese	+1.0 (-0.2 to +2.2)	+4.7 (+1.9 to +7.5)	0.010

\*Wilcoxon rank-sum test

Compared to those whose weight remained stable or increased, patients who were under or normal weight at baseline and lost weight also reported worse QOL two-year post-diagnosis, including scoring significantly worse for emotional, social, cognitive, and role function, as well as reporting more severe fatigue and arm symptoms. On the contrary, overweight or obese patients who lost weight reported significantly better physical function and body image, as well as reduced pain, dyspnea, and breast symptoms compared to those whose weight was stable or increased (**MS4-Supplementary Table 3**).

## Post-treatment weight changes and return-to-work

Rates of non-return to work in the overall cohort were 18.2% for those with stable weight, 26.0% for those who gained  $\geq 5\%$  weight, and 23.4% for those who lost  $\geq 5\%$  weight ( $p=0.0008$ ). When considering non-return to work according to BMI at breast cancer diagnosis, among patients who were under or normal weight, rates of non-return to work were 15.2% for those who remained stable, 20.6% for those who gained  $\geq 5\%$  weight, and 26.0% for those who lost  $\geq 5\%$  weight ( $p=0.0082$ ). Among those who were overweight or obese, rates of non-return to work were 24.3% for those who remained stable, 34.8% for those who gained  $\geq 5\%$  weight, and 20.9% for those who lost  $\geq 5\%$  weight ( $p=0.0065$ ).

Non-return to work was associated with weight changes when modeled as categorical variable in a

multivariable setting, with the effect of weight changes on return to work status being dependent on BMI at diagnosis ( $p_{\text{interaction}}=0.0002$ ). For under or normal weight women who lost  $\geq 5\%$  weight, the odds of non-return to work were two-fold (adjusted OR, 2.07; 95% CI, 1.20-3.56, vs. no weight loss,  $p=0.0086$ ), whereas for overweight or obese women who lost  $\geq 5\%$  weight, odds of non-return to work were halved (adjusted OR, 0.48; 95% CI, 0.24-0.97, vs. no weight loss,  $p=0.0418$ ) (**MS4-Table 4**). Similar results were obtained adjusting for working conditions (data not shown). Additionally, the continuous trend of weight gain on non-return to work was significant among overweight or obese patients (adjusted OR for each one-percent-unit increasing weight difference from baseline, 1.03; 95% CI, 1.01-1.06,  $p=0.030$ ) but not among under or normal weight women (adjusted OR 0.99; 95% CI, 0.97-1.02,  $p=0.823$ ) ( $p_{\text{interaction}}=0.036$ ) (**MS4-Supplementary Table 4**).

**MS4-Table 4. Association of weight changes (weight loss vs. non-weight loss [stability/gain]) with non-return to work in multivariable logistic regression models (N=1814).**

	Adjusted Odds Ratio*	95% Confidence Interval	<i>p</i>
<b>Whole cohort</b>			
Weight stability/gain	Ref.	-	-
Weight loss	1.11	0.73 - 1.68	0.632
<i>p</i> for interaction weight change-by-BMI=0.0002			
<b>Under/Normal weight</b>			
Weight stability/gain	Ref.	-	-
Weight loss	2.07	1.20 - 3.56	0.0086
<b>Overweight/Obese</b>			
Weight stability/gain	Ref.	-	-
Weight loss	0.48	0.24 - 0.97	0.0418

\*for factors in Table 2 + change in physical activity.

## Discussion

The CANTO cohort allowed us to explore how body weight and employment trends are related in early-stage breast cancer survivors, who make up a relevant portion of the modern workforce.<sup>201</sup> In this large, prospective, contemporary cohort, we have shown that excess body weight at breast cancer diagnosis is independently associated with increased rates of non-return to work two years afterwards, among young, previously employed breast cancer survivors.

From a societal perspective, overweight and obesity have multiple implications in the job market and excess weight correlates with worse occupational characteristics regardless of having a cancer history. Excess weight is a visible status, and can predispose individuals to stigma and bias.<sup>210</sup> Data indicate that there is substantial appearance-based discrimination in employment<sup>211</sup>, and that employers favor hiring workers whose BMI is in the normal range.<sup>212</sup> As a result, people with higher BMI, particularly individuals with obesity, tend to

be less likely to be hired and more frequently remain long-term unemployed.<sup>213</sup> Excess weight is also associated with lower education and income<sup>214</sup>, and with having lower job profiles, with worse monetary compensation as well as with less appealing non-pecuniary characteristics, including work content, job security, or work-related social prestige.<sup>215</sup> From a patient perspective, prior research suggests that reasons for unemployment among cancer survivors most frequently include physical limitations, cancer-related symptoms, and impairments in social and role functioning resulting from cancer treatment.<sup>195,216</sup> In a large meta-analysis, de Boer et al. reported that cancer survivors are 1.37 times more likely to be unemployed than healthy controls, with a pooled rate of unemployment of 33.8% overall and 35.6% specifically among breast cancer survivors, and authors concluded that the mechanism that most likely explains these higher figures among cancer survivors is a higher disability rate.<sup>217</sup> Analogously, among women in the Young Women's Breast cancer Study who were employed before breast cancer diagnosis and reported subsequent unemployment, half declared that they were unemployed for health reasons<sup>201</sup>, while work productivity and job performance were shown to be substantially and negatively impacted by symptom burden after breast cancer, with increased probability of work-related distress.<sup>200,201</sup> Moreover, supporting the notion that transitioning out of the workforce is more often due to health-related issues than to other reasons, previous studies showed that voluntary unemployment that is not linked to health conditions is infrequent unless patients benefit from sufficiently high alternative resources for income, other than their job compensation.<sup>195</sup> Overweight and obese patients are generally particularly susceptible to experience negative and long-lasting effects after cancer treatment, and are exposed to worse physical and psychological struggles. Patients with higher BMI more often develop fatigue, pain, and cognitive troubles that are prone to become chronic and can also affect return-to-work.<sup>218</sup>

Putting our results into the context of the existing literature, overweight and obese patients in our cohort were more likely to have lower education and to have low-ranking jobs, and more than half had also reported a low household income at diagnosis. These characteristics make it unlikely for these survivors to have remained voluntarily unemployed. Further, concomitant medical conditions also seemed to impair return to work ability of patients in this cohort, and indeed one in six overweight or obese women had at least one comorbidity at the time of breast cancer diagnosis. Presence of concomitant morbid conditions may have had also an implication in the higher observed proportion of overweight and obese patients that received a disability pension compared to under or normal weight patients, leading in turn to a reduced number of overweight and obese women that were actively seeking a job two years post-diagnosis. Finally, rates of patients that permanently retired after breast cancer were higher among overweight or obese compared to under or normal weight patients, despite a mean age of approximately forty-eight years at the time of diagnosis for the former group. This is a relatively premature age for retirement in a Country like France, where legal retirement age for women is 62 years, and specifically among women that were included in this cohort, all professionally active and mostly employed on long-term, permanent work contracts at the time of breast cancer diagnosis.

We also reported significant associations between weight changes, which are known to be common

after breast cancer,<sup>219</sup> and return-to-work. In CANTO, patients who were overweight or obese at diagnosis and who experienced a weight loss of at least 5% of initial body weight (corresponding to approximately 4 kilograms in this cohort), were less likely to be unemployed two years from diagnosis compared to those who did not lose weight. Several controlled trials have assessed the impact of weight loss interventions on a number of outcomes among overweight and obese breast cancer survivors. These interventions have been shown to be feasible, safe, and effective in improving physical fitness, cardiorespiratory parameters, and other health-related QOL outcomes.<sup>48,168,220</sup> Ongoing studies will confirm whether weight loss improves breast cancer-specific outcomes, including recurrence and survival.<sup>152</sup> Our results add to the existing literature showing an association of weight loss with return to work in overweight and obese women, for which there are several possible mediators. These include improved QOL, reduced psychophysical distress, attenuated downstream effects of cancer treatment and healthier overall physical status that can facilitate rejoining the workplace. Our findings also suggest that weight loss in patients that present with excess weight at diagnosis should be further explored as a way to facilitate re-employment, thus mitigating the societal and economic impact of surviving breast cancer. In this context, this study advocates for the urgent need of evaluating employment outcomes in large trials of weight management in cancer survivors, including the assessment of the etiology and duration of sick leave and absence from work, rates of re-employment, and longitudinal patterns of work ability, work capacity, and wage losses. Particularly, future trials should look beyond whether an overweight or obese patient has returned to work or not after cancer. For many cancer survivors, returning to work is indicative of a complete recovery and regained life routine.<sup>216</sup> However, although a survivor's wellbeing may be higher within the group of those that return to work compared to those that do not<sup>196,197</sup>, perceived health-related QOL may also range widely among those that do actually go back to work. Patients may be forced to change career tracks or not be able to perform at the same level as before their cancer, or experience particular physical, psychological, and financial challenges while trying to balance treatment side effects with several other employment concerns in daily life.<sup>201</sup> This may translate into worse QOL and increase distress and job dissatisfaction even after a patient has managed to successfully rejoin the workplace. All these aspects are relevant to overweight and obese individuals, who were shown to be particularly vulnerable to long-lasting and more severe physical and psychosocial stressors during the survivorship period compared to patients within a normal BMI range.<sup>221,222</sup>

The current study has a number of strengths. Previous studies have largely only included unemployment rates after cancer as a secondary outcome and there are few data concerning the relationship between body weight and job reintegration in cancer survivorship. Our findings are based on a prospective clinical study of patients recruited across France, strengthened by a large sample size. To be able to evaluate patients who would be available for labor market and seeking re-employment, we only identified those who were too young to be retired two years after breast cancer diagnosis, attempting to avoid including patients who would directly transition from cancer leave into permanent retirement. Additionally, body weight was objectively and longitudinally assessed by dedicated study nurses. Also, CANTO had availability of data

regarding other behavioral characteristics, including physical activity, with low rates of missing data. As such, in this study we were able to better describe behavioral traits of breast cancer survivors over time, and to conclude that overweight or obese patients who lost weight were also more likely to report significant increases in physical activity, which is an important component of weight management. In contrast, weight loss was not accompanied by a concomitant increase in physical activity for under or normal weight patients, who reported reduced or at most similar activity levels, possibly reflecting unintentional weight changes due to more severe symptom burden and treatment toxicity. These behavioral differences are also mirrored by differential patterns of QOL observed two-years after breast cancer diagnosis when analyzing patients by baseline BMI and weight change category. Women who were overweight or obese at diagnosis and who lost weight scored indeed significantly better on a number of functional and symptom domains compared to those whose weight was stable or increased, with no apparent detriments in QOL associated with their weight loss (consistently with a previous CANTO publication<sup>136</sup>), whereas women who were under or normal weight at diagnosis and had lost weight seemed to fare worse than those who reported a stable or increased weight, being more likely to complain of impaired functionality and more severe symptomatology.

Some limitations must also be acknowledged. First, we used an arbitrary cut-off of 5% to define weight change categories. However, this was based on previously observed clinically meaningful benefits of such a weight loss in the overweight patient population<sup>174</sup>, plus the association between non-return to work and weight changes remained consistent when weight change was modeled as continuous. Second, we used self-reported instruments for physical activity, with possible recall and reporting biases. Third, we acknowledge that our data does not allow to assess intentionality of weight changes. However, we provided additional descriptive information to better characterize patients whose weight decreased, particularly focusing on other closely-related health behaviors such as changes in physical activity, and we were able to access an extensive list of patient-reported outcomes that helped us better define several parameters of health-related QOL and correlate them with weight variations. Moreover, to rule out unintentional weight changes that could be due to disease progression, we upfront included only patients who were disease-free two years after diagnosis, without evidence of breast cancer recurrence or diagnosis of second cancers. Fourth, French law does not allow to collect race/ethnicity information, which we acknowledge as a potential confounder when assessing determinants of return-to-work. Fifth, we could not evaluate patients that had not provided information on work status at year-2 reassessment and this may have introduced some selection bias. However, respondents to work status questions were very similar to non-respondents in term of baseline characteristics. Finally, differences in insurance programs and social security systems may limit generalizability of our findings to work and healthcare systems that are different from France.

In conclusion, our data suggest that excess body weight at breast cancer diagnosis may be a significant barrier to return to work and that overweight and obese patients represent a vulnerable group for unemployment after breast cancer. However, while among overweight or obese women in this cohort there was an association between weight loss and higher rates of return-to-work, further weight gain was associated

with reduced likelihood of returning-to-work. Future research, including ongoing randomized studies testing interventions of weight management and weight loss among breast cancer survivors, should consider including measures of social rehabilitation and employment outcomes.

Data Supplement

MS4-Supplementary Table 1. Working conditions at breast cancer diagnosis.

N (%)	Whole cohort	By body mass index at breast cancer diagnosis		p*
		Under/Normal weight (<25 Kg/m <sup>2</sup> )	Overweight/Obese (≥25 Kg/m <sup>2</sup> )	
<b>Total</b>	1869 (100)	1180 (63.1)	689 (36.9)	
<b>Job position</b>				
Professionals and managers	455 (24.6)	331 (28.4)	124 (18.1)	<.0001
Technicians and associate professionals	445 (24.0)	287 (24.6)	158 (23.1)	
Clerks	728 (39.3)	430 (36.8)	298 (43.6)	
Manual workers	125 (6.7)	62 (5.3)	63 (9.2)	
Self-employed <sup>a</sup>	98 (5.3)	57 (4.9)	41 (6.0)	
Missing	18	13	5	
<b>Work sector</b>				0.324
Private	685 (39.4)	415 (37.7)	270 (42.2)	
Public	861 (49.5)	559 (50.8)	302 (47.3)	
Self-employed	138 (7.9)	90 (8.2)	48 (7.5)	
Other	55 (3.2)	36 (3.3)	19 (3.0)	
Missing	130	80	50	
<b>Type of job contract</b>				0.089
Permanent position	1386 (82.9)	861 (81.7)	525 (84.9)	
Fixed-term position	102 (6.1)	71 (6.7)	31 (5.0)	
Self-employed	69 (4.1)	40 (3.8)	29 (4.7)	
Other	115 (6.9)	82 (7.8)	33 (5.3)	
Missing	197	126	71	
<b>Workload</b>				0.337
Full-time	425 (24.6)	272 (24.8)	153 (24.3)	
Part-time (<40 hours/week)	983 (56.9)	612 (55.8)	371 (58.9)	
Part-time (≥40 hours/week)	319 (18.5)	213 (19.4)	106 (16.8)	
Missing	142	83	59	
<b>Length of daily commuting</b>				0.967
< one hour	1173 (65.3)	743 (65.3)	430 (65.2)	
≥ one hour	623 (34.7)	394 (34.6)	229 (34.7)	
Missing	73	43	30	

<sup>a</sup>Includes farmers, craftsmen, and shopkeepers. \*Chi square test.

**MS4-Supplementary Table 2. Multivariable logistic regression of factors associated with non-return-to-work, sensitivity analysis including late toxicity symptoms (N= 1869).**

	<b>Adjusted* Odds Ratio</b>	<b>95% Confidence Interval</b>	<b>p</b>
<b>BMI at diagnosis (vs. Underweight/Normal)</b>			
Overweight/Obese	1.40	1.05 - 1.88	0.022
<b>Age (continuous, 1-year increase)</b>			
	1.01	0.98 - 1.04	0.496
<b>Highest education level (vs. College graduate or higher)</b>			
Primary or lower High school	2.13 1.44	1.06 - 4.27 1.06 - 1.96	0.033 0.018
<b>Household Income (vs. ≥3000 Euro/month)</b>			
<3000 Euro/month	1.26	0.94 - 1.68	0.123
<b>Menopausal status (vs. premenopausal)</b>			
Postmenopausal	1.37	0.93 - 2.01	0.106
<b>Comorbidities (vs. Charlson 0)</b>			
Charlson 1+	1.39	0.95 - 2.02	0.085
<b>Anxiety (vs. Non-case)</b>			
Doubtful	1.30	0.90 - 1.87	0.153
Case	1.22	0.85 - 1.75	0.274
<b>Depression (vs. Non-case)</b>			
Doubtful	1.04	0.67 - 1.60	0.860
Case	1.16	0.67 - 1.99	0.597
<b>Smoking behavior (vs. Former/Never smoker)</b>			
Current smoker	1.44	1.04 - 1.99	0.029
<b>Physical activity (Travel, leisure) (continuous, 1-MET-hour/week increase)</b>			
	0.99	0.99 - 1.00	0.275
<b>Tumor stage (vs. I)</b>			
II	1.26	0.87 - 1.81	0.222
III	1.98	1.16 - 3.38	0.012
<b>Breast surgery (vs. Partial surgery)</b>			
Mastectomy	1.40	1.01 - 0.95	0.049
<b>Axillary surgery (vs. Sentinel lymph node)</b>			
Axillary dissection	1.09	0.75 - 1.59	0.647
<b>(Neo)adjuvant chemotherapy (vs. No)</b>			
Yes	1.03	0.69 - 1.53	0.874
<b>Adjuvant endocrine therapy (vs. No)</b>			
Yes	0.77	0.54 - 1.10	0.153
<b>Adjuvant anti-HER2 therapy (vs. No)</b>			
Yes	1.80	1.24 - 2.61	0.002
<b>Fatigue (continuous)</b>	1.011	1.005 - 1.017	0.0005
<b>Arm symptoms (continuous)</b>	1.013	1.008 - 1.019	<.0001
<b>Arthralgia (vs. No)</b>			
Any grade	1.079	0.80 - 1.46	0.621
<b>Myalgia (vs. No)</b>			
Any grade	1.36	1.02 - 1.83	0.039

BMI= Body Mass Index; MET= metabolic-equivalent-of-task; HER2= human-epidermal-growth-factor-receptor-2. \*for all factors in the Table.

**MS4-Supplementary Table 3. Associations between patient-reported quality of life at return to work assessment and weight changes. Data are presented by baseline body mass index.**

Domain	Under/Normal weight			Overweight/Obese		
	Weight stability/gain	Weight loss	<i>p</i> *	Weight stability/gain	Weight loss	<i>p</i> *
Global Health	67.59	63.78	0.065	64.42	65.46	0.693
Physical Function	88.45	86.87	0.066	83.73	87.55	0.015
Emotional Function	68.94	63.69	0.048	70.40	68.92	0.924
Social Function	85.12	80.76	0.020	82.99	87.00	0.146
Cognitive Function	74.27	69.05	0.038	75.39	74.50	0.762
Role Function	84.40	81.12	0.048	78.34	82.33	0.110
Fatigue	36.72	41.27	0.033	38.75	37.78	0.668
Pain	25.68	29.59	0.113	33.61	28.00	0.048
Insomnia	42.37	48.45	0.098	44.47	44.00	0.955
Nausea/Vomit	4.60	8.16	0.015	5.42	6.33	0.533
Dyspnea	15.93	14.29	0.515	22.76	14.00	0.001
Appetite Loss	8.13	14.29	0.006	5.24	10.33	0.007
Constipation	17.32	19.39	0.484	14.10	18.18	0.260
Diarrhea	6.56	9.52	0.262	9.58	9.33	0.295
Financial difficulties	9.31	14.63	0.076	9.93	6.80	0.416
Body Image	75.29	77.89	0.221	69.93	80.25	0.0002
Sexual Function	36.71	34.40	0.395	31.22	34.88	0.175
Sexual Enjoyment	61.84	60.32	0.879	57.54	59.68	0.407
Future Perspective	58.39	54.98	0.310	57.17	52.67	0.232
Side Effects	17.56	18.12	0.528	19.88	18.18	0.352
Breast Symptoms	19.75	20.49	0.919	23.88	19.19	0.032
Arm Symptoms	22.63	29.34	0.018	27.03	25.83	0.934
Upset by Hair Loss	40.55	47.06	0.451	41.95	41.27	0.960

Quality of life scores are summarized using mean scores. Standard scoring algorithms were applied, with higher scores reflecting better quality of life for global health or functional scales and greater severity for symptoms.

\*Wilcoxon rank-sum test

**MS4-Supplementary Table 4. Association of weight changes (continuous, difference from baseline) in multivariable logistic regression models.**

	Odds Ratio	95% Confidence Interval	<i>p</i>
<b>Whole cohort</b>			
Weight change, continuous (1 percent unit increase)	1.01	0.99-1.03	0.1597
P for interaction weight change-by-BMI=0.036			
<b>Under/Normal weight</b>			
Weight change, continuous (1 percent unit increase)	0.99	0.97-1.02	0.808
<b>Overweight/Obese</b>			
Weight change, continuous (1 percent unit increase)	1.03	1.01-1.06	0.030

Adjusted for age, menopausal status, comorbidities, education, income, smoking, stage, breast and axillary surgery, chemotherapy, endocrine therapy, anti-HER2 therapy, anxiety/depression, change in physical activity (travel, leisure). Weight changes modeled as continuous, odds ratios to be interpreted for one increasing percent-unit in weight from diagnosis.

## **RESULTS - PART II**

## MANUSCRIPT 5 (MS5):

### Setting up to predict long-term cancer-related fatigue: a conceptual framework in breast cancer survivorship care

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## **Abstract**

**Background:** While fatigue is one of the most distressing and common long-term side effects of cancer and cancer treatments, it is often poorly managed. Identification of factors associated with the development and persistence of fatigue would facilitate patient management and the development of early interventions.

**Patients and methods:** We prospectively collected assessments of global fatigue, physical, emotional and cognitive dimensions of fatigue, in 6,619 eligible patients with stage I-III BC enrolled in CANTO cohort from 2012-2015, using EORTC QLQ-C30 and -FA12 at diagnosis and 1, 2 and 4 years after diagnosis. Multiple iterations of logistic regression models predicted the risk of severe fatigue (score  $\geq 40/100$ ) after diagnosis, using clinical and behavioral features, treatment and symptoms at diagnosis. The final prediction model retained variables that met a pre-specified *P*-value of  $<0.05$ . Bootstrap was used to correct the c-indices for over-optimism.

**Results:** Prevalence of post-treatment severe fatigue reached 35.6% for global fatigue, 34.8% for physical, 21.8% for emotional and 13.4% for cognitive fatigue. Emotional distress including depression, and pain at diagnosis were significantly associated with all severe fatigue dimensions across the three post-diagnosis time points, whereas higher body mass index, current smoking, depression and insomnia were also significantly associated with global and physical severe fatigue. Lower income was associated with all severe fatigue dimensions at some time point. In addition, receipt of at least 2 years of adjuvant endocrine therapy represented a significant correlate of global and physical fatigue, with longer courses of treatment having an impact of increasingly larger magnitude. Tentative predictive equations had optimism-corrected c-statistic from 0.69-0.72.

**Conclusions:** Psychological distress, symptoms, lower socio-economic conditions and unhealthy behaviors play a significant role in the development of cancer-related fatigue. Treatment related factors, particularly chronic therapies such as endocrine therapy, also impact the persistence of this symptom. In this paper we present predictive equations for the upfront identification of patients at risk of severe long-term fatigue. Building on this tentative model, a conceptual framework is proposed, to help clinicians better manage this symptom and proactively propose specific interventions early over the survivorship trajectory.

## Introduction

Over the past four decades, breast cancer detection and treatment have improved remarkably, and now the vast majority of breast cancer patients are diagnosed with early breast cancer and are expected to be cured of their disease after treatment.<sup>6,222</sup> It is estimated that, in the United States and Europe, 5 million women are breast cancer survivors.<sup>223,224</sup> A substantial number of them will suffer from long-term effects of cancer treatments.<sup>20,225</sup> Increased awareness and better understanding of long-term effects of cancer treatments are therefore needed for improved management of issues faced by a growing population of breast cancer survivors.

One of the most distressing and common long-term side effects of cancer and cancer treatment is cancer-related fatigue.<sup>40</sup> Available data suggest that fatigue levels of breast cancer patients are high and remain high even years after treatment, with 30% of patients experiencing persistent fatigue after treatment completion.<sup>24,27,226,227</sup> Moreover, it is documented that cancer-related fatigue can result in substantial adverse physical, psychosocial, and socio-economic consequences, having a negative impact on the overall quality of life.<sup>226</sup> Nevertheless, prior studies indicate that fatigue is still rarely discussed or managed.<sup>228–230</sup>

Cancer-related fatigue is likely multidimensional in its manifestation, involving physical, psychological and cognitive dimensions. Prior data also indicate that cancer-related fatigue is probably multi-factorial, being determined by patient characteristics (e.g. contextual factors such as marital status and education, psychosocial, cognitive, and behavioral factors, such as depression, early stress, pre-treatment fatigue, and inactivity, pre-treatment comorbid conditions, biological factors (e.g. inflammation), disease characteristics (e.g. stage), and antineoplastic therapies (e.g. chemotherapy and radiotherapy)).<sup>40</sup>

Although many observational studies have described a range of severe fatigue symptoms,<sup>24,115,226</sup> current knowledge of the prevalence, long-term trajectory and risk factors of breast cancer related fatigue are still limited and we are not able to clearly identify those at risk of severe fatigue. Most of the studies are small, retrospective, cross-sectional, and do not have baseline information nor capture the long-term complexity and variability of symptoms over time. In addition, they do not provide detailed contextual, medical, treatment, psychological, cognitive, emotional, and biological information. Therefore, the absence of longitudinal and well-powered studies assessing fatigue among patients treated in the modern era, from pre-treatment up to the survivorship period, has been a barrier to identifying factors associated with the development and persistence of fatigue and potential targets for effective interventions in this setting.

The CANTO cohort (NCT01993498) was initiated in 2012 with the aim of better describing long-term toxicities of cancer and its correlates.<sup>60</sup> CANTO prospectively collects detailed longitudinal patient, tumor, treatment, patient-reported outcomes (including several quality of life, psychological and social questionnaires), and biological data on a large cohort of women with newly diagnosed breast cancer from 26 institutions across France, who will be followed for a minimum of 60 months after primary treatment completion (surgery, radiotherapy or chemotherapy, whichever ended last). In this study, we used CANTO data to define those at risk of global fatigue and specific dimensions of fatigue at 1, 2 and 4 years after diagnosis.

## Methods

### Study design and patient selection

We included 6,619 patients with stage I-III BC enrolled in CANTO cohort from March 2012 to April 2015, and used data collected at diagnosis (baseline) and at three distinct time points after diagnosis: approximately 3-6 months, 1 and 3 years after treatment completion, which correspond to 1 (T1), 2 (T2) and 4 (T3) years after diagnosis. All patients provided written informed consent.

To assess the potential bias introduced by the exclusion of patients with missing evaluation at different time points, the characteristics of such patients were compared with those of participating patients. Patients with missing evaluation at three time points tended to be unmarried, smokers, have lower income, higher daily consumption of alcohol, present higher tumor stage, triple-negative subtype, and report a higher depression score and more pain (data not shown).

### Fatigue assessment

The outcomes of interest were global fatigue and physical, emotional and cognitive dimensions of fatigue. We used European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30<sup>55</sup> for global fatigue and QLQ-FA12<sup>231</sup> for physical, emotional and cognitive dimensions of fatigue, defined as a binary variable (scores  $\geq 40/100$  defined severe fatigue). The threshold of severity was defined as in Abrahams et al.<sup>226</sup> for global fatigue, and the same was used for fatigue dimensions, based on correlation analyses showing satisfactory concordance. Outcome assessments were collected at all time points. We accessed information at diagnosis on covariates including: age, body mass index (BMI), marital status, education level, income, daily consumption of alcohol, tobacco, physical activity, tumor stage, tumor subtype, menopausal status, Charlson comorbidity index<sup>232</sup>, axillary management, type of breast surgery, receipt of, chemotherapy, radiotherapy, anti-human epidermal growth factor receptor 2 (HER2) therapy, endocrine therapy (medical record review) and emotional distress measured by anxiety and depression, insomnia, pain (self-reported questionnaires) and hot flashes (nurse assessment). Physical activity was assessed as per Global Physical Activity Questionnaire-16<sup>59</sup>, anxiety and depression as per the Hospital Anxiety and Depression Scale<sup>52</sup>, insomnia and pain as per EORTC QLQ-C30, whereas hot flashes as per Common Terminology Criteria for Adverse Events (CTCAE) v 4.0<sup>233</sup>.

### Statistical analysis

We fit multivariate logistic models to identify variables associated with the presence of severe fatigue (global, physical, emotional, and cognitive). We iterated the models 1) first with only clinical features, 2) second with clinical features + treatment factors, 3) then with clinical features + treatment factors + symptoms, and 4) finally with clinical features + treatment factors + symptoms including the baseline outcome (**MS5-Table 1**). We then selected the best performing model. The choice of the final model also compared the goodness of fit of models including or not the outcome variables assessed at baseline. We retained in a final association model

the variables that met a pre-specified  $p$ -value of  $<0.05$  using a backwards stepwise procedure. Receiver operating characteristic (ROC) curves were generated using assessment data at T1, T2 and T3, and areas under the ROC curve were estimated. Bootstrap was used to correct the c-indices for over-optimism.

Statistical analysis was performed using SAS statistical software Version 9.4 (SAS Institute Inc.) Statistical significance was defined with a 2-sided  $p$ -value  $<0.05$ .

## Results

### Patient characteristics

Of 6,619 patients enrolled in CANTO cohort, analysis was carried out for 5,640 patients (85.2%) at T1, 5,000 (75.5%) at T2, and 3,400 (51.4%) at T3 (**MS5-Supplementary Figure 1**). Cohort characteristics of patients reporting severe global fatigue at the three post-diagnosis time points are shown in **MS5-Table 1** (see **MS5-Supplementary Tables 1A, 1B** and **1C** for severe physical, emotional and cognitive fatigue, respectively).

Prevalence of severe fatigue reached 35.6% for global fatigue, 35.0% for physical, 21.9% for emotional and 13.3% for cognitive fatigue at T1 (closest to primary treatment completion) representing the highest prevalence across all time-points (with the exception of severe emotional fatigue, which was most prevalent at diagnosis [25.8%]), and remained relatively high and substantially unchanged until T3 (**MS5-Supplementary Figure 2**).

**MS5-Table 1. Distribution of cohort characteristics by severe overall fatigue at T1, T2, T3 after diagnosis, N (%).**

Characteristics	T1 (1 year after diagnosis)		T2 (2 years after diagnosis)		T3 (4 years after diagnosis)	
	Severe Fatigue N=2006 (35.6%)	Non-severe Fatigue N=3634 (64.4%)	Severe Fatigue N=1700 (34.0%)	Non-severe Fatigue N=3300 (66.0%)	Severe Fatigue N=1073 (31.6%)	Non-severe Fatigue N=2327 (68.4%)
<i>Clinical factors</i>						
<b>Age at diagnosis, years</b>						
Mean ± SD	54.5±11.3	57.2±11.2	54.2±11.3	57.3±11.0	55.1±11.3	57.4±10.7
Min-Max	25.0–89.0	22.0–88.0	23.0–88.0	22.0–88.0	26.0–88.0	22.0–85.0
<b>BMI at diagnosis, Kg/m<sup>2</sup></b>						
Mean ± SD	26.5±5.7	25.6±5.2	26.2±5.6	25.7±5.2	26.0±5.3	25.7±5.2
Missing	6	15	6	10	2	10
<b>Menopausal status</b>						
Premenopausal	847 (43.1)	1208 (33.8)	725 (43.5)	1102 (34.0)	437 (41.7)	743 (32.5)
Postmenopausal	1120 (56.9)	2366 (66.2)	942 (56.5)	2143 (66.0)	610 (58.3)	1545 (67.5)
Missing	39	60	33	55	26	39
<b>Charlson comorbidity index</b>						
0	1431 (77.6)	2710 (80.5)	1213 (78.1)	2492 (81.0)	788 (79.6)	1763 (81.1)
≥1	414 (22.4)	655 (19.5)	340 (21.9)	586 (19.0)	202 (20.4)	410 (18.9)
Missing	161	269	147	222	83	154
<b>Marital Status</b>						
Not partnered	560 (30.1)	862 (25.8)	457 (28.9)	766 (25.0)	278 (27.9)	536 (24.8)
Partnered	1303 (69.9)	2485 (74.2)	1126 (71.1)	2303 (75.0)	718 (72.1)	1621 (75.2)
Missing	143	287	117	231	77	170
<b>Education level</b>						
Primary school	287 (15.2)	522 (15.3)	223 (13.9)	469 (15.0)	135 (13.3)	357 (16.2)
High school	906 (48.1)	1595 (46.7)	754 (46.9)	1470 (47.0)	474 (46.7)	1034 (46.8)
College or higher	691 (36.7)	1301 (38.1)	631 (39.2)	1190 (38.0)	407 (40.1)	819 (37.1)
Missing	122	216	92	171	57	117
<b>Household income, Euros/month</b>						
< 1500	341 (19.4)	429 (13.6)	279 (18.6)	361 (12.5)	156 (16.2)	269 (13.2)
≥ 1500 to < 3000	688 (39.1)	1467 (46.6)	611 (40.7)	1381 (47.6)	413 (42.8)	959 (47.2)
≥ 3000	732 (41.6)	1251 (39.8)	611 (40.7)	1157 (39.9)	396 (41.0)	803 (39.5)
Missing	245	487	199	401	108	296
<b>Alcohol consumption behavior</b>						
Less than daily	1665 (85.6)	3051 (86.2)	1414 (85.8)	2743 (86.0)	879 (85.8)	1960 (86.6)
Daily	280 (14.4)	489 (13.8)	234 (14.2)	446 (14.0)	146 (14.2)	304 (13.4)
Missing	61	94	52	111	48	63
<b>Tobacco use behavior</b>						
Current smoker	424 (21.5)	506 (14.1)	367 (21.9)	424 (13.1)	201 (19.1)	314 (13.7)
Former smoker	429 (21.7)	775 (21.7)	394 (23.5)	671 (20.7)	229 (21.8)	447 (19.6)
Never smoker	1120 (56.8)	2296 (64.2)	913 (54.5)	2144 (66.2)	620 (59.0)	1525 (66.7)
Missing	33	57	26	61	23	41
<b>Physical activity (MET-h/week)</b>						
Median (Q1-Q3)	12.0 (0.0–36.0)	16.0 (0.3–40.0)	14.0 (0.0–38.0)	16.0 (0.7–40.0)	14.8 (0.0–40.0)	16.0 (0.7–40.0)
Missing	93	190	72	143	55	93
<b>Tumor stage</b>						
Stage I	903 (45.1)	1908 (52.5)	780 (45.9)	1755 (53.2)	531 (49.6)	1256 (54.0)
Stage II	867 (43.3)	1400 (38.5)	724 (42.6)	1270 (38.5)	462 (43.1)	890 (38.3)
Stage III	234 (11.7)	324 (8.9)	194 (11.4)	273 (8.3)	78 (7.3)	180 (7.7)
Missing	2	2	2	2	2	1
<b>Tumor subtype</b>						
HR+ HER2+	228 (11.5)	369 (10.2)	185 (10.9)	335 (10.2)	126 (11.8)	232 (10.0)
HR+ HER2-	1492 (75.0)	2783 (77.1)	1311 (77.5)	2510 (76.7)	828 (77.7)	1779 (77.0)
HR- HER2+	82 (4.1)	144 (4.0)	61 (3.6)	140 (4.3)	32 (3.0)	96 (4.2)
HR- HER2-	188 (9.4)	314 (8.7)	134 (7.9)	288 (8.8)	80 (7.5)	204 (8.8)
Missing	16	24	9	27	7	16

<i>Treatment-related factors</i>						
<b>Axillary surgery</b>						
None or sentinel	1124 (56.0)	2257 (62.1)	966 (56.8)	2084 (63.2)	651 (60.7)	1477 (63.5)
Dissection	882 (44.0)	1377 (37.9)	734 (43.2)	1216 (36.8)	422 (39.3)	850 (36.5)
<b>Breast cancer surgery</b>						
Conservative	1429 (71.2)	2706 (74.5)	1209 (71.1)	2475 (75.0)	792 (73.8)	1776 (76.3)
Mastectomy	577 (28.8)	928 (25.5)	491 (28.9)	825 (25.0)	281 (26.2)	551 (23.7)
<b>Chemotherapy</b>						
No	809 (40.3)	1825 (50.2)	709 (41.7)	1649 (50.0)	497 (46.3)	1181 (50.8)
Yes	1197 (59.7)	1808 (49.8)	991 (58.3)	1651 (50.0)	576 (53.7)	1146 (49.2)
Missing	0	1	0	0	0	0
<b>Radiotherapy</b>						
No	155 (7.7)	337 (9.3)	141 (8.3)	296 (9.0)	106 (9.9)	187 (8.0)
Yes	1851 (92.3)	3294 (90.7)	1558 (91.7)	3003 (91.0)	967 (90.1)	2139 (92.0)
Missing	0	3	1	1	0	1
<b>Hormonotherapy</b>						
No	377 (18.8)	669 (18.4)	275 (16.2)	614 (18.6)	159 (14.8)	451 (19.4)
Yes	1629 (81.2)	2964 (81.6)	1425 (83.8)	2686 (81.4)	914 (85.2)	1875 (80.6)
Missing	0	1	0	0	0	1
<b>Anti HER-2 therapy</b>						
No	1748 (87.1)	3232 (89.0)	1502 (88.4)	2927 (88.7)	944 (88.0)	2068 (88.9)
Yes	258 (12.9)	401 (11.0)	198 (11.6)	373 (11.3)	129 (12.0)	259 (11.1)
Missing	0	1	0	0	0	0
<i>Symptoms</i>						
<b>Anxiety</b>						
Non-case	576 (30.2)	1511 (44.0)	505 (31.2)	1360 (43.0)	316 (30.8)	973 (43.6)
Doubtful	512 (26.8)	915 (26.6)	409 (25.2)	852 (27.0)	259 (25.3)	608 (27.2)
Case	822 (43.0)	1011 (29.4)	706 (43.6)	948 (30.0)	450 (43.9)	651 (29.2)
Missing	96	197	80	140	48	95
<b>Depression</b>						
Non-case	1378 (72.1)	2997 (87.1)	1195 (73.7)	2731 (86.3)	757 (73.9)	1959 (87.7)
Doubtful	306 (16.0)	296 (8.6)	242 (14.9)	285 (9.0)	145 (14.1)	183 (8.2)
Case	226 (11.8)	146 (4.2)	185 (11.4)	147 (4.6)	123 (12.0)	93 (4.2)
Missing	96	195	78	137	48	92
<b>Insomnia</b>						
Mean ± SD	52.0±34.5	37.4±31.4	52.0±34.7	37.4±31.3	50.3±33.7	37.0±31.4
Missing	86	167	64	129	34	87
<b>Pain</b>						
Mean ± SD	23.6±25.1	11.8±18.3	23.1±24.6	11.4±17.9	23.1±25.2	11.2±17.6
Missing	74	144	54	106	31	72
<b>Hot flashes</b>						
No	633 (33.0)	919 (26.3)	511 (31.4)	843 (26.6)	292 (28.9)	601 (26.9)
Yes	1288 (67.0)	2572 (73.7)	1114 (68.6)	2327 (73.4)	718 (71.1)	1636 (73.1)
Missing	85	143	75	130	63	90
SD: Standard Deviation; Q: Quartile; BMI: Body Mass Index; MET-h: Metabolic-equivalent of task-hour; HR: hormone receptor, HER2: Human epidermal growth factor receptor 2. Anxiety and Depression scored according to the Hospital Anxiety and Depression Scale: non-case (score 0-7), doubtful (8-10), case (11-21).						

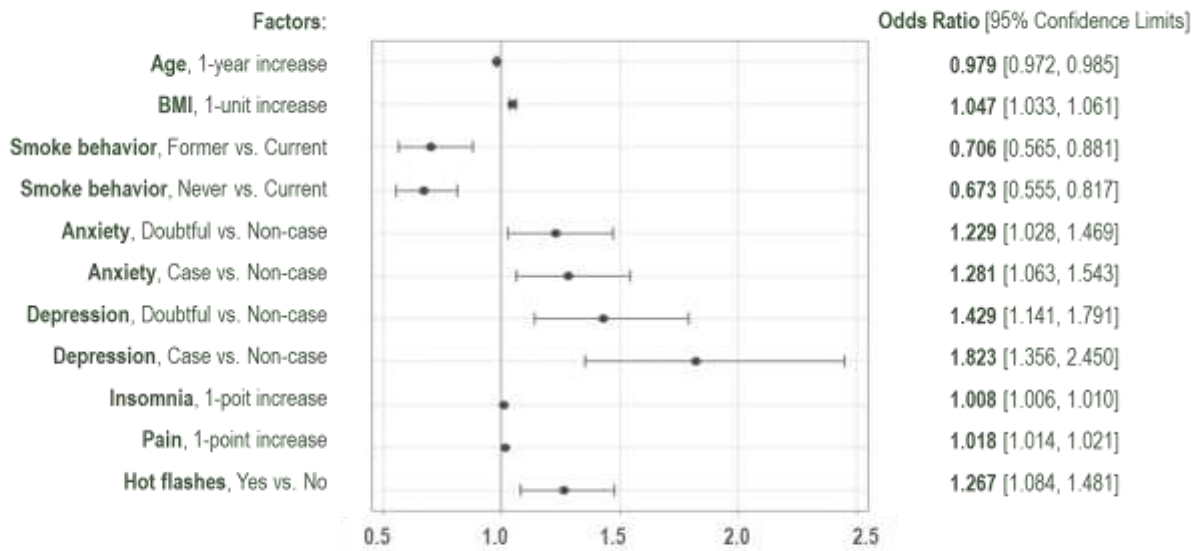
Severe Global fatigue

**MS5-Figure 1** shows the characteristics that were associated with severe global fatigue at each time point, with odds ratios, 95% Wald confidence limits and a tentative predictive equation. The best models were those including the combination of clinical features + treatment factors + symptoms. Severity of fatigue at baseline was highly correlated with presence of a severe outcomes at later time points, however models including the outcome variable at baseline as a covariate did not largely outperform models without the outcome variable (See **MS5-Supplementary Table 2** for the full model and performance information of models tested).

Higher BMI, active smoking, depression, insomnia and pain were consistently significant across the three time points. Younger age and hot flashes played a role at T1 and T2. Overall, severe fatigue was associated with lower income and comorbidities at 2 years after diagnosis (T2). Endocrine therapy represented a significant correlate of global fatigue after 2 years of initiation of therapy, with increasingly higher magnitude of overtime impact corresponding with longer courses of treatment. There was a significant association of receipt chemotherapy and global severe fatigue at T3. The optimism-corrected c-statistic was 0.70071, 0.71262 and 0.68730, at T1, T2 and T3, respectively.

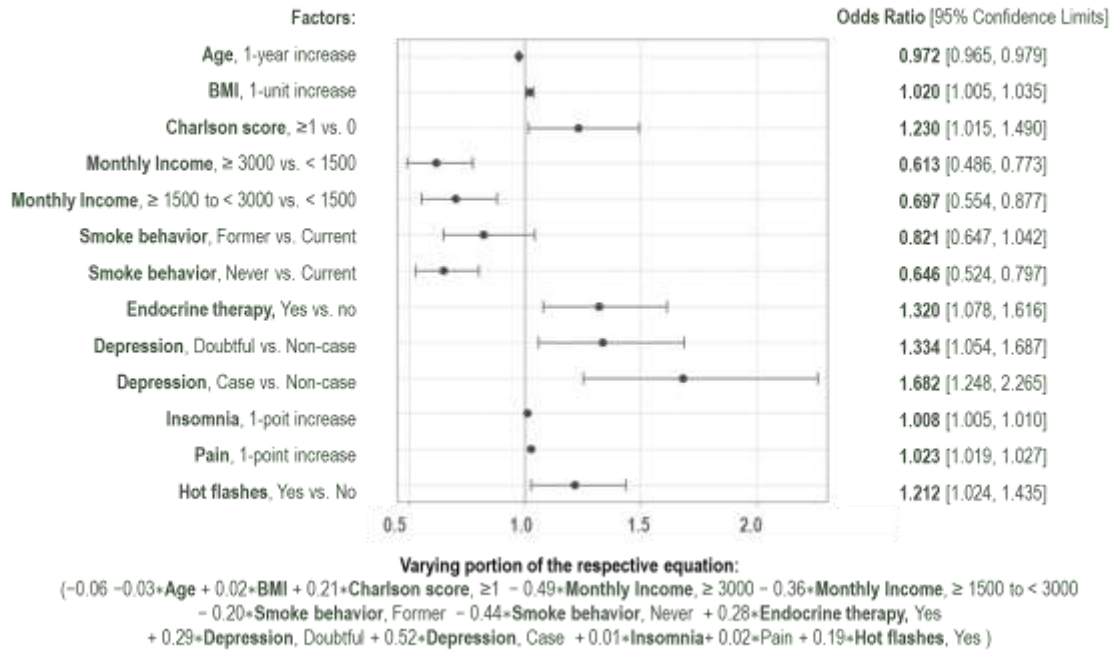
$$\text{Fatigue risk} = \frac{e^{(\text{varying portion of the equation for a given model})}}{1 + e^{(\text{varying portion of the equation for a given model})}}$$

**1A. Severe global fatigue, year-1 after diagnosis**

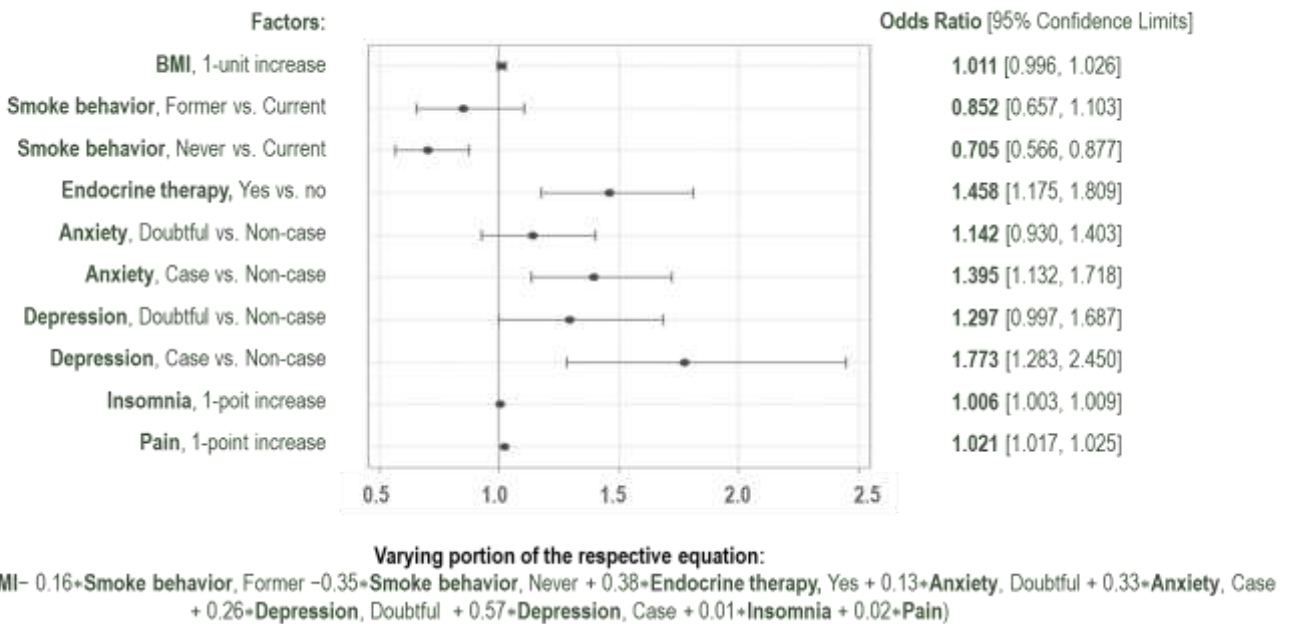


Varying portion of the respective equation:  
 (1.26 -0.02\*Age+ 0.05\*BMI - 0.35\*Smoke behavior, Former - 0.40\*Smoke behavior, Never + 0.20\*Anxiety, Doubtful + 0.25\*Anxiety, Case + 0.36\*Depression, Doubtful + 0.60\*Depression, Case + 0.01\*Insomnia + 0.02\*Pain + 0.24\*Hot flashes, Yes)

### 1B. Severe global fatigue, year-2 after diagnosis



### 1C. Severe global fatigue, year-4 after diagnosis

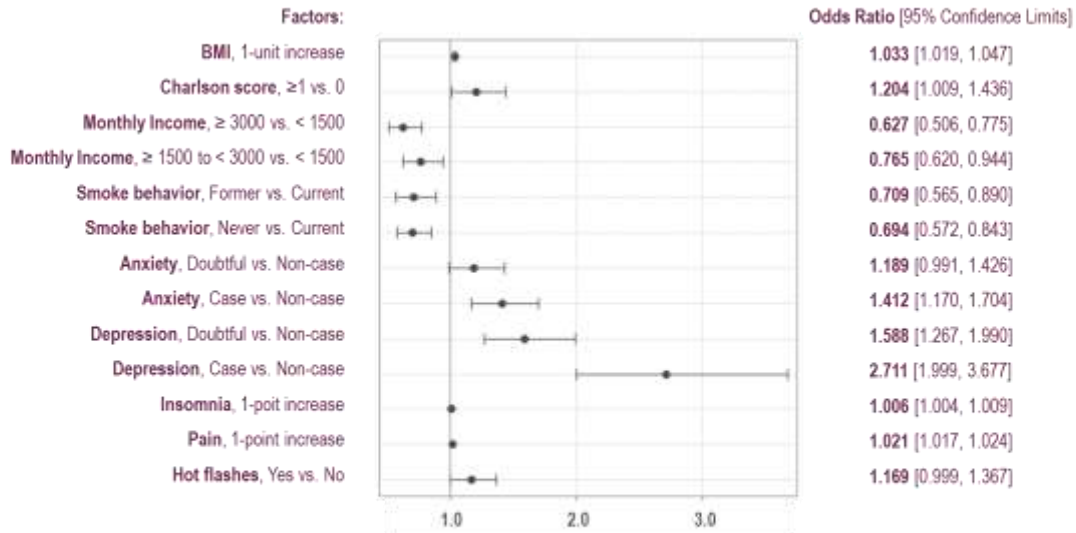


**Figure 1: Characteristics that predict severe global fatigue at T1 (1A), T2 (1B) and T3 (1C).** For continuous variables, the equation coefficient should be multiplied for the count value of the variable (e.g., if Age=51, then coefficient is multiplied by 51); For binary categorical variables coefficient is multiplied by 0 if patient belongs to reference category level, by 1 if to the alternate level (e.g., if Chemotherapy=No [Ref.], then coefficient is multiplied by 0, if Chemotherapy=Yes, then coefficient is multiplied by 1); For categorical variables with three levels, both coefficients are multiplied by 0 if patient belongs to reference level, the first coefficient is multiplied by 1 if patients belongs to the first level of the variable by order of appearance in the plot area or to 0 if to the second level (vice versa for the second coefficient; e.g. if Smoke behavior= Current [Ref.], then both coefficients are multiplied by 0, if Smoke behavior=Former, first coefficient is multiplied by 1 and second by 0, if Smoke behavior=Never, first coefficient is multiplied by 0 and second by 1); A practical example is provided in the Discussion section.

## Severe Physical fatigue

Similar associations with those observed for global fatigue were found to severe physical fatigue (**MS5-Figure 2**; see **MS5-Supplementary Table 3** for the full model). The optimism-corrected c-statistic was 0.71149, 0.69371 and 0.69188, at T1, T2 and T3, respectively.

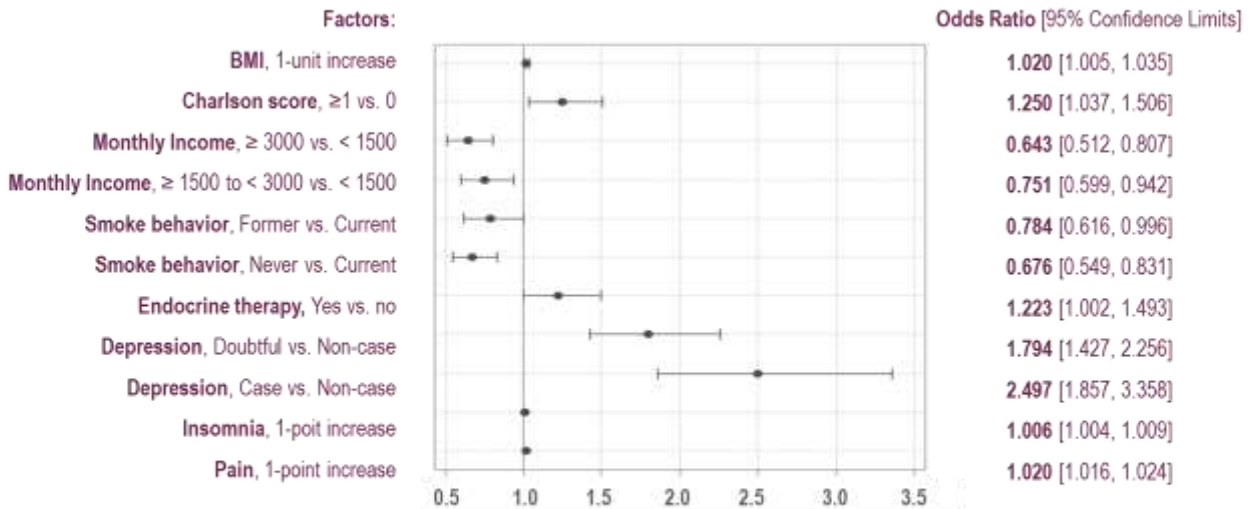
### 2A. Severe physical fatigue, year-1 after diagnosis



Varying portion of the respective equation:

$$(-1.86 + 0.03 \cdot \text{BMI} + 0.19 \cdot \text{Charlson score, } \geq 1 - 0.47 \cdot \text{Monthly Income, } \geq 3000 - 0.27 \cdot \text{Monthly Income, } \geq 1500 \text{ to } < 3000 - 0.34 \cdot \text{Smoke behavior, Former} - 0.37 \cdot \text{Smoke behavior, Never} + 0.17 \cdot \text{Anxiety, Doubtful} + 0.35 \cdot \text{Anxiety, Case} + 0.46 \cdot \text{Depression, Doubtful} + 0.99 \cdot \text{Depression, Case} + 0.01 \cdot \text{Insomnia} + 0.02 \cdot \text{Pain} + 0.16 \cdot \text{Hot flashes, Yes})$$

### 2B. Severe physical fatigue, year-2 after diagnosis



Varying portion of the respective equation:

$$(-1.57 + 0.02 \cdot \text{BMI} + 0.22 \cdot \text{Charlson score, } \geq 1 - 0.44 \cdot \text{Monthly Income, } \geq 3000 - 0.29 \cdot \text{Monthly Income, } \geq 1500 \text{ to } < 3000 - 0.24 \cdot \text{Smoke behavior, Former} - 0.39 \cdot \text{Smoke behavior, Never} + 0.20 \cdot \text{Endocrine therapy, Yes} + 0.58 \cdot \text{Depression, Doubtful} + 0.92 \cdot \text{Depression, Case} + 0.01 \cdot \text{Insomnia} + 0.02 \cdot \text{Pain})$$

### 2C. Severe physical fatigue, year-4 after diagnosis

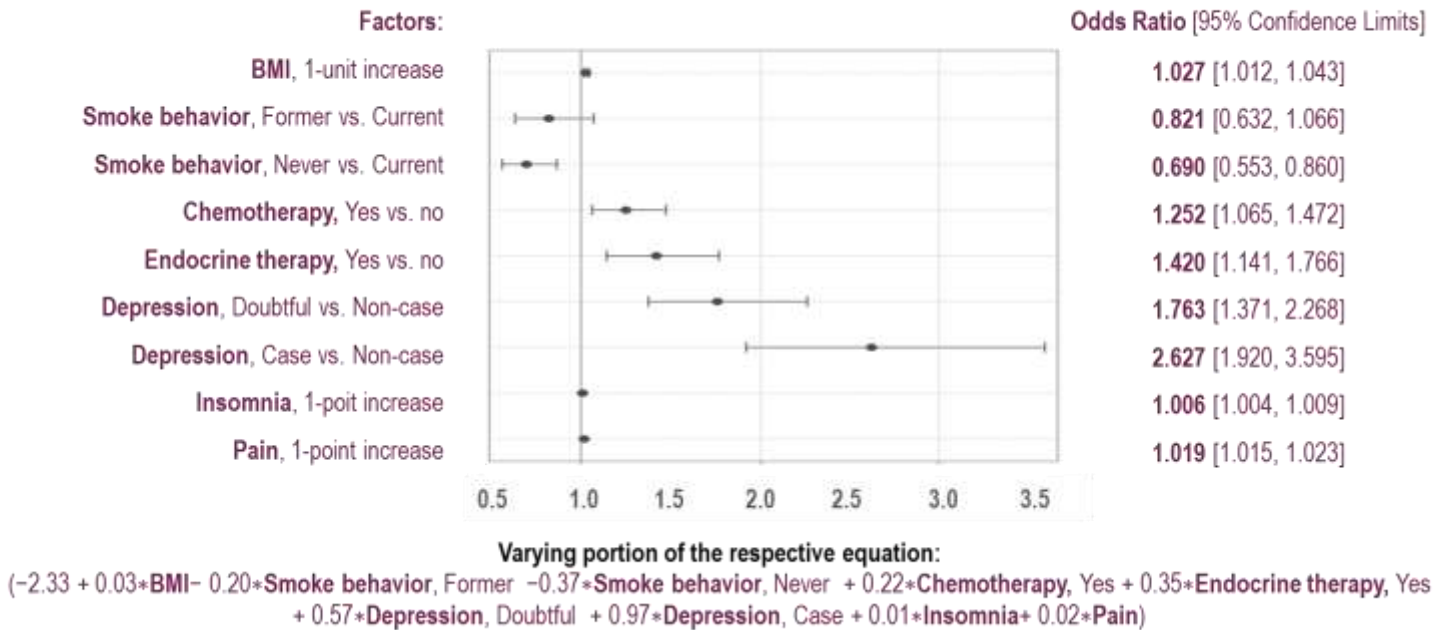
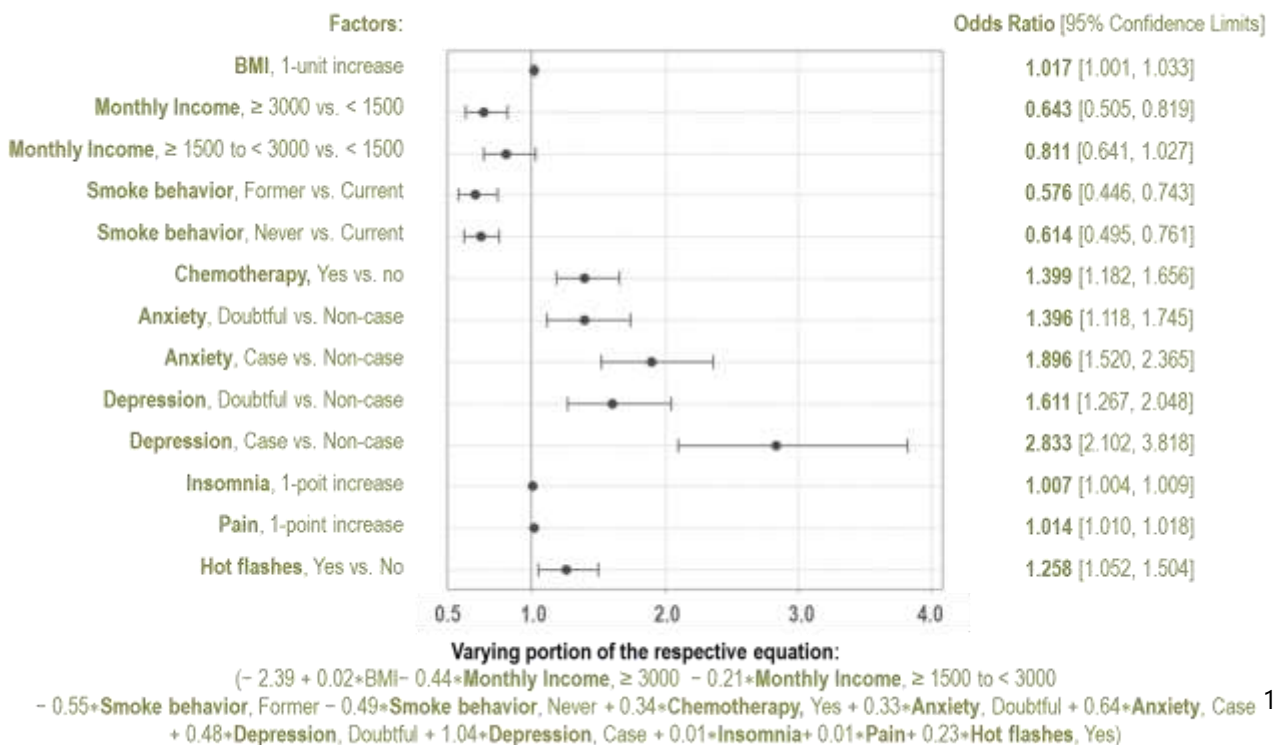


Figure 2: Characteristics that predict severe physical fatigue at T1 (2A), T2 (2B) and T3 (2C).

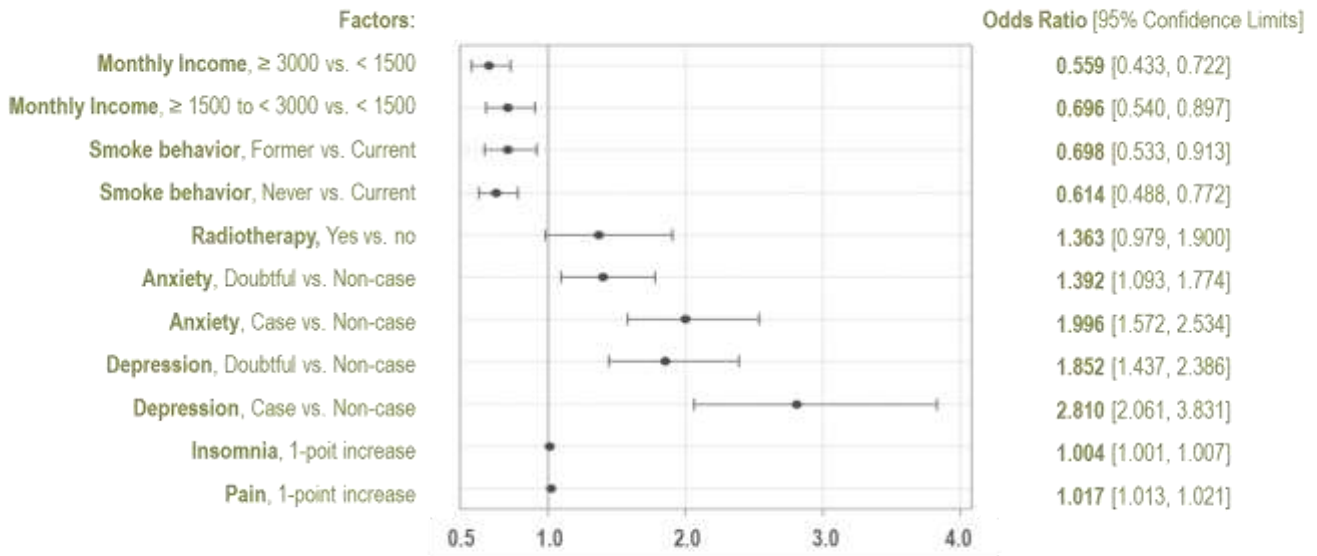
#### Severe Emotional fatigue

Active smoking, anxiety, depression and pain were consistently significant associations of severe emotional fatigue across the three time points (MS5-Figure 3; see MS5-Supplementary Table 4 for the full model). In addition, lower income was associated with severe emotional fatigue, especially at T1 and T2. The optimism-corrected c-statistic was 0.72309, 0.72391 and 0.70474, at T1, T2 and T3, respectively.

### 3A. Severe emotional fatigue, year-1 after diagnosis



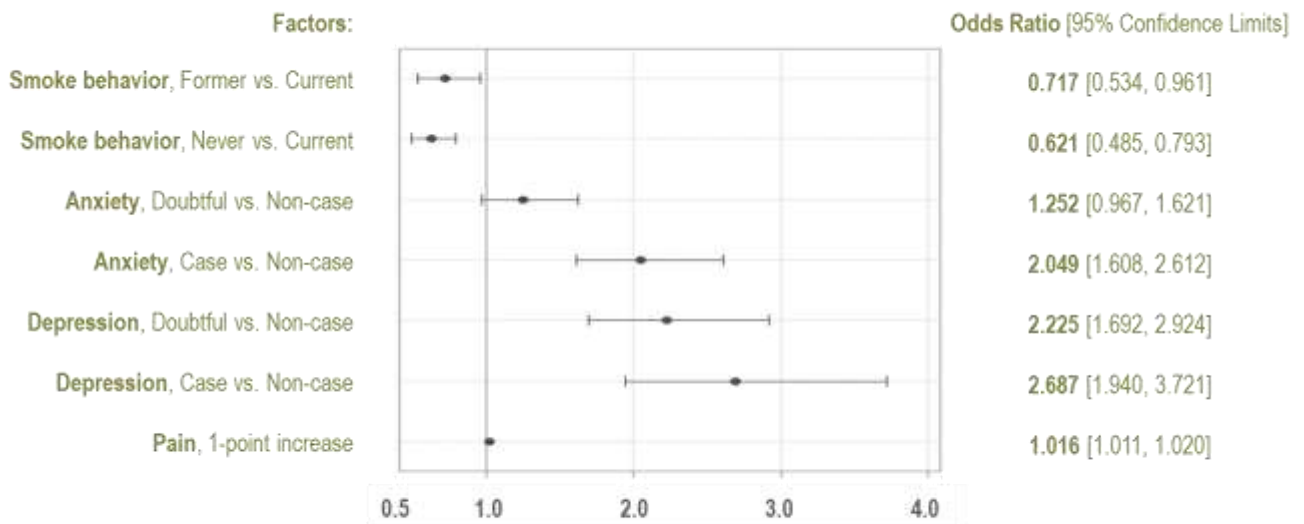
### 3B. Severe emotional fatigue, year-2 after diagnosis



Varying portion of the respective equation:

$$(-1.93 - 0.58 * \text{Monthly Income, } \geq 3000 - 0.36 * \text{Monthly Income, } \geq 1500 \text{ to } < 3000 - 0.36 * \text{Smoke behavior, Former} - 0.49 * \text{Smoke behavior, Never} + 0.31 * \text{Radiotherapy, Yes} + 0.33 * \text{Anxiety, Doubtful} + 0.69 * \text{Anxiety, Case} + 0.62 * \text{Depression, Doubtful} + 1.03 * \text{Depression, Case} + 0.01 * \text{Insomnia} + 0.02 * \text{Pain})$$

### 3C. Severe emotional fatigue, year-4 after diagnosis



Varying portion of the respective equation:

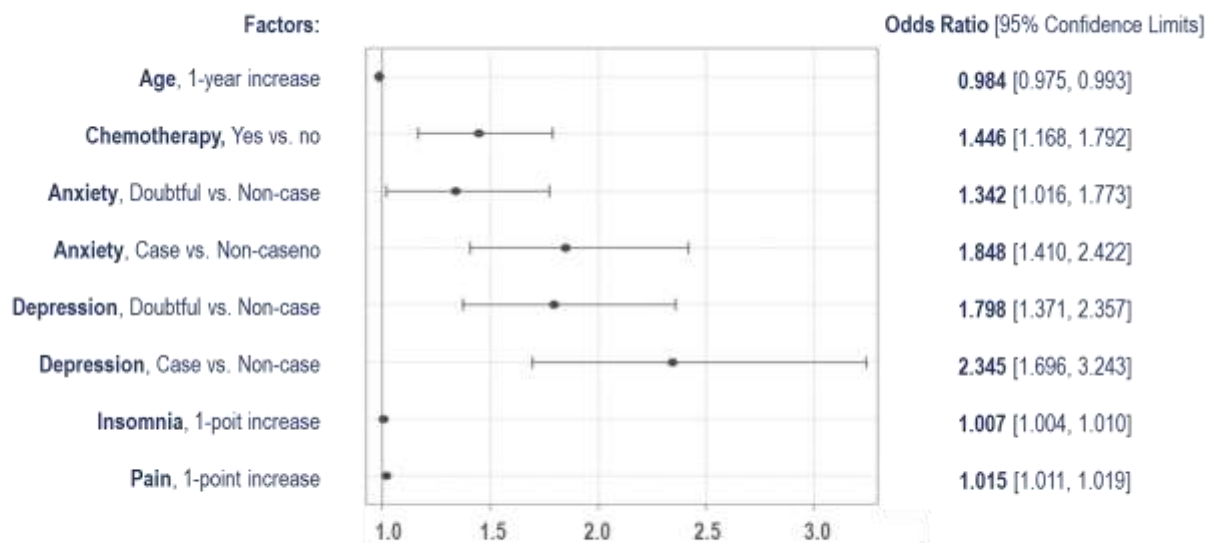
$$(1.88 - 0.33 * \text{Smoke behavior, Former} - 0.48 * \text{Smoke behavior, Never} + 0.23 * \text{Anxiety, Doubtful} + 0.72 * \text{Anxiety, Case} + 0.80 * \text{Depression, Doubtful} + 0.99 * \text{Depression, Case} + 0.02 * \text{Pain})$$

**Figure 3: Characteristics that predict severe emotional fatigue at T1 (3A), T2 (3B) and T3 (3C).**

#### Severe Cognitive fatigue

Correlates of severe cognitive fatigue were similar to those of emotional severe fatigue. Anxiety, depression, insomnia and pain were consistently significant across the three time points (**MS5-Figure 4**; see **MS5-Supplementary Table 5** for the full model). Severe cognitive fatigue was impacted by chemotherapy at T1, namely the time point that is closest to the end of active chemotherapy, and by lower income at T2 and T3. The optimism-corrected c-statistic was 0.72640, 0.70868 and 0.70464, at T1, T2 and T3, respectively.

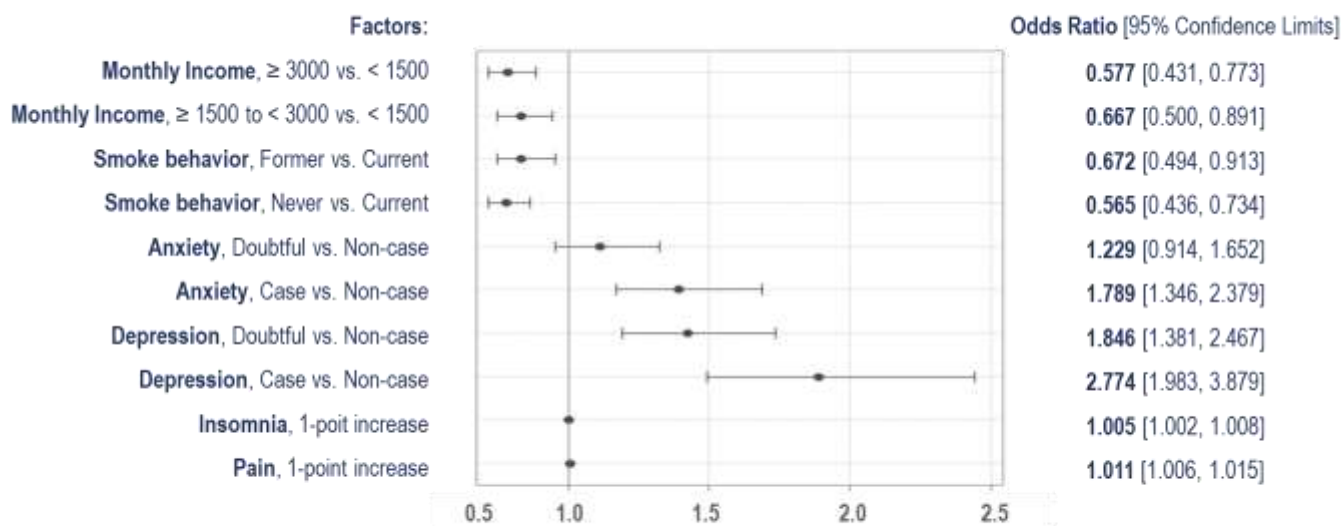
#### 4A. Severe cognitive fatigue, year-1 after diagnosis



Varying portion of the respective equation:

$$(-2.36 - 0.02 \cdot \text{Age} + 0.37 \cdot \text{Chemotherapy, Yes} + 0.29 \cdot \text{Anxiety, Doubtful} + 0.61 \cdot \text{Anxiety, Case} + 0.59 \cdot \text{Depression, Doubtful} + 0.85 \cdot \text{Depression, Case} + 0.01 \cdot \text{Insomnia} + 0.02 \cdot \text{Pain})$$

#### 4B. Severe cognitive fatigue, year-2 after diagnosis



Varying portion of the respective equation:

$$(-2.02 - 0.55 \cdot \text{Monthly Income, } \geq 3000 - 0.40 \cdot \text{Monthly Income, } \geq 1500 \text{ to } < 3000 - 0.40 \cdot \text{Smoke behavior, Former} - 0.57 \cdot \text{Smoke behavior, Never} + 0.21 \cdot \text{Anxiety, Doubtful} + 0.58 \cdot \text{Anxiety, Case} + 0.61 \cdot \text{Depression, Doubtful} + 1.02 \cdot \text{Depression, Case} + 0.01 \cdot \text{Insomnia} + 0.01 \cdot \text{Pain})$$

#### 4C. Severe cognitive fatigue, year-4 after diagnosis

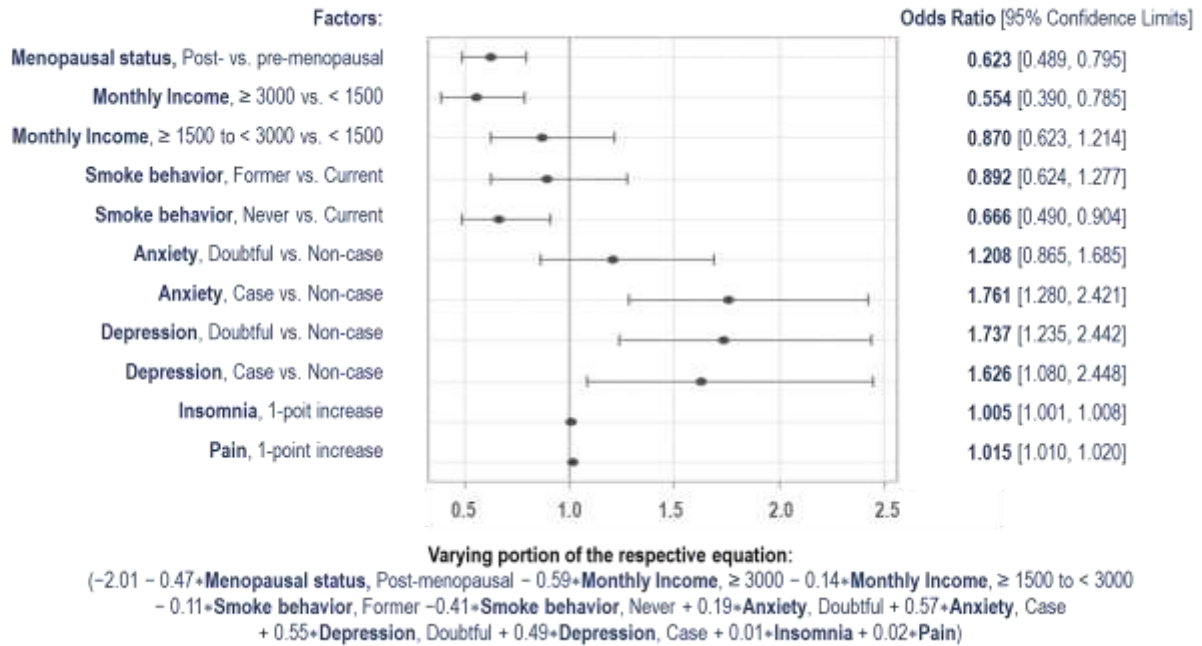


Figure 4: Characteristics that predict severe cognitive fatigue at T1 (4A), T2 (4B) and T3 (4C).

#### Discussion

Fatigue is a very common side effect of breast cancer and cancer treatment, and the vast majority of breast cancer patients are expected to experience fatigue during the active phase of treatment. While it typically improves after treatment completion, about a third of patients endure fatigue post-treatment, which can last several years. The characteristics that emerge from this study give us a sense of the patient population who are at risk of developing persistent fatigue: these seem to correspond to those who are medically, socially and economically fragile at the time of diagnosis. Surprisingly, the associations that we found were often similar across the different dimensions of fatigue, pointing at a group of patients with specific and consistent characteristics that should be helped aggressively since the beginning of the cancer trajectory.

Several prior studies (mainly retrospective and cross-sectional) identified associations with severe cancer-related fatigue after breast cancer treatment. Consistent with previous data, we identified that preexisting psychological distress, symptoms and lifestyle factors play an important role in the presence of fatigue over time.<sup>115,234–239</sup> However, while most studies have focused on fatigue during or immediately after treatment, we evaluated the risk factors for fatigue among breast cancer survivors at different time points up to 4 years after diagnosis.

Findings of our study are novel since they suggest that most of fatigue correlates are shared across the distinct fatigue domains and over the temporal trajectory, as they significantly persist overtime. However, there are some factors that are subject to significant variation in the way they impact fatigue and its different domains. Notably, distinct types of treatment impact fatigue with varying patterns. On the short term, an

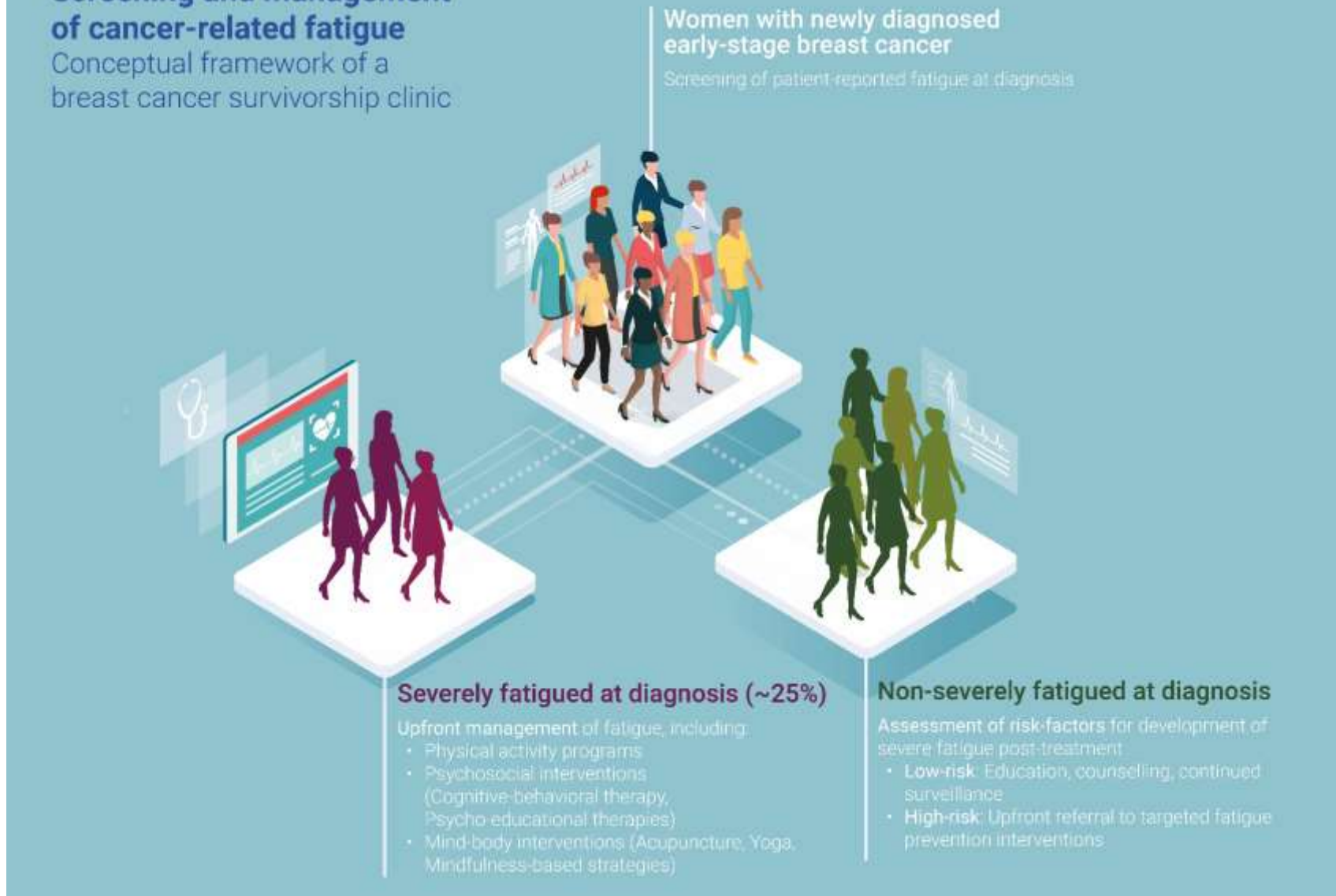
impact of chemotherapy on cognitive fatigue was present, which seemed resolve at later assessments. This is in line with previous reports suggesting that cognitive impairment is transitory and mostly described in the aftermath of chemotherapy in breast cancer survivors.<sup>240,241</sup> In contrast, on the long term, a negative impact of endocrine therapy was found, appearing at 1 year after initiation of adjuvant endocrine therapy and with increasing magnitude over time.

Currently, there is substantial evidence that cancer-related fatigue is under addressed. Recently, our group suggested a suboptimal utilization of strategies to manage cancer-related fatigue, including inadequate physical activity levels and referral for psychosocial services among survivors reporting severe fatigue. There is therefore a major need to improve fatigue management pathways in clinical care. The present study can serve as a model to implement the screening of patients for long-term fatigue in a conceptual framework for a breast cancer survivorship clinic. Such model may be integrated in a comprehensive fatigue management algorithm, which we propose in **MS5-Figure 5**. Briefly, we may envision an ideal clinical care setting, with screening of severe fatigue at diagnosis, in order to filter patients that need: A) upfront management of fatigue because they already experience severe fatigue before treatment, being therefore in need of strategies to mitigate symptoms, vs. B) assessment of risk-factors that include medical, treatment factors, psychological distress, pain and other symptoms, in order to detect the presence of warning signs for those patients at high-risk to face development of severe fatigue in the aftermath of treatment and during their cancer treatment trajectory. Particularly, the latter would allow the definition of a patient profile risk that prompts referral to dedicated fatigue prevention interventions. Therefore, we produced predictive equations that can potentially be integrated in such algorithm, eventually taking advantage of modern digital tools that will be increasingly implemented in clinical settings over the next years.<sup>242</sup> CANTO data enabled us to build a tentative predicting equation for each domain of fatigue at 1, 2 and 4 years after diagnosis. As an example of application of our equations, we may consider a patient of age 51, treated with chemotherapy, with HADS scores suggestive of overt anxiety and depression, and scoring 100/100 on the insomnia and pain scales of EORTC QLQ-C30. For this patient, our equation would return a high risk score for severe cognitive fatigue at T1, of 81% (see example of equation below, with reference to model/equation displayed in **MS5-Figure 4A**):

$$\frac{-2.36 - (0.02*51 [Age] + (0.37*1 [Receipt chemotherapy]) + (0.61*1 [Anxiety case]) + (0.84*1 [Depression case]) + (0.01*100 [Insomnia score]) + (0.02*100 [Pain score])}{1 + e^{(-2.36 - (0.02*51 [Age] + (0.37*1 [Receipt chemotherapy]) + (0.61*1 [Anxiety case]) + (0.84*1 [Depression case]) + (0.01*100 [Insomnia score]) + (0.02*100 [Pain score])}}$$

## Screening and management of cancer-related fatigue

Conceptual framework of a breast cancer survivorship clinic



MS5-Figure 5. Screening and management of cancer-related fatigue. A conceptual framework of a breast cancer survivorship clinic.

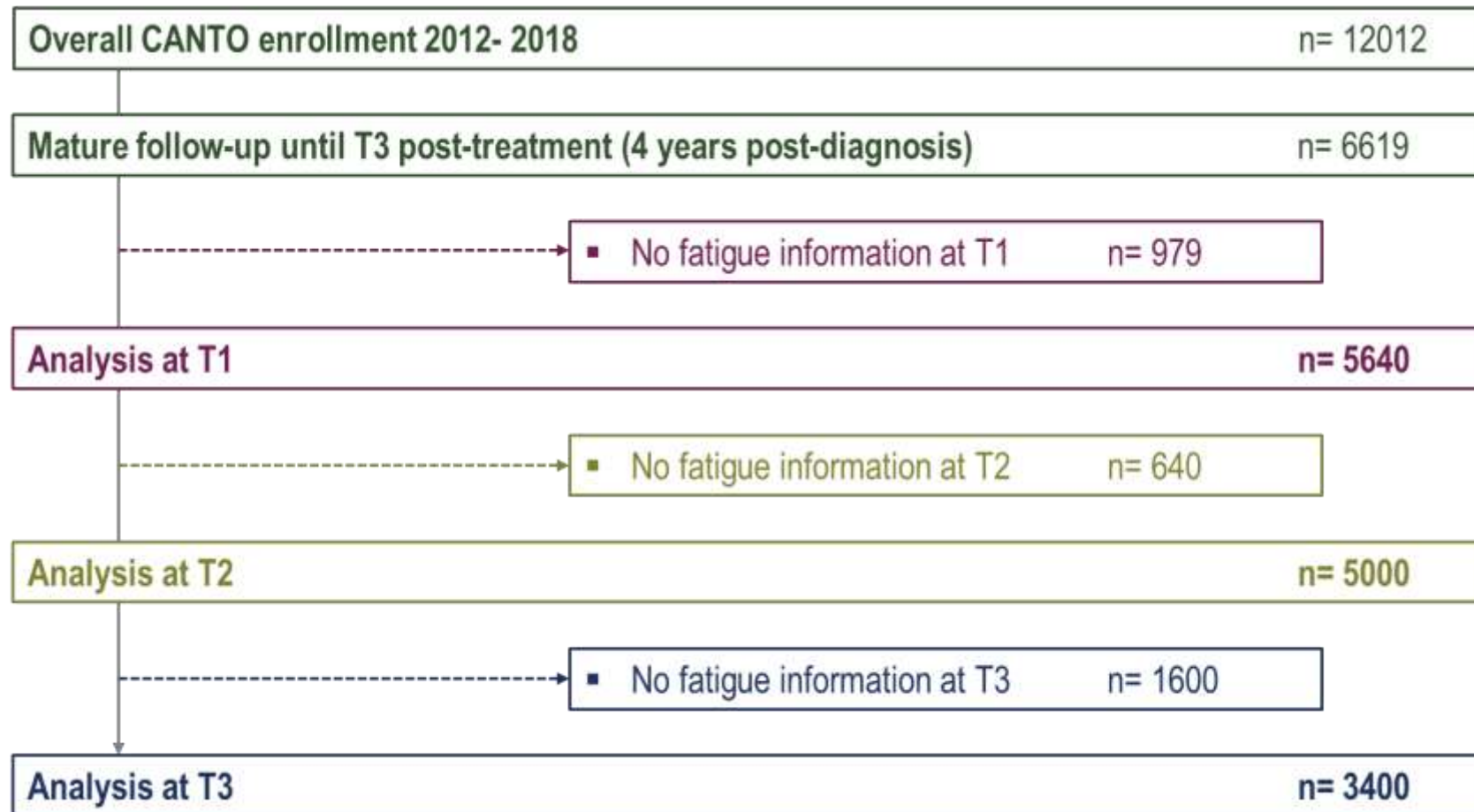
We acknowledge that our predictive equations and their utility in a clinical care setting require validation in dedicated clinical trials. However, our analysis generated a number of tentative predictive equations, involving model reiterations for distinct domains of fatigue and at several longitudinal time points. We could clearly observe a very consistent pattern for clinico-behavioral associations, supporting a notion of robustness and internal validity for our findings. Our models may therefore already provide a useful framework in breast cancer survivorship care, setting up to predict cancer-related fatigue following breast cancer treatment.

Lately, the use of digital platforms to serve cancer research and patients care has resulted in greater awareness and better management of symptoms, turning into improved quality of life and survival in specific indications. In 2017, Basch et al. proposed a system that integrates self-reporting of common symptoms during chemotherapy (and that would then trigger alerts to clinicians), applicable to several types of metastatic solid tumors.<sup>243</sup> In the intervention of Basch and colleagues, symptom reporting resulted not only in higher quality of life and less emergency room visits, but also in a survival benefit exceeding five months compared to usual care. Such benefit compares to other recent treatment advances in medical oncology: routine symptom monitoring was indeed able to outperform the overall survival advantage of all the medical oncology treatments approved in 2016 by the FDA for various indications. Gustave Roussy recently Developed CAPRI ("Cancérologie Parcours de soins Région Ile-de-France"), a tool used in a randomized controlled trial that tested the use of a mobile application combined with a nursing-led follow-up to manage symptoms and assess toxicities, adherence to oral treatment and supportive care needs of cancer survivors, which proved to contribute to better treatment delivery.<sup>242</sup> We can envision that the use of these digital strategies can be tested with the aim of improving long-term symptomatology in breast cancer survivors, including fatigue.

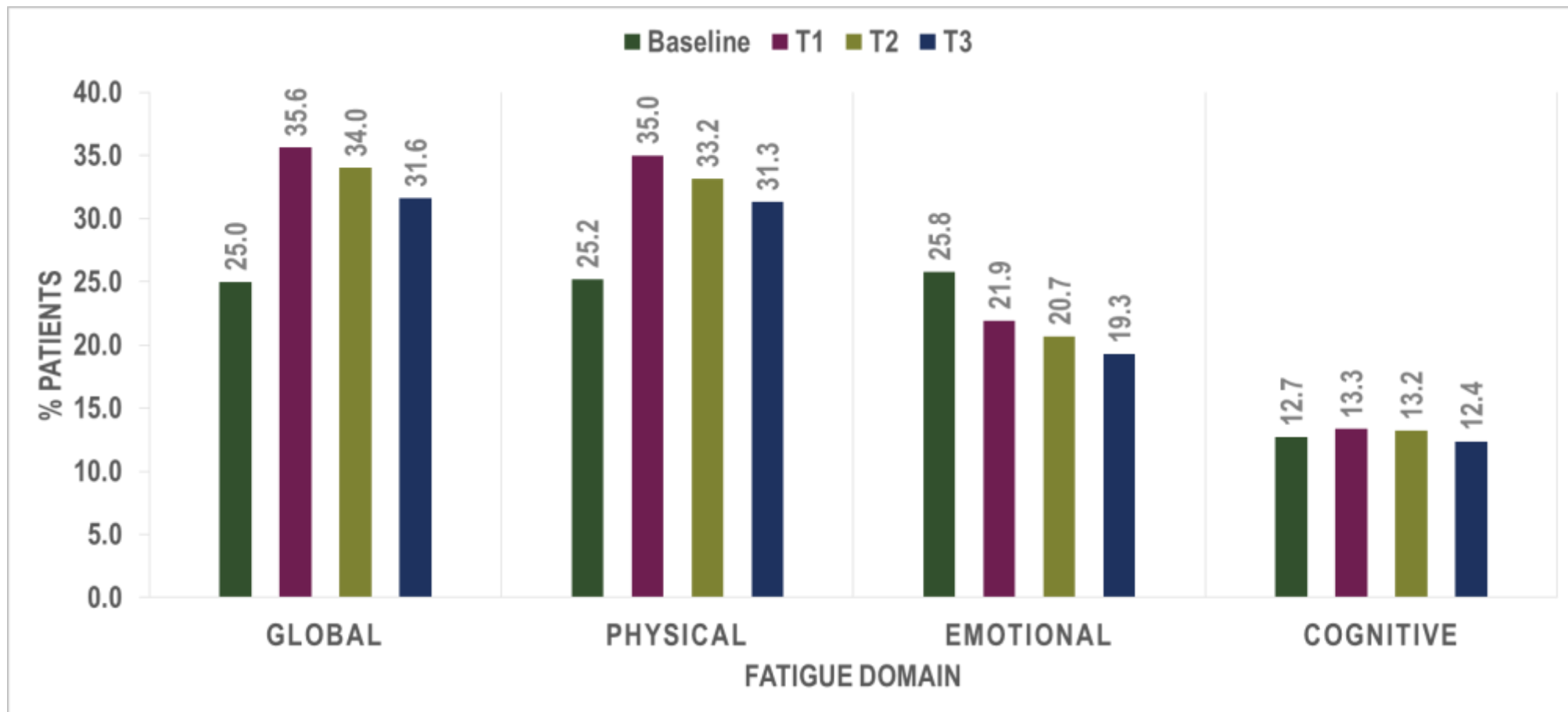
The strengths of this study are the large cohort, the prospective and longitudinal design that followed patients from treatment completion into the survivorship period, and the evaluation of different domains of fatigue. The study's limitations must be acknowledged. CANTO is a longitudinal study, and reduction of patient retention over the years is inevitable and expected. The cohort lost about half of patients (49%) at 4 years following diagnosis. When comparing the patients who are included and excluded at different time points, the characteristics of patients who were excluded (mostly for not coming back for follow-up visits) were very similar to those who experienced persistent fatigue, presenting unhealthy behaviors, lower income, psychological distress and symptoms. Also, while this was a relatively large study, patient loss limits the generalizability of results. In addition, although the models were re-run internally and are very consistent across domains and time, we acknowledge a need of validation in an external cohort.

In conclusion, we have developed predictive models of severe global and specific dimensions of severe fatigue in the years following breast cancer treatment completion. These models can help clinicians with the early management of patients at risk of developing persistent fatigue. Better understanding of mechanisms of fatigue and implementation of fatigue screening and prevention algorithms in a clinical care setting are needed to develop efficient fatigue-reducing interventions.

Data Supplement



MS5-Supplementary Figure 1. Study Flowchart.



**MS5-Supplementary Figure 2.** Prevalence of severe global fatigue and of severe fatigue by dimension over time.

**MS5-Supplementary Table 1A. Distribution of cohort characteristics by severe physical fatigue at T1, T2, T3 after diagnosis, N (%).**

Characteristics	T1 (1 year after diagnosis)		T2 (2 years after diagnosis)		T3 (4 years after diagnosis)	
	Severe Fatigue N=1966 (35.0%)	Non-severe Fatigue N=3651 (65.0%)	Severe Fatigue N=1644 (33.2%)	Non-severe Fatigue N=3315 (66.8%)	Severe Fatigue N=1054 (31.3%)	Non-severe Fatigue N=2312 (68.7%)
<i>Clinical factors</i>						
<b>Age at diagnosis, years</b>						
Mean ± SD	55.3±11.5	56.8±11.2	55.2±11.5	56.7±11.0	55.6±11.3	57.1±10.7
Min-Max	25.0–88.0	22.0–89.0	23.0–88.0	22.0–88.0	26.0–88.0	22.0–85.0
<b>BMI at diagnosis, Kg/m<sup>2</sup></b>						
Mean ± SD	26.7±5.8	25.5±5.1	26.3±5.5	25.6±5.2	26.3±5.3	25.6±5.2
Missing	10	11	5	11	4	8
<b>Menopausal status</b>						
Premenopausal	771 (40.2)	1279 (35.5)	658 (40.8)	1158 (35.5)	416 (40.1)	754 (33.3)
Postmenopausal	1149 (59.8)	2319 (64.5)	953 (59.2)	2103 (64.5)	621 (59.9)	1510 (66.7)
Missing	46	53	33	54	17	48
<b>Charlson comorbidity index</b>						
0	1387 (76.8)	2743 (81.1)	1156 (76.8)	2524 (81.7)	757 (78.1)	1773 (81.9)
≥1	420 (23.2)	639 (18.9)	349 (23.2)	565 (18.3)	212 (21.9)	391 (18.1)
Missing	159	269	139	226	85	148
<b>Marital Status</b>						
Not partnered	555 (30.5)	861 (25.5)	459 (29.9)	754 (24.5)	279 (28.5)	523 (24.4)
Partnered	1265 (69.5)	2509 (74.5)	1075 (70.1)	2329 (75.5)	699 (71.5)	1623 (75.6)
Missing	146	281	110	232	76	166
<b>Education level</b>						
Primary school	299 (16.2)	506 (14.7)	229 (14.7)	454 (14.5)	150 (15.0)	334 (15.2)
High school	900 (48.6)	1591 (46.4)	740 (47.4)	1467 (46.7)	465 (46.5)	1026 (46.7)
College or higher	652 (35.2)	1335 (38.9)	593 (38.0)	1217 (38.8)	385 (38.5)	835 (38.0)
Missing	115	219	82	177	54	117
<b>Household income, Euros/month</b>						
< 1500	352 (20.4)	416 (13.2)	273 (18.7)	361 (12.4)	151 (15.9)	268 (13.3)
≥ 1500 to < 3000	651 (37.7)	1499 (47.4)	573 (39.3)	1407 (48.3)	395 (41.6)	970 (48.1)
> 3000	726 (42.0)	1246 (39.4)	611 (41.9)	1145 (39.3)	403 (42.5)	780 (38.7)
Missing	237	490	187	402	105	294
<b>Alcohol consumption behavior</b>						
Less than daily	1625 (85.1)	3070 (86.4)	1362 (85.7)	2767 (86.2)	865 (85.3)	1942 (86.7)
Daily	285 (14.9)	483 (13.6)	228 (14.3)	444 (13.8)	149 (14.7)	299 (13.3)
Missing	0	98	54	104	40	71
<b>Tobacco use behavior</b>						
Current smoker	416 (21.5)	511 (14.2)	346 (21.4)	440 (13.5)	196 (19.0)	314 (13.8)
Former smoker	424 (21.9)	779 (21.7)	363 (22.4)	693 (21.3)	221 (21.4)	451 (19.9)
Never smoker	1098 (56.7)	2299 (64.1)	911 (56.2)	2122 (65.2)	616 (59.6)	1504 (66.3)
Missing	0	62	24	60	21	43
<b>Physical activity (MET-h/week)</b>						
Median (Q1-Q3)	12.0 (0.0–36.0)	16.0 (0.7–40.0)	13.2 (0.0–40.0)	16.0 (1.3–40.0)	14.0 (0.0–40.0)	16.0 (1.3–40.0)
Missing	99	182	68	145	47	98
<b>Tumor stage</b>						
Stage I	910 (46.3)	1890 (51.8)	775 (47.2)	1742 (52.6)	524 (49.8)	1247 (54.0)
Stage II	834 (42.4)	1422 (39.0)	702 (42.8)	1272 (38.4)	445 (42.3)	892 (38.6)
Stage III	221 (11.2)	336 (9.2)	164 (10.0)	300 (9.1)	84 (8.0)	171 (7.4)
Missing	1	3	3	1	1	2
<b>Tumor subtype</b>						
HR+ HER2+	228 (11.7)	366 (10.1)	190 (11.6)	327 (9.9)	117 (11.2)	239 (10.4)
HR+ HER2-	1459 (74.7)	2797 (77.2)	1259 (77.1)	2529 (76.9)	820 (78.2)	1764 (76.8)
HR- HER2+	82 (4.2)	144 (4.0)	52 (3.2)	145 (4.4)	34 (3.2)	91 (4.0)
HR- HER2-	185 (9.5)	317 (8.7)	133 (8.1)	288 (8.8)	77 (7.3)	202 (8.8)
Missing	12	27	10	26	6	16

<i>Treatment-related factors</i>						
<b>Axillary surgery</b>						
None or sentinel	1124 (57.2)	2241 (61.4)	956 (58.2)	2071 (62.5)	630 (59.8)	1477 (63.9)
Dissection	842 (42.8)	1410 (38.6)	688 (41.8)	1244 (37.5)	424 (40.2)	835 (36.1)
<b>Breast cancer surgery</b>						
Conservative	1421 (72.3)	2694 (73.8)	1184 (72.0)	2471 (74.5)	783 (74.3)	1762 (76.2)
Mastectomy	545 (27.7)	957 (26.2)	460 (28.0)	844 (25.5)	271 (25.7)	550 (23.8)
<b>Chemotherapy</b>						
No	817 (41.6)	1802 (49.4)	712 (43.3)	1621 (48.9)	471 (44.7)	1190 (51.5)
Yes	1149 (58.4)	1848 (50.6)	932 (56.7)	1694 (51.1)	583 (55.3)	1122 (48.5)
Missing	0	1	0	0	0	0
<b>Radiotherapy</b>						
No	146 (7.4)	345 (9.5)	141 (8.6)	293 (8.8)	91 (8.6)	199 (8.6)
Yes	1820 (92.6)	3303 (90.5)	1502 (91.4)	3021 (91.2)	963 (91.4)	2112 (91.4)
Missing	0	3	1	1	0	1
<b>Hormonotherapy</b>						
No	360 (18.3)	684 (18.7)	258 (15.7)	623 (18.8)	162 (15.4)	439 (19.0)
Yes	1606 (81.7)	2966 (81.3)	1386 (84.3)	2692 (81.2)	892 (84.6)	1872 (81.0)
Missing	0	1	0	0	0	1
<b>Anti HER-2 therapy</b>						
No	1713 (87.1)	3247 (89.0)	1456 (88.6)	2937 (88.6)	934 (88.6)	2049 (88.6)
Yes	253 (12.9)	403 (11.0)	188 (11.4)	378 (11.4)	120 (11.4)	263 (11.4)
Missing	0	1	0	0	0	0
<i>Symptoms</i>						
<b>Anxiety</b>						
Non-case	548 (29.5)	1532 (44.1)	469 (29.8)	1382 (43.6)	305 (30.2)	970 (43.8)
Doubtful	483 (26.0)	938 (27.0)	411 (26.1)	836 (26.4)	265 (26.3)	597 (26.9)
Case	827 (44.5)	1000 (28.8)	693 (44.1)	952 (30.0)	439 (43.5)	650 (29.3)
Missing	108	181	71	145	45	95
<b>Depression</b>						
Non-case	1294 (69.6)	3066 (88.3)	1116 (70.9)	2780 (87.7)	730 (72.3)	1960 (88.3)
Doubtful	315 (16.9)	286 (8.2)	257 (16.3)	265 (8.4)	151 (15.0)	173 (7.8)
Case	250 (13.4)	120 (3.5)	202 (12.8)	126 (4.0)	128 (12.7)	87 (3.9)
Missing	107	179	69	144	45	92
<b>Insomnia</b>						
Mean ± SD	51.4±34.7	37.8±31.4	50.9±35.0	38.2±31.4	50.2±33.9	37.2±31.3
Missing	91	158	55	136	36	82
<b>Pain</b>						
Mean ± SD	24.0±25.5	11.7±17.9	22.8±24.6	11.6±18.1	22.7±24.6	11.4±18.1
Missing	76	139	45	113	31	69
<b>Hot flashes</b>						
No	620 (33.0)	925 (26.3)	486 (31.1)	856 (26.8)	285 (28.6)	595 (26.8)
Yes	1257 (67.0)	2588 (73.7)	1079 (68.9)	2336 (73.2)	713 (71.4)	1623 (73.2)
Missing	89	138	79	123	56	94
SD: Standard Deviation; Q: Quartile; BMI: Body Mass Index; MET-h: Metabolic-equivalent of task-hour; HR: hormone receptor, HER2: Human epidermal growth factor receptor 2. Anxiety and Depression scored according to the Hospital Anxiety and Depression Scale: non- case (score 0-7), doubtful (8-10), case (11-21).						

**MS5-Supplementary Table 1B. Distribution of cohort characteristics by severe emotional fatigue at T1, T2, T3 after diagnosis, N (%).**

Characteristics	T1 (1 year after diagnosis)		T2 (2 years after diagnosis)		T3 (4 years after diagnosis)	
	Severe Fatigue N=1227 (21.9%)	Non-severe Fatigue N=4368 (78.1%)	Severe Fatigue N=1025 (20.7%)	Non-severe Fatigue N=3928 (79.3%)	Severe Fatigue N=645 (19.3%)	Non-severe Fatigue N=2700 (80.7%)
<i>Clinical factors</i>						
<b>Age at diagnosis, years</b>						
Mean ± SD	54.8±11.1	56.6±11.3	55.2±11.2	56.5±11.2	55.5±11.1	56.8±10.8
Min-Max	26.0–85.0	22.0–89.0	26.0–88.0	22.0–88.0	26.0–88.0	22.0–85.0
<b>BMI at diagnosis, Kg/m<sup>2</sup></b>						
Mean ± SD	26.5±5.7	25.8±5.3	26.3±5.6	25.7±5.2	26.1±5.3	25.7±5.2
Missing	5	16	6	10	4	8
<b>Menopausal status</b>						
Premenopausal	506 (42.1)	1538 (35.8)	402 (39.8)	1413 (36.6)	243 (38.1)	926 (35.0)
Postmenopausal	696 (57.9)	2756 (64.2)	607 (60.2)	2444 (63.4)	394 (61.9)	1717 (65.0)
Missing	25	74	16	71	8	57
<b>Charlson comorbidity index</b>						
0	863 (77.1)	3250 (80.2)	725 (77.8)	2949 (80.7)	475 (80.0)	2040 (81.0)
≥1	257 (22.9)	800 (19.8)	207 (22.2)	707 (19.3)	119 (20.0)	480 (19.0)
Missing	107	318	93	272	51	180
<b>Marital Status</b>						
Not partnered	336 (30.0)	1075 (26.5)	271 (28.4)	935 (25.6)	175 (29.5)	616 (24.5)
Partnered	784 (70.0)	2980 (73.5)	682 (71.6)	2723 (74.4)	418 (70.5)	1896 (75.5)
Missing	107	313	72	270	52	188
<b>Education level</b>						
Primary school	182 (15.8)	621 (15.1)	158 (16.4)	525 (14.1)	92 (15.0)	383 (14.9)
High school	581 (50.5)	1904 (46.3)	463 (48.1)	1741 (46.6)	285 (46.3)	1199 (46.8)
College or higher	387 (33.7)	1591 (38.7)	341 (35.4)	1468 (39.3)	238 (38.7)	980 (38.3)
Missing	77	252	63	194	30	138
<b>Household income, Euros/month</b>						
< 1500	214 (19.9)	553 (14.5)	182 (20.1)	449 (13.0)	105 (18.2)	307 (12.9)
≥ 1500 to < 3000	399 (37.1)	1746 (45.9)	340 (37.6)	1641 (47.4)	229 (39.6)	1135 (47.8)
> 3000	462 (43.0)	1503 (39.5)	383 (42.3)	1369 (39.6)	244 (42.2)	932 (39.3)
Missing	152	566	120	469	67	326
<b>Alcohol consumption behavior</b>						
Less than daily	1002 (84.5)	3674 (86.3)	834 (84.7)	3288 (86.3)	524 (84.7)	2264 (86.6)
Daily	184 (15.5)	581 (13.7)	151 (15.3)	521 (13.7)	95 (15.3)	351 (13.4)
Missing	40	113	40	119	26	85
<b>Tobacco use behavior</b>						
Current smoker	288 (23.9)	635 (14.8)	238 (23.6)	548 (14.2)	139 (21.9)	370 (14.0)
Former smoker	253 (21.0)	948 (22.1)	224 (22.2)	828 (21.5)	136 (21.4)	534 (20.2)
Never smoker	665 (55.1)	2716 (63.2)	547 (54.2)	2483 (64.3)	360 (56.7)	1742 (65.8)
Missing	20	69	16	69	10	54
<b>Physical activity (MET-h/week)</b>						
Median (Q1-Q3)	12.0 (0.0–39.3)	14.7 (0.3–38.0)	12.0 (0.0–40.0)	16.0 (1.3–40.0)	14.0 (0.0–42.0)	16.0 (1.3–40.0)
Missing	73	204	55	158	30	115
<b>Tumor stage</b>						
Stage I	539 (44.0)	2248 (51.5)	483 (47.2)	2034 (51.8)	311 (48.3)	1450 (53.7)
Stage II	538 (43.9)	1710 (39.2)	432 (42.2)	1537 (39.2)	277 (43.0)	1051 (39.0)
Stage III	149 (12.2)	407 (9.3)	109 (10.6)	354 (9.0)	56 (8.7)	197 (7.3)
Missing	1	3	1	3	1	2
<b>Tumor subtype</b>						
HR+ HER2+	131 (10.7)	463 (10.7)	113 (11.1)	400 (10.3)	74 (11.6)	280 (10.4)
HR+ HER2-	919 (75.1)	3319 (76.6)	796 (77.9)	2990 (76.8)	498 (77.8)	2069 (77.1)
HR- HER2+	51 (4.2)	173 (4.0)	33 (3.2)	164 (4.2)	22 (3.4)	103 (3.8)
HR- HER2-	122 (10.0)	378 (8.7)	80 (7.8)	341 (8.8)	46 (7.2)	231 (8.6)
Missing	4	35	3	33	5	17

<i>Treatment-related factors</i>						
<b>Axillary surgery</b>						
None or sentinel	684 (55.7)	2667 (61.1)	579 (56.5)	2447 (62.3)	373 (57.8)	1722 (63.8)
Dissection	543 (44.3)	1701 (38.9)	446 (43.5)	1481 (37.7)	272 (42.2)	978 (36.2)
<b>Breast cancer surgery</b>						
Conservative	885 (72.1)	3214 (73.6)	732 (71.4)	2921 (74.4)	464 (71.9)	2066 (76.5)
Mastectomy	342 (27.9)	1154 (26.4)	293 (28.6)	1007 (25.6)	181 (28.1)	634 (23.5)
<b>Chemotherapy</b>						
No	475 (38.7)	2129 (48.7)	459 (44.8)	1875 (47.7)	290 (45.0)	1357 (50.3)
Yes	751 (61.3)	2239 (51.3)	566 (55.2)	2053 (52.3)	355 (55.0)	1343 (49.7)
Missing	0	0	0	0	0	0
<b>Radiotherapy</b>						
No	103 (8.4)	385 (8.8)	84 (8.2)	348 (8.9)	68 (10.5)	221 (8.2)
Yes	1124 (91.6)	3980 (91.2)	941 (91.8)	3578 (91.1)	577 (89.5)	2478 (91.8)
Missing	0	3	0	2	0	1
<b>Hormonotherapy</b>						
No	231 (18.8)	810 (18.5)	163 (15.9)	718 (18.3)	105 (16.3)	491 (18.2)
Yes	995 (81.2)	3558 (81.5)	862 (84.1)	3210 (81.7)	540 (83.7)	2208 (81.8)
Missing	0	0	0	0	0	1
<b>Anti HER-2 therapy</b>						
No	1070 (87.3)	3870 (88.6)	907 (88.5)	3485 (88.7)	565 (87.6)	2398 (88.8)
Yes	156 (12.7)	498 (11.4)	118 (11.5)	443 (11.3)	80 (12.4)	302 (11.2)
Missing	0	0	0	0	0	0
<i>Symptoms</i>						
<b>Anxiety</b>						
Non-case	262 (22.7)	1814 (43.7)	222 (22.9)	1627 (43.2)	150 (24.4)	1117 (43.1)
Doubtful	283 (24.5)	1131 (27.2)	223 (23.0)	1019 (27.1)	138 (22.5)	717 (27.7)
Case	610 (52.8)	1210 (29.1)	525 (54.1)	1121 (29.8)	326 (53.1)	757 (29.2)
Missing	72	213	55	161	31	109
<b>Depression</b>						
Non-case	735 (63.6)	3613 (86.9)	616 (63.4)	3275 (86.9)	398 (64.8)	2276 (87.7)
Doubtful	224 (19.4)	373 (9.0)	190 (19.6)	331 (8.8)	119 (19.4)	203 (7.8)
Case	196 (17.0)	172 (4.1)	165 (17.0)	163 (4.3)	97 (15.8)	115 (4.4)
Missing	72	210	54	159	31	106
<b>Insomnia</b>						
Mean ± SD	55.0±34.8	39.0±31.9	54.5±35.3	39.3±31.9	52.2±34.5	38.7±31.7
Missing	59	186	40	150	18	100
<b>Pain</b>						
Mean ± SD	25.3±26.3	13.3±19.4	24.5±25.3	13.0±19.2	23.6±25.0	12.7±19.3
Missing	49	161	34	124	18	81
<b>Hot flashes</b>						
No	386 (33.1)	1154 (27.5)	321 (32.9)	1021 (27.0)	181 (29.7)	693 (26.8)
Yes	779 (66.9)	3050 (72.5)	654 (67.1)	2755 (73.0)	429 (70.3)	1892 (73.2)
Missing	62	164	50	152	35	115
SD: Standard Deviation; Q: Quartile; BMI: Body Mass Index; MET-h: Metabolic-equivalent of task-hour; HR: hormone receptor, HER2: Human epidermal growth factor receptor 2. Anxiety and Depression scored according to the Hospital Anxiety and Depression Scale: non- case (score 0-7), doubtful (8-10), case (11-21).						

**MS5-Supplementary Table 1C. Distribution of cohort characteristics by severe cognitive fatigue at T1, T2, T3 after diagnosis, N (%).**

Characteristics	T1 (1 year after diagnosis)		T2 (2 years after diagnosis)		T3 (4 years after diagnosis)	
	Severe Fatigue N=748 (13.3%)	Non-severe Fatigue N=4866 (86.7%)	Severe Fatigue N=655 (13.2%)	Non-severe Fatigue N=4306 (86.8%)	Severe Fatigue N=416 (12.4%)	Non-severe Fatigue N=2947 (87.6%)
<i>Clinical factors</i>						
<b>Age at diagnosis, years</b>						
Mean ± SD	53.1±10.4	56.7±11.4	54.1±11.3	56.5±11.2	54.3±10.9	56.9±10.9
Min-Max	26.0–86.0	22.0–89.0	26.0–88.0	22.0–88.0	26.0–88.0	22.0–85.0
<b>BMI at diagnosis, Kg/m<sup>2</sup></b>						
Mean ± SD	26.3±5.7	25.9±5.3	26.2±5.3	25.8±5.3	25.8±5.1	25.8±5.2
Missing	3	18	2	14	1	11
<b>Menopausal status</b>						
Premenopausal	350 (47.7)	1700 (35.5)	291 (45.3)	1524 (36.0)	187 (45.9)	982 (34.0)
Postmenopausal	383 (52.3)	3082 (64.5)	352 (54.7)	2707 (64.0)	220 (54.1)	1909 (66.0)
Missing	15	84	12	75	9	56
<b>Charlson comorbidity index</b>						
0	535 (78.6)	3592 (79.7)	480 (79.9)	3198 (80.1)	305 (80.1)	2223 (80.8)
≥1	146 (21.4)	913 (20.3)	121 (20.1)	797 (19.9)	76 (19.9)	527 (19.2)
Missing	67	361	54	311	35	197
<b>Marital Status</b>						
Not partnered	206 (30.5)	1209 (26.8)	172 (28.4)	1041 (25.9)	108 (27.9)	692 (25.3)
Partnered	470 (69.5)	3302 (73.2)	434 (71.6)	2971 (74.1)	279 (72.1)	2042 (74.7)
Missing	72	355	49	294	29	213
<b>Education level</b>						
Primary school	116 (16.7)	689 (15.0)	104 (16.9)	580 (14.2)	73 (18.8)	410 (14.6)
High school	332 (47.9)	2160 (47.1)	308 (50.1)	1897 (46.4)	187 (48.2)	1303 (46.5)
College or higher	245 (35.4)	1738 (37.9)	203 (33.0)	1610 (39.4)	128 (33.0)	1091 (38.9)
Missing	55	279	40	219	28	143
<b>Household income, Euros/month</b>						
< 1500	141 (21.5)	626 (14.8)	124 (21.3)	510 (13.5)	73 (19.7)	345 (13.3)
≥ 1500 to < 3000	242 (36.8)	1906 (45.1)	219 (37.7)	1761 (46.5)	125 (33.8)	1240 (47.8)
> 3000	274 (41.7)	1698 (40.1)	238 (41.0)	1517 (40.0)	172 (46.5)	1009 (38.9)
Missing	91	636	74	518	46	353
<b>Alcohol consumption behavior</b>						
Less than daily	622 (85.9)	4072 (86.0)	542 (85.8)	3586 (86.0)	346 (85.6)	2458 (86.3)
Daily	102 (14.1)	664 (14.0)	90 (14.2)	583 (14.0)	58 (14.4)	390 (13.7)
Missing	24	130	23	137	12	99
<b>Tobacco use behavior</b>						
Current smoker	168 (22.9)	758 (15.8)	165 (25.6)	622 (14.7)	94 (22.8)	416 (14.4)
Former smoker	169 (23.0)	1034 (21.6)	143 (22.2)	910 (21.5)	88 (21.4)	583 (20.2)
Never smoker	398 (54.1)	2997 (62.6)	337 (52.2)	2699 (63.8)	230 (55.8)	1888 (65.4)
Missing	13	77	10	75	4	60
<b>Physical activity (MET-h/week)</b>						
Median (Q1-Q3)	14.0 (0.0–42.0)	14.0 (0.0–38.0)	12.0 (0.0–42.0)	15.0 (0.7–40.0)	14.0 (0.0–48.0)	16.0 (0.7–40.0)
Missing	47	234	31	183	26	119
<b>Tumor stage</b>						
Stage I	308 (41.2)	2491 (51.2)	296 (45.2)	2220 (51.6)	193 (46.4)	1578 (53.6)
Stage II	329 (44.0)	1926 (39.6)	284 (43.4)	1691 (39.3)	187 (45.0)	1147 (39.0)
Stage III	111 (14.8)	445 (9.2)	75 (11.5)	391 (9.1)	36 (8.7)	219 (7.4)
Missing	0	4	0	4	0	3
<b>Tumor subtype</b>						
HR+ HER2+	86 (11.5)	508 (10.5)	75 (11.5)	443 (10.4)	59 (14.2)	297 (10.2)
HR+ HER2-	537 (71.9)	3717 (77.0)	504 (77.2)	3284 (76.9)	302 (72.6)	2279 (77.9)
HR- HER2+	33 (4.4)	192 (4.0)	19 (2.9)	179 (4.2)	16 (3.8)	109 (3.7)
HR- HER2-	91 (12.2)	411 (8.5)	55 (8.4)	366 (8.6)	39 (9.4)	240 (8.2)
Missing	1	38	2	34	0	22

<i>Treatment-related factors</i>						
<b>Axillary surgery</b>						
None or sentinel	394 (52.7)	2968 (61.0)	372 (56.8)	2654 (61.6)	237 (57.0)	1868 (63.4)
Dissection	354 (47.3)	1898 (39.0)	283 (43.2)	1652 (38.4)	179 (43.0)	1079 (36.6)
<b>Breast cancer surgery</b>						
Conservative	522 (69.8)	3589 (73.8)	456 (69.6)	3202 (74.4)	289 (69.5)	2253 (76.5)
Mastectomy	226 (30.2)	1277 (26.2)	199 (30.4)	1104 (25.6)	127 (30.5)	694 (23.5)
<b>Chemotherapy</b>						
No	261 (34.9)	2357 (48.4)	278 (42.4)	2056 (47.7)	173 (41.6)	1486 (50.4)
Yes	487 (65.1)	2508 (51.6)	377 (57.6)	2250 (52.3)	243 (58.4)	1461 (49.6)
Missing	0	1	0	0	0	0
<b>Radiotherapy</b>						
No	51 (6.8)	440 (9.0)	57 (8.7)	376 (8.7)	46 (11.1)	244 (8.3)
Yes	697 (93.2)	4423 (91.0)	598 (91.3)	3928 (91.3)	370 (88.9)	2702 (91.7)
Missing	0	3	0	2	0	1
<b>Hormonotherapy</b>						
No	148 (19.8)	895 (18.4)	106 (16.2)	777 (18.0)	75 (18.0)	526 (17.9)
Yes	600 (80.2)	3970 (81.6)	549 (83.8)	3529 (82.0)	341 (82.0)	2420 (82.1)
Missing	0	1	0	0	0	1
<b>Anti HER-2 therapy</b>						
No	645 (86.2)	4313 (88.7)	575 (87.8)	3819 (88.7)	354 (85.1)	2626 (89.1)
Yes	103 (13.8)	552 (11.3)	80 (12.2)	487 (11.3)	62 (14.9)	321 (10.9)
Missing	0	1	0	0	0	0
<i>Symptoms</i>						
<b>Anxiety</b>						
Non-case	148 (21.0)	1932 (41.8)	142 (22.9)	1707 (41.4)	98 (25.0)	1175 (41.5)
Doubtful	168 (23.9)	1251 (27.1)	135 (21.8)	1112 (27.0)	89 (22.7)	772 (27.3)
Case	388 (55.1)	1438 (31.1)	342 (55.3)	1305 (31.6)	205 (52.3)	884 (31.2)
Missing	44	245	36	182	24	116
<b>Depression</b>						
Non-case	426 (60.3)	3934 (85.1)	387 (62.4)	3509 (85.0)	254 (64.8)	2434 (85.9)
Doubtful	151 (21.4)	448 (9.7)	120 (19.4)	402 (9.7)	75 (19.1)	248 (8.8)
Case	129 (18.3)	240 (5.2)	113 (18.2)	216 (5.2)	63 (16.1)	152 (5.4)
Missing	42	244	35	179	24	113
<b>Insomnia</b>						
Mean ± SD	57.4±35.3	40.3±32.3	55.2±35.4	40.4±32.4	53.8±34.4	39.5±32.1
Missing	36	213	26	164	13	105
<b>Pain</b>						
Mean ± SD	26.1±26.5	14.4±20.4	24.2±25.2	14.0±20.1	25.2±25.8	13.4±19.8
Missing	34	181	23	135	14	86
<b>Hot flashes</b>						
No	240 (34.0)	1303 (27.8)	202 (32.8)	1142 (27.6)	130 (32.8)	750 (26.6)
Yes	465 (66.0)	3379 (72.2)	414 (67.2)	3001 (72.4)	266 (67.2)	2067 (73.4)
Missing	43	184	39	163	20	130
SD: Standard Deviation; Q: Quartile; BMI: Body Mass Index; MET-h: Metabolic-equivalent of task-hour; HR: hormone receptor, HER2: Human epidermal growth factor receptor 2. Anxiety and Depression scored according to the Hospital Anxiety and Depression Scale: non- case (score 0-7), doubtful (8-10), case (11-21).						

MS5-Supplementary Table 2A. Full logistic regression models of factors associated with severe global fatigue at each time point.															
	OR	Severe global fatigue at T1				Severe global fatigue at T2				Severe global fatigue at T3					
		95% Wald CI	p-value	global p-value	OR	95% Wald CL	p-value	global p-value	OR	95% Wald CL	p-value	global p-value			
<b>Clinical factors</b>															
<b>Age</b> , 1-year increase	0.983	0.972	0.994	0.0028	0.0028	0.972	0.960	0.983	<.0001	<.0001	0.995	0.980	1.010	0.5282	0.5282
<b>Menopausal status</b> , Post- vs. pre-menopausal	0.905	0.713	1.148	0.4095	0.4095	1.069	0.826	1.384	0.6107	0.6107	0.827	0.600	1.138	0.2426	0.2426
<b>BMI</b> , 1-unit increase	1.044	1.030	1.059	<.0001	<.0001	1.020	1.005	1.036	0.0099	0.0099	1.019	1.000	1.038	0.0555	0.0555
<b>Charlson score</b> , ≥1 vs. 0	1.128	0.942	1.351	0.1897	0.1897	1.260	1.037	1.532	0.0200	0.0200	1.084	0.851	1.380	0.5130	0.5130
<b>Education</b> , High school vs. primary	1.033	0.812	1.313	0.7934	0.8959	1.111	0.853	1.446	0.4349	0.3572	1.167	0.844	1.612	0.3507	0.0992
<b>Education</b> , College vs. primary	1.063	0.811	1.395	0.6570		1.224	0.912	1.643	0.1789		1.421	0.991	2.039	0.0562	
<b>Marital status</b> , Partnered vs. no	0.849	0.702	1.026	0.0902	0.0902	0.865	0.704	1.062	0.1670	0.1670	0.816	0.637	1.047	0.1102	0.1102
<b>Monthly Income</b> , ≥ 3000 vs. < 1500	0.814	0.619	1.071	0.1410	0.3385	0.660	0.493	0.885	0.0055	0.0207	0.992	0.685	1.436	0.9657	0.6515
<b>Monthly Income</b> , ≥ 1500 to < 3000 vs. < 1500	0.872	0.690	1.102	0.2523		0.743	0.578	0.957	0.0214		1.091	0.791	1.504	0.5970	
<b>Smoke behavior</b> , Former vs. Current	0.716	0.572	0.897	0.0037	0.0006	0.837	0.657	1.065	0.1479	<.0001	0.860	0.633	1.168	0.3332	0.0294
<b>Smoke behavior</b> , Never vs. Current	0.681	0.559	0.829	0.0001		0.650	0.526	0.804	<.0001		0.715	0.549	0.932	0.0131	
<b>Stage</b> , II vs. I	1.017	0.846	1.224	0.8551	0.4167	1.081	0.887	1.317	0.4402	0.4838	1.106	0.873	1.401	0.4026	0.4654
<b>Stage</b> , III vs. I	1.208	0.889	1.642	0.2273		1.226	0.877	1.714	0.2332		0.907	0.578	1.424	0.6717	
<b>Physical Activity</b> , 1 MET-hour/week increase	1.000	0.999	1.001	0.7347	0.7347	1.000	0.999	1.001	0.6275	0.6275	1.000	0.999	1.002	0.5322	0.5322
<b>Treatment-related factors</b>															
<b>Axillary surgery</b> , Dissection sentinel	0.927	0.764	1.124	0.4401	0.4401	1.010	0.821	1.243	0.9234	0.9234	0.897	0.699	1.151	0.3931	0.3931
<b>Breast surgery</b> , Mastectomy vs Conservative	0.994	0.816	1.212	0.9552	0.9552	0.991	0.798	1.230	0.9322	0.9322	1.063	0.806	1.401	0.6646	0.6646
<b>Radiotherapy</b> , Yes vs No	1.155	0.863	1.544	0.3323	0.3323	1.082	0.793	1.477	0.6180	0.6180	0.934	0.644	1.357	0.7210	0.7210
<b>Chemotherapy</b> , Yes vs No	1.162	0.963	1.403	0.1166	0.1166	1.042	0.854	1.271	0.6864	0.6864	1.009	0.792	1.286	0.9404	0.9404
<b>Endocrine therapy</b> , Yes vs No	1.067	0.885	1.286	0.4962	0.4962	1.291	1.048	1.591	0.0165	0.0165	1.450	1.119	1.880	0.0050	0.0050
<b>Anti HER-2</b> , Yes vs No	1.069	0.853	1.340	0.5615	0.5615	0.928	0.726	1.187	0.5530	0.5530	1.161	0.854	1.579	0.3413	0.3413
<b>Symptoms</b>															
<b>Anxiety</b> , Doubtful vs. Non-case	1.221	1.019	1.463	0.0303	0.0181	1.086	0.893	1.321	0.4068	0.4401	1.200	0.945	1.523	0.1352	0.0521
<b>Anxiety</b> , Case vs. Non-case	1.291	1.069	1.560	0.0081		1.141	0.929	1.400	0.2093		1.362	1.059	1.751	0.0162	

<b>Depression</b> , Doubtful vs. Non-case	1.402	1.115	1.761	0.0038	0.0001	1.305	1.018	1.672	0.0357	0.0079	1.300	0.951	1.776	0.1001	0.0191
<b>Depression</b> , Case vs. Non-case	1.747	1.293	2.361	0.0003		1.544	1.126	2.117	0.0071		1.682	1.132	2.501	0.0101	
<b>Insomnia</b> , 1-point increase	1.008	1.006	1.011	<.0001	<.0001	1.007	1.005	1.010	<.0001	<.0001	1.007	1.004	1.010	<.0001	<.0001
<b>Pain</b> , 1-point increase	1.017	1.014	1.021	<.0001	<.0001	1.023	1.019	1.027	<.0001	<.0001	1.022	1.018	1.027	<.0001	<.0001
<b>Hot flashes</b> , Yes vs. No	1.286	1.095	1.511	0.0022	0.0022	1.223	1.028	1.456	0.0232	0.0232	1.106	0.891	1.373	0.3594	0.3594
<b>Hosmer and Lemeshow Goodness-of-Fit Test</b>	0.0053					0.2532					0.3742				
<b>AUC</b>	0.7094					0.7207					0.7052				

MS5-Supplementary Table 2B. Full logistic regression models of factors associated with severe physical fatigue at each time point.															
	Severe physical fatigue at T1					Severe physical fatigue at T2					Severe physical fatigue at T3				
	OR	95% Wald CI		p-value	global p-value	OR	95% Wald CL		p-value	global p-value	OR	95% Wald CL		p-value	global p-value
<b>Clinical factors</b>															
<b>Age</b> , 1-year increase	0.998	0.986	1.009	0.6687	0.6687	0.993	0.981	1.005	0.2243	0.2243	1.004	0.989	1.020	0.5893	0.5893
<b>Menopausal status</b> , Post- vs. pre-menopausal	0.912	0.715	1.163	0.4572	0.4572	0.938	0.724	1.217	0.6311	0.6311	0.758	0.549	1.047	0.0924	0.0924
<b>BMI</b> , 1-unit increase	1.038	1.024	1.053	<.0001	<.0001	1.028	1.012	1.043	0.0005	0.0005	1.030	1.011	1.050	0.0020	0.0020
<b>Charlson score</b> , ≥1 vs. 0	1.267	1.057	1.518	0.0104	0.0104	1.353	1.116	1.640	0.0021	0.0021	1.261	0.994	1.600	0.0564	0.0564
<b>Education</b> , High school vs. primary	1.221	0.959	1.555	0.1058	0.1653	1.323	1.018	1.719	0.0363	0.0505	1.194	0.868	1.643	0.2762	0.1005
<b>Education</b> , College vs. primary	1.303	0.990	1.714	0.0592		1.441	1.073	1.934	0.0150		1.437	1.005	2.053	0.0468	
<b>Marital status</b> , Partnered vs. no	0.987	0.814	1.195	0.8898	0.8898	0.903	0.736	1.109	0.3306	0.3306	0.866	0.675	1.111	0.2583	0.2583
<b>Monthly Income</b> , ≥ 3000 vs. < 1500	0.565	0.429	0.744	<.0001	0.0002	0.600	0.448	0.803	0.0006	0.0026	0.888	0.614	1.285	0.5277	0.3375
<b>Monthly Income</b> , ≥ 1500 to < 3000 vs. < 1500	0.715	0.566	0.904	0.0050		0.728	0.567	0.935	0.0128		1.053	0.765	1.449	0.7535	
<b>Smoke behavior</b> , Former vs. Current	0.711	0.565	0.896	0.0038	0.0041	0.788	0.617	1.006	0.0564	0.0213	0.859	0.631	1.169	0.3332	0.0435
<b>Smoke behavior</b> , Never vs. Current	0.725	0.593	0.887	0.0018		0.739	0.596	0.915	0.0055		0.726	0.556	0.948	0.0185	
<b>Stage</b> , II vs. I	1.002	0.831	1.209	0.9816	0.8031	0.933	0.765	1.136	0.4893	0.4330	0.880	0.692	1.117	0.2928	0.5603
<b>Stage</b> , III vs. I	0.915	0.667	1.254	0.5811		0.799	0.568	1.123	0.1959		0.854	0.547	1.334	0.4880	
<b>Physical Activity</b> , 1 MET-hour/week increase	0.999	0.998	1.000	0.2308	0.2308	1.000	0.999	1.001	0.6188	0.6188	1.000	0.998	1.001	0.5129	0.5129
<b>Treatment-related factors</b>															
<b>Axillary surgery</b> , Dissection sentinel	0.966	0.794	1.174	0.7255	0.7255	1.120	0.910	1.377	0.2841	0.2841	0.954	0.741	1.227	0.7125	0.7125
<b>Breast surgery</b> , Mastectomy vs Conservative	0.991	0.810	1.212	0.9274	0.9274	1.081	0.870	1.343	0.4802	0.4802	0.987	0.748	1.302	0.9244	0.9244
<b>Radiotherapy</b> , Yes vs No	1.188	0.884	1.595	0.2527	0.2527	1.102	0.809	1.500	0.5386	0.5386	1.157	0.789	1.696	0.4541	0.4541
<b>Chemotherapy</b> , Yes vs No	1.147	0.948	1.389	0.1593	0.1593	1.085	0.889	1.324	0.4221	0.4221	1.305	1.025	1.663	0.0309	0.0309
<b>Endocrine therapy</b> , Yes vs No	1.109	0.918	1.341	0.2837	0.2837	1.279	1.039	1.575	0.0205	0.0205	1.394	1.079	1.802	0.0111	0.0111
<b>Anti HER-2</b> , Yes vs No	1.219	0.970	1.532	0.0898	0.0898	0.964	0.753	1.234	0.7716	0.7716	0.852	0.623	1.165	0.3151	0.3151
<b>Symptoms</b>															
<b>Anxiety</b> , Doubtful vs. Non-case	1.180	0.981	1.418	0.0785	0.0023	1.150	0.946	1.399	0.1610	0.1457	1.233	0.972	1.564	0.0840	0.0722
<b>Anxiety</b> , Case vs. Non-case	1.406	1.161	1.703	0.0005		1.218	0.992	1.497	0.0600		1.322	1.026	1.703	0.0309	

<b>Depression, Doubtful vs. Non-case</b>	1.564	1.244	1.965	0.0001	<.0001	1.688	1.324	2.153	<.0001	<.0001	1.613	1.183	2.200	0.0025	<.0001
<b>Depression, Case vs. Non-case</b>	2.651	1.944	3.614	<.0001		2.220	1.621	3.039	<.0001		2.197	1.475	3.273	0.0001	
<b>Insomnia, 1-point increase</b>	1.006	1.004	1.009	<.0001	<.0001	1.005	1.003	1.008	<.0001	<.0001	1.007	1.004	1.010	<.0001	<.0001
<b>Pain, 1-point increase</b>	1.020	1.017	1.024	<.0001	<.0001	1.020	1.016	1.024	<.0001	<.0001	1.020	1.015	1.025	<.0001	<.0001
<b>Hot flashes, Yes vs. No</b>	1.251	1.063	1.472	0.0072	0.0072	1.182	0.993	1.406	0.0594	0.0594	1.067	0.859	1.325	0.5568	0.5568
<b>Hosmer and Lemeshow Goodness-of-Fit Test</b>	0.2338					0.5239					0.1059				
<b>AUC</b>	0.7211					0.7062					0.7086				

MS5-Supplementary Table 2C. Full logistic regression models of factors associated with severe emotional fatigue at each time point.															
	Severe emotional fatigue at T1					Severe emotional fatigue at T2					Severe emotional fatigue at T3				
	OR	95% Wald CI		p-value	global p-value	OR	95% Wald CL		p-value	global p-value	OR	95% Wald CL		p-value	global p-value
<b>Clinical factors</b>	0.995	0.982	1.008	0.4398	0.4398	0.996	0.982	1.011	0.6162	0.6162	0.993	0.975	1.011	0.4397	0.4397
<b>Age</b> , 1-year increase	0.919	0.695	1.215	0.5521	0.5521	0.996	0.735	1.351	0.9796	0.9796	1.233	0.842	1.807	0.2823	0.2823
<b>Menopausal status</b> , Post- vs. pre-menopausal	1.016	1.000	1.033	0.0478	0.0478	1.014	0.996	1.032	0.1268	0.1268	1.020	0.998	1.043	0.0774	0.0774
<b>BMI</b> , 1-unit increase	1.144	0.930	1.407	0.2043	0.2043	1.061	0.845	1.330	0.6115	0.6115	1.035	0.778	1.378	0.8116	0.8116
<b>Charlson score</b> , ≥1 vs. 0	1.040	0.789	1.370	0.7813	0.9467	1.132	0.840	1.525	0.4161	0.7176	1.056	0.727	1.535	0.7745	0.1152
<b>Education</b> , High school vs. primary	1.017	0.742	1.395	0.9152		1.123	0.800	1.577	0.5021		1.379	0.906	2.097	0.1334	
<b>Education</b> , College vs. primary	0.900	0.722	1.121	0.3465	0.3465	1.011	0.795	1.285	0.9304	0.9304	0.922	0.687	1.237	0.5873	0.5873
<b>Marital status</b> , Partnered vs. no	0.677	0.495	0.926	0.0146	0.0385	0.568	0.407	0.792	0.0009	0.0038	0.701	0.457	1.075	0.1033	0.1387
<b>Monthly Income</b> , ≥ 3000 vs. < 1500	0.832	0.640	1.082	0.1697		0.681	0.513	0.903	0.0077		0.902	0.626	1.300	0.5809	
<b>Monthly Income</b> , ≥ 1500 to < 3000 vs. < 1500	0.587	0.453	0.760	<.0001	<.0001	0.660	0.501	0.870	0.0032	0.0001	0.767	0.541	1.088	0.1370	0.0026
<b>Smoke behavior</b> , Former vs. Current	0.629	0.504	0.785	<.0001		0.595	0.468	0.757	<.0001		0.597	0.441	0.809	0.0009	
<b>Smoke behavior</b> , Never vs. Current	1.219	0.982	1.512	0.0721	0.1042	1.010	0.800	1.276	0.9333	0.9505	1.027	0.776	1.360	0.8503	0.9314
<b>Stage</b> , II vs. I	1.419	0.994	2.026	0.0540		0.957	0.643	1.423	0.8265		1.104	0.660	1.845	0.7063	
<b>Stage</b> , III vs. I	1.000	0.999	1.001	0.5027	0.5027	1.000	0.999	1.001	0.5799	0.5799	1.000	0.999	1.002	0.8422	0.8422
<b>Physical Activity</b> , 1 MET-hour/week increase															
<b>Treatment-related factors</b>	0.802	0.640	1.006	0.0565	0.0565	1.155	0.903	1.477	0.2501	0.2501	1.038	0.774	1.392	0.8055	0.8055
<b>Axillary surgery</b> , Dissection sentinel	0.883	0.700	1.114	0.2934	0.2934	1.090	0.846	1.404	0.5071	0.5071	0.999	0.724	1.377	0.9938	0.9938
<b>Breast surgery</b> , Mastectomy vs Conservative	0.926	0.660	1.299	0.6565	0.6565	1.464	1.004	2.135	0.0477	0.0477	0.869	0.567	1.332	0.5180	0.5180
<b>Radiotherapy</b> , Yes vs No	1.349	1.081	1.682	0.0079	0.0079	0.892	0.705	1.129	0.3416	0.3416	1.050	0.786	1.403	0.7423	0.7423
<b>Chemotherapy</b> , Yes vs No	1.007	0.811	1.250	0.9516	0.9516	1.217	0.951	1.559	0.1190	0.1190	1.059	0.788	1.425	0.7031	0.7031
<b>Endocrine therapy</b> , Yes vs No	0.923	0.710	1.200	0.5484	0.5484	0.986	0.735	1.323	0.9257	0.9257	1.278	0.900	1.816	0.1708	0.1708
<b>Anti HER-2</b> , Yes vs No															
<b>Symptoms</b>	1.375	1.098	1.722	0.0056	<.0001	1.371	1.072	1.752	0.0118	<.0001	1.291	0.952	1.750	0.1000	<.0001
<b>Anxiety</b> , Doubtful vs. Non-case	1.858	1.484	2.325	<.0001		1.920	1.504	2.451	<.0001		2.128	1.572	2.881	<.0001	
<b>Anxiety</b> , Case vs. Non-case	1.595	1.250	2.037	0.0002	<.0001	1.864	1.440	2.412	<.0001	<.0001	2.015	1.451	2.798	<.0001	<.0001

<b>Depression</b> , Doubtful vs. Non-case	2.773	2.047	3.758	<.0001		2.676	1.946	3.679	<.0001		2.502	1.671	3.746	<.0001	
<b>Depression</b> , Case vs. Non-case	1.007	1.004	1.010	<.0001	<.0001	1.004	1.002	1.007	0.0027	0.0027	1.003	1.000	1.007	0.0683	0.0683
<b>Insomnia</b> , 1-point increase	1.014	1.010	1.018	<.0001	<.0001	1.016	1.012	1.020	<.0001	<.0001	1.015	1.010	1.020	<.0001	<.0001
<b>Pain</b> , 1-point increase	1.287	1.069	1.551	0.0078	0.0078	1.211	0.991	1.481	0.0609	0.0609	1.118	0.866	1.442	0.3918	0.3918
<b>Hot flashes</b> , Yes vs. No	0.3155					0.3795					0.0562				
<b>Hosmer and Lemeshow Goodness-of-Fit Test</b>	0.7304					0.7304					0.7252				
<b>AUC</b>	0.995	0.982	1.008	0.4398	0.4398	0.996	0.982	1.011	0.6162	0.6162	0.993	0.975	1.011	0.4397	0.4397

MS5-Supplementary Table 2D. Full logistic regression models of factors associated with severe cognitive fatigue at each time point.															
	Severe cognitive fatigue at T1					Severe cognitive fatigue at T2				Severe cognitive fatigue at T3					
	OR	95% Wald CI		p-value	global p-value	OR	95% Wald CL		p-value	global p-value	OR	95% Wald CL		p-value	global p-value
<b>Clinical factors</b>															
<b>Age</b> , 1-year increase	0.981	0.966	0.997	0.0170	0.0170	0.994	0.978	1.011	0.5160	0.5160	1.005	0.984	1.027	0.6292	0.6292
<b>Menopausal status</b> , Post- vs. pre-menopausal	0.854	0.614	1.188	0.3493	0.3493	0.831	0.582	1.186	0.3081	0.3081	0.540	0.344	0.849	0.0076	0.0076
<b>BMI</b> , 1-unit increase	1.015	0.996	1.034	0.1328	0.1328	1.010	0.989	1.031	0.3500	0.3500	1.003	0.977	1.030	0.8181	0.8181
<b>Charlson score</b> , ≥1 vs. 0	1.162	0.907	1.489	0.2357	0.2357	0.900	0.685	1.182	0.4485	0.4485	0.951	0.676	1.339	0.7735	0.7735
<b>Education</b> , High school vs. primary	0.794	0.571	1.104	0.1698	0.3769	0.901	0.642	1.266	0.5479	0.1320	0.714	0.471	1.082	0.1119	0.2765
<b>Education</b> , College vs. primary	0.788	0.540	1.149	0.2157		0.713	0.480	1.058	0.0930		0.719	0.443	1.165	0.1804	
<b>Marital status</b> , Partnered vs. no	0.791	0.607	1.031	0.0830	0.0830	0.981	0.739	1.303	0.8965	0.8965	1.124	0.790	1.601	0.5154	0.5154
<b>Monthly Income</b> , ≥ 3000 vs. < 1500	0.925	0.635	1.346	0.6823	0.8788	0.663	0.451	0.975	0.0367	0.0803	0.552	0.336	0.909	0.0194	0.0312
<b>Monthly Income</b> , ≥ 1500 to < 3000 vs. < 1500	0.922	0.673	1.263	0.6121		0.705	0.509	0.976	0.0351		0.810	0.534	1.228	0.3213	
<b>Smoke behavior</b> , Former vs. Current	0.922	0.681	1.248	0.5980	0.4927	0.672	0.490	0.920	0.0132	0.0004	0.997	0.664	1.495	0.9867	0.0227
<b>Smoke behavior</b> , Never vs. Current	0.854	0.653	1.116	0.2481		0.574	0.436	0.755	<.0001		0.681	0.475	0.977	0.0372	
<b>Stage</b> , II vs. I	1.218	0.941	1.575	0.1343	0.0819	1.125	0.857	1.478	0.3960	0.6166	0.979	0.705	1.360	0.8994	0.9905
<b>Stage</b> , III vs. I	1.585	1.055	2.383	0.0267		1.225	0.776	1.933	0.3835		0.967	0.531	1.763	0.9134	
<b>Physical Activity</b> , 1 MET-hour/week increase	1.001	1.000	1.002	0.2420	0.2420	1.000	0.999	1.001	0.9932	0.9932	1.001	0.999	1.002	0.3266	0.3266
<b>Treatment-related factors</b>															
<b>Axillary surgery</b> , Dissection sentinel	0.821	0.628	1.073	0.1486	0.1486	0.995	0.747	1.325	0.9725	0.9725	0.947	0.671	1.337	0.7562	0.7562
<b>Breast surgery</b> , Mastectomy vs Conservative	0.954	0.729	1.249	0.7335	0.7335	1.159	0.864	1.554	0.3250	0.3250	1.252	0.863	1.818	0.2367	0.2367
<b>Radiotherapy</b> , Yes vs No	1.071	0.709	1.618	0.7454	0.7454	1.192	0.778	1.827	0.4193	0.4193	0.800	0.494	1.296	0.3655	0.3655
<b>Chemotherapy</b> , Yes vs No	1.345	1.030	1.758	0.0297	0.0297	0.911	0.690	1.202	0.5099	0.5099	1.133	0.803	1.599	0.4777	0.4777
<b>Endocrine therapy</b> , Yes vs No	1.004	0.777	1.296	0.9778	0.9778	1.267	0.943	1.702	0.1156	0.1156	0.977	0.690	1.384	0.8969	0.8969
<b>Anti HER-2</b> , Yes vs No	1.042	0.774	1.402	0.7885	0.7885	1.056	0.755	1.477	0.7515	0.7515	1.226	0.819	1.836	0.3228	0.3228
<b>Symptoms</b>															
<b>Anxiety</b> , Doubtful vs. Non-case	1.357	1.024	1.798	0.0336	<.0001	1.206	0.895	1.626	0.2188	0.0017	1.309	0.907	1.888	0.1505	0.0164
<b>Anxiety</b> , Case vs. Non-case	1.841	1.399	2.423	<.0001		1.673	1.251	2.238	0.0005		1.703	1.182	2.454	0.0043	

<b>Depression, Doubtful vs. Non-case</b>	1.762	1.336	2.323	<.0001	<.0001	1.863	1.386	2.504	<.0001	<.0001	1.791	1.223	2.622	0.0028	0.0028
<b>Depression, Case vs. Non-case</b>	2.262	1.619	3.159	<.0001		2.930	2.076	4.137	<.0001		1.790	1.126	2.847	0.0138	
<b>Insomnia, 1-point increase</b>	1.007	1.004	1.010	<.0001	<.0001	1.005	1.002	1.008	0.0038	0.0038	1.006	1.001	1.010	0.0082	0.0082
<b>Pain, 1-point increase</b>	1.013	1.009	1.018	<.0001	<.0001	1.010	1.005	1.014	<.0001	<.0001	1.015	1.009	1.021	<.0001	<.0001
<b>Hot flashes, Yes vs. No</b>	1.260	1.008	1.576	0.0427	0.0427	1.210	0.956	1.530	0.1129	0.1129	1.331	0.988	1.793	0.0597	0.0597
<b>Hosmer and Lemeshow Goodness-of-Fit Test</b>	0.0893					0.0001					0.4597				
<b>AUC</b>	0.7419					0.7285					0.7266				

## MANUSCRIPT 6 (MS6):

### Uptake of recommendations for post-treatment cancer-related fatigue among breast cancer survivors

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**Previous Presentations:** Findings of this study were partly presented in the proffered paper session (Oral Presentation) at the European Society for Medical Oncology (ESMO) Breast Cancer Virtual Meeting, May 23-24, 2020. Ref: "183O - Use of physical activity (PA) and supportive care (SC) among patients (pts) with early breast cancer (BC) reporting cancer-related fatigue (CRF"; Annals of Oncology (2020) 31 (suppl\_2): S83-S87. 10.1016/annonc/annonc123). Portions of this work were also highlighted in the official ESMO Press Release (<https://www.esmo.org/newsroom/press-office/esmo-congress-breast-2020-breast-supportive-care-fatigue-dimeglio>) and the ASCO Post (<https://ascopost.com/news/may-2020/physical-activity-supportive-care-to-relieve-cancer-related-fatigue-may-be-underutilized-by-breast-cancer-survivors/>).

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## **Abstract**

**Background:** Physical Activity (PA) and psychosocial interventions are recommended management strategies for Cancer-Related Fatigue (CRF). Randomized trials support the use of mind-body techniques, whereas no data show benefit for homeopathy or naturopathy.

**Methods:** We used data from CANTO (NCT01993498), a multicenter, prospective study of stage I-II-III breast cancer (BC). CRF, evaluated post-primary treatment completion using EORTC QLQ-C30 (global CRF) and QLQ-FA12 (physical, emotional and cognitive dimensions), served as independent variable (severe [score  $\geq 40/100$ ] vs. non-severe). Outcomes of interest were adherence to PA recommendations ( $\geq 10$  MET-hours/week [GPAQ-16]) and participation in consultations with a psychologist, psychiatrist, acupuncturist, or other complementary-alternative medicine (CAM) practitioner (homeopath and/or naturopath) following CRF assessment. Multivariable logistic regression examined associations between CRF and outcomes, adjusting for socio-demographic, psychological, tumor and treatment characteristics.

**Results:** Among 7902 women diagnosed from 2012-2017, 36.4% reported severe global CRF, and 35.8%, 22.6% and 14.1% reported severe physical, emotional and cognitive CRF, respectively. Patients reporting severe global CRF were less likely to adhere to PA recommendations (60.4% vs. 66.7%; adjusted odds ratio [aOR] 0.82, [95%CI 0.71-0.94],  $p=0.004$ ), and slightly more likely to see a psychologist (13.8% vs. 7.5%; aOR 1.29 [1.05-1.58],  $p=0.014$ ), psychiatrist (10.4% vs. 5.0%; aOR 1.39 [1.10-1.76],  $p=0.0064$ ), acupuncturist (9.8% vs. 6.5%; aOR 1.46 [1.17-1.82],  $p=0.0008$ ) or CAM practitioner (12.5% vs. 8.2%; aOR 1.49 [1.23-1.82],  $p<.0001$ ). There were differences in recommendation uptake by CRF dimension, including that severe physical CRF was associated with lower adherence to PA (aOR 0.74 [0.63-0.86];  $p=0.0001$ ) and severe emotional CRF with higher likelihood of psychology consultations (aOR 1.37 [1.06-1.79];  $p=0.018$ ).

**Conclusions:** Uptake of recommendations to improve CRF, including adequate PA and use of psychosocial services, seemed suboptimal among early-stage BC patients, while there was a non-negligible interest in homeopathy and naturopathy. This large study calls for the need to implement recommendations for CRF in clinical practice.

## Introduction

Improved cure rates and prolonged survival after breast cancer (BC) treatment resulted in a growing population of survivors being faced with varying degrees of chronic side effects and treatment-related symptoms.<sup>1,6,244,245</sup> Among these, cancer-related fatigue (CRF) is extremely common and persistent.<sup>24,226,246,247</sup> Compared to fatigue experienced by individuals without cancer, CRF is described as more intense, distressing, and less responsive to rest.<sup>30,248,249</sup> Its manifestations can include generalized weakness, decreased motivation and interest to engage in usual activities or emotional lability, and diminished concentration or attention.<sup>250–252</sup> CRF is a multifactorial symptom. Younger age, lower socio-economic status, psychological distress, comorbidities and concomitant symptomatology, unhealthy behaviors such as tobacco use, inactivity and higher body mass index (BMI), were often associated with higher risk of developing CRF.<sup>40,226</sup> Multiple life domains are negatively impacted by CRF, as it can interfere with normal functioning, mood, social relationships, work, sleep and daily activities.<sup>30,247,253,254</sup>

Building on the mechanisms and pathophysiology underpinning CRF, particularly an increased expression of genes encoding pro-inflammatory cytokines or other mediators of immunologic activation<sup>250,255–259</sup>, some treatment strategies were tested and are now recommended. Meta-analyses, systematic reviews, and randomized trials demonstrated that initiating or maintaining adequate levels of physical activity (PA) can improve CRF for BC survivors both on-treatment and in the post-treatment setting, by acting on the modulation of inflammatory mediators.<sup>48,150,260–262</sup> Given its multi-factorial etiology and strong link with psychological distress level, the effect of PA on CRF may also be exerted through an action on self-esteem and depressive status.<sup>263</sup> Engaging in an active lifestyle and sport activities can help cancer patients improve global functionality and facilitate cognitively demanding tasks such as health-related decision-making processes, empowering their ability to manage symptoms like CRF. PA was suggested to work on specific skills like improving problem-solving schemes, training attention and coping, strengthening strategy, tactics and creativity, and enhancing self/introspection processes.<sup>264</sup> Research has also demonstrated how these skills can be adapted from PA experiences and transferred to a cancer and symptom management context.<sup>265,266</sup>

Reductions in CRF were also observed with psychosocial therapy that included cognitive-behavioral or psycho-educational approaches targeting non-adaptive thoughts, such as catastrophizing.<sup>48,250,267</sup> Mind-body interventions, focused on the interactions among brain, mind, body, and behavior<sup>268</sup>, include a variety of practices such as acupuncture, yoga, and mindfulness-based meditation that have also been tested to treat CRF.<sup>48,228</sup> Data from several reviews and clinical trials suggested that acupuncture may be beneficial for persistent CRF.<sup>228,269–275</sup> To date, there are no data showing benefits of other complementary-alternative medicine (CAM) strategies such as homeopathy or naturopathy for post-treatment BC survivors.<sup>48,228,276</sup>

Regular screening, assessment, education and appropriate treatment of CRF are considered as priorities in modern survivorship care. PA and referral to psychosocial service providers are strongly encouraged to reduce CRF, especially for patients reporting at least moderate-to-severe CRF.<sup>48,228</sup> Particularly, NCCN includes PA and psychosocial interventions as category 1 recommendations for CRF in patients post-

treatment (high-level evidence, with uniform NCCN consensus that the intervention is appropriate).<sup>228</sup> Nevertheless, large scale data on the real-world utilization of recommended strategies for CRF are lacking. We aimed to describe the uptake of strategies that can help reduce CRF among patients with early-stage BC that have completed primary treatment.

## Methods

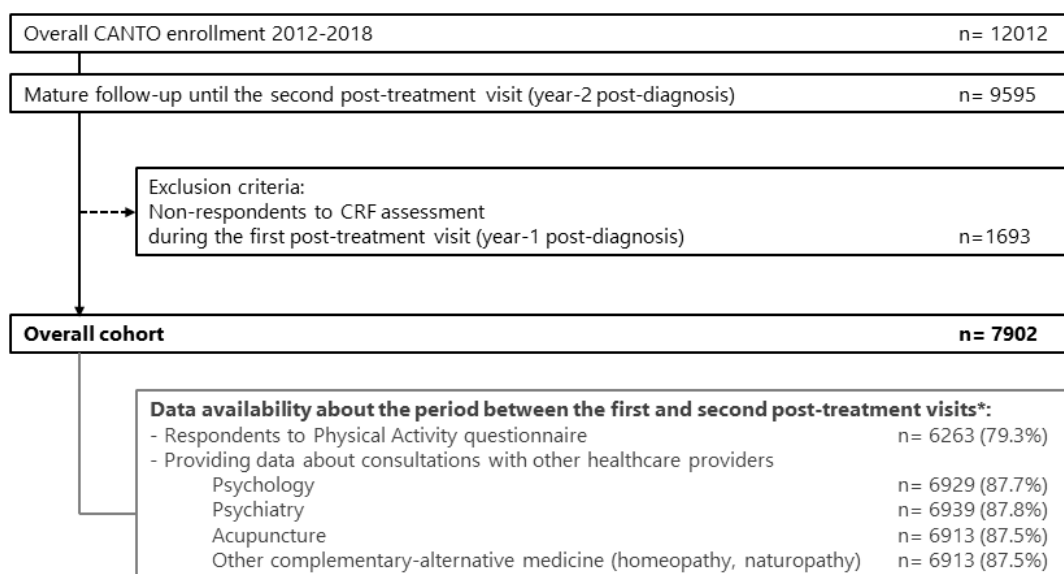
### Data source

This study used CANTO data (ClinicalTrials.gov NCT01993498). Study procedures were previously described.<sup>60</sup> Briefly, CANTO is a prospective, multicentric cohort of women with stage I-II-III BC, designed to study BC toxicities. Patients exit CANTO at any BC recurrence (other than local) or second cancers. We used data that was collected at diagnosis and during the first and second post-primary treatment completion visits (approximately year-1 and -2 post-diagnosis). Primary treatment included surgery, chemo- and/or radiation-therapy. Endocrine and anti-human epidermal growth factor receptor (HER)-2 treatment could be ongoing. Extensive sociodemographic, clinical, tumor and treatment information was assessed by trained clinical research nurses during health examinations.

All participants provided informed consent and the study was approved by the national regulatory and ethics committee (ID-RCB:2011-A01095-36,11-039).

### Study cohort

Mature follow-up until the second post-treatment visit was available among 9595 patients that entered CANTO from 2012-2017. Women with CRF assessment at the first post-treatment visit (N=7902, 82.4%) were included (**MS6-Figure 1**).



**MS6-Figure 1.** CONSORT diagram of patient population. CRF= Cancer-Related Fatigue. \*Note: Patients providing data on PA and healthcare consultations were more likely to be better educated and enrolled from larger CANTO centers, although no major differences were present compared to non-respondents.

## Variables of interest

### *Outcome variables.*

Outcomes of interest were assessed at second post-treatment completion visit (approximately 1 year after primary treatment completion):

*PA.* The Global PA Questionnaire (GPAQ)-16 (World Health Organization [WHO]) was used to assess duration and intensity of PA as well as sedentary behavior.<sup>59</sup> As per WHO recommendations, patients reporting  $\geq 10$  metabolic-equivalents of task (MET)-hours/week qualified as “sufficiently-active” (corresponding to 150 minutes/week of moderate-intensity or 75 minutes/week of vigorous intensity, or an equivalent combination), whereas patients engaging in  $< 10$  MET-hours/week as “insufficiently-active”.<sup>59</sup> Categories for change in PA between the first and second post-treatment visits were therefore: “maintained or increased” (sufficiently-active before and after *or* insufficiently-active before and sufficiently-active after) vs. “decreased or persistently-insufficient” activity (sufficiently-active before and insufficiently-active after *or* insufficiently-active before and after).

*Consultations with other healthcare providers.* Per CANTO protocol, patients were systematically asked if and how many times they had consulted with one of the following providers since the first post-treatment visit: psychologist, psychiatrist, acupuncturist, or other CAM practitioner (homeopath and/or naturopath). Therefore, these types of consultations were explored as outcomes.

### *Independent variable.*

CRF was reported at the first post-treatment visit using the validated French versions of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 and QLQ-FA12.<sup>56,57,60,121,123,124</sup> CRF was categorized as severe if patients scored 40/100 or higher, based on previously defined thresholds of clinical importance<sup>226,277</sup> (details in the **MS6-Data Supplement**).

### *Covariates*

Cohort characteristics were categorized as per **MS6-Table 1**.

## Statistical analysis

Cohort characteristics were summarized for the whole cohort and described by global CRF status at first post-treatment visit (severe vs. not severe). Uptake of PA recommendations and other consultations were analyzed in relation to CRF status. We used multivariable logistic regression models to evaluate odds of maintaining or increasing PA and of participating in other consultations between the first and second post-treatment visit according to CRF status as reported at the first post-treatment visit, adjusting by age, body mass index, comorbidities, anxiety and depression, education, income, tumor stage and subtype, breast and axillary surgery, chemotherapy, and center volume. Two sets of models were fit by outcome, including 1) global CRF and 2) physical, emotional, and cognitive CRF dimensions as independent variables. We used a distinct regression model for each outcome.

Variations in sedentary time (continuous) were assessed using multivariable random-effect mixed-models, adjusted by CRF, time, CRF-by-time interaction, and covariates.

Sensitivity analyses were performed as follows: 1) factors potentially influencing use of specific strategies (affecting ability to participate in PA or prompting other consultations) were included, particularly: i) patient-reported outcomes (PROs) such as pain (EORTC QLQ-C30), systemic-therapy side effects and arm symptoms (EORTC QLQ-B23), ii) clinician-documented toxicities such as arthralgia, myalgia, and neuropathy (Common Terminology Criteria for Adverse Events [CTCAE] V4.0); 2) CRF was modeled as continuous; and 3) endocrine and anti-HER2 therapy were included after removing subtype.

We hypothesized that women experiencing severe CRF would rely more heavily on strategies that are highly recommended to relieve this symptom (i.e. PA and mental health care services delivering psychosocial interventions [NCCN Category 1]<sup>228</sup>). We also hypothesized a substantial diversity in the way these strategies are integrated in the care pathway, due to variance in circumstances and resources.<sup>228</sup> Statistical analysis was performed using SAS statistical software Version 9.4. Statistical significance was defined with a 2-sided p-value < 0.017 (to accommodate for some multiple comparisons among primary outcomes of interest [i.e., PA, psychology and psychiatry consultations]). Acupuncture and CAM service use were considered as exploratory outcomes.

## Results

### Cohort characteristics

Among the whole cohort, mean global CRF score was 36.2 (Standard Deviation [SD] 25.7) and 2873 patients (36.4%) reported severe global CRF (score  $\geq 40$ )<sup>226</sup> during the first post-treatment visit. Patients with severe CRF were younger, heavier, had worse anxiety and/or depression scores, lower educational level and/or income, worse PROs and treatment-related toxicities compared to patients without severe CRF (**MS6-Table 1**).

Patients reported a mean score of 33.2 (SD 24.3) for physical, 23.3 (SD 26.5) for emotional, and 18.0 (SD 23.4) for cognitive CRF, whereas severe CRF was prevalent among 35.8% (N= 2814), 22.6% (N= 1776), and 14.1% (N=1107) for each dimension, respectively.

<b>MS6-Table 1. Cohort characteristics; participants with post-treatment CRF data (N= 7902).</b>				
<b>N (%)</b>	<b>Whole cohort</b>	<b>By global cancer-related CRF status</b>		
		<b>Non severe N= 5029 (63.6%)</b>	<b>Severe N= 2873 (36.4%)</b>	<b>p*</b>
<b>Age at diagnosis, years</b>				
Mean (SD)	56.2 (11.2)	57.2 (11.1)	54.4 (11.2)	<.0001
Missing	-			
<b>Body Mass Index**, Kg/m<sup>2</sup></b>				
Mean (SD)	26.0 (5.4)	25.7 (5.1)	26.6 (5.9)	<.0001
Missing	334			
<b>Initial level of physical activity**, MET-h/week</b>				
Median (Q1-Q3)	16.0 (40-41.3)	18.0 (5.0-42.0)	14.0 (0.0-37.3)	<.0001
Missing	-			
<b>Menopausal status</b>				
Premenopausal	2893 (37.3)	1670 (33.8)	1223 (43.5)	<.0001
Postmenopausal	4858 (62.7)	3267 (66.2)	1591 (56.5)	
Missing	151			
<b>Charlson comorbidity score</b>				
0	5859 (80.6)	3785 (81.6)	2074 (78.7)	0.0027
≥1	1414 (19.4)	853 (18.4)	561 (21.3)	
Missing	629			
<b>Anxiety**</b>				
Non-case (score 0-7)	4355 (56.6)	3286 (65.8)	1069 (37.6)	<.0001
Doubtful (score 8-10)	1886 (24.1)	1083 (21.7)	803 (28.2)	
Case (score 11-21)	1598 (20.4)	626 (12.5)	972 (34.2)	
Missing	64			
<b>Depression**</b>				
Non-case (score 0-7)	6362 (81.2)	4564 (91.3)	1798 (63.3)	<.0001
Doubtful (score 8-10)	941 (12.0)	337 (6.7)	604 (21.2)	
Case (score 11-21)	535 (6.8)	95 (1.9)	440 (15.5)	
Missing	64			
<b>Highest education level</b>				
Primary school	1075 (14.5)	684 (14.4)	391 (14.6)	0.482
High School	3470 (46.8)	2192 (46.3)	1278 (47.6)	
College degree or higher	2875 (38.7)	1858 (39.2)	1017 (37.9)	
Missing	1036			
<b>Monthly household income</b>				
<3,000 Euro	3804 (55.4)	2295 (52.8)	1509 (59.8)	<.0001

≥3,000 Euro Missing	3062 (44.6) 1036	2049 (47.2)	1013 (40.2)	
<b>Stage^</b>				
I	3966 (50.2)	2638 (52.5)	1328 (46.3)	<.0001
II	3141 (39.8)	1921 (38.2)	1220 (42.5)	
III	789 (10.0)	468 (9.3)	321 (11.2)	
Missing	6			
<b>Subtype</b>				
HR+/HER2-	5956 (76.0)	3831 (76.7)	2125 (74.7)	0.115
HR±/HER2+	1165 (14.9)	724 (14.5)	441 (15.5)	
HR-/HER2-	717 (9.1)	438 (8.8)	279 (9.8)	
Missing	64			
<b>Breast cancer surgery</b>				
Mastectomy	2085 (26.4)	1278 (25.4)	807 (28.1)	0.0094
Partial breast surgery	5817 (73.6)	3751 (74.6)	2066 (71.9)	
Missing	-			
<b>Axillary surgery</b>				
Axillary dissection	2988 (37.8)	1803 (35.8)	1185 (41.2)	<.0001
Sentinel node	4914 (62.2)	3226 (64.1)	1688 (58.7)	
Missing	-			
<b>Chemotherapy</b>				
Yes	3749 (47.4)	2488 (49.5)	1664 (57.9)	<.0001
No	4152 (52.5)	2540 (50.5)	1209 (42.1)	
Missing	-			
<b>Radiation therapy</b>				
Yes	7253 (91.9)	4597 (91.5)	2656 (92.5)	0.126
No	643 (8.1)	427 (8.5)	216 (7.5)	
Missing	6			
<b>Endocrine therapy</b>				
Yes	6453 (81.7)	4111 (81.8)	2342 (81.5)	0.783
No	1445 (18.3)	915 (18.2)	530 (18.4)	
Missing	4			
<b>Anti-HER2 therapy</b>				
Yes	949 (12.0)	576 (11.5)	373 (13.0)	0.045
No	6951 (88.0)	4451 (88.5)	2500 (87.0)	
Missing	-			

<b>Center volume, based on number of patients recruited in CANTO</b>				
Small to medium (<1000)	5956 (75.4)	3776 (75.1)	2180 (75.9)	0.430
Large (≥1000)	1946 (24.6)	1253 (24.9)	693 (24.1)	
Missing	-			
<b>Pain (EORTC QLQ-C30)**</b>				
Mean (SD)	28.3 (26.3)	18.3 (19.2)	45.9 (27.8)	<.0001
Missing	15			
<b>Systemic Therapy Side Effects (EORTC QLQ-C30)**</b>				
Mean (SD)	19.9 (16.4)	14.5 (12.3)	29.5 (18.4)	<.0001
Missing	65			
<b>Arm Symptoms (EORTC QLQ-B23)**</b>				
Mean (SD)	27.2 (27.8)	20.4 (22.6)	39.2 (29.8)	<.0001
Missing	72			
<b>Arthralgia***</b>				
Any grade	3784 (48.4)	2121 (42.6)	1663 (58.5)	<.0001
No	4030 (51.6)	2852 (57.3)	1178 (41.5)	
Missing	88			
<b>Myalgia**</b>				
Any grade	2082 (26.6)	1084 (21.8)	998 (35.1)	<.0001
No	5732 (73.4)	3889 (78.2)	2843 (64.9)	
Missing	88			
<b>Neuropathy**</b>				
Any grade	349 (4.5)	179 (3.6)	170 (6.0)	<.0001
No	7419 (95.5)	4762 (96.4)	2657 (94.0)	
Missing	134			
<p>*Using chi-square tests and Wilcoxon rank sum tests for categorical and continuous variables, as appropriate.</p> <p>**Variables collected during the first post-treatment visit (after completion of primary treatment). Anxiety and depression were assessed using the validated Hospital Anxiety and Depression Scale (HADS) (Zigmond AS et al. <i>Acta Psychiatr Scand</i> 1983; Bjelland I et al. <i>J Psychosom Res</i> 2002). All other variables were assessed at breast cancer diagnosis.</p> <p>^Breast cancer stage definition followed the American Joint Committee on Cancer 7th edition classification.</p> <p>CRF= Cancer-Related Fatigue; SD= Standard Deviation; MET= Metabolic-equivalent of task; Q1= Quartile 1; Q3= Quartile 3; HR= Hormone Receptor; HER2= Human Epidermal Growth Factor Receptor 2; EORTC QLQ= European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire.</p>				

**MS6-Table 2** and **MS6-Supplementary Table 1** describe exposure to PA and use of consultations with other healthcare providers between first and second post-treatment visits by global CRF status and by CRF dimension, respectively.

Overall, 4035 patients (64.4%) met recommendations on PA between the first and second post-treatment visits (**MS6-Table 2**). Patients with severe global CRF at first visit had lower odds of meeting activity recommendations between first and second visit (60.4% vs. 66.7%; adjusted Odds Ratio [aOR] 0.82 [95% Confidence Interval [CI] 0.71-0.94],  $p=0.004$ ) compared to those with non-severe CRF. Particularly, the proportion of patients maintaining sufficient levels of activity was lower among severely fatigued patients (44.0% vs. 53.7% vs. non-severely fatigued, **MS6-Table 2**). Accordingly, sedentary time significantly increased for patients with severe CRF that were sufficiently active at first visit, but not among those that were insufficiently active (mean change [95%CI]: +0.30 [+0.03, +0.51] and -0.07 [-0.37, +0.22] hours/day, respectively;  $p_{\text{interaction}} < .0001$ , **MS6-Supplementary Table 2**),

<b>MS6-Table 2. Physical activity and consultations with other healthcare providers by global CRF status.</b>				
	Whole cohort	Global CRF*		
N (%)		Non-severe	Severe	P***
<b>Physical Activity** (N=6263)</b>				<.0001
Maintained <i>or</i> Increased	4035 (64.4)	2697 (66.7)	1338 (60.4)	
<i>Maintained</i>	3147 (50.2)	2172 (53.7)	975 (44.0)	
<i>Increased</i>	888 (14.2)	525 (13.0)	363 (16.4)	
Decreased <i>or</i> Persistently-insufficient	2228 (35.6)	1349 (33.3)	879 (39.6)	
<i>Decreased</i>	1392 (22.2)	830 (20.5)	562 (25.3)	
<i>Persistently-insufficient</i>	836 (13.3)	519 (12.8)	317 (14.3)	
<b>Psychology Consultations** (N=6929)</b>				0.424
No	6252 (90.2)	4116 (92.5)	2136 (86.2)	
Yes	677 (9.8)	335 (7.5)	342 (13.8)	
<i>Median N. times consulted (q1-q3)</i>	5 (2-10)	4 (2-9)	5 (2-10)	
<b>Psychiatrist Consultations** (N=6939)</b>				0.291
No	6460 (93.1)	4234 (95.0)	2226 (89.6)	
Yes	479 (6.9)	221 (5.0)	258 (10.4)	
<i>Median N. times consulted (q1-q3)</i>	6 (3-12)	6 (3-11)	6 (3-13)	
<b>Acupuncture Consultations** (N=6913)</b>				0.523
No	6384 (92.3)	4158 (93.5)	2226 (90.2)	
Yes	529 (7.7)	288 (6.5)	241 (9.8)	
<i>Median N. times consulted (q1-q3)</i>	3 (1-6)	3 (2-6)	3 (1-6)	
<b>CAM practitioner** (N=6913)</b>				0.457
No	6238 (90.2)	4079 (91.7)	2159 (87.5)	
Yes	675 (9.8)	367 (8.2)	308 (12.6)	
<i>Median N. times consulted (q1-q3)</i>	2 (1-4)	2 (1-3)	2 (1-4)	
*Global CRF status was assessed during the first post-treatment visit.				
**Physical activity and participation in consultations with other healthcare providers were assessed over the course of the year following the CRF assessment.				
****Using chi-square tests and Wilcoxon rank sum tests for categorical and continuous variables, as appropriate.				
CRF= Cancer-Related Fatigue; q= quartile; CAM= Complementary-alternative Medicine.				

There were 677 (9.8%) patients who consulted with a psychologist, 479 (6.9%) with a psychiatrist, 529 (7.6%) with an acupuncturist, and 675 (9.8%) with a CAM practitioner. Compared to patients without severe global CRF, those with severe CRF had a slightly higher propensity to participate in a psychology (13.8% vs. 7.5%; aOR 1.29 [95%CI 1.05-1.58],  $p=0.014$ ), psychiatry (10.4% vs. 5.0%; aOR 1.39 [1.10-1.76],  $p=0.0064$ ), acupuncture (9.8% vs. 6.5%; aOR 1.46 [1.17-1.82],  $p=0.0008$ ), or CAM (12.5% vs. 8.2%; aOR 1.49 [1.23-1.82],  $p<.0001$ ) consultation. Among those that did so, the number of consultations did not differ between patients with and without severe CRF (**MS6-Table 2**).

Of note, no significant interactions between severe CRF and anxiety or depressive symptoms on the use of either psychology or psychiatry services service emerged from models. Overall, among those that qualified as non-cases of anxiety or depression, rates of use of mental health care services were consistently almost twofold for severely vs. non-severely fatigued patients. For example, 12.8% vs. 6.9% of them saw a psychologist and 7.3% vs. 4.3% saw a psychiatrist, respectively. However, mental health care services did not seem to be particularly used. Use rates were generally higher among patients that had at least doubtful anxiety or depression symptoms, reflecting data from regression models. In addition, psychology consultations were more frequent among patients without severe CRF if overt symptoms of anxiety were present (16.5% vs. 20.2% for patients with and without severe CRF, respectively, among anxiety cases) (**MS6-Supplementary Figure 1**).

**MS6-Table 3** presents all relevant associations of uptake of PA recommendations and consultations with other healthcare providers with demographical, clinical, tumor and treatment-related covariates.

**MS6-Table 3. Association between global CRF, uptake of physical activity recommendations and consultations with other healthcare providers. Adjusted\* odds ratios (95% Confidence Intervals).**

	Maintained or increased physical activity 4,035/6,263 (64.4%) 3,139/4,803 (65.3%)	Other consultations			
Event rate, N (%) <i>Rate on actual N. observations used</i>		Psychologist 677/6,929 (9.8%) 530/5,232 (10.1%)	Psychiatrist 479/6,939 (6.9%) 386/5,237 (7.4%)	Acupuncturist 529/6,913 (7.6%) 426/5,221 (8.1%)	CAM Practitioner 675/6,913 (9.8%) 549/4,672 (10.5%)
<b>Global CRF status**</b>					
Non-severe	1.00	1.00	1.00	1.00	1.00
Severe	<b>0.82 (0.71-0.94)</b>	<b>1.29 (1.05-1.58)</b>	<b>1.39 (1.10-1.76)</b>	<b>1.46 (1.17-1.82)</b>	<b>1.49 (1.23-1.82)</b>
<b>Age at diagnosis, years</b>					
Continuous, 1-year increment	0.99 (0.99-1.00)	<b>0.97 (0.96-0.98)</b>	<b>0.98 (0.97-0.99)</b>	0.99 (0.98-1.00)	1.00 (0.99-1.01)
<b>Body Mass Index**, Kg/m<sup>2</sup></b>					
Continuous, 1-unit increment	<b>0.95 (0.94-0.96)</b>	0.99 (0.98-1.01)	0.99 (0.97-1.01)	0.99 (0.97-1.01)	0.98 (0.97-1.00)
<b>Charlson comorbidity score</b>					
0	1.00	1.00	1.00	1.00	1.00
≥1	1.01 (0.86-1.18)	0.99 (0.79-1.28)	0.89 (0.66-1.20)	0.95 (0.73-1.25)	0.90(0.71-1.15)
<b>Anxiety**</b>					
Non-case	1.00	1.00	1.00	1.00	1.00
Doubtful	1.07 (0.92-1.24)	<b>2.26 (1.79-2.85)</b>	<b>1.33 (1.01-1.76)</b>	1.20 (0.93-1.54)	1.18 (0.94-1.47)
Case	<b>1.28 (1.07-1.53)</b>	<b>2.79 (2.17-3.59)</b>	<b>2.04 (1.53-2.71)</b>	<b>1.61 (1.23-2.22)</b>	1.09 (0.85-1.42)
<b>Depression**</b>					
Non-case	1.00	1.00	1.00	1.00	1.00
Doubtful	0.83 (0.67-1.01)	1.22 (0.92-1.60)	<b>1.79 (1.31-2.44)</b>	0.74 (0.53-1.04)	1.06 (0.79-1.41)
Case	<b>0.63 (0.48-0.83)</b>	<b>1.51 (1.08-2.13)</b>	<b>2.96 (2.07-4.22)</b>	0.75 (0.48-1.17)	1.04 (0.71-1.54)
<b>Highest education level</b>					
College degree or higher	1.00	1.00	1.00	1.00	1.00
High School	<b>0.71 (0.62-0.83)</b>	<b>0.70 (0.57-0.87)</b>	<b>0.46 (0.36-0.58)</b>	<b>0.61 (0.49-0.77)</b>	<b>0.65 (0.54-0.80)</b>
Primary school	<b>0.56 (0.45-0.69)</b>	<b>0.36 (0.23-0.57)</b>	<b>0.22 (0.13-0.40)</b>	<b>0.45 (0.29-0.69)</b>	<b>0.27 (0.17-0.41)</b>
<b>Monthly household income</b>					
≥3,000 Euro	1.00	1.00	1.00	1.00	1.00
<3,000 Euro	0.99 (0.876-1.15)	0.96 (0.79-1.17)	1.01 (0.80-1.27)	0.98 (0.79-1.21)	1.11 (0.92-1.35)

<b>Stage</b>					
I	1.00	1.00	1.00	1.00	1.00
II	0.96 (0.82-1.12)	1.11 (0.88-1.41)	1.01 (0.76-1.33)	0.91 (0.70-1.18)	0.94 (0.74-1.18)
III	1.10 (0.85-1.44)	0.99 (0.66-1.46)	1.04 (0.66-1.64)	0.99 (0.65-1.51)	0.70 (0.47-1.04)
<b>Subtype</b>					
HR+/HER2-	1.00	1.00	1.00	1.00	1.00
HR±/HER2+	1.04 (0.86-1.25)	1.19 (0.92-1.53)	1.24 (0.92-1.67)	1.27 (0.96-1.66)	0.99 (0.77-1.28)
HR-/HER2-	1.00 (0.80-1.27)	0.90 (0.63-1.27)	0.85 (0.56-1.29)	0.92 (0.63-1.34)	<b>0.70 (0.49-0.99)</b>
<b>Breast cancer surgery</b>					
Partial breast surgery	1.00	1.00	1.00	1.00	1.00
Mastectomy	0.95 (0.82-1.12)	<b>1.31 (1.05-1.64)</b>	0.89 (0.67-1.15)	0.99 (0.77-1.28)	0.92 (0.73-1.15)
<b>Axillary surgery</b>					
Sentinel node	1.00	1.00	1.00	1.00	1.00
Axillary dissection	0.97 (0.82-1.15)	0.87 (0.68-1.11)	1.11 (0.83-1.47)	0.89 (0.68-1.17)	1.02 (0.80-1.29)
<b>Chemotherapy</b>					
No	1.00	1.00	1.00	1.00	1.00
Yes	0.98 (0.83-1.15)	1.01 (0.79-1.29)	0.94 (0.71-1.25)	1.27 (0.98-1.66)	1.49 (1.18-1.89)
<b>Center volume, number of patients recruited</b>					
Large (≥1000)	1.00	1.00	1.00	1.00	1.00
Small to medium (<1000)	0.99 (0.86-1.25)	0.87 (0.70-1.08)	1.21 (0.92-1.58)	1.12 (0.87-1.43)	1.03 (0.83-1.28)
*Adjusted for all factors in the table.					
**Variables collected during the first post-treatment visit (after completion of primary treatment). All other variables were assessed at breast cancer diagnosis. Physical activity and participation in consultations with other healthcare providers were assessed over the course of the year following the CRF assessment. CRF= Cancer-Related Fatigue; CAM= Complementary-alternative Medicine; HR= Hormone Receptor; HER2= Human Epidermal Growth Factor Receptor 2.					

## CRF dimensions and recommendations uptake

Severe physical CRF was associated with reduced engagement in PA (aOR 0.74 [95%CI 0.63-0.86];  $p=0.0001$ ), whereas severe emotional CRF with increased odds of psychology consultations (aOR 1.37 [1.06-1.79];  $p=0.018$ ) and severe cognitive CRF with increased psychiatry (aOR 1.56 [1.16-2.11];  $p=0.0037$ ) and acupuncture consultations (aOR 1.49 [95% CI 1.10-2.04;  $p=0.011$ ). No specific patterns emerged for CAM consultations (**MS6-Table 4**).

## Sensitivity analyses

Analyses incorporating PROs and CTCAE toxicities showed some additional relevant associations, including between pain, systemic therapy side effects, and acupuncture use (**MS6-Supplementary Table 3**). Consistent results with main analyses were found modeling CRF as continuous (**MS6-Supplementary Table 4**) and in models including endocrine and anti-HER2 therapy as covariates (data not shown).

<b>MS6-Table 4. Association between CRF dimensions, uptake of physical activity recommendations and consultations with other healthcare providers. Adjusted* odds ratios (95% Confidence Intervals).</b>					
Event rate, N (%)	Maintained or increased physical activity 4,035/6,263 (64.4%)	Other consultations			
		Psychologist 677/6,929 (9.8%)	Psychiatrist 479/6,939 (6.9%)	Acupuncturist 529/6,913 (7.6%)	CAM Practitioner 675/6,913 (9.8%)
<b>Physical CRF **</b>					
Non-severe	1.00	1.00	1.00	1.00	1.00
Severe	0.74 (0.63-0.86)	1.26 (1.01-1.60)	1.33 (1.01-1.75)	1.12 (0.86-1.44)	1.20 (0.95-1.50)
<b>Emotional CRF **</b>					
Non-severe	1.00	1.00	1.00	1.00	1.00
Severe	0.98 (0.80-1.19)	1.37 (1.06-1.79)	1.02 (0.75-1.39)	1.11 (0.82-1.51)	1.09 (0.83-1.44)
<b>Cognitive CRF **</b>					
Non-severe	1.00	1.00	1.00	1.00	1.00
Severe	1.19 (0.96-1.48)	1.10 (0.84-1.44)	1.56 (1.16-2.11)	1.49 (1.10-2.04)	1.29 (0.97-1.71)

\*Models were adjusted for age, body mass index, comorbidities, anxiety and depression, education, income, tumor stage and subtype, breast cancer and axillary surgery, receipt of chemotherapy, center volume. CRF= Cancer-Related Fatigue; CAM= Complementary-alternative Medicine.

\*\*Variables collected during the first post-treatment visit (after completion of primary treatment). Physical activity and participation in consultations with other healthcare providers were assessed over the course of the year following the CRF assessment.

## Discussion

We evaluated the association between CRF and uptake of specific CRF management strategies in the year post treatment completion among patients with early-stage BC. Reporting severe global CRF was associated with reduced uptake of recommended activity levels and with a slightly higher likelihood of consultations with other healthcare practitioners over the year following CRF evaluation. Among patients with severe CRF, 40% did not adhere to PA recommendations, while only 14% and 10% consulted with psychologists and psychiatrists, respectively, and 10% with acupuncturists, similar to a nearly 13% who saw a CAM practitioner offering homeopathy and/or naturopathy strategies. There were differential associations across physical, emotional, and cognitive dimensions of CRF.

Recommendations for CRF exist for survivors in the post-treatment setting, including dedicated NCCN and ASCO practice guidelines.<sup>48,228</sup> Our study highlights a need to optimize the implementation of available options.

Rest and limitation of physically demanding tasks are often mistakenly reported by patients and providers as strategies to relieve CRF.<sup>263</sup> In fact, survivors suffering from CRF should be encouraged to avoid physical inactivity, and to engage in any activity type, pace, and intensity to meet exercise recommendations.<sup>48,278</sup> However, significant increments in sedentary behavior, which includes time spent sitting or reclining while at work, at home or traveling, were present among patients that initially qualified as sufficiently active and that also reported severe CRF. Compared to patients without severe CRF, fewer of these patients maintained their initial levels of activity. Severe CRF seemed therefore to represent a major barrier to exercise in our cohort, particularly its physical dimension, which is known to have highest correlation with global CRF<sup>48</sup>. Other factors were previously cited as barriers for cancer patients to engage in PA, including therapy-related symptoms, higher BMI, more severe depression, or financial difficulties.<sup>263</sup> In this study we could also investigate the contribution of such factors to adherence to PA recommendations, which was, as expected, lower among women with higher adiposity and worse depression. In contrast, symptoms like pain and other treatment-related *sequelae* seemed to play only a marginal role compared to CRF, which was significantly associated with reduced uptake of PA recommendations after accounting for all these relevant clinical and contextual factors.

Indications exist to refer cancer survivors to mental health services specialized in cancer to address CRF.<sup>48</sup> Cognitive behavioral therapy, by targeting dysfunctional thoughts, poor coping strategies, and alterations in sleep patterns, as well as psychoeducational therapies that offer information about CRF and that correct maladaptive thoughts like over-dramatizing, are capable of improve CRF significantly.<sup>279,280</sup> In CANTO, the use of consultations with psychologists and psychiatrists seemed to be appropriately impacted by the presence of severe CRF.

However, this observation should be discussed in the context of the strong interplay between CRF and symptoms of psychological distress<sup>40</sup>, as the use of mental health services is also indicated for such symptoms both in the presence and absence of CRF. Severe CRF is indeed rarely isolated, and often occurs as part of the

somatic expression of more complex mental conditions, clustering with physical and emotional symptoms of depression, and, to a lesser extent, of anxiety.<sup>48,281,282</sup> Particularly, CRF can represent a symptom of depression, but might also determine precipitation of a depressed mood by interference with regular functioning and activities.<sup>40</sup>

In our models, we tried to isolate the contribution of CRF and psychological distress as drivers of utilization of psychology and psychiatry services, showing an independent association with CRF regardless of adjustment for anxiety and depression levels, and reporting non-significant interaction terms. We acknowledge that statistical controls may not be able to fully disentangle this relationship. Use of mental health services was indeed substantially more common if patients reported at least doubtful symptoms of emotional distress, and psychology support was more frequently used in the absence of severe CRF by patients qualifying as cases of overt depression. Furthermore, strategies adopted for CRF in our study were strongly correlated to specific symptom dimensions, with psychology consultations being more commonly used by women with severe emotional CRF complains (i.e., frequently reporting “feelings of helplessness” or “frustration” [EORTC QLQ-FA12]). We may therefore assume that what we are observing is also part of the referral pattern to mental health services of women with a history of BC that experience actual mood disorders, struggling with clinically-meaningful symptoms of psychological distress in addition to severe CRF. Nevertheless, our data also speak to the fact that only a minority of women reported to have seen a mental healthcare provider (9.8% and 6.9% a psychologist or psychiatrist, respectively), similar to the 10% rate reported among the general French population suffering from psychological distress.<sup>283,284</sup>

Although CANTO is an observational clinical study, describing a routinely treated clinical population where no specific efforts are made to educate patients on how to manage CRF, our data can generate several considerations. We may propose different explanations for the observed low rates of services utilization. Firstly, patients and providers may be unaware of the rationale and efficacy of using psychosocial approaches to treat CRF, as there is often limited attention to CRF correlates falling outside of strictly physical attributes, and insufficient understanding of the applicability of approaches such as cognitive-behavioral therapy outside of the context of mental or mood disorders.<sup>285,286</sup> Secondly, socio-environmental pressure still persists, building on negative stereotypes and prejudicial beliefs towards mental health services.<sup>287</sup> Patients could feel hesitant to seek psychosocial support, or may be inclined to under-report utilization. For similar reasons, the referral may occur quite late, when patients are already experiencing severe CRF or overt emotional distress symptoms, and not upfront, during the organization of the post-treatment survivorship care plan. This may urge a paradigm shift. When needed, BC patients should be promptly referred to psycho-oncology services, and psychotherapists should be included in the multidisciplinary discussions as early as possible. The involvement of general mental healthcare from services in the community should as well be considered. Stigmatization may also exert a differential impact on attitudes towards access to psychology vs. psychiatry services. Caregivers, patients, and their families seem to tend to first approach less stigmatizing health professionals, such as psychologists (but also neurologists and general practitioners), further delaying help-seeking, and resourcing

poorly particularly to psychiatrists.<sup>287-289</sup> Education on the availability of mental health services to manage CRF should target both providers and patients<sup>228,287</sup>, working on reducing the stigmatization associated with the prevention and management of mental conditions and psychological distress, which can in turn translate into severe CRF symptoms. Thirdly, to increase utilization rates of psycho-social services among patients with CRF, more work is also needed towards the establishment of an improved (and less paternalistic) patient-physician “partnership model”. This model should promote a more active involvement of patients along the pathway of care, supporting a systematic assessment of CRF and other patient-reported symptoms, and using tools to monitor psycho-emotional status and availability of coping resources, eventually serving as a shared decision aid to trigger timely and effective patients’ participation in consultations with a mental health specialist.<sup>290,291</sup> Finally, psychological therapy comes with non-reimbursed, out-of-pocket costs for patients during post-treatment follow-up in France, representing an additional relevant barrier.

Acupuncture can also be helpful for patients with CRF.<sup>48,228</sup> However, only one-tenth of severely fatigued survivors reported participation in post-treatment acupuncture sessions, with pain and other systemic therapy-related effects (particularly related to receipt chemotherapy, as captured by the EORTC QLQ-BR23) also emerging as significant associations with its use. In contrast, we observed very consistent associations linking severe CRF with subsequent consultations with CAM practitioners offering homeopathy and/or naturopathy. CANTO patients reported an interest in strategies for which we have robust evidence, like psychotherapy, at roughly the same rates as these CAM approaches lacking solid efficacy data and that therefore should not be recommended for CRF in the post-treatment setting.<sup>276</sup>

Some study limitations should be acknowledged, including risk of misreporting, recall bias, and residual Hawthorne effect, as the “awareness of being observed” could affect reported or actual PA among individuals that are cognizant to be on study. Nevertheless, as previously observed, this effect is minimized by the long-term observation and data collection.<sup>92</sup> Further, use of mind-body strategies including yoga and mindfulness approaches was not granularly documented. We also acknowledge that CAM therapies encompass a broad range of practices<sup>276</sup>, not limited to homeopathy and naturopathy, which we grouped under this definition upon data availability in CANTO. Reason for consultation of healthcare providers and information about decision-making actors of referral plans was not collected in this is observational study. Sensitivity analyses correcting for healthcare settings could not be performed (e.g., academic vs general hospital), as center of care is not identifiable by law. However, we assessed volume of patients enrolled by center to address this limitation. Patients were mainly included from reference facilities, in centralized cancer care systems and urban areas, therefore this analysis may mirror practice at larger centers. Nevertheless, this further stresses the need of better CRF care plans, which currently do not seem to be optimally implemented even at facilities exclusively focused on cancer care. Referral patterns and uptake of recommendations may be impacted by availability of physical activity programs and mental health services as well as by access- and cost-related issues within different healthcare systems outside of France. However, our results should be generalizable to other Countries with equivalent systems.

CANTO has a number of strengths that we want to highlight, representing an unparalleled effort in the modern survivorship research arena, one of the largest, longitudinal study of women with early BC worldwide addressing complex and multifaceted issues.<sup>60</sup> Specific to the present analysis, a wealth of medical, patient-reported, CRF and healthcare strategies data made CANTO a unique dataset to explore CRF-related questions. CRF was extensively evaluated using a unidimensional scale (QLQ-C30, brief, easy-to-use, mostly capturing the physical impact of CRF), complemented with a multidimensional scale (QLQ-FA12) incorporating emotional and cognitive impact. Completion rates were high at time-points of interest. Finally, several sensitivity analyses confirmed the robustness of our findings.

CANTO data show that, among many post-treatment BC survivors complaining of severe CRF -nearly one-in-four- strategies that could help improving their condition, such as adhering to exercise guidelines or use of psychosocial services, risk to be largely underutilized and not optimally implemented. Concomitantly, there seems to be a non-negligible interest in non-evidence based CAM approaches like homeopathy and naturopathy. Personalized survivorship care plans can help optimize the use of strategies to improve a highly prevalent condition like CRF, while patients transition from their primary care into long-term follow-up. Better coordination of care among oncologists, exercise specialists, and other supportive care providers, as part of an integrated CRF management team that also incorporates community-based services, is needed to improve patient education and provide adequate guidance to alleviate CRF, a complex syndrome with substantial downstream impact.

## Data Supplement

### MS-6Supplementary Methods. Details of questionnaires used to assess physical activity (PA) and Cancer-Related Fatigue (CRF).

**GPAQ-16.** The Global PA Questionnaire (GPAQ)-16 assesses PA in three different domains (work, transportation [travel to/from places] and leisure [e.g., sports and fitness]), as well as sedentary behavior (i.e., sitting or reclining including at work, at home, watching television, or travelling, but not including time spent sleeping). Activity was reported in metabolic equivalents of task [MET]-hours/week.

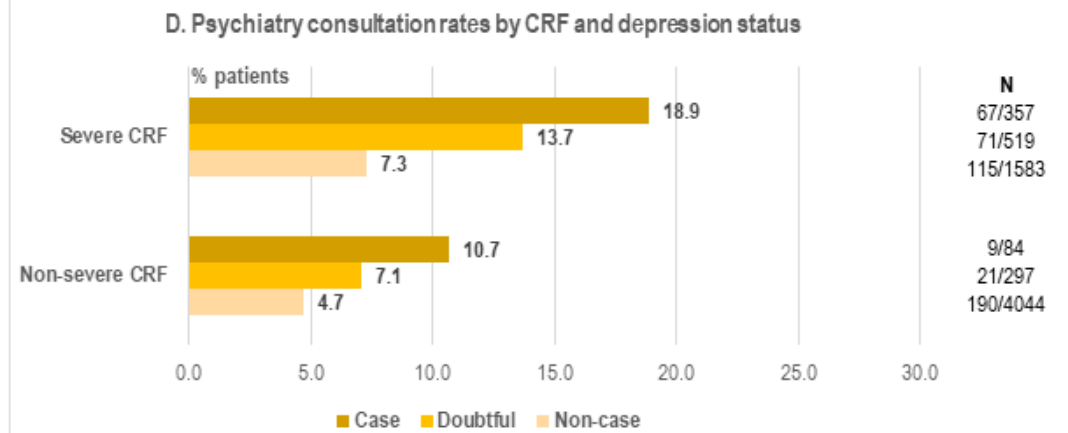
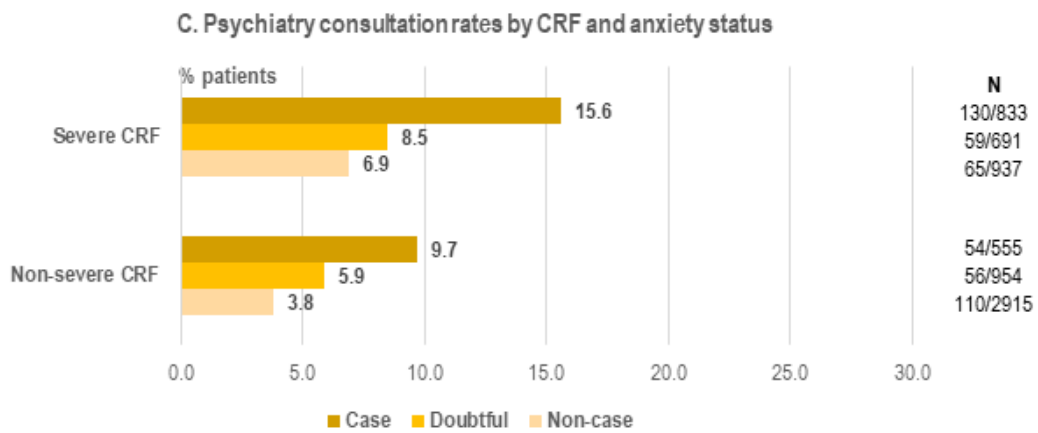
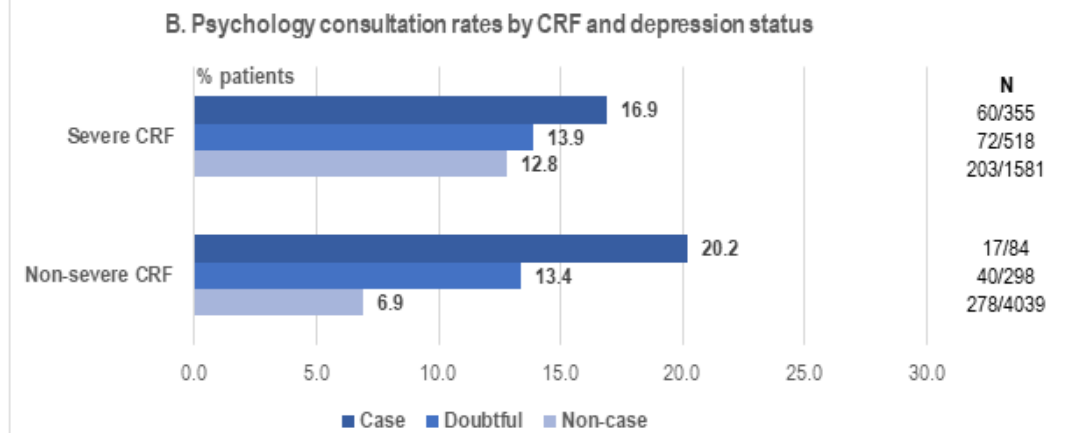
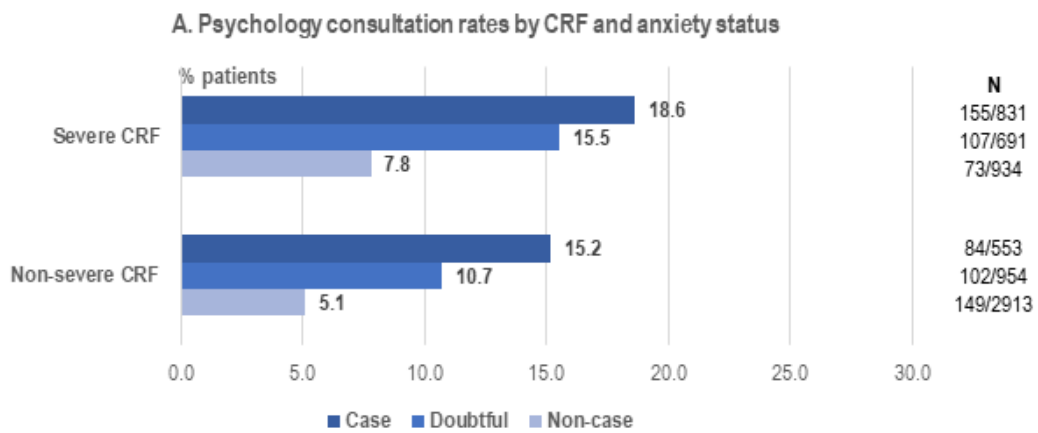
**EORTC QLQ-C30 and EORTC QLQ-FA12.** The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 (EORTC QLQ-C30) is a 30-item questionnaire with a three-item global CRF subscale (i.e., Over the past week: "Did you need to rest?", "Have you felt weak", "Were you tired"), independently validated as separate fatigue measure. The EORTC QLQ-FA12 explores the physical (e.g., lack of energy, exhaustion), emotional (e.g., feelings of helplessness, frustration), and cognitive (e.g., trouble thinking clearly, confusion) dimensions of CRF.[1,2] Questionnaires provide 4-point Likert scale responses for each item: 'not at all', 'a little', 'quite a bit, and 'very much'. All items are subsequently converted to a 0-100 scale using a standard scoring algorithm, where higher scores reflect greater symptom severity. A validated French version of EORTC QLQ-C30 and QLQ-FA12 is available in CANTO. [1,3–6] CRF was categorized as severe if patients scored 40 or higher.[7]

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<b>MS6-Supplementary Table 1. Prevalence of severe CRF among respondents providing data on physical activity and consultations with other healthcare providers.</b>				
	<b>Global CRF</b>	<b>CRF Dimensions</b>		
		<b>Physical</b>	<b>Emotional</b>	<b>Cognitive</b>
<b>Whole cohort with CRF data available</b>				
Reporting severe CRF, N (%)	2873/7902 (36.4)	2814/7867 (35.8)	1776/7841 (22.6)	1107/7865 (14.1)
Mean (SD)	36.2 (25.7)	33.2 (24.3)	23.3 (26.5)	18.0 (23.4)
Missing	-	35	61	37
<b>Physical Activity questionnaires respondents</b>				
Reporting severe CRF, N (%)	2217/6263 (35.4)	2176/6239 (34.9)	1338/6222 (21.5)	837/6239 (13.4)
Mean (SD)	35.5 (25.3)	32.5 (24.0)	22.5 (26.1)	17.5 (23.2)
Missing	-	24	41	24
<b>Psychology consultations respondents</b>				
Reporting severe CRF, N (%)	2478/6929 (35.8)	2441/6899 (35.4)	1511/6879 (22.0)	954/6899 (13.8)
Mean (SD)	35.8 (25.5)	32.9 (24.1)	22.8 (26.3)	17.8 (23.2)
Missing	-	30	50	30
<b>Psychiatry consultation respondents</b>				
Reporting severe CRF, N (%)	2484/6939 (35.8)	2445/6909 (35.4)	1515/6889 (22.0)	655/6909 (13.8)
Mean (SD)	35.8 (25.5)	32.9 (24.1)	22.8 (26.3)	17.8 (23.2)
Missing	-	30	50	30
<b>Acupuncture consultation respondents</b>				
Reporting severe CRF, N (%)	2467/6913 (35.7)	2436/6883 (35.4)	1506/6863 (21.9)	949/6883 (13.8)
Mean (SD)	35.8 (25.5)	32.9 (24.1)	22.8 (26.3)	17.8 (23.2)
Missing	-	30	50	30
<b>CAM consultations respondents</b>				
Reporting severe CRF, N (%)	2467/6913 (35.7)	2436/6883 (35.4)	1506/6863 (21.9)	949/6883 (13.8)
Mean (SD)	35.8 (25.5)	32.9 (24.1)	22.8 (26.3)	17.8 (23.2)
Missing	-	30	50	30
CRF data were collected during the first post-treatment visit (after completion of primary treatment). Physical activity and participation in consultations with other healthcare providers were assessed over the course of the year following the CRF assessment. CRF= Cancer-Related Fatigue; SD= Standard Deviation; CAM= Complementary-alternative Medicine.				

<b>MS6-Supplementary Table 2. Sedentary time (hours/day) by severe global CRF; mean (95% confidence interval for the mean).</b>			
	<b>Whole cohort</b> (N= 6,263)	<b>Insufficiently active at first assessment</b> (N= 2,280)	<b>Sufficiently active at first assessment</b> (N= 3,983)
<i>Patients with non-severe CRF</i>			
At first post-treatment visit	5.57 (5.31, 5.82)	6.09 (5.64, 6.55)	5.26 (4.9, 5.58)
Variation by second post-treatment visit	+0.09 (-0.04, +0.22)	+0.04 (-0.21, +0.28)	+0.10 (-0.05, +0.27)
<i>Patients with severe CRF</i>			
At first post-treatment visit	5.79 (5.53, 6.05)	6.44 (6.00, 6.87)	5.35 (5.02, 5.67)
Variation by second post-treatment visit	+0.13 (-0.04, +0.32)	-0.07 (-0.37, +0.22)	<b>+0.30 (+0.03, +0.51)</b>
<p>CRF data were collected during the first post-treatment visit (after completion of primary treatment). Physical activity and participation in consultations with other healthcare providers were assessed over the course of the year following the CRF assessment.</p> <p>Estimates are obtained using a multivariable-adjusted mixed model that includes CRF status, time, interaction time * CRF status, age, body mass index, comorbidities, anxiety and depression, education, income, tumor stage and subtype, breast cancer and axillary surgery, receipt of chemotherapy, center volume.</p> <p>Results are bolded to highlight within-group changes that were statistically significant (95% confidence interval around the mean change not crossing 0). Models were first fit for the whole cohort and then separately among patients who were insufficiently or sufficiently active at first post-treatment assessment.</p> <p>CRF= Cancer-Related Fatigue.</p>			



**MS6- Supplementary Figure 1.** Rates of patients consulting with a psychologist (**A, B**) and psychiatrist (**C, D**) by CRF and psychological distress status (anxiety and depression, assessed using two separate subscales of the Hospital Anxiety and Depression Scale [HADS]). CRF and psychological distress data were collected during the first post-treatment visit (after completion of primary treatment). Use of psychological healthcare services (psychology and psychiatry consultations) was assessed over the course of the year following the CRF assessment. CRF= Cancer-Related Fatigue.

<b>MS6-Supplementary Table 3. Association between global CRF, uptake of physical activity recommendations and consultations with other healthcare providers: Sensitivity Analyses.</b>					
	<b>Maintained or increased physical activity</b>	<b>Other consultations</b>			
		<b>Psychologist</b> 677/6,929 (9.8%)	<b>Psychiatrist</b> 479/6,939 (6.9%)	<b>Acupuncturist</b> 529/6,913 (7.6%)	<b>CAM Practitioner</b> 675/6,913 (9.8%)
<b>Sensitivity Model A - Inclusion of patient-reported outcomes*</b>					
<b>Global CRF status**</b>					
Non-severe	1.00	1.00	1.00	1.00	1.00
Severe	0.84 (0.72-0.98)	1.10 (0.87-1.38)	1.36 (1.05-1.77)	1.22 (0.95-1.57)	1.39 (1.11-1.73)
<b>Pain (EORTC QLQ-C30)**</b>					
Continuous	0.99 (0.99-1.00)	1.007 (1.003-1.012)	1.00 (0.99-1.00)	1.005 (1.000-1.009)	1.00 (0.99-1.00)
<b>Systemic Therapy Side Effects (EORTC QLQ-C30)**</b>					
Continuous	1.00 (0.99-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	1.007 (1.000-1.014)	1.00 (0.99-1.00)
<b>Arm Symptoms (EORTC QLQ-B23)**</b>					
Continuous	1.00 (0.99-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)
<b>Sensitivity Model B - Inclusion of CTCAE toxicities*</b>					
<b>Global CRF status**</b>					
Non-severe	1.00	1.00	1.00	1.00	1.00
Severe	0.82 (0.72-0.95)	1.24 (1.01-1.53)	1.30 (1.02-1.66)	1.39 (1.11-1.74)	1.46 (1.19-1.78)
<b>Arthralgia**</b>					
No	1.00	1.00	1.00	1.00	1.00
Any grade	0.97 (0.86-1.10)	1.09 (0.90-1.33)	1.04 (0.83-1.30)	1.05 (0.85-1.29)	1.32 (1.09-1.59)
<b>Myalgia**</b>					
No	1.00	1.00	1.00	1.00	1.00
Any grade	0.98 (0.85-1.13)	1.35 (1.10-1.66)	1.28 (1.01-1.63)	1.44 (1.15-1.79)	1.17 (0.96-1.43)
<b>Neuropathy**</b>					
No	1.00	1.00	1.00	1.00	1.00
Any grade	0.91 (0.68-1.21)	1.85 (1.28-2.67)	1.04 (0.64-1.67)	1.88 (0.77-1.83)	1.43 (0.99-2.08)
*Models were also adjusted for age, body mass index, comorbidities, anxiety and depression, education, income, tumor stage and subtype, breast cancer and axillary surgery, receipt of chemotherapy, center volume. **Variables collected during the first post-treatment visit (after completion of primary treatment). Physical activity and participation in consultations with other healthcare providers were assessed over the course of the year following the CRF assessment. CRF= Cancer-Related Fatigue; CAM= Complementary-alternative Medicine.; EORTC QLQ= European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; CTCAE= Common Terminology Criteria for Adverse Events.					

<b>MS6-Supplementary Table 4. Association between global CRF and CRF dimensions, uptake of physical activity recommendations and consultations with other healthcare providers: Sensitivity Analyses.</b>					
	<b>Maintained or increased physical activity</b>	<b>Other consultations</b>			
		<b>Psychologist</b>	<b>Psychiatrist</b>	<b>Acupuncturist</b>	<b>CAM Practitioner</b>
<b>Event rate, N (%)</b>	4,035/6,263 (64.4%)	677/6,929 (9.8%)	479/6,939 (6.9%)	529/6,913 (7.6%)	675/6,913 (9.8%)
<b>Model A - Global CRF*</b>					
<b>Global CRF**</b>					
Continuous	0.996 (0.993-0.998)	1.009 (1.004-1.013)	1.009 (1.04-1.013)	1.010 (1.006-1.014)	1.007 (1.003-1.011)
<b>Model B - CRF Dimensions*</b>					
<b>Physical CRF**</b>					
Continuous	0.993 (0.989-0.997)	1.006 (1.000-1.011)	1.006 (1.000-1.013)	1.004 (0.998-1.010)	1.000 (0.0994-1.005)
<b>Emotional CRF**</b>					
Continuous	0.999 (0.995-1.003)	1.006 (1.001-1.012)	1.002 (0.996-1.008)	1.003 (0.997-1.009)	1.004 (0.999-1.010)
<b>Cognitive CRF**</b>					
Continuous	1.005 (1.000-1.008)	1.002 (0.997-1.007)	1.009 (1.004-1.015)	1.006 (1.001-1.012)	1.003 (0.998-1.008)
*Models were adjusted for age, body mass index, comorbidities, anxiety and depression, education, income, tumor stage and subtype, breast cancer and axillary surgery, receipt of chemotherapy, center volume.					
**Variables collected during the first post-treatment visit (after completion of primary treatment). Physical activity and participation in consultations with other healthcare providers were assessed over the course of the year following the CRF assessment.					
CRF= Cancer-Related Fatigue; CAM= Complementary-alternative Medicine.					

## **RESULTS - PART III**

## MANUSCRIPT 7 (MS7):

### A phase III randomized trial of weight loss to reduce cancer-related fatigue among overweight and obese breast cancer patients: MEDEA study design

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**Previous Presentations:** Presented during the Ongoing Trials session at the 2020 San Antonio Breast Cancer Symposium®, December 8-12, 2020, San Antonio, TX, US. Ref: "Abstract #1176, MEDEA: A randomized trial of weight loss to reduce cancer-related fatigue (CRF) among overweight and obese breast cancer (BC) patients". OT-38-01 - Weight Loss Intervention.

**Publication:** Submitted for publication in November 2020.

**Abstract**

**Background:** Motivating to Exercise and Diet, and Educating to healthy behaviors After breast cancer (MEDEA) is a multi-center, randomized-controlled trial evaluating the impact of weight loss on cancer-related fatigue (CRF) in overweight or obese breast cancer (BC) patients. Herein we described the MEDEA methodology.

**Methods:** Patients are randomized 1:1 to health education alone vs. a personalized telephone-based weight loss intervention plus health education. Patients with stage I-II-III BC with BMI  $\geq 25$  kg/m<sup>2</sup>, completing treatment within 12 months of enrollment, and able to walk  $\geq 400$  meters are eligible to enroll. Both arms receive a health education program focusing on healthy living. Patients in the intervention arm are paired with an individual lifestyle coach, who delivers the intervention through 24 semi-structured telephone calls of 30-60 minutes each, supplemented by a participant workbook, in three phases over one year: intensive phase (weeks 1-12; 12 weekly calls); consolidation phase (weeks 13-24; six bi-weekly calls); maintenance phase (weeks 25-52; one monthly call). Intervention goals include weight loss  $\geq 10\%$  of baseline, caloric restriction of 500-1000 Kcal/day, increased physical activity (PA) to 150 (initial phase) and 225-300 minutes/week (maintenance phase). Tailored toolbox solutions facilitate reaching intervention goals. Primary endpoint is the difference in self-reported CRF (EORTC QLQ-C30) between arms. Secondary endpoints include: quality of life (EORTC QLQ-C30, -B45, -FA12), anxiety and depression (HADS); weight and body mass index (BMI), dietary habits and quality, PA, sleep; healthcare costs (hospital-admissions, all-drug consumption, sick leaves) and cost-effectiveness (cost per quality-adjusted life-year QALY); patient motivation and satisfaction. The primary analysis of MEDEA will compare CRF scores 12-month post-randomization between arms. Overall sample size is 220 patients (inflated for drop outs), with 90.0% power (two-sided  $\alpha=0.05$ ) to detect a standardized effect size of 0.40.

**Status:** Recruitment started in 06/2020.

**Conclusions:** MEDEA is among the first studies testing the impact of a weight loss intervention on CRF. ClinicalTrials.gov NCT04304924.

## Background and Study Rationale

### 1.1 Treatment-related sequelae among breast cancer survivors: Cancer-Related Fatigue (CRF)

Over 80% of patients with early-stage breast cancer can nowadays expect long-term disease-free intervals after primary treatment. As a result, breast cancer survivors currently make up a substantial proportion of the population, as almost three million women in the United States (US), two million in Europe and 250000 in France live with a history of breast cancer.<sup>1,7,20</sup> Improved survival rates led to the emergence of a number of new, often unmet, clinical needs in survivorship care. Particularly, those related to the management of late and chronic side effects of cancer therapies and treatment-related symptoms represent key priorities.<sup>292</sup>

CRF is one of the most common and persistent *sequelae* of cancer treatments<sup>246</sup>, with a prevalence reaching 30-40% one year and up to 20% ten years after treatment completion.<sup>24,226,247</sup> CRF is a complex and multifaceted syndrome, described as heavily distressing and impactful from a patient perspective. Its subjective expressions not only include generalized weakness and physical manifestations, but also emotional lability and loss of capacity to concentrate, which can interfere with normal functioning in a multitude of life domains spanning from usual daily activities, job tasks, and social relationships.<sup>30,247-254</sup>

From a biological standpoint, a positive association between cytokine deregulation, particularly levels of pro-inflammatory markers, and CRF was documented, with increased expression of genes encoding pro-inflammatory cytokines or other mediators of immunologic activation and alterations in the immune and neuroendocrine systems in survivors with persistent CRF.<sup>250,255-259</sup>

### 1.2 Excess body weight, CRF, and other treatment-related sequelae

The epidemic of overweight and obesity is a relevant public health issue in the general population worldwide, increasingly among breast cancer patients. Data suggest that up to 75% of women are overweight or obese at the time of breast cancer diagnosis<sup>47,293,294</sup> and there is a well described increased risk of weight gain after breast cancer.<sup>218,295</sup> Excess body weight, and particularly obesity, poses individuals at risk for several serious and possibly life-threatening conditions, including hypertension, diabetes, sleep apnea, and coronary heart disease.<sup>296</sup> Physical and psychosocial morbidity including physical dysfunction, reduced capacity for physical activity and increased chronic fatigue, dyspnea, diminished sexual functioning, poor body image and depression are commonly linked to higher body adiposity.<sup>170,297,298</sup>

A significantly higher prevalence of CRF among heavier as compared to leaner breast cancer survivors was also observed in several reports<sup>30-32</sup> Particularly, obesity emerged as a strong predictor of post-treatment CRF among obese vs. non-obese women after completion of therapy.<sup>30</sup> Among women with breast cancer enrolled in the Women's Healthy Eating and Living (WHEL) study, obesity was also associated with significantly worse physical function and with worse physical health, vitality, pain and overall health-related quality of life (QOL).<sup>29</sup>

Our understanding of the biologic nature of the link between excess adiposity, obesity, and cancer suggests the presence of a complex interplay between the adipose tissue, its fat-containing microenvironment,

and the whole patient. Adipose tissue is expanded and reprogrammed in obese individuals, with specific metabolic activations leading to localized inflammation and altered cytokine/adipokine secretion. Additional interactions occur between local changes and alterations in systemic physiology. This complex interplay can be responsible of direct and indirect effects that trigger worse cancer treatment-related symptomatology in obese individuals, including worse and more persistent CRF, effects that are substantially mediated by the activity of the cancer-associated inflammatory *milieu*.<sup>33</sup>

### 1.3 Weight loss interventions among breast cancer survivors

Calorie restriction, while maintaining high diet quality, physical activity and behavioral counselling (promoting interactions between environmental, personal and motivational elements determining behavioral change)<sup>299</sup> are the cornerstones of weight loss. In-person or remotely-delivered weight loss interventions are now deemed feasible and also safe in breast cancer survivors with excess body weight. Examples of completed studies of large lifestyle interventions conducted in the US among overweight or obese breast cancer survivors include the Exercise and Nutrition Enhance Recovery and Good Health for You (ENERGY) and the Lifestyle Intervention Study for Adjuvant Treatment of Early breast cancer (LISA) studies.<sup>167,300</sup> These interventions showed great potential in improving a number of outcomes for breast cancer survivors. A mean weight loss of 6% of baseline in the interventional arm of ENERGY and a mean weight loss of 4-5 Kg in the LISA intervention were indeed linked to a more likely preservation of physical function, greater increases in physical condition, and improvement in a multitude of functional and symptom domains.<sup>167,300</sup> In addition, recent observational evidence from the French CANcer TOxicity (CANTO) study showed how weight changes occurring shortly after adjuvant therapy are related to long-term quality of life, and that weight loss among obese survivors is associated with more favorable variations in patient-reported outcomes compared to the pre-treatment period, including CRF.<sup>135</sup> Taken together, these data show that there is rationale to test intentional weight loss during the early survivorship period as a strategy to mitigate downstream *sequelae* of primary breast cancer treatment. However, randomized data are still lacking showing that a combined lifestyle intervention of weight loss, incorporating multiple components of diet, exercise (which is already known as the most effective strategy to treat CRF by modulating inflammation), and motivational counseling improves CRF among overweight and obese survivors of breast cancer.

#### **Scope of the trial**

Motivating to Exercise and Diet, and Educating to healthy behaviors After breast cancer (MEDEA) is a pragmatic randomized controlled trial (RCT) focused on overweight and obese (Body mass index [BMI]  $\geq 25$  Kg/m<sup>2</sup>) adult patients recruited after their initial breast cancer treatment that aims to evaluate the impact of a personalized telephone-based weight loss intervention on post-treatment CRF, QOL, and several other general and breast cancer-specific outcomes.

## Study development

A number of small-to-moderate sized studies looked at the feasibility and benefits of weight loss interventions in cancer survivors.<sup>301–307</sup> The largest weight loss intervention study reported in breast cancer patients to date was the multicenter LISA study, which tested a 2-year, telephone-based weight loss intervention, modeled on the Diabetes Prevention Program (DPP) and focused on diet, physical activity and motivational factors.<sup>167</sup> More recently, the Breast cancer Weight Loss study (BWEL, NCT02750826, PI Jennifer A. Ligibel) started in the US and Canada, testing the impact of a weight loss program on invasive disease-free survival (IDFS) among overweight (BMI  $\geq 27$  Kg/m<sup>2</sup>) patients with early-stage breast cancer. The BWEL weight loss intervention is standardized using the approaches developed as part of the DPP and the LISA study.<sup>151</sup> These studies also provide data demonstrating the feasibility of conducting a lifestyle intervention in a cooperative group setting, serving as a model for a study testing the impact of lifestyle changes on outcomes of breast cancer survivors outside the US.

The MEDEA study is based on the telephone-based weight loss program that was standardized as part of BWEL. Study materials were obtained and adapted from BWEL. Materials include a standard health education program and a personalized telephone-based follow-up intervention. Materials underwent language adaptation from English to French and were thoroughly reviewed by a MEDEA study expert board that includes medical oncologists, psychologists, nutrition, exercise, and behavioral counselling experts. Patient advocates were extensively involved during study preparation and review of materials. The study board systematically included investigators from BWEL. A continuous exchange of intervention materials, tools, feedback and expertise from the BWEL study ensured high standards in the process of conceptualization, funding acquisition, materials adaptation and writing of the study protocol for MEDEA. This process lasted approximately 18 months and it resulted in a simplified version of BWEL, including a 1-year intervention in MEDEA vs. 2-year intervention offered in BWEL, and the thematic adaptation of intervention content to cultural, societal and dietary habits of French participants.

The MEDEA study is supported by a grant from the French National Cancer Institute (Institut National du Cancer [InCA]; grant RISP 2018-13684. MEDEA is sponsored by Gustave Roussy (Villejuif, France). Patient advocacy and dissemination groups are actively involved in the MEDEA study, including the “Ligue nationale contre le cancer<sup>308</sup>”, and the “Seintinelles<sup>309</sup>” network.

## Study objectives

*Primary objective.* The primary objective of the MEDEA trial is to compare the effect of a personalized telephone-based weight loss program based on motivational coaching, exercise and diet versus a standard health educational program control on CRF of overweight or obese breast cancer patients (reported by patients using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of life Questionnaire (QLQ)-C30<sup>56,121</sup>

*Secondary objectives.* Secondary objectives of MEDEA include (1) the evaluation of the impact of the weight loss intervention on (i) specific CRF dimensions, including physical, emotional, and cognitive CRF, (ii) QOL, including domains such as Global health status, emotional, social, role, cognitive function, sleep, pain, body image and systemic therapy side effects, (iii) sleep quality, (iv) anxiety and depression; weight and body mass index, dietary habits and quality, and PA; (2) the feasibility of the dissemination/implementation of the intervention, adapted from a US setting, in the French healthcare setting; and (3) healthcare costs (hospital-admissions, all-drug consumption, sick leaves) and cost-effectiveness (cost per quality-adjusted life-year QALY); patient motivation and satisfaction. Finally, (4) adverse musculoskeletal events including fractures, sprains, tendon or ligament injuries, and orthopedic surgeries will be assessed.

*Exploratory objectives.* MEDEA will also have the following exploratory objectives: (1) impact of the weight loss intervention on cancer-related outcomes (IDFS and overall survival [OS]), (2) assess adherence to intervention by qualitative and quantitative evaluation. For the qualitative assessment, focus groups will be performed with selected study participants to understand barriers and facilitators to uptake and adherence to the intervention, including satisfaction and suggestions for improvement regarding the weight loss program. Focus groups are envisioned at least once halfway through the intervention (month 6) and once at completion of the intervention (month 12). **MS7-Table 1** summarizes MEDEA study outcomes.

### **Study design**

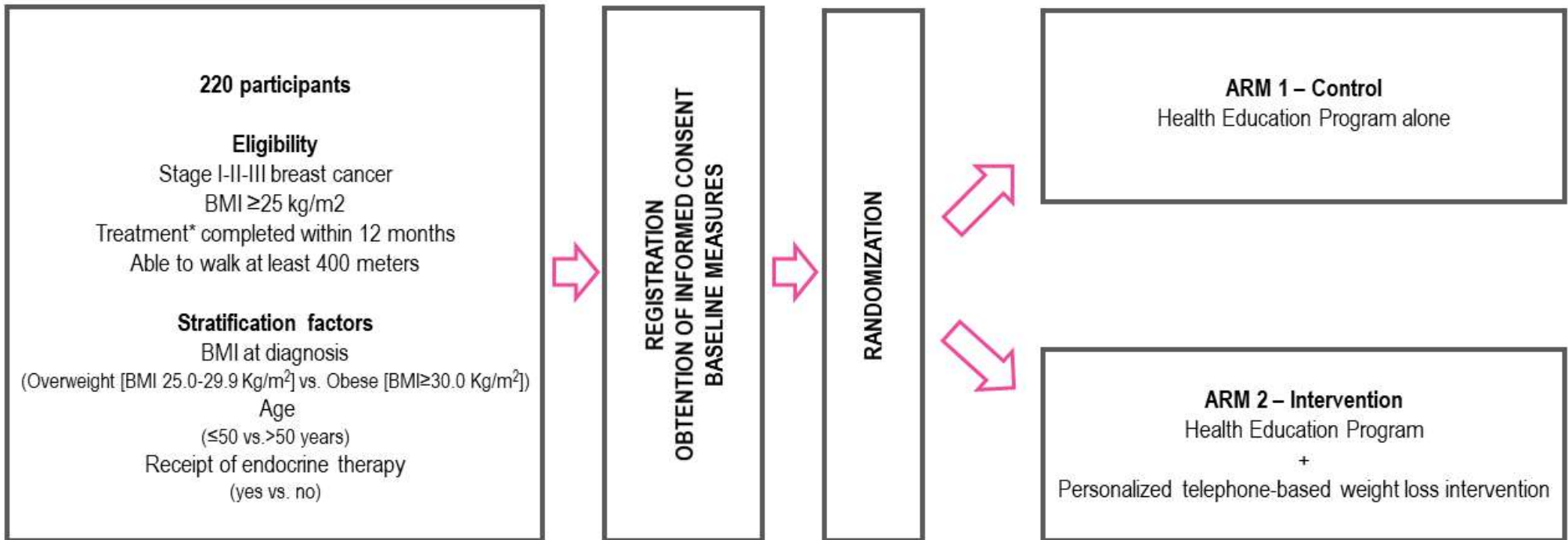
MEDEA is a RCT evaluating the effect of health education alone vs. weight loss intervention plus health education on CRF in overweight and obese women with early-stage breast cancer. Patients are offered to participate in this study during routine consultations. Participants are randomized to a standard health education program (Arm 1 control) vs. a 1-year personalized telephone-based health education weight loss follow-up (Arm 2 interventional). A permuted block randomization is applied in a 1:1 randomization ratio. Stratification occurs on the basis of BMI at diagnosis (Overweight [BMI 25.0-29.9 Kg/m<sup>2</sup>] vs. Obese [BMI ≥30.0 Kg/m<sup>2</sup>]), age (≤50 vs. >50 years), and receipt of endocrine therapy (yes vs. no) (**MS7-Figure 1**). Patients are enrolled through local clinic sites and the weight loss intervention is delivered remotely by trained study coaches. Target enrollment is 220 patients.

MS7-Table 1. MEDEA study outcomes, measures and assessment.							
Outcome		Measure	Type of assessment	Schedule of data collection			
				Baseline M0	M6	M12	M18
Quality of life, depression and anxiety	Fatigue	EORTC QLQ-C30 <sup>1</sup>	Self-reported	X	X	X	X
		EORTC QLQ-FA12 <sup>2</sup>	Self-reported	X	X	X	X
	Other Quality of life Domains*	EORTC QLQ-C30 <sup>1</sup>	Self-reported	X	X	X	X
		EORTC QLQ-B45 <sup>3</sup>	Self-reported	X	X	X	X
	Anxiety/Depression	HADS <sup>4</sup>	Self-reported	X	X	X	X
Health behaviors	Dietary habits	Food questionnaire <sup>5</sup>	Self-reported	X	X	X	X
	Physical Activity	WHO GPAQ-16 <sup>6</sup>	Self-reported	X	X	X	X
	Intensity of physical activity	Actigraph Accelerometer <sup>7</sup>	Device-based	X	X	X	X
	Energy expenditure	Actigraph Accelerometer <sup>7</sup>	Device-based	X	X	X	X
	Daily steps	Actigraph Accelerometer <sup>7</sup>	Device-based	X	X	X	X
Weight and body composition	Weight	Clinical visit	Hospital-based	X	X	X	X
	Body mass index	Clinical visit	Hospital-based	X	X	X	X
	Waist and hip circumference	Clinical visit	Hospital-based	X	X	X	X
Cost-effectiveness	Length of all-cause hospitalizations	Direct medical costs	**	Throughout whole study duration			
	Drug consumption antidepressants, anxiolytics, pain-killers, anti-inflammatory drugs (name, start date, duration of use)	Direct medical costs	**	Throughout whole study duration			
	Sick leave (number, duration and reason)	Indirect costs	**	Throughout whole study duration			
	Utility / QALY	EuroQol 5D 3L <sup>8</sup>	Self-reported	X	X	X	X
Survival outcomes	Invasive DFS	Relapses	**	Throughout whole study duration			
	OS	Death	**	Throughout whole study duration			
Satisfaction and adherence	Motivation and Satisfaction with intervention	Qualitative	Focus group	Halfway through intervention (month 6) + once at intervention completion (month 12)			
	% delivered / planned phone calls % patients who achieve intervention goals % phone calls/total by patient/coaches	Quantitative	Centrally assessed (study manager)	End of study			

1. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J. Natl. Cancer Inst.* 1993;85(5):365–376. 2. Weis J, Tomaszewski KA, Hammerlid E, et al. International Psychometric Validation of an EORTC Quality of Life Module Measuring Cancer Related Fatigue (EORTC QLQ-FA12). *J. Natl. Cancer Inst.* 2017;109(5):. 3. Bjelic-Radisic V, Cardoso F, Cameron D, et al. An international update of the EORTC questionnaire for assessing quality of life in breast cancer patients: EORTC QLQ-BR45. *Ann. Oncol.* 2020;31(2):283–288. 4. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr. Scand.* 1983;67(6):361–70. 5. Gazan R, Vieux F, Darmon N, Maillot M. Structural Validation of a French Food Frequency Questionnaire of 94 Items. *Front. Nutr.* 2017;4:62. 6. Global Physical Activity Questionnaire Analysis Guide GPAQ Analysis Guide Global Physical Activity Questionnaire (GPAQ) Analysis Guide. 7. Eslinger DW, Tremblay MS. Technical reliability assessment of three accelerometer models in a mechanical setup. *Med. Sci. Sports Exerc.* 2006;38(12):2173–2181. 8. EQ-5D. \*Including: Global health status, physical, emotional, social, role, cognitive function, Pain, Insomnia, Nausea/Vomit, Dyspnea, Appetite Loss, Constipation, Diarrhea, Financial difficulties, Body Image, Future perspective, Sexual function and enjoyment, systemic therapy side effects, arm and breast symptoms, endocrine therapy, skin, and sexual symptoms. \*\* National health, Insurance, Hospital-based records, ad hoc questionnaire. M=Month



## STUDY DESIGN



\*surgery, adjuvant chemotherapy and/or radiation therapy, as applicable

MS7-Figure 1. MEDEA Study design.

## **Eligibility**

Patients are eligible if they have histologically confirmed Stage I-II-III breast cancer without evidence of distant metastatic or locally recurrent disease at inclusion. Participants with history of invasive breast cancer in the five years prior to study registration other than the current diagnosis are ineligible for enrollment. Prior Ductal Carcinoma in situ (DCIS) at any time does not make a patient ineligible. Subjects must have a BMI  $\geq 25$  kg/m<sup>2</sup>, either objectively assessed at the time of eligibility evaluation or reported in the medical records within 56 days prior to study registration. All adjuvant or neoadjuvant chemotherapy, radiation, and surgery must have been completed no more than 12 months before enrollment. Patients may have breast reconstruction during protocol participation, but definitive breast cancer surgery must be completed prior to registration. Biologic therapy, hormonal therapy, and bisphosphonates are acceptable to be ongoing while on study. Participants should have an ECOG Performance Status of  $\leq 1$  and self-reported ability to walk at least 400 meters (at any pace). Each participant should understand, sign, and date the written informed consent form prior to any protocol-specific procedures, and be able and willing to comply with study visits and procedures as per protocol.

Participants in both arms are allowed to pursue weight loss and PA programs on their own, but participation in another weight loss, PA or dietary intervention clinical trial at a time is not allowed. Comorbid conditions, such as other malignancy, diabetes, inflammatory bowel disease, history of severe cardiovascular, respiratory or musculoskeletal disease that would preclude adherence to the study diet or PA program or significantly affect the physical status, or the ability to give an informed consent make a patient ineligible for enrollment. Secondary overweight or obesity must not be documented or suspected at the time of enrollment. Chronic consumption of corticosteroids or self-reported pregnancy or intent to become pregnant in the year after enrollment also represent ineligibility criteria.

## **Study intervention**

### **7.1 Health Education Program (Arms 1 and 2).**

All patients in both the health education control and the intervention group receive a standardized Health Education Program focusing on healthy living. This includes a welcome letter, paper brochures and links to websites focused on cancer-related topics. Covered themes include healthy eating, exercising, nutrition and cancer.

In addition, all study participants receive a quarterly newsletter with additional materials, including invitations to join Webinars/conferences that focus on breast cancer and other health topics, (e.g., treatment updates in breast cancer, management of specific side effects, general cancer screening). Finally, patients are provided with updates about study and enrollment progress.

### **7.2 Weight loss intervention (Arm 2).**

Patients randomized in the interventional arm of MEDEA receive behavioral support to facilitate lifestyle change based on caloric restriction and increased PA, delivered remotely by a weight loss coach.

Personalized coaching is crucial for the MEDEA intervention, therefore participants are paired with an individual coach who works with them through all phases of the weight loss program. Lifestyle coaches are required to have expertise in diet/nutrition and received initial training in behavioral change, PA, and/or weight loss in cancer patients.

The behavioral change program is based on Social Cognitive Theory, which hypothesizes that the interactions between environmental, personal and behavioral elements determine behavioral change.<sup>299</sup>

The intervention is implemented through 24 semi-structured and standardized telephone calls, delivered over one year, supplemented by a detailed participant workbook that is mailed to participants after randomization. Participants are encouraged to review the content of the call beforehand using the workbook in order to facilitate the telephone interactions with their coach. Calls scheduled at the participant's convenience. Each call lasts approximately 30 minutes, although the first four calls last longer (up to 45-60 minutes). Calls are scheduled as follows: intensive phase (weeks 1-12; 12 weekly calls); consolidation phase (weeks 13-24; six bi-weekly calls); maintenance phase (weeks 25-52; one monthly call). Every effort is made to ensure that a core of 16 calls (the minimum number required to ensure success of the intervention) take place during the first six months and that the frequency is greatest early in the intervention, when participants are making the most rapid changes. **MS7-Table 2** outlines the 24 telephone calls with respective thematic content.

Lifestyle coaches individualize the call content as necessary to address individual problems (ensuring that key aspects of each call are covered) and are trained to address motivational and emotional issues as they arise, partnering with participants to overcome barriers to success. Data on compliance, changes in diet, PA and weight reported by participants are captured and discussed with coaches during the calls. Coaches prepare a brief written summary of motivational, behavioral, diet and exercise issues discussed during each call.

A toolbox approach that allows for tailoring the intervention to the individual participant is available to facilitate reaching intervention goals and losing weight. Toolbox solutions also aim at optimizing the intervention to meet the needs of specific ethnic, socioeconomic or other patient populations. Toolbox materials were partly developed by coaches during the preparation phase of the study and reviewed by the MEDEA study expert board. Examples of MEDEA Toolbox solutions are listed in **MS7-Table 3**.

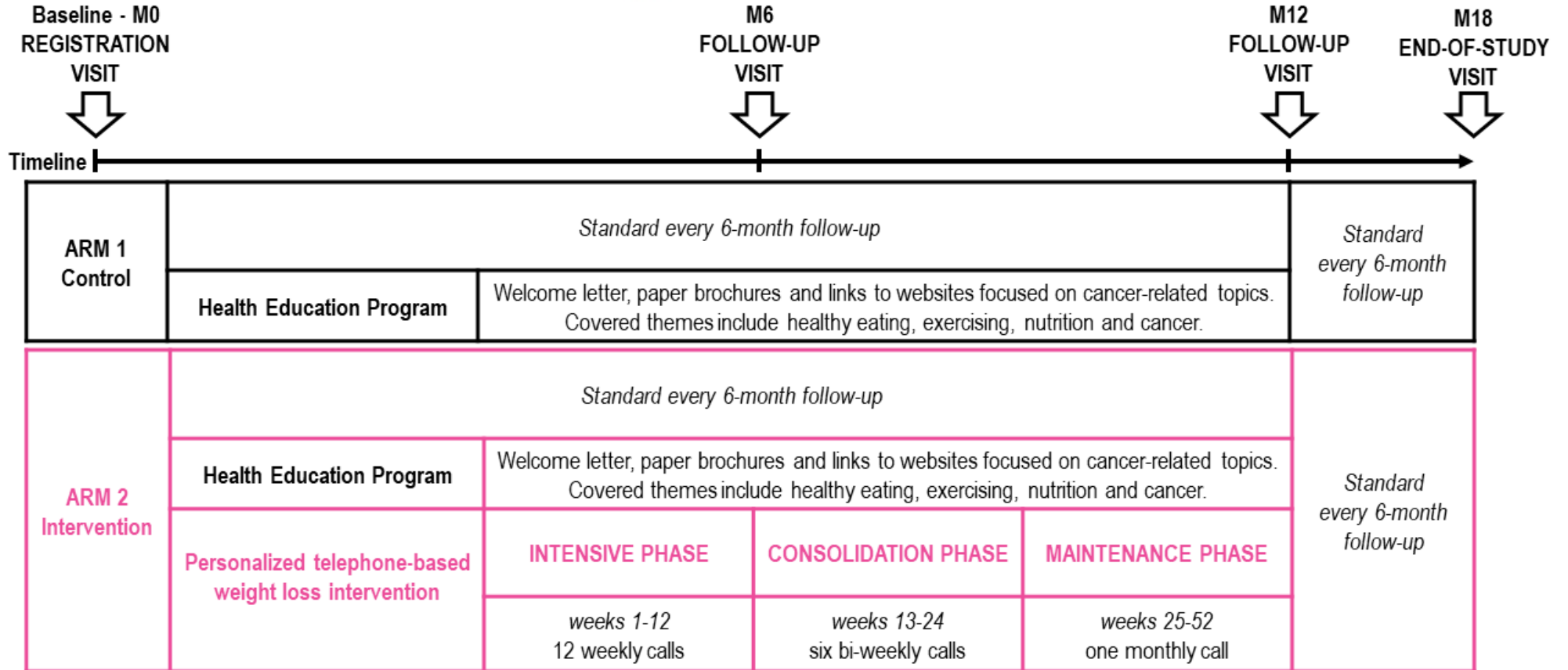
The MEDEA Study schema and timeline is displayed in **MS7-Figure 2**.

<b>MS7-Table 2. MEDEA telephone-based intervention sessions: schedule and thematic content.</b>				
<b>Intervention phase</b>	<b>Phone call</b>	<b>Week</b>	<b>Title</b>	<b>Thematic Content</b>
<b>Intensive phase</b> Weekly calls	<b>1</b>	1	Welcome to the MEDEA Program	Introduction to program
	<b>2</b>	2	Getting Started: Tipping the Calorie Balance	Caloric restriction
	<b>3</b>	3	Not All Fats Are Created Equal: Eat Less of Most, More of Some	Caloric restriction
	<b>4</b>	4	Cutting Calories by Controlling Your Portions	Caloric restriction
	<b>5</b>	5	Move Those Muscles!	Physical activity
	<b>6</b>	6	Working With What's Around You: Cue Control	Behavioral support
	<b>7</b>	7	Problem Solving	Behavioral support
	<b>8</b>	8	Being Active: A Way of Life	Physical activity
	<b>9</b>	9	Healthy Eating	Caloric restriction
	<b>10</b>	10	Healthy Eating and Breast Cancer	Breast cancer and nutrition
	<b>11</b>	11	Preparing a better breakfast, lunch, and dinner	Caloric restriction and Behavioral support
	<b>12</b>	12	Summary and Progress Review	Summary and evaluation
<b>Consolidation phase</b> Bi-weekly calls	<b>13</b>	14	Talk Back to Negative Thoughts	Behavioral support
	<b>14</b>	16	The Slippery Slope of Lifestyle Change	Behavioral support
	<b>15</b>	18	Stepping Up Your Physical Activity	Physical activity
	<b>16</b>	20	Ten Ways to Control Your Hunger	Behavioral support
	<b>17</b>	22	Handling Holidays, Vacations, and Special Events	Behavioral support
	<b>18</b>	24	Taking Stock and Celebrating Your Success	Summary and evaluation
<b>Maintenance phase</b> Monthly calls	<b>19</b>	30	Ways to Stay Motivated	Behavioral support
	<b>20</b>	34	Recovering from Overeating	Behavioral support
	<b>21</b>	38	Weight loss review	Caloric restriction
	<b>22</b>	42	Adapting to long-lasting success	Behavioral support
	<b>23</b>	46	Preparing for What Comes Next	Summary and evaluation
	<b>24</b>	50	Congratulations! You finished the MEDEA program!	Summary and evaluation

<b>MS7-Table 3. Examples of content for MEDEA Toolbox approaches</b>	
<b>Eating patterns and meal plans</b>	<ul style="list-style-type: none"> <li>- High protein / low carb eating pattern</li> <li>- Mediterranean eating pattern</li> </ul>
<b>Cooking and shopping tips</b>	<ul style="list-style-type: none"> <li>- Using your hands to estimate portions</li> <li>- Weighing and measuring foods</li> <li>- Food shopping on a budget</li> <li>- Commercial protein bars</li> <li>- Meal prep and batch cooking</li> </ul>
<b>Activity and symptoms</b>	<ul style="list-style-type: none"> <li>- Three examples of resistance training</li> <li>- 50 ideas to increase daily steps</li> <li>- Apps, videos, books, and tutorials to exercise</li> <li>- Being active with neuropathy</li> <li>- Being active with joint pain</li> <li>- Being active with lymphedema</li> </ul>
<b>Miscellaneous</b>	<ul style="list-style-type: none"> <li>- Sports and cancer</li> <li>- Managing weight when you quit smoking</li> <li>- "Use" your hunger</li> </ul>



## STUDY SCHEMA AND TIMELINE



MS7-Figure 2. MEDEA Study schema and timeline.

### 7.3 Intervention Goals

MEDEA study goals include:

- Weight loss: Weight loss  $\geq 10\%$  of baseline weight (0.5-1.0 Kg per week) until a BMI no less than 21 Kg/m<sup>2</sup>.
- Caloric restriction: Caloric deficit of 500-1000 Kcal per day based on current weight and weight loss target. Recommended calorie levels are based on body weight and standardized tables: calorie levels range from 1200-1499 Kcal/day for participants weighing <110Kg at baseline and 1500-1800 Kcal/day for individuals weighing  $\geq 110$  Kg at baseline. Caloric goals are modified as necessary to assist participants in reaching their goals. The basic diet used in the MEDEA materials supports a low fat, high fruit and vegetable diet.
- Physical Activity: the primary focus of the physical activity portion of the weight loss intervention will be on moderate intensity aerobic activity. Gradual increase in moderate intensity aerobic activity has a target goal of 150 minutes/week during the initial phase of the intervention and 225-300 minutes/week in the maintenance phase of the intervention.

To maximize standardization of goals, tables of target weight loss (based on current weight and BMI), calorie intake (based on current weight and weight loss target) and physical activity (based on current physical activity) are used.

### 7.4 Standardization of the Intervention and quality control

Approaches to standardization of the intervention include the following: 1) A standardized training protocol for the coaches that was piloted in the BWEL study was developed by the MEDEA and BWEL investigators. Training involved the use of printed materials (e.g., protocol, coach's manual, and sample of call scripts) and in-person activities (e.g., behavioral/motivational interviewing techniques, role playing, review of telephone tapes). 2) Standardized supervision of coaches: regular meetings with coaches and the MEDEA study board and coordinators are held on a weekly basis to review progress and troubleshoot problems associated with delivery of the intervention. Coaches have the ability to discuss their calls summary and to receive feedback on relevant aspects of their interactions with study participants. Regular participation of lead nutrition, exercise, and behavioral experts to MEDEA meetings is assured to address specific issues. 3) Recording and centralized review of 5% randomly selected phone calls: these calls are reviewed by the MEDEA study board and coordinators with the coaches for adherence to the study intervention, and standardized feedback is provided to the individual coaches. 4) Centralized calculation of individual weight. 5) Centralized response to diet and physical activity problems arising between telephone calls. Participants are provided with contacts of the MEDEA study coordinators, to alert study personnel of issues that develop during participation in the intervention. Medical problems are referred to the participants' treating oncologist or generalist. 6) Centralized feedback system: coaches have the ability to refer to the MEDEA team at any time for questions and to troubleshoot problems arising during the delivery of the intervention, through a centralized e-mail managed by a dedicated study manager.

## Study Measures

MEDEA study assessments include a baseline (Month [M]0) assessment (at time of enrollment), two “on-health education-intervention visits” (M6 and M12), and a final follow-up visit (M18). Participants undergo study visits at their local site. Collected measures include CRF, quality of life, depression and anxiety, health behaviors, anthropometric measures, cost-effectiveness measures, assessment of disease status and adverse events, adherence and satisfaction with the study intervention. Details about study measures type and frequency of assessment are reported in **MS7-Table 1**.

All patients in MEDEA are provided with Actigraph accelerometers<sup>310</sup>, recording the duration and intensity of physical activity. Readings are obtained centrally through the use of ACTILIFE software<sup>311</sup>. Participants do not receive any feedback from the accelerometer unit. Participants wear the accelerometer for seven days at all four time points (M0, M6, M12, and M18). Accelerometers are mailed to participants by the study manager along with an instruction sheet regarding its use and a diary form to indicate the dates that the accelerometer was worn. Participants return the accelerometer to Gustave Roussy site along with a pre-addressed return mailer. For the first visit they wear the accelerometer before start of the intervention if randomized to Arm 2. For subsequent assessments, a pre-paid mailer is included in the packet so that participants can directly return materials to Gustave Roussy. Dietary Assessment is performed using a 94-item food frequency questionnaire.<sup>312</sup> Weight assessments are performed by healthcare professionals in the clinic during follow-up visits.

Direct medical costs and indirect costs will be assessed from the perspective of the French national health insurance using data linkage to SNDS (“Système national des données de santé” – National Health data system<sup>313</sup>) database for each patient (indirect matching using the date of birth, zip code of the patient’s residence, type/date/hospital identification code for any breast cancer treatment, health insurance characteristics). Resource use includes all-cause hospitalizations (distinguishing between breast cancer related hospitalizations and hospitalizations for other causes), all drugs consumption and sick leaves. Quality-Adjusted Life Years (QALYs) are measured using utility values derived from the Euroqol-5D (EQ-5D-3L)<sup>314</sup> at all four time points (M0, M6, M12, and M18).

Participants in both study arms are asked about the following musculoskeletal events during each follow up visit: fractures, sprains, tendon or ligament injuries, orthopedic surgeries. Non-solicited adverse events such as post-surgical wound infections or side effects from hormonal therapy such as hot flashes, are not required to be reported for this trial.

Adherence to the intervention is measured by the number of completed phone calls/total number of calls scheduled. To define the intervention as completed, a minimum of 16 calls have to be completed. Satisfaction with the intervention will be also assessed with qualitative analyses and dedicated focus groups.

Invasive DFS (IDFS) will be defined as time from randomization to any one of the following: distant, invasive, or locoregional recurrence, ipsilateral or contralateral invasive breast cancer, second primary invasive cancer (non-breast cancer other than basal or squamous cell carcinoma of the skin that has been adequately

treated, and carcinoma in situ of the cervix), or death from any cause. The analyses of objectives including IDFS as an endpoint will be performed in an intention-to-treat manner. Overall survival will be defined as time from randomization to death from any cause. Patients who withdraw consent to be followed will be censored at that time point, and patients who are lost-to-follow-up will be censored at the time point they were last determined to be disease-free.

### **Statistical considerations**

Previous meta-analyses indicated that exercise was more effective than control in reducing CRF, with a standardized effect size  $\sim 0.40$ <sup>48,150,262,278</sup> but there are limited data on the effect of weight loss on CRF. To detect an effect size of 0.40, a sample size of 101 evaluable patients per arm will provide 90.0% power using a two-sided  $\alpha=0.05$  two-sample test. This effect size (0.40) is considered as small to moderate by Cohen.<sup>315</sup> Taking some potential drop-out into account, the final sample size for this study is inflated to 220 patients. The primary comparison of CRF among intervention assignments will be performed in the intent-to treat population of all randomized patients.

The primary analysis of MEDEA will compare the primary endpoint of CRF scores at the M12 post-randomization time point between arms. This comparison between arms will employ a linear mixed model with random patient effect using time as categorical variable, treatment arm and a treatment by time interaction with patient-reported CRF measured by appropriate EORTC QLQ-C30 subscale scores. In a sensitivity analysis, baseline characteristics will be added as fixed covariates to the model.

All other measures/time points/analyses will be considered secondary or exploratory analyses. Similar analyses as those specified for the primary endpoint will be performed for other scales. For binary endpoints, chi-squared tests will be used. Further analyses will include analyses of continuous endpoints using mixed-effects models and binary endpoints using generalized estimating equations.

For all statistical analyses, two-sided p-values  $<0.05$  will be considered statistically significant. For interpreting the clinical significance of effects, 0.2, 0.5, and 0.8 standard deviation effects will be considered as small, moderate, and large.<sup>315</sup>

### **Trial status and data availability**

The MEDEA study received regulatory approval by the institutional review board of Gustave Roussy and by the National review board of France in February 2020. Recruitment was activated in June 2020. Accrual completion is anticipated for 2021, with results available in approximately 2022.

The data are not yet available for the MEDEA Study as the trial is still in progress. ClinicalTrials.gov Identifier: NCT04304924.<sup>153</sup>

## OVERALL CONCLUSIONS

This thesis gathers several projects exploiting data of the CANcer TOxicity study (CANTO; NCT01993498), aimed to understand the potential of health behaviors to improve overall health and preserve quality of life (QOL) of breast cancer survivors. **Several key findings emerge from this work:**

1. The majority of women with early-stage breast cancer in a large, nationwide, French cohort of breast cancer survivors, seem to pursue a healthy lifestyle at the moment of diagnosis. Over the first two years after diagnosis, a sizable proportion of them also seem to improve unhealthy behaviors. However, **unhealthy behaviors such as physical inactivity, tobacco use, and daily alcohol consumption, when present at diagnosis, tend to persist**, with a complex interplay among multiple risk factors that include contextual, clinical, and treatment-related characteristics.
2. There are varying trajectories of patient-reported Quality of Life (QOL) among breast cancer patients receiving chemotherapy. We identified four longitudinal trajectories until 4 years after diagnosis, respectively characterized by "Excellent", "Very good", "Deteriorating", and "Poor" QOL. **Women clustering in the "Deteriorating" group reported fairly good QOL at diagnosis that significantly worsened in the aftermath of chemotherapy and never recovered to pre-treatment values.** Factors associated with membership to this group included younger age, comorbidities, extensive axillary surgery and endocrine therapy. Healthy behaviors were positively and consistently associated with better performing trajectory-groups. In contrast, excess body weight, inactivity, and smoking persistence were particularly prevalent among the "Deteriorating" trajectory-group.
3. Among obese breast cancer survivors, QOL after breast cancer treatment tended to worsen compared to assessments obtained at diagnosis. Nevertheless, **obese women who gained further weight seemed to score the worst in several QOL domains, whereas weight loss was associated with more favorable variations in QOL.** Importantly, there was no association between weight loss and worsened QOL after treatment.
4. Overweight and obesity have important implications in occupational reintegration after breast cancer. We have shown that **excess body weight at breast cancer diagnosis is independently associated with increased rates of non-return to work** two years afterwards, among young, previously employed breast cancer survivors, and that weight changes are also related to return to work.
5. By focusing on a core case-study in breast cancer survivorship, **we defined prevalence and risk factors for severe global fatigue and for severe physical, emotional, and cognitive fatigue at different longitudinal time points after diagnosis.** We also produced a set of tentative predictive equations.

6. Using CANTO as a pool of real-world data, we described how strategies that are recommended to improve cancer-related fatigue seem to be underutilized. Among these, **health behaviors such as uptake of recommended physical activity levels among patients with severe fatigue are underutilized.**
7. In its final part, **this thesis generated a clinical trial protocol for a randomized interventional study (MEDEA)** aimed at reducing fatigue among one of the frail populations identified, namely breast cancer survivors that are overweight or obese.

There are many ways in which findings produced with the preparation of this thesis can help **move forward the knowledge in the field of health behaviors and breast cancer survivorship:**

1. At this time, limited to no specific efforts are generally made to support patients' choices to maintain or initiate a healthy behavior after a cancer diagnosis, and referral to behavior improving programs is not usual standard of care. An integrated effort is strongly needed to urgently develop tailored, patient-centered, and easily accessible programs for health promotion, which have the greatest impact if targeted at women who are most inclined to unhealthy lifestyle choices. **Our work will inform targeted behavioral interventions for patients that are at risk of picking up an unhealthy behavior or persisting in their unhealthy lifestyle.**
2. The portrait of post-chemotherapy QOL is dynamic and involves differential trajectories that may not be evident by analyzing only overall population characteristics. We identified and characterized patients at risk of steep and clinically meaningful decline in QOL. Most of the identified risk factors were non-modifiable, including socio-demographics and receipt of more extensive treatment. Behavioral factors were consistently associated with QOL trajectory-groups. Weight modulation, physical activity uptake, and smoke abstinence are modifiable factors that may represent a potential tool to combat functional health impairment and symptoms exacerbation, mitigating the detrimental impact of chemotherapy. **Our results offer further insight on how to screen relevant patient-level factors and identify clusters of at-risk patients that are suitable for tailored interventions aimed at preservation of QOL, including healthy lifestyle support programs.**
3. **Our data suggest that prevention of weight gain and purposeful weight loss during the early survivorship period should be tested in dedicated studies as strategies to mitigate many downstream sequelae of primary breast cancer treatment for obese survivors.** Answering this question has important implications, as it would help reduce the burden that secondary effects of breast cancer treatment pose on the care of this frail population. The MEDEA clinical trial is one first step trying to answer this question.

4. Our data suggest that excess body weight at breast cancer diagnosis may be a significant barrier to return to work and that overweight and obese patients represent a vulnerable group for unemployment after breast cancer. However, while among overweight or obese women in this cohort there was an association between weight loss and higher rates of return-to-work, further weight gain was associated with reduced likelihood of returning-to-work. **Future research, including ongoing randomized studies testing interventions of weight management and weight loss among breast cancer survivors, should consider including measures of social rehabilitation and employment outcomes.**
  
5. We have developed predictive models of severe global and specific dimensions of severe fatigue in the years following breast cancer treatment completion. **These models can help clinicians with the early management of patients at risk of developing persistent fatigue. We also provide a conceptual framework of a breast cancer survivorship clinic that can be implemented as a screening and management tool of cancer-related fatigue.** The models that we developed are however complex and still suboptimal in terms of performance, calling for the incorporation of further biological components, including genomics, proteomics, and metabolomics. This is an ongoing effort that will represent the continuation of the present work (see next section).
  
6. CANTO data show that, among many post-treatment BC survivors complaining of severe CRF -nearly one-in-four- strategies that could help improving their condition, such as adhering to exercise guidelines, risk to be largely underutilized and not optimally implemented. **Our data point at the need of better coordination of care among oncologists, exercise specialists, and other supportive care providers, as part of an integrated fatigue management team.**
  
7. Finally, by informing a targeted behavioral weight loss intervention to reduce fatigue among overweight and obese breast cancer patients, **our result will have an impact on (i) reducing symptom burden and improving well-being for patients, (ii) improve quality, effectiveness and cost-effectiveness of survivorship care, (iii) improve clinical guidelines and policy recommendations for survivorship care, (iv) reduce economic and societal burden of survivorship care, and (v) pave the way for the development of the same care strategy for other chronic symptoms and cancer types.**

In conclusion, in the modern era of targeted and personalized medicine, this body of work calls for the need of also personalizing survivorship care. Enhancing health and QOL for cancer survivors has become a major public health goal. Optimizing the integration of health behaviors is a core component of such process of personalization of the survivorship care pathway, shaping the survivorship experience to the needs and priorities of the individual patient. Nevertheless, many challenges remain in this process.

- **The first challenge** is (i) to **identify the optimal type of behavioral intervention**, taking into consideration cultural factors, comorbidities, and functional status of cancer survivors, and tailoring interventions to specific patient's needs and preferences (e.g., medically supervised programs vs community programs vs home-based interventions), and (ii) to **identify the specific goal of the intervention** (e.g., management of a specific conditions, such as obesity or cancer-related fatigue).
- **The second challenge** is identifying **how to deliver behavioral interventions**, both in medical settings and in the community, or through the use of technology (e.g., mHealth solutions). Facilitation of referrals from oncologists and other health care professionals to these interventions should be also considered as a priority. This requires (i) **more education** of health care providers about the importance of behavioral interventions and (ii) **better information** delivered to survivors in order to increase awareness and improve knowledge about behavioral strategies and recommendations.
- **The third challenge** is to **inform health care payer decisions to cover behavioral interventions**. Reimbursement would make interventions more affordable and widespread available. In order to do this, solid evidence is needed to convince payers about the need of covering the integration of weight management, physical activity, and tobacco and alcohol abuse cessation programs as part of standards of care in the "after-cancer".

**Despite these great challenges, the opportunities in the field of full integration of health behaviors in cancer survivorship are multiple and exciting. Collaboration across disciplines, including oncologists, exercise specialists, supportive care providers, key clinical stakeholders, payers and insurers, patients and advocacy groups is crucial in this mission.**

## OTHER RELATED PROJECTS AND COLLABORATIONS

- **A qualitative evaluation of the use of interventions to treat fatigue among cancer survivors: a health care provider's view.** Martin E, Zingarello A, **Di Meglio A**, Baciarello G, Matias M, Charles C, Arvis J, Dumas A, Menvielle G, Vaz-Luis I. *European Journal of Cancer Care*, 2020 (in press)
- **Association of body mass index and cardiotoxicity related to anthracyclines and trastuzumab in early breast cancer: French CANTO cohort study.** Kaboré EG, Guenancia C, Vaz-Luis I, **Di Meglio A**, Pistilli B, Coutant C, Cottu P, Lesur A, Petit T, Dalenc F, Rouanet P, Arnaud A, Arsene O, Ibrahim M, Wassermann J, Boileau-Jolimoy G, Martin AL, Lemonnier J, André F, Arveux P. *PLoS Med.* 2019 Dec 23;16(12):e1002989. doi: 10.1371/journal.pmed.1002989. PMID: 31869400; PMCID: PMC6927582.
- **Long-Term Fatigue and Cognitive Disorders in Breast Cancer Survivors.** Joly F, Lange M, Dos Santos M, Vaz-Luis I, **Di Meglio A**. *Cancers (Basel)*. 2019 Nov 28;11(12):1896. doi: 10.3390/cancers11121896. PMID: 31795208; PMCID: PMC6966680.
- **Differential impact of endocrine therapy and chemotherapy on quality of life of breast cancer survivors: a prospective patient-reported outcomes analysis.** Ferreira AR, **Di Meglio A**, Pistilli B, Gbenou AS, El-Mouhebb M, Dauchy S, Charles C, Joly F, Everhard S, Lambertini M, Coutant C, Cottu P, Lerebours F, Petit T, Dalenc F, Rouanet P, Arnaud A, Martin A, Berille J, Ganz PA, Partridge AH, Delalogue S, Michiels S, Andre F, Vaz-Luis I. *Ann Oncol.* 2019 Nov 1;30(11):1784-1795. doi: 10.1093/annonc/mdz298. PMID: 31591636.
- **Fatigue and physical activity in cancer survivors: A cross-sectional population-based study.** Matias M, Baciarello G, Neji M, **Di Meglio A**, Michiels S, Partridge AH, Bendiane MK, Fizazi K, Ducreux M, Andre F, Vaz-Luis I. *Cancer Med.* 2019 May;8(5):2535-2544. doi: 10.1002/cam4.2060. Epub 2019 Mar 12. PMID: 30864301; PMCID: PMC6536944.
- **Use of oral complementary-alternative medicine and fatigue among early breast cancer patients.** Lapidari P, Djehal N, Havas J, Gbenou A, Martin E, Charles C, Dauchy S, Pistilli B, Cadeau C, Arveux P, Everhard S, Lemonnier J, Coutant C, Cottu P, Lesur A, Menvielle G, Dumas A, Andre F, Michiels S, Vaz-Luis I, **Di Meglio A**  
*Publication status:* Presented in poster form at the European Breast Cancer Conference (EBCC 12) 2020; submitted for publication in November 2020
- **A qualitative exploration of the use of mHealth to increase physical activity among breast cancer survivors with fatigue.** Martin A, **Di Meglio A**, Charles C, Ferreira AR, Gbenou A, Blond M, Fagnou B, Pistilli B, Saghatchian M, Vaz-Luis I. *Publication status:* Presented in poster form at the ESMO Breast Cancer conference 2019; submitted for publication in October 2020
- **QualiFatigue study - A qualitative exploration of the use of specific interventions to relieve fatigue among breast cancer survivors**  
Charles C, **Di Meglio A**, Arnedos M, Arvis J, Baciarello G, Blanchard P, Djehal N, Dumas A, Hollbecque A, Martin E, Matias M, Menvielle G, Zingarello A, Dauchy S, Vaz-Luis I. *Publication status:* submitted for publication in October 2020
- **Overweight, obesity and weight gain after breast cancer (BC): a prospective clinical study.** **A. Di Meglio**, M. El-Mouhebb, S. Michiels, L. Jones, M. Annonay, A. Zingarello, M. Matias, S. Everhard, A.L. Martin, P. Arveux, O. Tredan, P. Soulie, P.H. Cottu, A.H. Partridge, L. Del Mastro, J.A. Ligibel, F. André, I. Vaz-Luis. *Publication status:* Presented in the poster discussion session at the ESMO Congress 2018, manuscript in preparation. Awarded with an **ESMO Merit Award 2018**.
- **Breast Cancer (BC) related fatigue: a longitudinal investigation of its prevalence, domains and correlates.** I. Vaz Luis, **A. Di Meglio**, M. El-Mouhebb, A. Dumas, C. Charles, G. Menvielle, C. Mesleard, A.L.

Martin, P.H. Cottu, F. Lerebours, C. Coutant, A. Lesur, S. Dauchy, P. Arveux, S. Delaloge, N. Lin, P. Ganz, A.H. Partridge, S. Michiels, F. André. *Publication status*: Presented in the poster discussion session at the ESMO Congress 2018, submitted for publication in November 2020

- **Neuropathy and Health Behaviors in Cancer Survivors treated with Chemotherapy (CT).** M. Matias, **A. Di Meglio**, A. Zingarello, S. Michiels, A.H. Partridge, M.K. Bendiane, M.P. Ducreux, F. André, I. Vaz Luis. *Publication status*: Presented in the poster discussion session at the ESMO Congress 2018, manuscript in preparation

## PERSPECTIVES: CAREER DEVELOPMENT PLAN

I am a medical oncologist focused on the care of breast cancer patients. I devoted a considerable amount of my training to clinical and translational research methodology, including biostatistics and acquisition of programming skills. I have a specific interest in breast cancer survivorship research that prompted me to engage in dedicated fellowships.

I successfully completed a research fellowship in the Breast Oncology Program at Dana-Farber Cancer Institute / Harvard Cancer Center (Boston, MA) in 2016. I was then the recipient of a research grant from the European Society of Medical Oncology (ESMO Clinical Research Fellowship) that enabled me to join Gustave Roussy in 2017, supporting my research under the outstanding mentorship of Dr. Ines Vaz-Luis. At Gustave Roussy I had the privilege to be involved in one of the largest contemporary clinical studies in breast cancer survivorship, the CANcer TOxicity study (CANTO), and to work with Prof. Fabrice Andre, CANTO PI and director of our research Unit. Following the completion of my fellowship, I was offered the opportunity to further my training exploiting CANTO data in a dedicated PhD program in breast cancer survivorship, under the co-direction of Prof. Andre and Dr. Vaz-Luis.

In CANTO, I focused on characterizing behavioral factors and their relationship with treatment-related toxicity among breast cancer survivors, with a spotlight on obesity and cancer-related fatigue (CRF). This thesis includes the body of work that I performed over the past years in this field. The CANTO work that I developed informed a phase III randomized trial for CRF, currently active and recruiting (MEDEA / NCT04304924).

In addition, I have been collaborating in a number of projects assessing other types of toxicities among breast cancer survivors (e.g., cardiotoxicity), and their medical and social impact, including adherence to therapy and re-employment. At GR, I also have the opportunity to mentor younger medical oncologists and biostatisticians.

At this point, I am fully committed to pursue a career in applied breast oncology and breast cancer survivorship research, as I embrace survivorship and symptom management as my specific fields of interest.

My overarching career goals include the following:

- 1. To conduct collaborative, interdisciplinary, and patient-centered research**
- 2. To become an independent physician-scientist**, to then:
  - a. transition to a faculty position with instructor and teaching responsibilities
  - b. lead my own research group
- 3. To promote an immediate and meaningful impact of research**, in particular:
  - a. Design and test targeted interventions to prevent and manage treatment-related toxicities
- 4. To be a player in implementing research innovation into clinical practice**, and specifically to:
  - a. be involved with relevant clinical stakeholders activities
  - b. promote patient and advocates engagement



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*“The delicate balance of mentoring someone is not creating them in your own image, but giving them the opportunity to create themselves”*

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I also owe a word to all my friends, near and far, to my good old folks from Ischia and Genova, those I more recently met at Cité Internationale Universitaire de Paris (which gave me shelter for the past years -including quarantine times-), and the many friends that live here and there around the world, but who always find the time and energy to keep connected with me. Thanks for being part of my global family, and for sharing the good and bad times. Little or big, you all gave -maybe unintentionally- a great contribution to my PhD adventure.

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**Titre : Les comportements de santé dans l'après cancer du sein**

**Mots clés :** Cancer du sein, Après cancer, Toxicités liées aux traitements, Comportements de santé, CANTO

**Résumé :** Les survivantes du cancer du sein (CS) de stade précoce ont souvent un impact considérable et persistant des symptômes liés aux traitements.

Cette thèse rassemble plusieurs projets exploitant les données de l'étude CANcer TOxicity (CANTO; NCT01993498) pour comprendre le potentiel des comportements de santé (CSAN), notamment le maintien d'un indice de masse corporelle (IMC) sain, le respect des recommandations en matière d'activité physique (AP), l'arrêt du tabac et la limitation de la consommation d'alcool, pour préserver la qualité de vie (QV) chez les survivantes du CS. CANTO est une cohorte multicentrique et prospective de CS de stade I-II-III. La cohorte recueille des informations clinico-comportementales (IMC, consommation de tabac et d'alcool, AP [GPAQ-16]), psychologiques (HADS), sociodémographiques, et liées au traitement. Les toxicités sont évaluées par les « patient-reported outcomes (PROs)» (EORTC QLQ-C30, -BR23 et -FA12) et par CTCAE. Les patientes font l'objet d'un suivi longitudinal annuel à compter du moment du diagnostic.

Un certain nombre de méthodes statistiques ont été utilisées pour l'analyse des données, notamment la régression linéaire et logistique multivariable, la régression multinomiale, les modèles mixtes à effets aléatoires et les analyses de classe latente.

Dans une première partie, cette thèse vise à (1) décrire les CSAN dans l'après CS, en se concentrant sur les facteurs de risque (FR) de persistance des comportements malsains. Ensuite, ce travail vise (2) à caractériser les toxicités et à définir leur interaction avec les CSAN. Des groupes de patientes spécifiques à a priori risque élevés des toxicités ont été évalués, notamment: (2a) les patientes recevant une chimiothérapie (CT) adjuvante, afin de décrire la QV et sa relation avec les CSAN, et (2b) les patientes obèses, afin d'explorer l'association des PROs avec les changements de poids, l'impact social du CS et sa relation avec l'IMC.

Les principales conclusions sont les suivantes : (1) certaines femmes ont amélioré leur CSAN après CS, bien que la plupart des comportements malsains de base aient persisté, avec des déterminants cliniques, sociodémographiques et psychologiques fluctuant selon le CSAN ; (2a) il y a une grande variabilité dans les trajectoires de la QV après la CT, un groupe de patientes ayant une forte détérioration des PROs, et étant également particulièrement enclin à des comportements malsains ; (2b) parmi les patientes obèses, la perte de poids était associée à de meilleurs PROs après traitement et à des taux plus élevés de retour au travail.

Dans une deuxième partie, cette thèse a exploré une étude de cas spécifique, en se concentrant sur la fatigue liée au cancer (FAT). Dans un premier temps, (3) la prévalence et les FR de la FAT sévère (globale, physique, émotionnelle et cognitive) ont été évalués. Nous avons ensuite (4) caractérisé la mise en œuvre des stratégies de gestion recommandées pour améliorer la FAT, y compris l'AP.

Les résultats ont révélé que : (3) il existe une forte prévalence et persistance de la FAT sévère après CS, avec une multitude de FR comprenant la détresse psychologique, les symptômes concomitants et les comportements malsains, en particulier surpoids et tabagisme (des équations prédictives préliminaires ont également été générées) ; et que (4) l'application des recommandations pour améliorer la FAT, ainsi qu'en matière d'AP, semblait sous-optimale.

L'objectif principal de cette thèse était d'éclairer les interventions comportementales ciblées pour les patientes à risque de toxicité persistante. Ce travail a donc abouti (5) à la génération d'un protocole d'étude pour un essai randomisé de phase III : « Motivating to Exercise and Diet, and Educating to healthy behaviors After breast cancer - MEDEA ». Cette étude, visant à évaluer l'impact d'une intervention personnalisée de perte de poids sur la FAT liée au cancer chez les survivantes de CS en surpoids et obèses, est actuellement en cours (NCT04304924).

## Title : Health Behaviors And Breast Cancer Survivorship

**Keywords :** Breast Cancer, Survivorship, Treatment-related toxicities, Health Behaviors, CANTO

**Abstract:** Survivors of early-stage breast cancer (BC) often face relevant late and long-term health-related *sequelae*, downstream functional impact of treatments and persistent symptoms.

This thesis gathers several projects exploiting data of the CANcer TOxicity study (CANTO; NCT01993498), to understand the potential of health behaviors (HB), including maintenance of a healthy body mass index (BMI), adherence to physical activity (PA) recommendations, tobacco abstinence and limitation of alcohol consumption, to improve overall health and preserve quality of life (QOL) of BC survivors. CANTO is a nationwide, prospective cohort of patients with stage I-II-III BC. Longitudinal clinico-behavioral (e.g., nurse-reported BMI, tobacco and alcohol use, PA [GPAQ-16]), psychological (HADS), socio-demographic, and treatment data are available at diagnosis and yearly afterwards. Treatment-related toxicities are extensively assessed by patient-reported outcomes (PROs; EORTC QLQ-C30, -BR23, and -FA12) and by provider's evaluation (CTCAE).

A number of statistical analytic methods were involved in this thesis, including multivariable linear and logistic regression, multinomial regression, random-effects mixed-models, and latent-class analyses (i.e., group-based trajectory models).

In the first part, this thesis aimed at (1) describing HB over the survivorship period, focusing on risk factors for persistent unhealthy behaviors, and at (2) characterizing the evolution of treatment-related toxicities and defining their interplay with HB. We assessed QOL in two specific and frail populations, at risk of severe downstream treatment impact: (2a) among patients receiving adjuvant chemotherapy (CT) and (2b) among obese BC survivors, where we also specifically studied the social impact of BC and its relationship with BMI.

Key findings included the following: (1) most women pursue a healthy lifestyle and some are prone to improvements after diagnosis, although unhealthy behaviors tend to persist, with varying clinico-demographic and psychological determinants by HB (Manuscript [MS]1); (2a) there is great variability in

trajectories of post-CT QOL, with a clinically relevant cluster of patients reporting severely deteriorating QOL, never recovering to pre-treatment levels for over 4 years, and being also particularly prone to unhealthy behaviors (MS2); (2b) among obese survivors, those that lose weight report less of a decline in PROs, without evidence of worsened functionality or symptomatology in any QOL domain (MS3). Moreover, excess weight seems to represent a barrier to occupational reintegration, and weight loss is associated with higher rates of return to work after BC (MS4).

In its second part, the thesis explored a core case-study, cancer-related fatigue (CRF). First, (3) prevalence and risk factors for severe CRF were evaluated, analyzing global CRF and its physical, emotional, and cognitive dimensions. We then (4) characterized the uptake of recommended management strategies to improve CRF, including PA.

Findings revealed that: (3) there is a high prevalence of post-treatment severe CRF, which stays persistently elevated over time, with a multitude of risk factors including psychological distress, concomitant symptoms, and unhealthy behaviors, particularly excess weight and tobacco use (preliminary predictive equations were also generated) (MS5); (4) recommendations uptake, including PA adherence, seems suboptimal and in need of implementation in clinical practice (MS6).

The overarching goal of this thesis was to inform targeted behavioral interventions for patients at risk of persistent toxicities. This work resulted therefore in (5) the generation of a study protocol for a phase III randomized trial: "Motivating to Exercise and Diet, and Educating to healthy behaviors After breast cancer - MEDEA". This study, aimed to evaluate the impact of a personalized telephone-based weight loss intervention on CRF in overweight and obese BC survivors, is currently ongoing (NCT04304924) (MS7).

Further interventional studies informed by this thesis work are planned.

