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Cancer-related fatigue

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Cancer-related fatigue in breast cancer survivors

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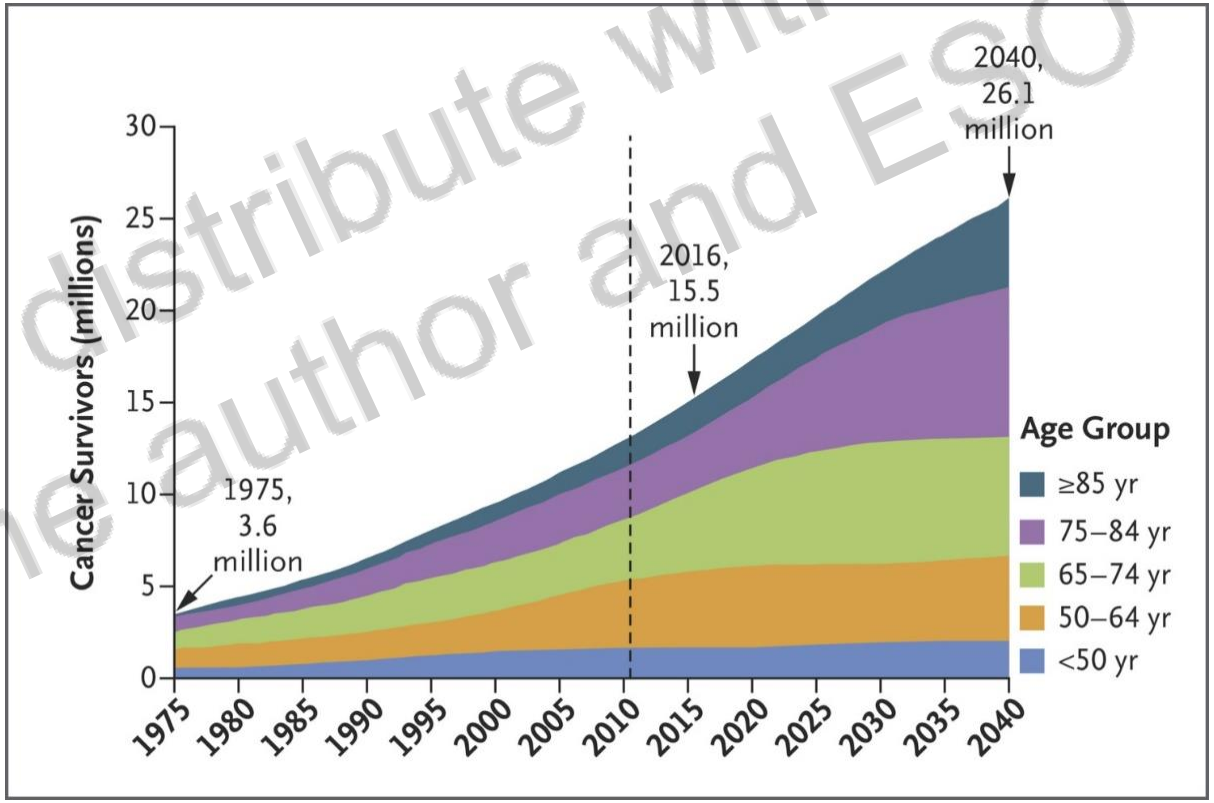
Disclosures

Honoraria: AstraZeneca, Amgen, Pfizer, Novartis

Cancer Survivorship

Cancer Survivorship

- A "**cancer survivor**" is "anyone with history of cancer, from the time of diagnosis and for the remainder of life" (Rowland, 2006)
- Currently, over **18 million** individuals living with a history of cancer, numbers expected to increase to over **26 million** by 2040
- Women diagnosed with **breast cancer** encompass over 3 million in US and 2million in EU
- Corresponding with improved survival, an awareness increased of **survivorship care challenges**, **new research priorities and needs**
- Need to focus on **minimizing the physical, psychological and social burden** of surviving breast cancer

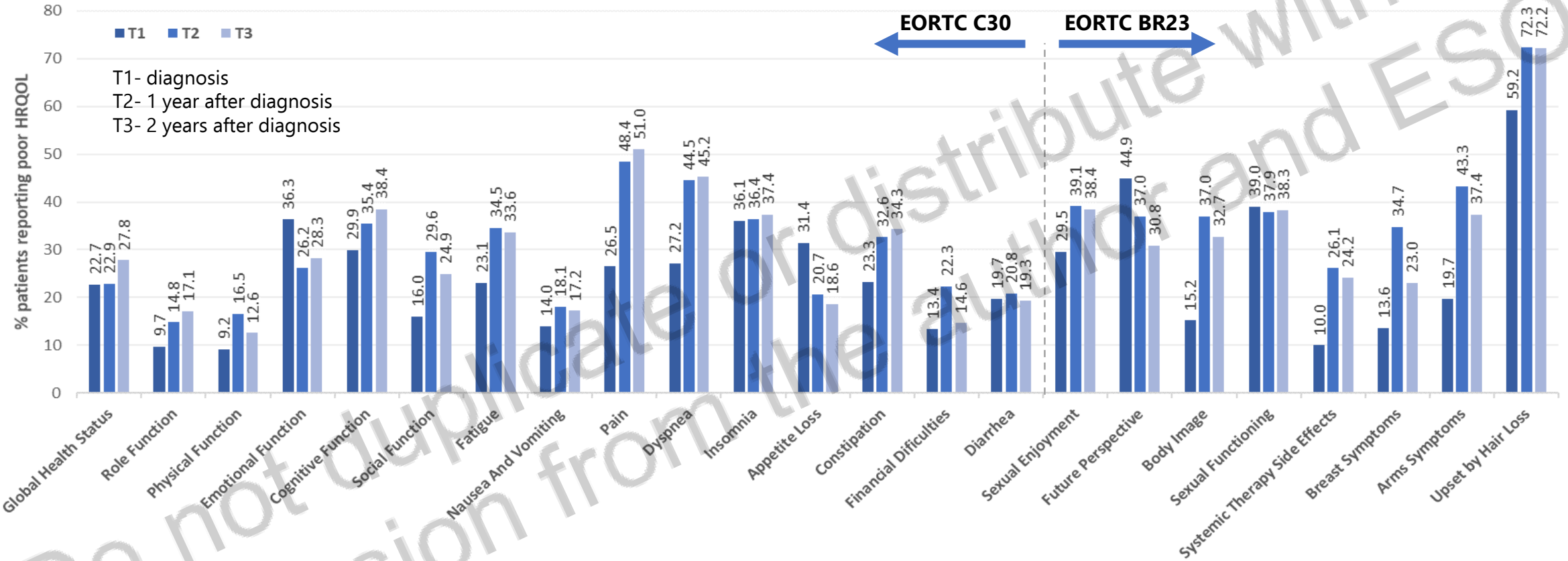


Cancer Survivors worldwide, by age group 1975-2040.
Adapted from Shapiro CL, *NEJM* 2018

Cancer Survivorship

Ferreira AR, Di Meglio A, Vaz-Luis I, Ann Oncol 2019
CANTO data

Impact of breast cancer and its treatment



- **Variety** of treatment-related *sequelae* and severe deterioration of quality of life among breast cancer survivors
- **Dramatic and persistent** downstream impact of treatments on psychological, functional and social dimensions of quality of life
- **Substantial under-diagnosis and inadequate management**

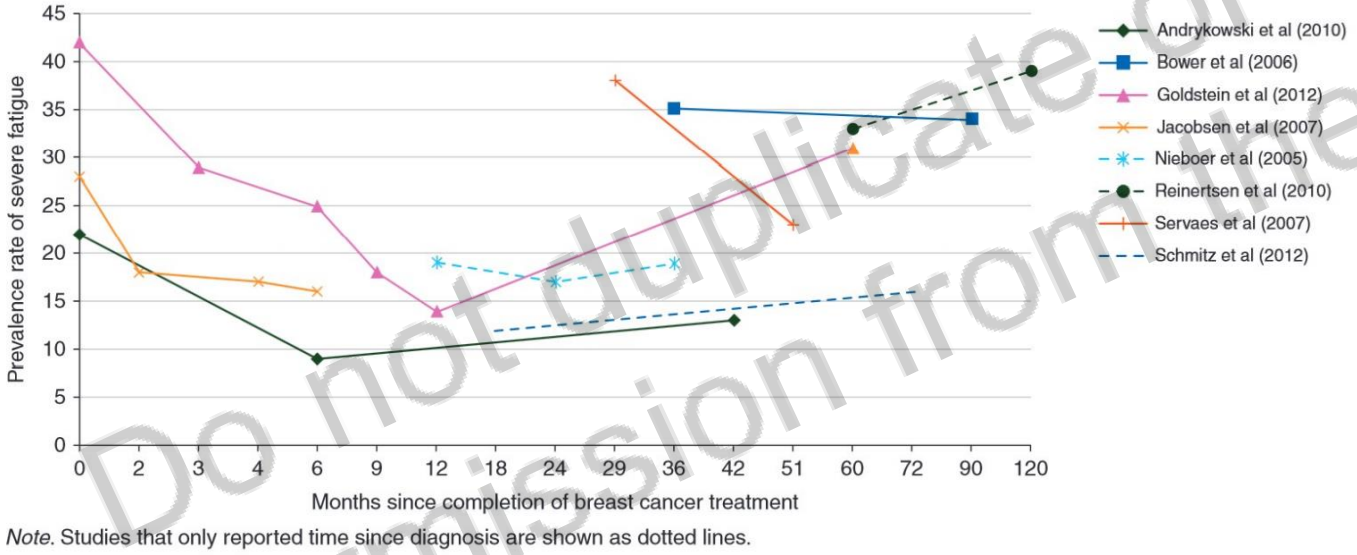
Cancer-related Fatigue

"A distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning."

National Comprehensive Cancer Network®

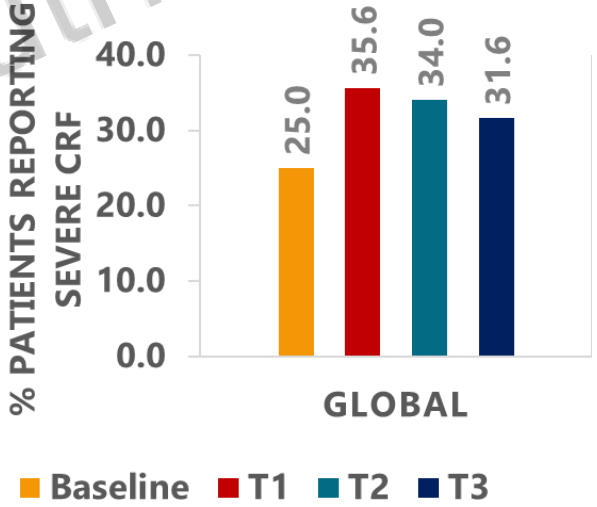
Extremely common, persistent, and subjective

- 90% during treatment
- Up to 40% in the year following primary treatment
- Up to 20% 10 years afterwards
- More intense, distressing, and less responsive to rest than regular fatigue



Note. Studies that only reported time since diagnosis are shown as dotted lines.

Prevalence of severe cancer related Fatigue (CRF) over time, Abrahams HJG – Ann Oncol, 2016



Baseline= Breast Cancer Diagnosis
T1= Year-1 after diagnosis
T2= Year-2 after diagnosis
T3= Year-4 after diagnosis

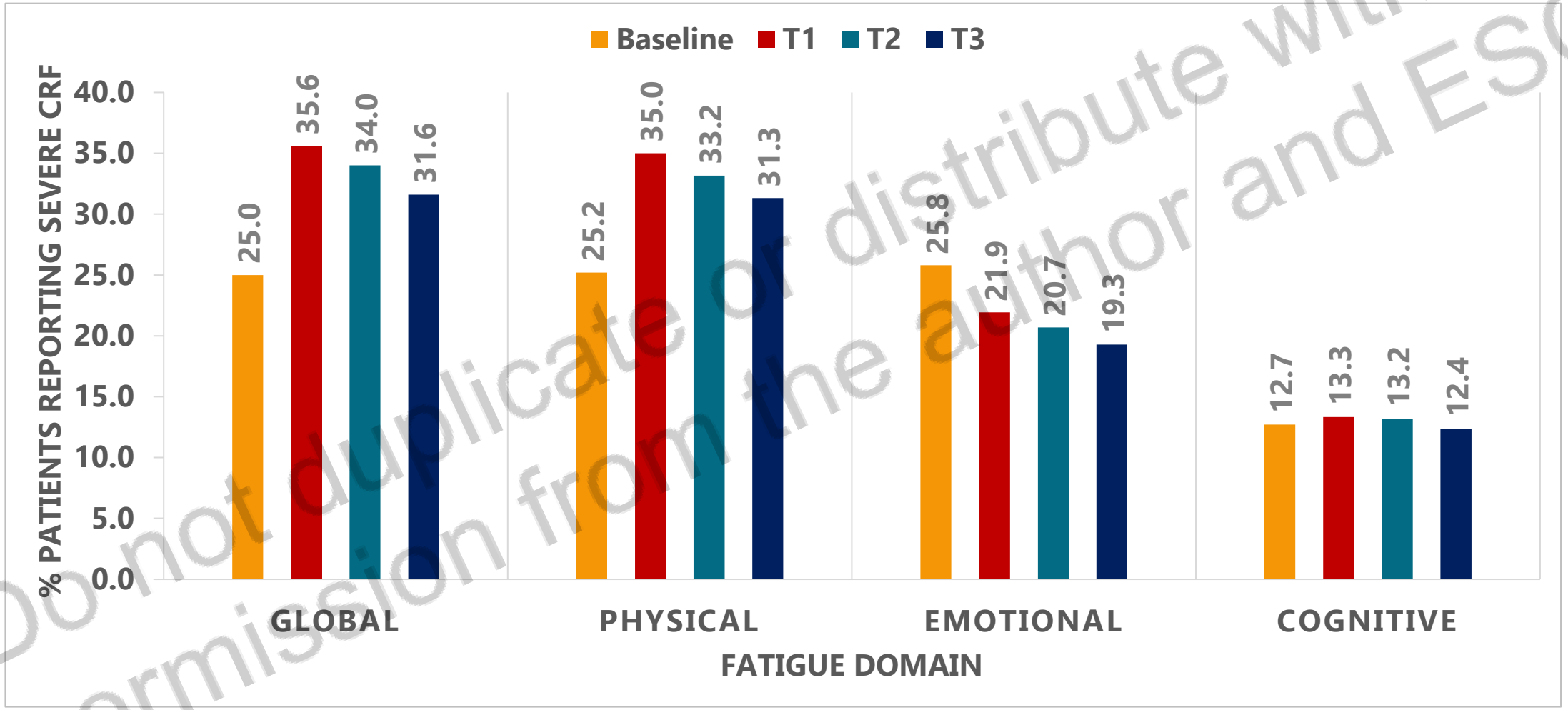
Prevalence of severe CRF over time. Severe CRF defined by a score of 40 or higher on EORTC QLQ-C30 (Global CRF) of QLQ-FA12 (CRF Dimensions), Vaz-Luis, ESMO, 2018

Abrahams HJG – Ann Oncol, 2016; Bower JE –JCO, 2000; Bower JE – Cancer, Vaz-Luis, ESMO, 2018

Cancer-related Fatigue – Multidimensional symptom

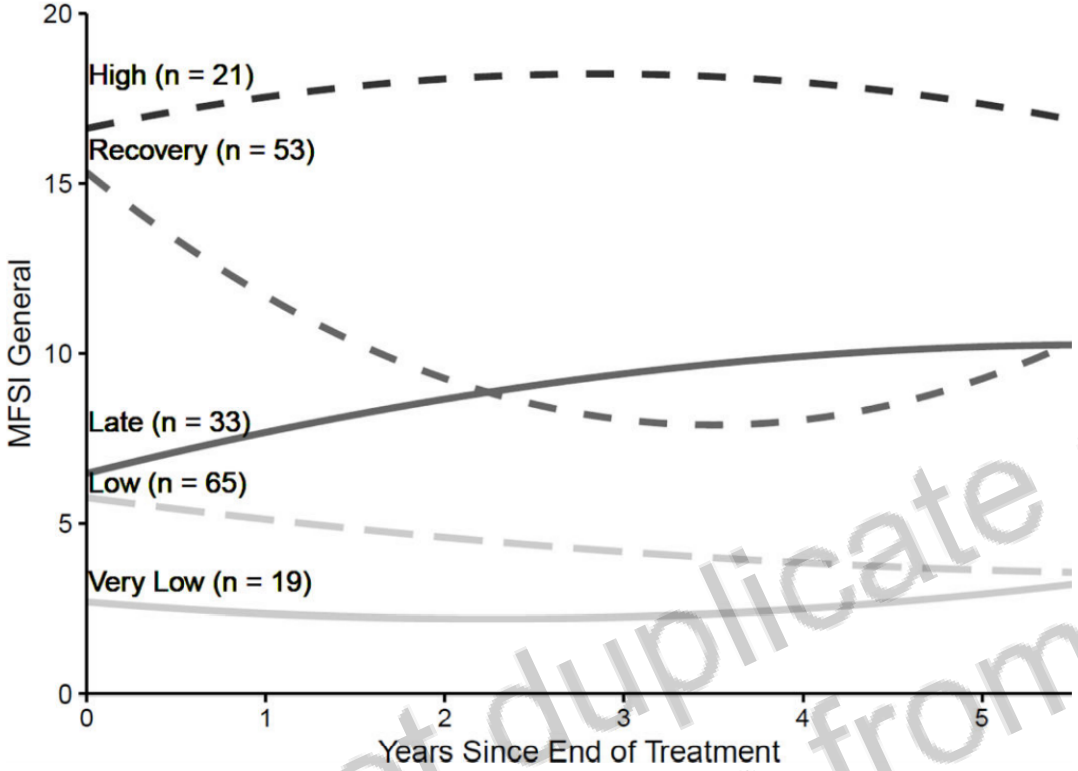
Multidimensional

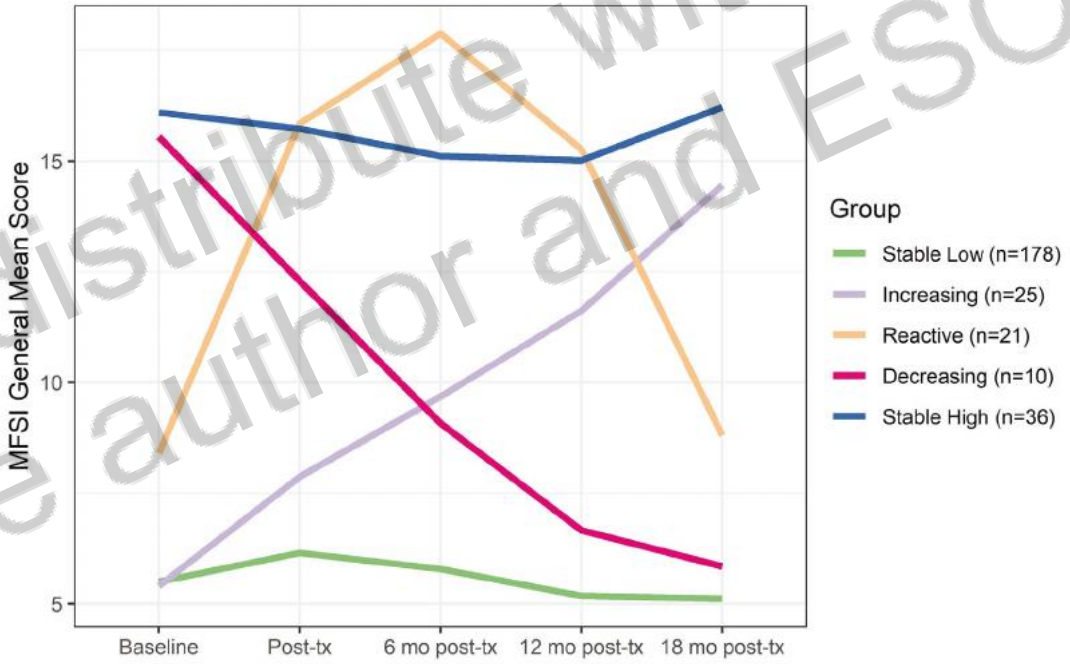
- Involves physical, emotional and cognitive dimensions



Prevalence of severe CRF over time. Severe CRF defined by a score of 40 or higher on EORTC QLQ-C30 (Global CRF) of QLQ-FA12 (CRF Dimensions). Vaz-Luis, ESMO, 2018

Cancer-related Fatigue-Trajectories

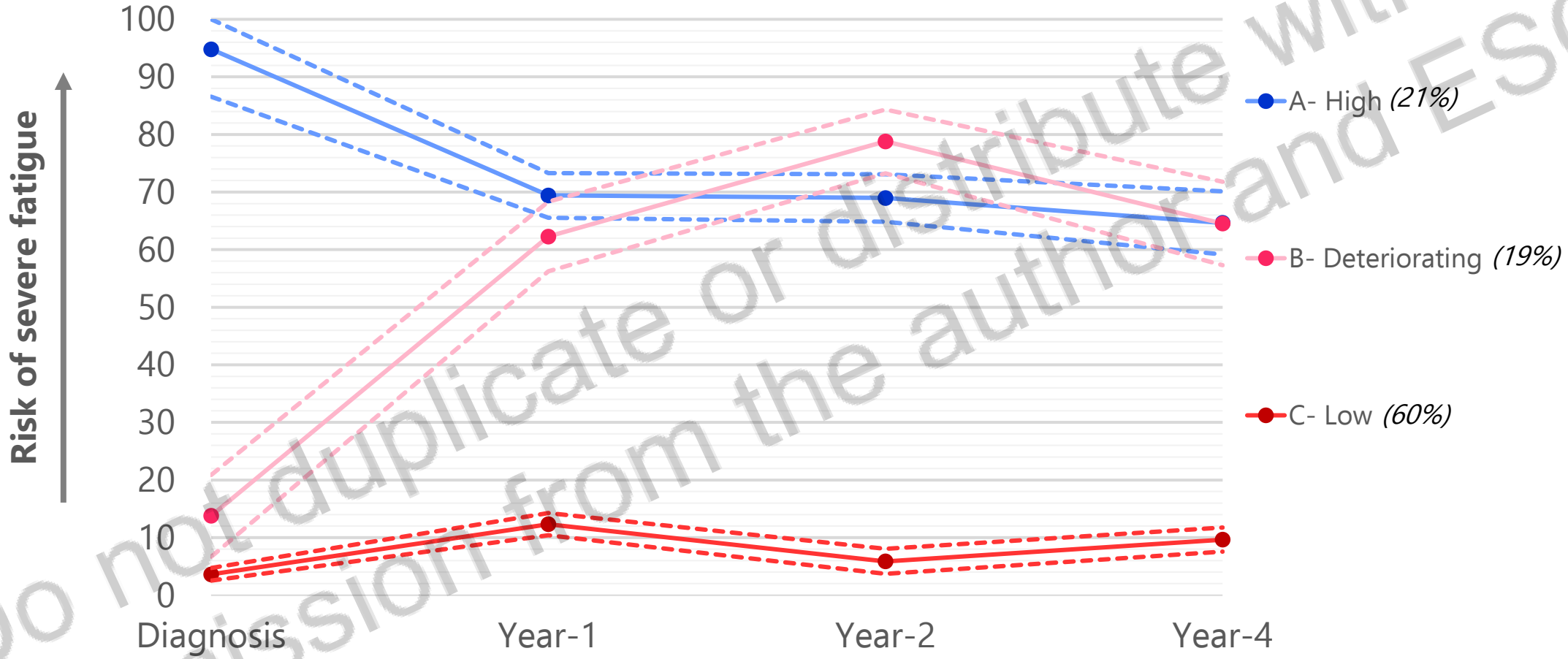




Mean scores on the MFSI general fatigue subscale are shown for the latent trajectory groups at each study assessment

Bower JE –Health Psychol, 2018; Bower JE – Cancer, 2021

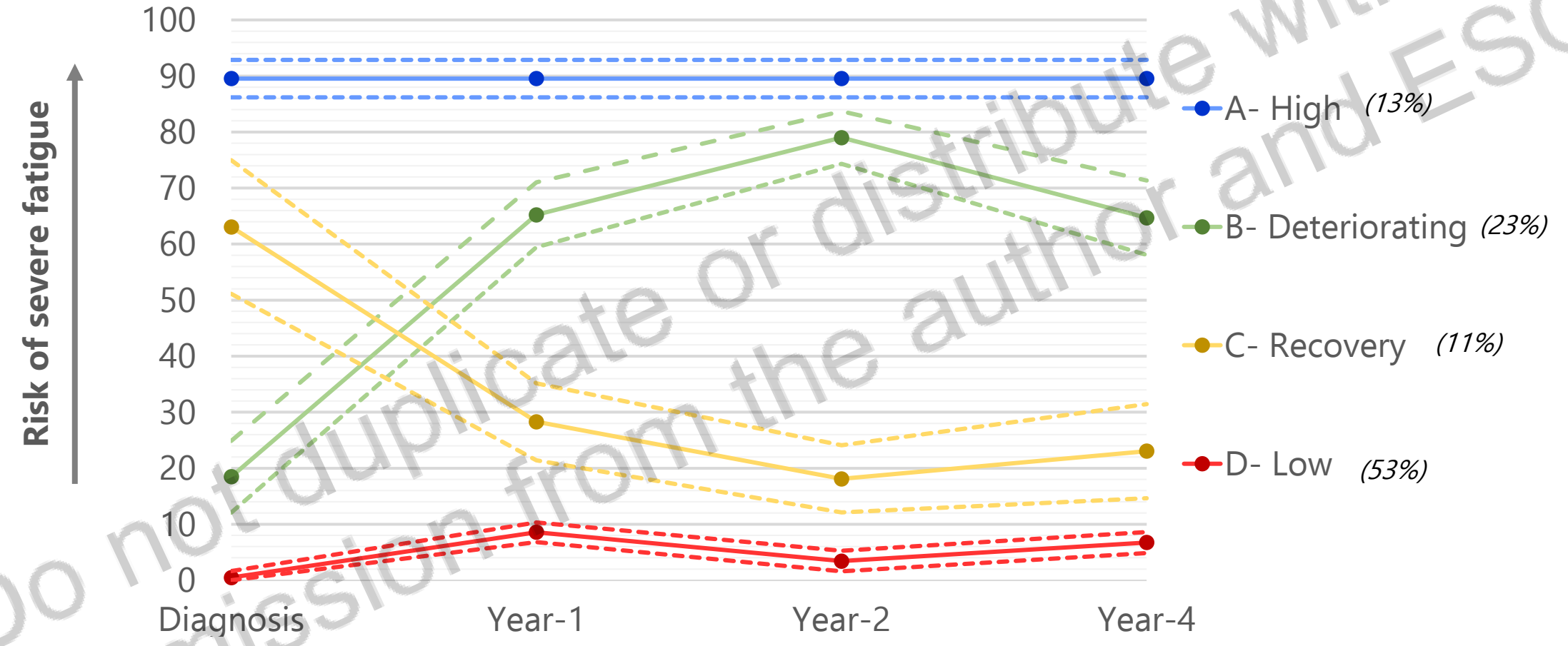
Cancer-related Fatigue-Trajectories



EORTC QLQ-C30 Severe global fatigue

Vaz-Luis I, ESMO, 2018

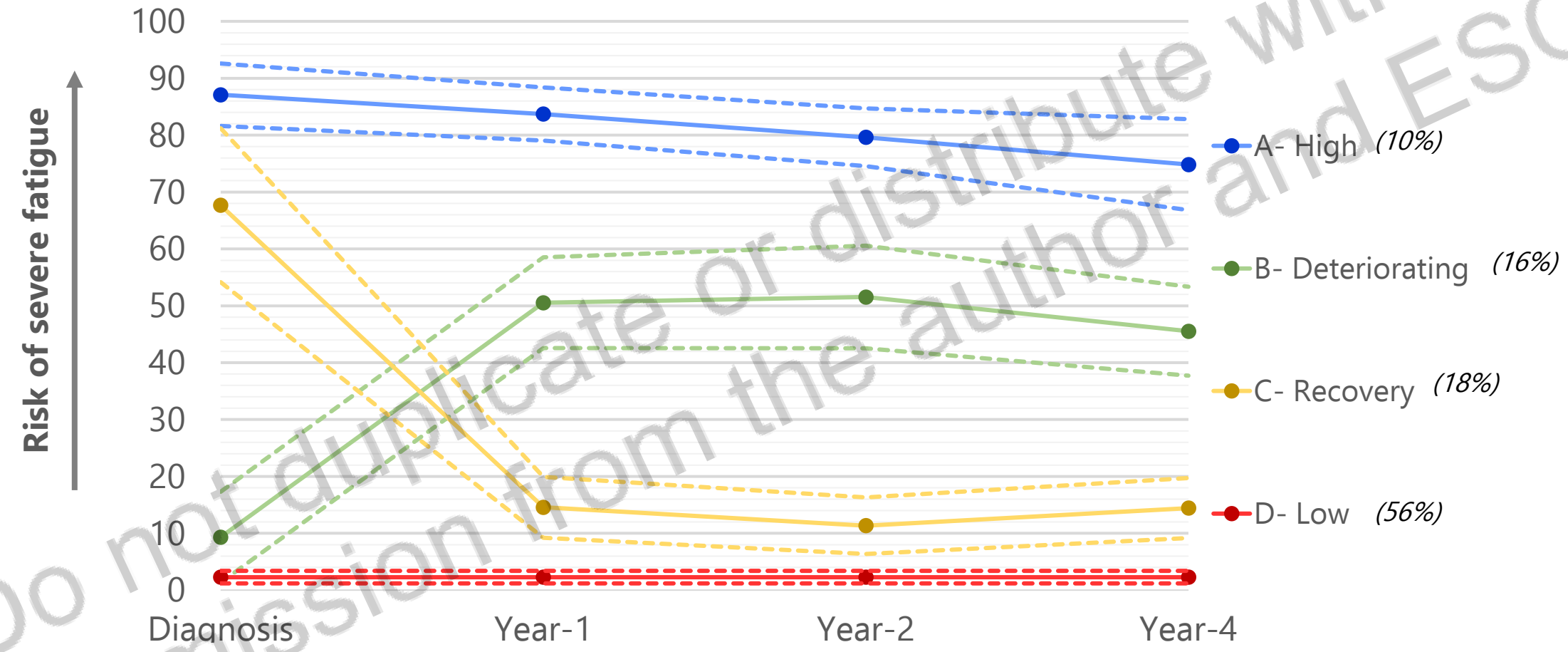
Cancer-related Fatigue-Trajectories



EORTC QLQ-C30 Severe physical fatigue

Vaz-Luis I, ESMO, 2018

Cancer-related Fatigue-Trajectories



EORTC QLQ-C30 Severe emotional fatigue

Vaz-Luis I, ESMO, 2018

Cancer-related Fatigue-Trajectories

EORTC QLQ-C30 Severe cognitive fatigue

Vaz-Luis I, ESMO, 2018

Cancer-related Fatigue- Impact

Impact

- Can interfere with normal functioning, and greatly deteriorate quality of life

Affects all aspects of Quality of Life (QOL)

- Considered more distressing than pain to a higher proportion of patients
- Ability to work (61%)
- Ability to care for family (42%)
- Concerns about survival/hope fighting cancer (33%) / Treating fatigue as important as treat cancer (16%)

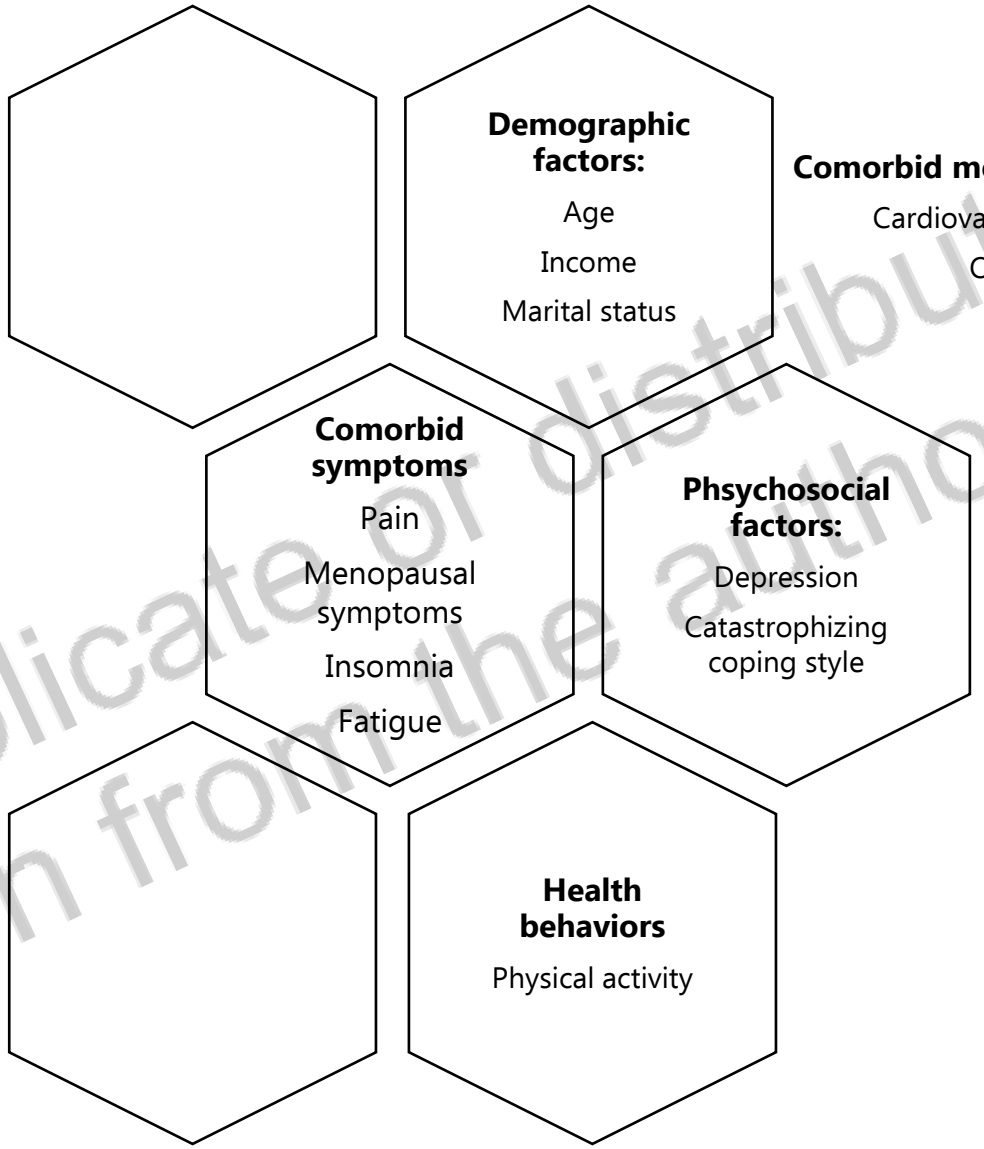
Decreased probability of receipt of treatment and trend towards reduced probability of return to work

	Odds Ratio of non adherence to endocrine therapy	95% CI
Severe fatigue (vs no)	1.65	(1.07-2.54)

	Odds Ratio of non returning to work	95% CI
Severe emotional fatigue (vs no)	1.45	(0.98-2.12)
Severe physical fatigue (vs. no)	1.30	(0.93-1.83)

Vogelzang- Semin Hemato, 1997; Pistilli B – JCO, 2020; Dumas – JCO, 2020

Cancer-related Fatigue- Associations



Abrahams HJG – Ann Oncol, 2016; Bower JE - Nature reviews Clin Onc, 2014

Cancer-related Fatigue-Associations

Multivariable logistic regression models of associations with severe global CRF, Variables retained after stepwise backward selection (threshold p<0.05)									
Characteristics	T1: Year-1			T2: Year-2			T3: Year-4		
	Estimate	95% CI		Estimate	95% CI		Estimate	95% CI	
Age, 1-year increase	**0.985**	0.979	0.992	**0.981**	0.974	0.988	-	-	-
Menopause, post vs. pre	-	-	-				**0.755**	0.640	0.891
BMI, 1-unit increase	**1.041**	1.028	1.055	**1.022**	1.008	1.036	-	-	-
Smoke behavior, Former vs. Current	**0.753**	0.609	0.932	**0.844**	0.671	1.060	-	-	-
Smoke behavior, Never vs. Current	**0.717**	0.596	0.862	**0.676**	0.554	0.824	-	-	-
Income, ≥ 3000 vs. < 1500	**0.734**	0.600	0.897	**0.634**	0.510	0.787	-	-	-
Income, > 1500 - 3000 vs. < 1500	**0.815**	0.669	0.994	**0.734**	0.592	0.910	-	-	-
Chemotherapy, Yes vs. No	**1.296**	1.125	1.493	-	-	-	-	-	-
Endocrine therapy, Yes vs. No	-	-	-	**1.280**	1.056	1.551	**1.448**	1.165	1.799
Anxiety, Doubtful vs. Non-case	-	-	-	**1.079**	0.897	1.298	**1.137**	0.924	1.398
Anxiety, Case vs. Non-case	-	-	-	**1.249**	1.044	1.493	**1.460**	1.196	1.781
Depression, Doubtful vs. Non-case	**1.379**	1.119	1.701	-	-	-	-	-	-
Depression, Case vs. Non-case	**1.625**	1.239	2.130	-	-	-	-	-	-
Insomnia, 1-point increase	**1.006**	1.004	1.008	**1.004**	1.002	1.007	**1.004**	1.001	1.007
Pain, 1-point increase	**1.010**	1.007	1.014	**1.015**	1.011	1.019	**1.016**	1.012	1.021
Hot flashes, Yes vs. No	**1.302**	1.123	1.509	**1.230**	1.048	1.442	-	-	-
Severe CRF at diagnosis	**3.007**	2.537	3.564	**3.254**	2.722	3.890	**2.480**	2.022	3.042
AUC	**0.74**			**0.75**			**0.71**		

Di Meglio A, ASCO 2021

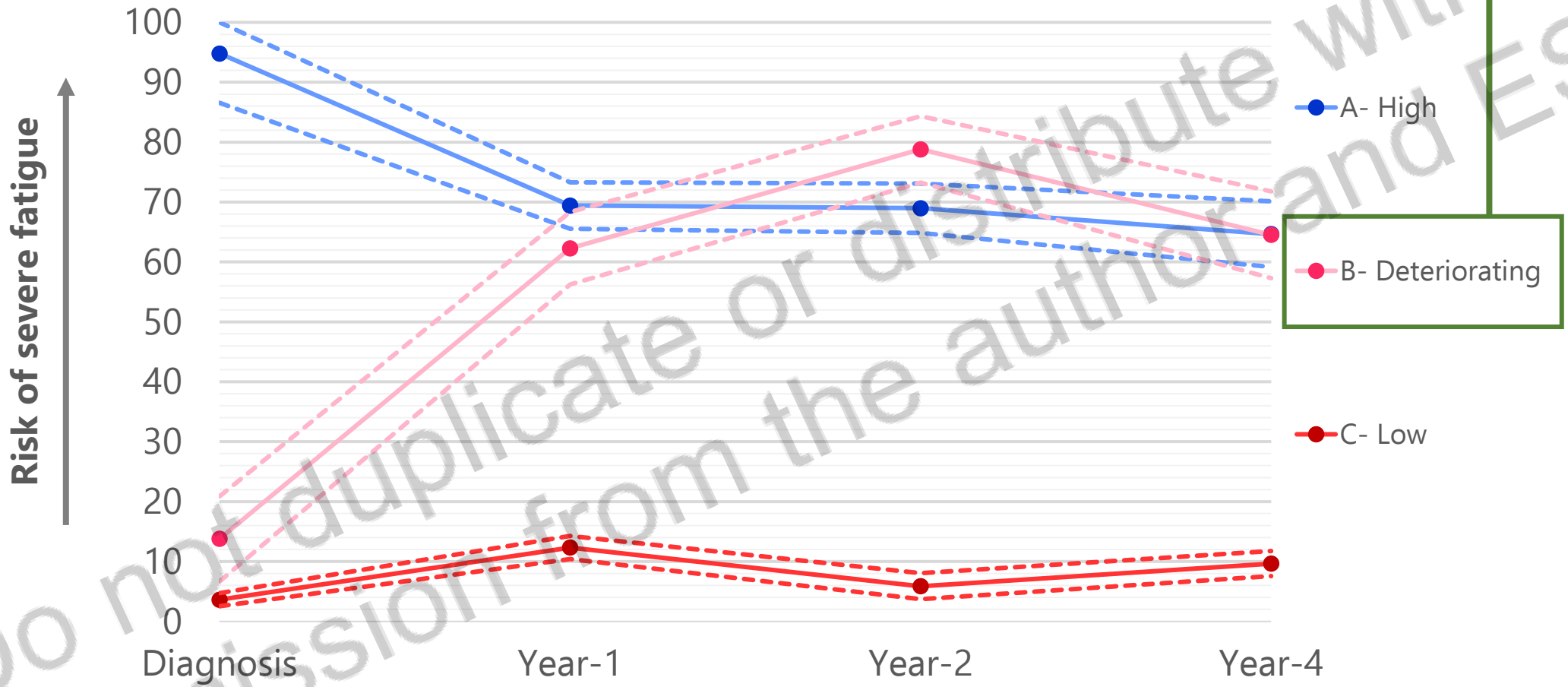
Cancer-related Fatigue- Associations

Example of clinical application	
Patient characteristics	
Age	55 years
BMI	28 Kg/m^2
Smoke behavior	Current smoker
Monthly income	<1500 Euros
Receipt of Endocrine therapy	Yes
HADS Score Anxiety	Case
C30 Pain Score	100/100
C30 Insomnia Score	100/100
Hot Flashes	Yes
Severe fatigue at diagnosis	Yes
Predicted risk of Severe Global CRF at Year-2 after diagnosis	**93%**

Di Meglio A, ASCO 2021

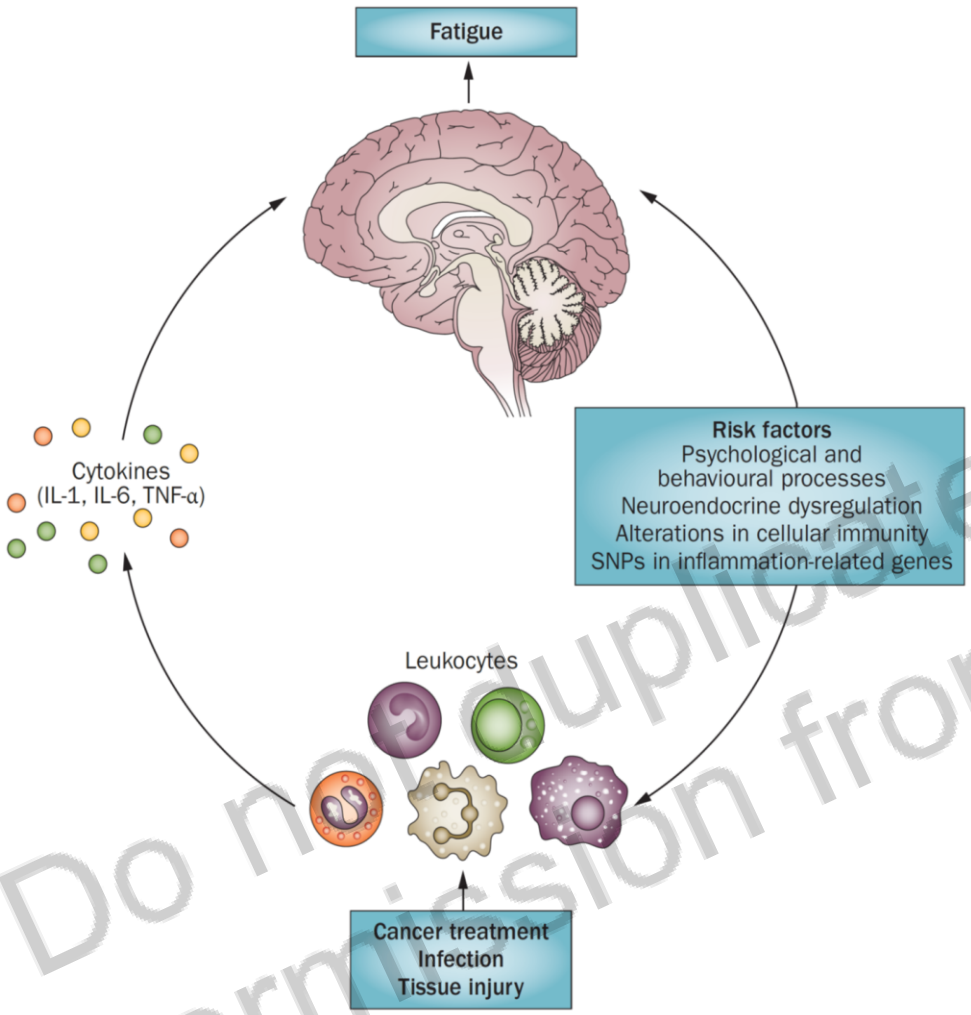
Cancer-related Fatigue-Associations

Clinical: Younger, heavier, smokers, single, higher income,
Treatment: Chemo-treated, hormonotherapy-treated,
Symptoms: More depression, pain, insomnia, hot flashes



EORTC QLQ-C30 Severe global fatigue

Cancer-related Fatigue - Biology

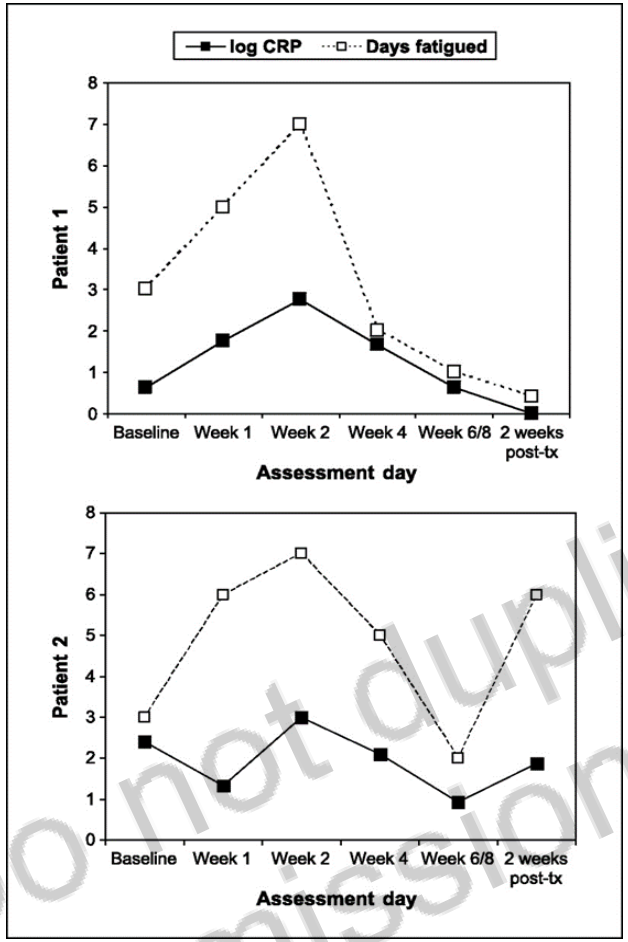


Biological substrate of onset and persistence of CRF.
Adapted from Bower JE - Nature reviews Clin Onc, 2014

Cancer survivors with persistent fatigue show elevated markers of inflammatory activity

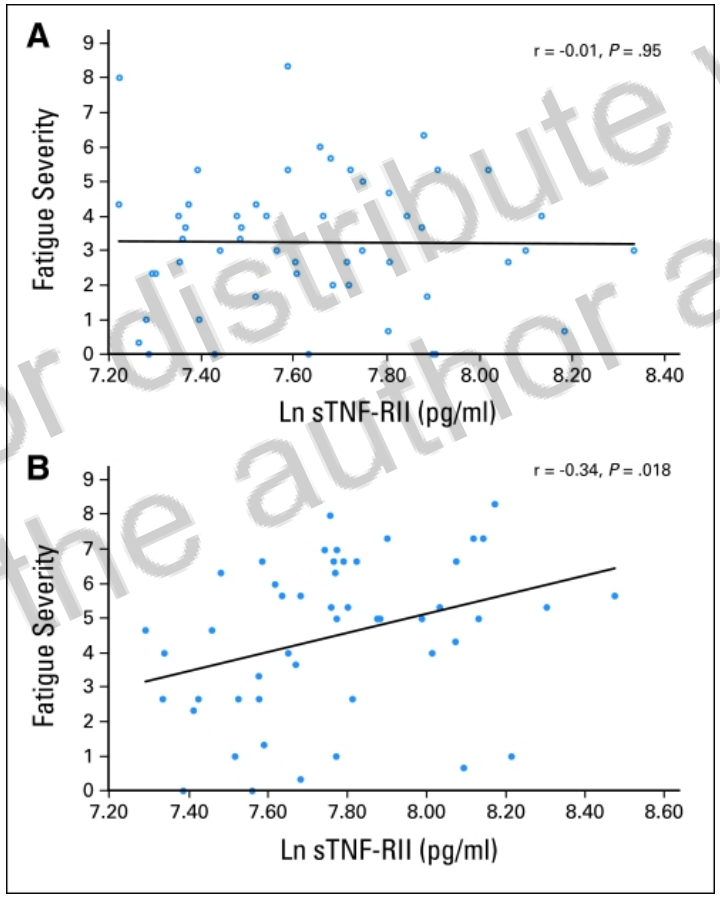
- This may reflect increased activity of pro-inflammatory cytokines, signaling the brain to produce symptoms of fatigue
- Individuals who are prone to produce more inflammatory cytokines may be at higher risk for cancer related fatigue

Cancer-related Fatigue - Biology



Longitudinal assessement in 2 patients of fatigue and CRP

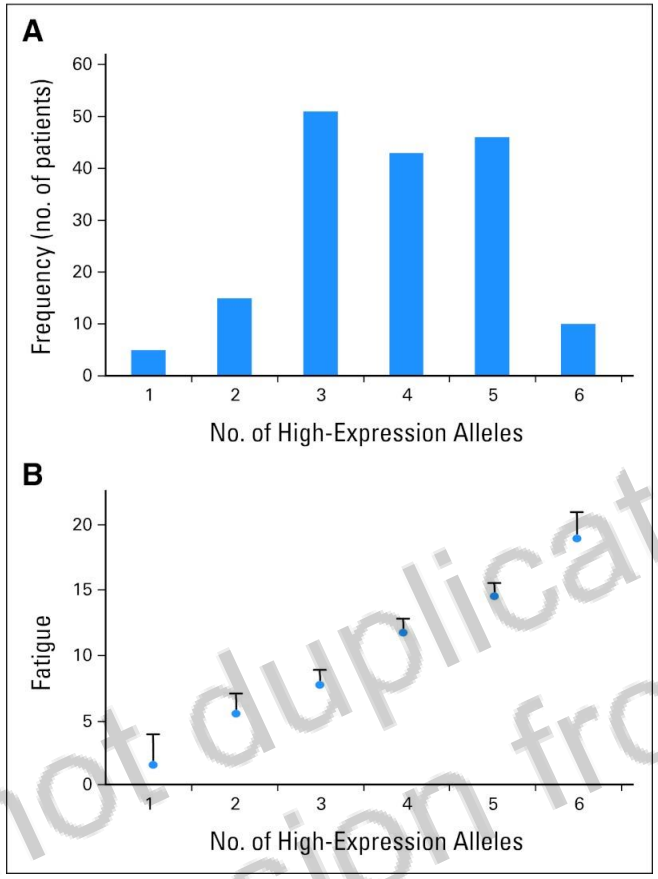
Bower JE- Clin Cancer Res 2009



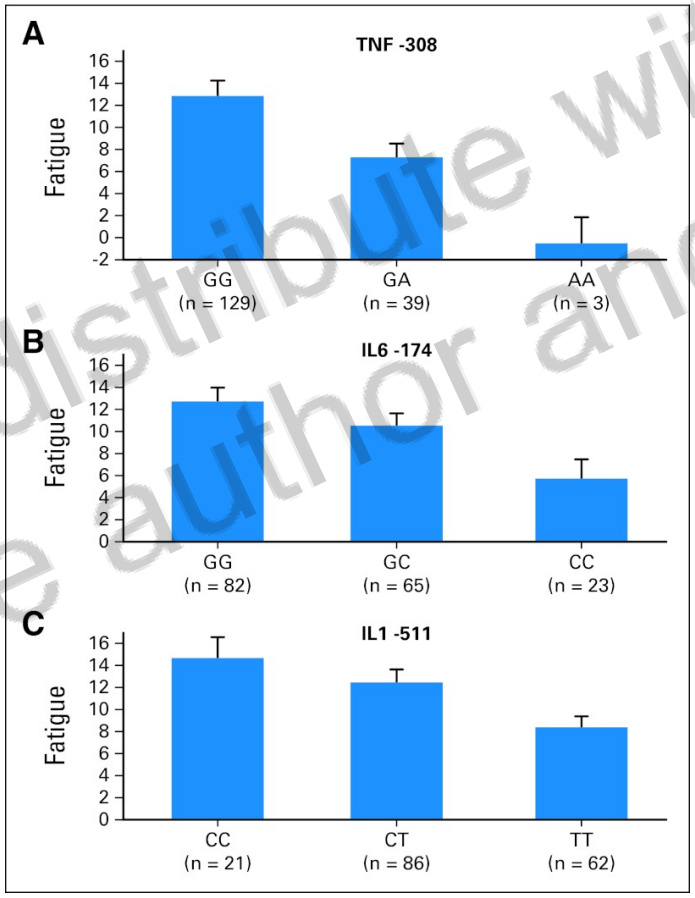
Correlation between fatigue severity and TNF-RII A) no chemotherapy B) chemotherapy

Bower JE- JCO 2011

Cancer-related Fatigue- Biology



A- Frequency of patients at each level of an additive genetic risk socre summing the number of high risk alleles B- Predicted scores on the MFSI-SF at each level of the additive genetic risk score



Associations between 3 individual SNPs and CRF

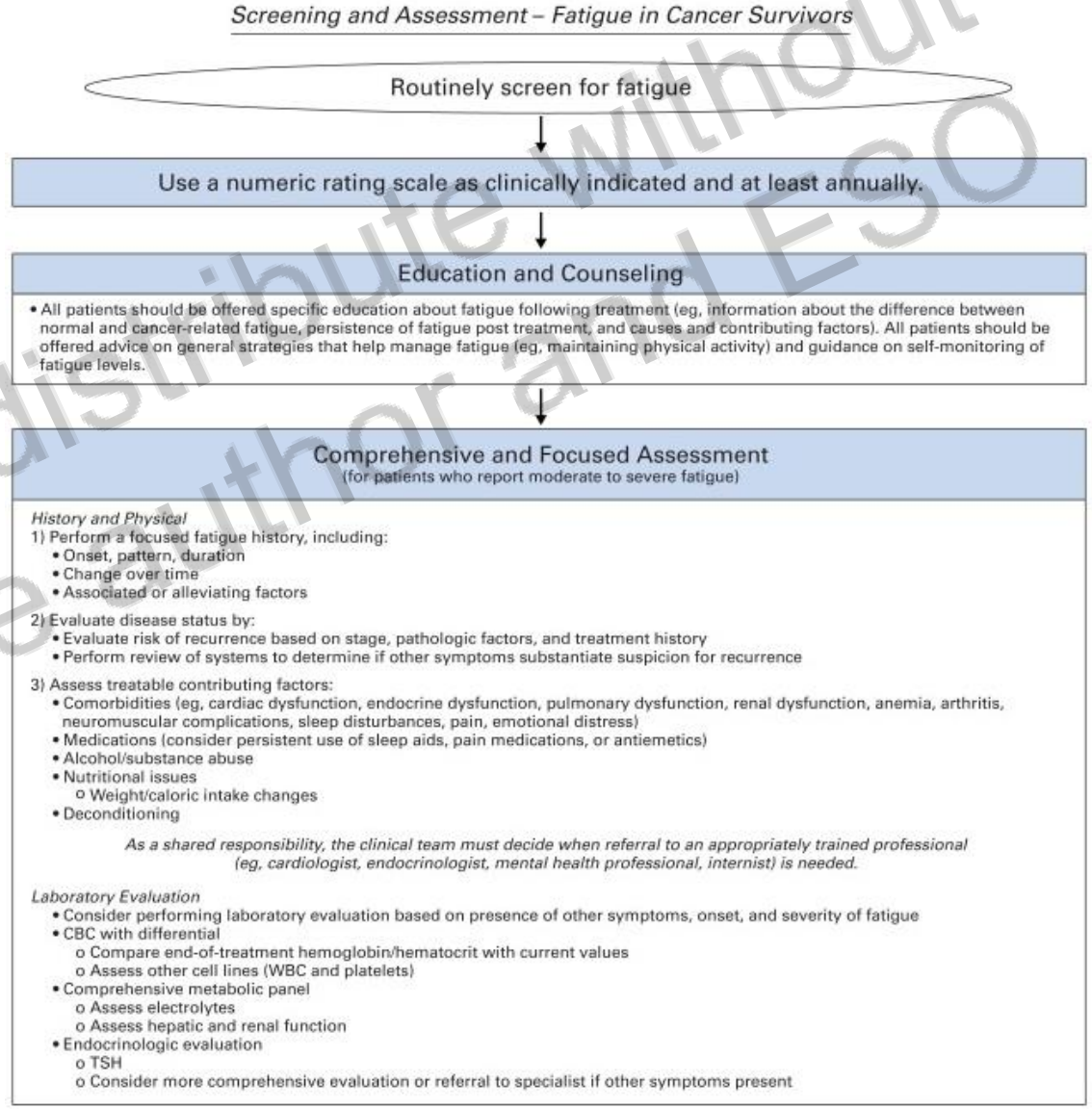
Bower JE- JCO 2013

Cancer related Fatigue – Management

Complex management

- Often untreated and unaddressed
- Regular screening and assessment, close monitoring
- Interdisciplinary/Multidisciplinary management
- Education and training programs
- Availability of effective approaches (e.g., promotion of more active lifestyle, cognitive-behavioral and psycho-social approaches, acupuncture and other mind-body interventions)

- If possible, identify and treat underlying contributing factors
- If these cannot be identified, non-specific interventions may be useful



Bower JE- JCO 2014

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Cancer-Related Fatigue

Nonpharmacologic

- Physical activity (category 1)
  - Maintain optimal level of activity
  - Consider initiation and/or encourage maintenance of a physical activity/exercise program, as appropriate per health care provider, consisting of cardiovascular endurance (walking, jogging, or swimming) and resistance (weights) training[k]
  - Cautions in determining level of activity:
    - Late effects of treatment (eg, cardiomyopathy)
    - Safety issues (ie, assessment of risk of falls)
  - Consider referral to rehabilitation: physical therapy, occupational therapy, and physical medicine
  - Yoga (category 1)
- Psychosocial interventions (category 1)
  - CBT[k]/BT (category 1)[m]
  - Mindfulness-based stress reduction (category 1)
  - Psycho-educational therapies/Educational therapies (category 1)
  - Supportive expressive therapies (category 1)[n]
- CBT[l] for sleep (category 1)
  - Stimulus control
  - Sleep restriction
  - Sleep hygiene
- Bright white light therapy
- Acupuncture
- Nutrition consultation

Pharmacologic[q]

- Consider psychostimulants[p] (methylphenidate) after ruling out other causes of fatigue
- Treat for pain, emotional distress, and anemia as indicated per NCCN Guidelines (See NCCN Guidelines for Adult Cancer Pain, Distress Management, and Hematopoietic Growth Factors)
- Optimize treatment for sleep dysfunction, nutritional deficit/imbalance, and comorbidities

National Comprehensive Cancer Network®

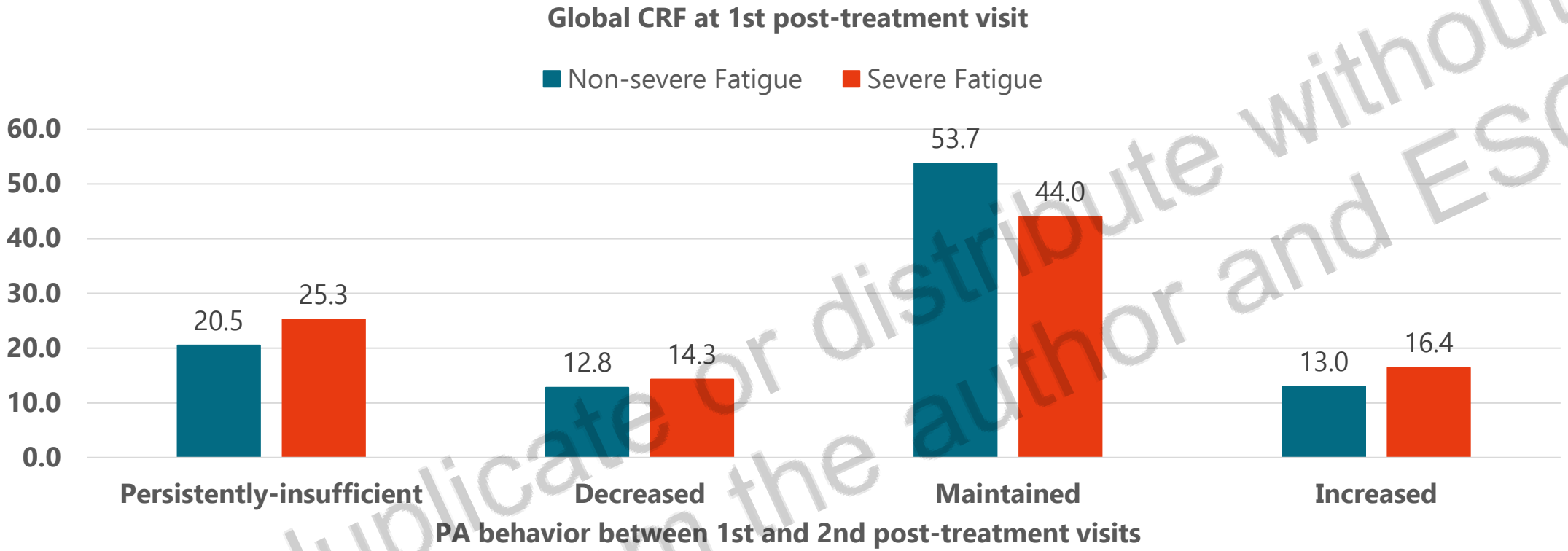
Cancer related Fatigue –Management

PA and other types of consultations between 1st and 2nd post-treatment visits	
Overall N= 7902	**(%)**
PA	
Persistently insufficient (always <10*)	13.4%
Reduced activity (from ≥10 to <10)	22.2%
Maintained activity (always ≥10)	50.2%**
Increased activity (from <10 to ≥10)	14.2%**
	**Adherent to WHO recommendations on PA
Consultations with other health care providers	
Psychologist consultations	9.8%
Psychiatrist consultations	6.9%
Acupuncturist consultations	7.7%
CAM practitioner consultations (homeopathy or naturopathy)	9.8%

*MET-hours/week;
**corresponding to 150 minutes/week of moderate-intensity or 75 minutes/week of vigorous intensity or an equivalent combination

Di Meglio A, JNCCN 2021 (in press)

Cancer related Fatigue –Management



Prevalence severe CRF=36.4%

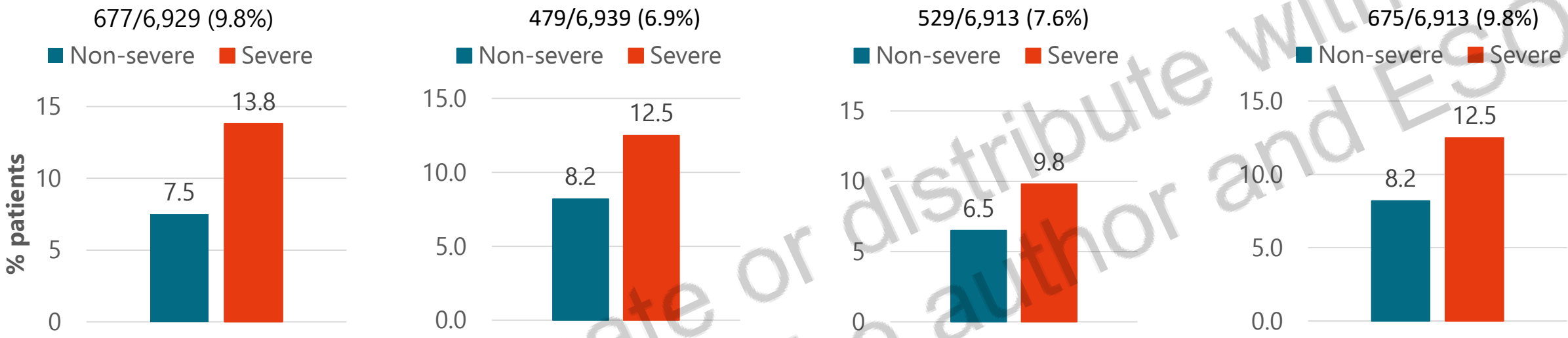
Maintained or increased physical activity ≥10 MET-hours/week 4035/6263 (64.4%)	
% aOR* (95%CI)	**60.4% vs. 66.7%; 0.82 (0.71-0.94),** p= 0.004

*Severe vs. Non-severe CRF group; Adjusted by: Age, BMI, comorbidities, anxiety and depression, education, income, centre volume, breast cancer subtype and stage, breast and axillary surgery, receipt of chemotherapy

Di Meglio A, JNCCN 2021 (in press)

Cancer related Fatigue –Management

Global CRF at 1st post-treatment visit



Consultations with other health care providers between 1st and 2nd post-treatment visits

Psychologist		Psychiatrist		Acupuncturist		CAM Practitioner	
aOR* (95% CI)	1.29 (1.05-1.58) p= 0.014	aOR* (95% CI)	1.39 (1.10-1.76) p= 0.0064	aOR* (95% CI)	1.46 (1.17-1.82) p= 0.0008	aOR* (95% CI)	1.49 (1.23-1.82) p<.0001

*Severe vs. Non-severe CRF group; Adjusted by: Age, BMI, comorbidities, anxiety and depression, education, income, centre volume, breast cancer subtype and stage, breast and axillary surgery, receipt of chemotherapy

Di Meglio A, JNCCN 2021 (in press)

Cancer related Fatigue – Preferences and barriers to Management (patient perspective)

	FATIGUE CHARACTERISTICS				USE OF HEALTH BEHAVIOR INTERVENTIONS		USE OF OTHER RESOURCES	
Patients (No.)	Global level of fatigue (NS)	Physical fatigue (FA-12)	Emotional fatigue (FA-12)	Cognitive fatigue (FA-12)	Physical activity	Mind-body interventions	Complementary and alternative medicine	Dietary changes
1	7	46.67	66.67	16.67	-	-	-	+
2	6	46.67	66.67	66.67	++	Yoga	Vitamin D, osteopathy	-
3	7	66.67	44.44	100	++	Sophrology	-	+
4	7	93.33	55.56	100	+	-	Vitamin C, Ginseng, Acerola	-
5	8	13.33	0	16.67	-	-	-	-
6	7	40	66.67	33.33	++	-	Osteopathy	-
7	5	60	33.33	33.33	++	-	-	-
8	7	80	44.44	50	+	-	Osteopathy	-
9	5	40	33.33	0	-	-	-	-
10	8	60	88.89	66.67	-	Sophrology	-	-
11	6	26.67	11.11	0	++	-	Homeopathy, acupuncture, magnesium, probiotics, thermal cure	+
12	7	60	77.78	0	-	-	-	-
13	7	46.67	0	0	-	-	Vitamins	-
14	5	26.67	22.22	33.33	++	-	-	-
15	6	80	77.78	50	+	-	-	-
Mean (SD)	6.53 (0.99)	52.44 (22.09)	45.93 (28.75)	36.90 (34.20)	9 (60)	3 (20)	6 (40)	3 (20)
Or N (%)								

Charles C, Supportive Care Cancer 2021

Cancer related Fatigue – Preferences and Barriers to Management (patient perspective)

All patients who were not physically active (n=6) declared that they *"should move more"* however only one had a defined project (individual coaching).

Barriers to physical activity:
- Physical: such as fatigue ("*fear of not being able to keep pace with the group and of being misjudged by others"*), pain, overweight ("*I have trouble breathing as soon as I walk a little bit so walking is good for others")*
- Psychological and socio-professionals: lack of motivation, lack of social support, family responsibility and workload
- Environmental: distances from places to practice, weather

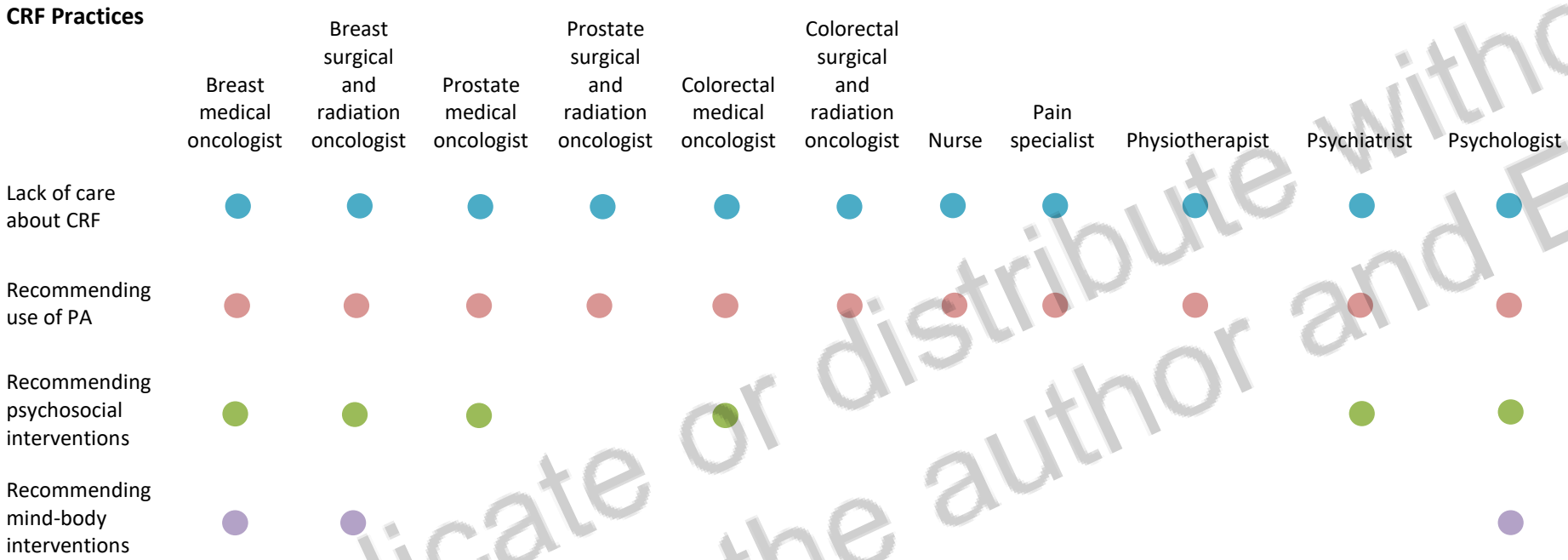
Motivational levers:
- Being accompanied by a friend, joining a group with people in a similar life situation or in the same age range
- Practicing adapted physical activity close to home
- Being encouraged to go out and exercise by someone, being advised by a coach.

Representations of Physical activity:
- Majority expressed positive representations about physical activity
- None of the respondents reported negative representations about physical activity.

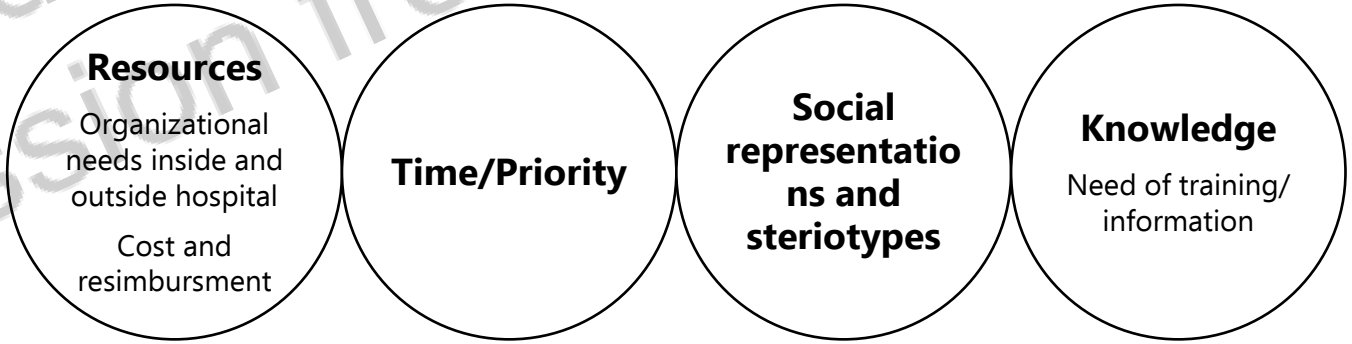
Benefits of physical activity
General ("*It feels good*")
Specific benefits
- Morale support,
- Relief of symptoms (fatigue – *"It is another kind of fatigue"*, *"It is a good fatigue"*, pain, sleep disorders)
- Relief of stress *("clear or change one's mind"*, *"think about something other than illness"*)
- Maintenance and strengthening of physical capacities (*"exercise muscles"*, *"lose weight"*, *"this helps circulate blood"*, *"keep oneself in good physical shape"*)
- Getting some fresh air or seeing other people

Charles C, Supportive Care Cancer 2021

Cancer related Fatigue – Needs and Barriers to Management (providers perspective)



CRF Practices among distinct HCP categories. The circle represents that at least one HCP within each professional category indicated to view them represented in the described category. Note: CRF: cancer-related fatigue, HCP: health care providers.



Martin E, European Journal of Cancer Care 2021

Cancer related Fatigue – Can mHealth be a solution?

World tour gamification to promote physical activity

Main themes emerging during the Focus Groups	
Focus Group - App-based mHealth group challenge	
Positive Aspects	***Negative Aspects***

Main themes emerging during the Focus Groups

Positive Aspects	***Negative Aspects***
Motivating (7/9)	Time consuming (4/9)
Making them feel good physically and morally (6/9)	Lack of explanations (4/9)
Generating good habits (5/9)	Only optimized for walking (4/9)
Group activity (4/9)	Technical problems (3/9)
Tracking of physical activity (3/9)	
Seeing they are able to do it (2/9)	

STEPPING-STONe A STEpwise research Program to Promote INGeniouS ONline supportive solutions in the relief of cancer-related fatigue

Martin E, JMIR, 2021; C Charles, INCA PI

Cancer related Fatigue – Can a personalized clinic be a solution?

Methods

Population: 32 BC pts received at the fatigue clinic from October 2018 to May 2019

Instrument: Ad-hoc questionnaire sent by mail

MAIN RESULTS

Response rate: 15/32 (46.9%)

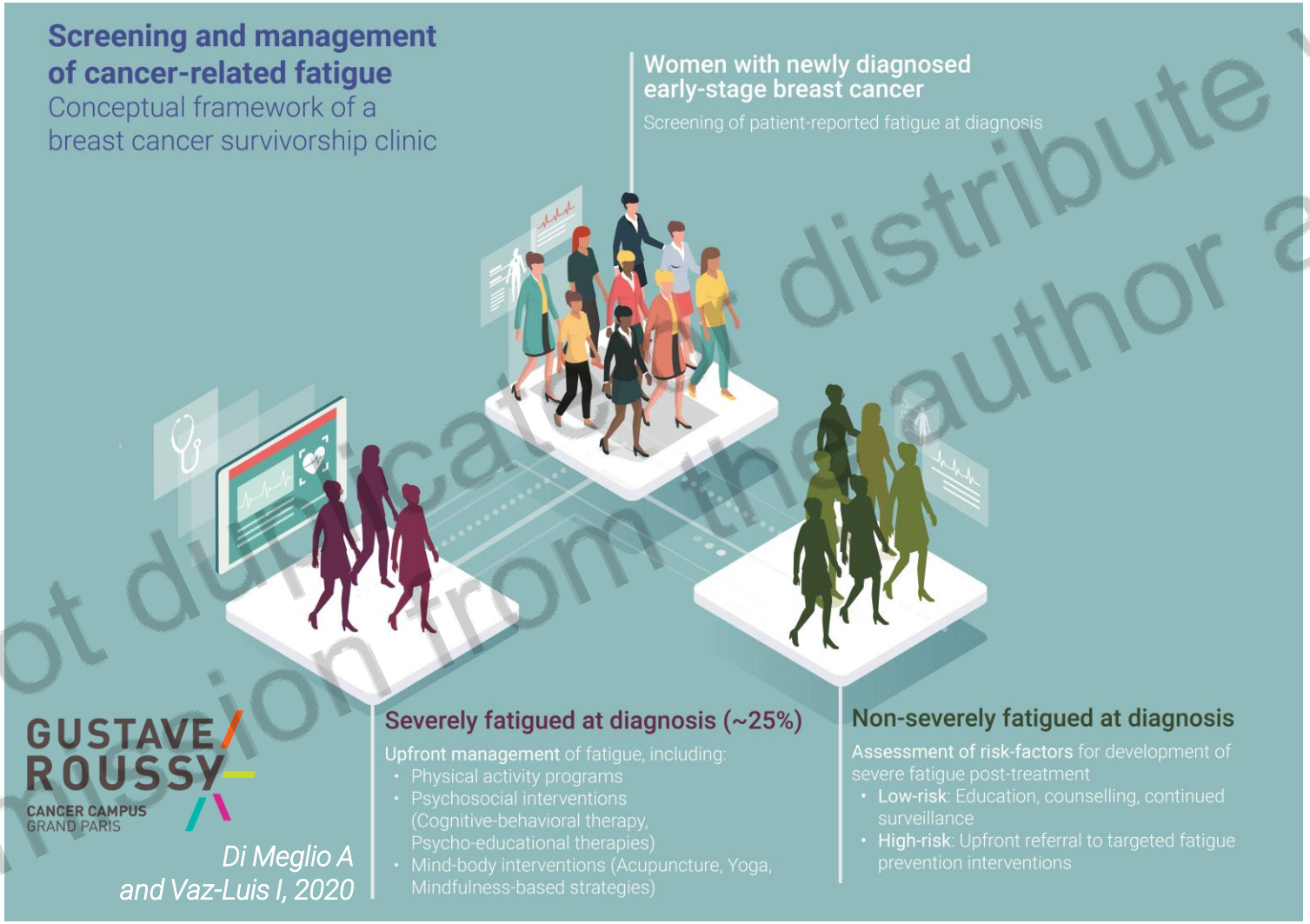
- **Organization and setting:** Globally a **good level of satisfaction** with respect to appointment scheduling, reception and information received
- **Expectations:** Partially addressed
  - Better understanding of the causes of fatigue
  - Being advised to fight against fatigue
  - Being informed on the adverse effects related to cancer treatments (e.g. hormone therapy)
- **Perceived usefulness:** Moderate to very useful
  - Reinsurance (cancer recurrence)
  - Guidance
  - Confirmation of personal assumptions about the causes of fatigue
  - Putting the problem into words / recognizing it
- **Application of recommendations:** 14% not at all vs. **86%** a little to very much (43% a lot)
- **Evolution of fatigue (B/A consultation):** 50% similar situation vs. 50% decrease of fatigue

Unpublished data

Should we move in each direction?

A Comprehensive Bio-behavioral Approach To Tackle Toxicities In Breast Cancer Survivors

Screening and management of CRF: a conceptual framework and model



Conclusions

- **Cancer related- fatigue is a highly distressing and prevalent symptom**

- **Predicting cancer-related fatigue (CRF):**

Development of predictive equations of CRF
  - **Need to improve predictive ability**
  - **Other factors to integrate (biology)**

- **Treating CRF:**

Need to optimize the **implementation of available strategies for CRF**

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