ONCONET-SUDOE

Expert Report

Workshop on Nutrition, Physical Activity & Cancer

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European Regional Development Fund

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CONFERENCE BACKGROUND

Rationale

Cancers are among the leading causes of morbidity and mortality worldwide, and the number of new cases is expected to rise significantly over the next decades. According to the World Health Organization, between 30-50% of all cancer cases could be prevented mainly through healthy lifestyle choices, such as diet and physical activity. A healthy diet and engaging in regular physical activity are not only established risk factors for cancer incidence but they are also important after the diagnosis of cancer.

As Work Package 1.1 Coordinator for Onconet, ICO brought together a panel of experts who specialize in the mechanisms of nutrition and exercise science on cancer. The conference took place on March 14th, 2019 at Hospital Duran i Reynals, in Barcelona (Spain). The overall aim of the workshop was to analyse and discuss current research on diet, nutrition, physical activity and their influence on the prevention and management of cancer in patients and survivors.

This document presents a detailed summary of the main topics discussed.

Program - Thursday, March 14th. 2019

8:30h – Registration

Workshop opening and welcome

9 – 9:30h – **Dr. Josep María Vilà**, President, Catalan Institute of Oncology (ICO)
– Representatives of the ONCONET-SUDOE

Session I – Diet and cancer prevention (I)

Chair: Paula Jakszyn (ONCONET-SUDOE; Unit of Nutrition and Cancer-UNAC, ICO)

9:30 – 10:05h – **DORA ROMAGUERA.** Instituto de Salud Global (ISGlobal). Barcelona, Spain
Topic: *The WCRF / AICR cancer prevention recommendations 2007 vs. 2018: lessons learned and current challenges in the operationalization of an index score.*

10:05 – 10:40h – **ANTONIO AGUDO.** Head of the Unit of Nutrition and Cancer. Catalan Institute of Oncology (ICO). ICO Coordinator for Onconet.
Topic: *Nutritional quality as represented by the Nutri-Score label and cancer risk in Europe.*

10:40 – 11:15h – **CECILIA GALBETE.** MG Nutrición 3G S.L. Noain (Navarra), Spain
Topic: *Mediterranean diet: a technical review of its definition and the implication on cancer risk.*

11:15 – 11:45h - Coffee Break.

Diet and cancer prevention (II).

Chair: Paula Jakszyn (ONCONET-SUDOE; UNAC, ICO)

11:45 – 12:20h – **ANA RAMIREZ DE MOLINA.** Deputy Director and Director of the precision nutrition program for cancer. IMDEA Food Institute.
Topic: *Lipid metabolism in colorectal cancer.*

12:20 – 12:55h – **GEMMA CASTAÑO-VINYALS.** Instituto de Salud Global (ISGlobal). Barcelona, Spain
Topic: *Mistimed eating patterns and cancer risk.*

12:55 – 13:30h – **Open discussion**

13:30 – 14:45 - Lunch.

Session II – Physical activity, sedentary behavior and cancer.

Chair: Antonio Agudo (ONCONET-SUDOE; Head of the Unit of Nutrition and Cancer. Catalan Institute of Oncology (ICO). ICO Coordinator for Onconet.)

14:45 – 15:30h – **ANNE M. MAY.** University Medical Center Utrecht, Julius Center. Utrecht, The Netherlands
Topic: *The role of physical activity before and after a cancer diagnosis: Current evidence.*

15:30 – 16:00h – **GUILLERMO R. OVIEDO.** Faculty of Psychology, Education and Sport Sciences. Ramon Llull University. Barcelona, Spain
Topic: *Physical activity interventions in patients with chronic conditions.*

16:00 – 16:30h – **SORAYA CASLA.** Asociación Española Contra el Cáncer (AECC). Madrid, Spain
Topic: *Regular exercise interventions in cancer patients.*

16:30 – 17:00h – **MIREIA FÉLEZ.** Research, Innovation and Teaching Unit. Parc Sanitari Sant Joan de Déu-CIBERSAM. Barcelona, Spain
Topic: *Measuring physical activity and sedentary behavior in free-living environments: methodologies, considerations and limitations.*

17:00 – 17:30h – **Open discussion**

Closing

17:30h – **Representatives of the ONCONET-SUDOE**
Antonio Agudo, Paula Jakszyn (ONCONET-SUDOE; UNAC, ICO).

INTRODUCTION

Cancers are among the leading causes of morbidity and mortality worldwide, and the number of new cases is expected to rise significantly over the next decades. According to the World Health Organization, between 30-50% of all cancer cases could be prevented mainly through healthy lifestyle choices, such as diet and physical activity. A healthy diet and engaging in regular physical activity are not only established protective factors for cancer incidence but they are also important after the diagnosis of cancer.

In this context, the Catalan Institute of Oncology (ICO) brought together a panel of experts who specialize in the mechanisms of nutrition and exercise science on cancer. The workshop was held as part of the Onconet project. The latter was a European cooperation project in oncology, coordinated by the University of Toulouse III Paul Sabatier and co-financed by Interreg Sudoe Program 2016-2019, as well as the European Region Development Fund.

The overall aim of the workshop was to analyze and discuss current research on diet, nutrition and, physical activity and their influence on the prevention and management of cancer in patients and survivors.

During the workshop, the panel of experts provided background information and the latest research on key questions and controversies in the field.

This report gathers some of the main ideas which were discussed and highlights relevant aspects which could be worth exploring in the future.

THE ONCONET-SUDOE PROGRAM

The Onconet Project was co-financed by Interreg Sudoe, a program which aims to reduce social and economic inequalities between geographical areas. In this particular case, the Onconet aimed to promote collaboration and exchange of clinical practices among 6 regions of South-Western Europe. A total of 7 partner institutions, together with their associated partners, took part of it. Their actions brought research, clinical practices and innovation to a large number of institutions, research and health specialists.

The general objective of the project was to analyze and to compare professional practices and public health policies in cancer prevention, diagnosis, therapeutic innovation and medical data processing, in the participating regions.

The specific objectives of the project were to share resources, skills and means to access innovation, to exchange good practices, to achieve a critical mass in the field of research and to harmonize therapeutic practices.

The activities of the ONCONET Project focused the improvement of the ecosystem of medical innovation and was targeted at the following key aspects:

- Nutritional prevention.
- Diagnostic and personalized medicine.
- Innovative approaches for the treatment of cancer.
- Communication of health systems and technological innovation.

You can find out more on the Onconet-Sudoe program, its events, publications and products by accessing the following website: https://www.onconet-sudoe.eu/en/

Session I

Diet and cancer prevention

THE WCRF / AICR CANCER PREVENTION RECOMMENDATIONS 2007 *vs.* 2018: LESSONS LEARNED AND CURRENT CHALLENGES IN THE OPERATIONALIZATION OF AN INDEX SCORE

Dora Romaguera

Instituto de Salud Global (ISGlobal). Barcelona, Spain.

The World Cancer Fund and the American Institute of Cancer Research are two charities that work on the combination of all available evidence analyzing the association of nutritional factors, physical activity and obesity, and how these factors affect the development of cancer. Within the WCRF, the Continuous Update Project analyzes the published evidence and reviews all available studies —mainly epidemiological— on nutrition and cancer, and prepares a meta-analysis of these accessible reports on cancer. With regard to the 2007 report, evidence allowed to infer the relationship of the data analysed and their level of association with the risk of cancer. Based on the by then existing evidence, 10 recommendations for cancer prevention were published. These recommendations were based on: nutritional factors (diet, obesity, physical activity), taking into account the origin of foods, types of foods rich in fiber, unnecessary intake of supplements. The recommendations on foods of plant origin established that we must consume a variety of vegetables, fruits, whole grains and legumes, on a daily basis. The 2018 report presents up-to-date relationships of certain habits with certain types of cancer. An example of this would be colorectal cancer, which is associated with several risk factors, such as alcohol intake or body mass index. In this new report, another series of 10 recommendations was made, which reflect some difference in comparison to the previous list. For instance, the recommendation which initially included foods and drinks which promote weight gain has now turned into two separate recommendations, one for fast foods and the other for sugar sweetened drinks. Recommendations for plant foods remains similar, although cut-off points have changed, and the current recommendation is that people take 30 grams of fiber, instead of 25. Alcoholic drinking recommendations for cancer prevention have become clearer: it is best not to drink alcohol at all, than to drink it with moderation. The recommendation on preservation processes and preparation has disappeared. The recommendation on dietary supplements is unchanged: aim to meet your nutritional needs through di*et al.*one. Finally, a recommendation on breast-feeding is also provided.

WCRF/AICR 2018 Cancer prevention recommendations

Adapted from the WCRF/AICR Cancer Prevention Recommendations and Cancer Risk in the European Prospective Investigation into Cancer and Nutrition (EPIC).

Within the framework of the European Prospective Investigation into Cancer and Nutrition (EPIC), a WCRF-funded research project was carried out and published in 2009, by the Imperial College of London. This project allowed for the creation of an *ad hoc* index score that can be applied in the analysis of epidemiological studies, with an established range of punctuation: 0-6 points in men and 0- 7 points in women.

The WCRF/AICR score 2017

	1	0.5	0
	FOODS THAT PROMOTE WEIGHT GAIN (FWG)		
Average **3.1 -Limit** Consumption of **energy-dense foods**	ED ≤ 125 kcal/100 g	125 < ED < 275 kcal/100 g	ED ≥ 125 kcal/100 g
3.2 -Avoid sugary drinks	0 g/d	≤ 250 g/d	> 250 g/d
	PLANT FOODS (PF)		
Average **4.1** –Eat at least 5 servings **fruit and vegetables** a day	≥400 g/d	200 - <400 g/d	<200 g/d
4.2 –Eat **unprocessed cereals and pulses**	Dietary fibre ≥25 g/d	Dietary fibre 12.5 - <25 g/d	Dietary fibre <12.5 g/d

	1	0.5	0
	MEAT CONSUMPTION (MEAT)		
5 -Limit consumption of **red meats** and avoid **processed meats**	Red + Processed meats <500 g/d *and* Processed meat <3 g/d	Red + Processed meats <500 g/d *and* Processed meat 3 - <50 g/d	Red + Processed meats ≥500 g/d *and/or* Processed meat ≥50 g/d
	ALCOHOL INTAKE (ALC)		
6 -Limit alcoholic drinks to 2 for men and 1 for women a day	Ethanol ≤ 20 g/d men ≤ 10 g/d women	Ethanol >20-30 g/d men >10-20 g/d women	Ethanol >30 g/d men >20 g/d women

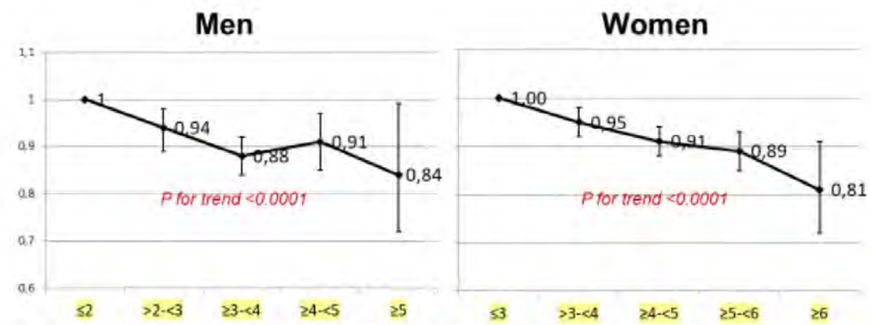
	1	0.5	0
7 -Limit consumption of **salty foods**	*Insufficient data avaible*		
8 -Don´t use supplements to protect against cancer	*Not applicable*		
	BREAST FEEDING (BF)		
9 -Breastfeed exclusively for up to 6 months	Cumulative BF ≥ 6 months	Cumulative BF >0 - <6 months	Cumulative BF 0 months
10 -Cancer survivors should **follow the recommendations**	*Not applicable*		

Score Range:
0 – 6 points in Men
0 – 7 points in Women

Adapted from WCRF/AICR score 2007 Romaguera *et al.*, *AJCN* 2012.

The application of this score to the EPIC study cohort (378,864 participants) enabled the researchers to analyze the association between adherence to nutritional recommendations and cancer risk . For most cancers, the risk decreased as the score increased. A one-point increase in the score was associated with a lower risk of several cancers, although for prostate, pancreatic and ovarian cancer the results were not statistically significant. Regarding mortality, the greater the adherence to the WCRF recommendations, the lower the risk of death in the EPIC study cohort, both in men and in women.

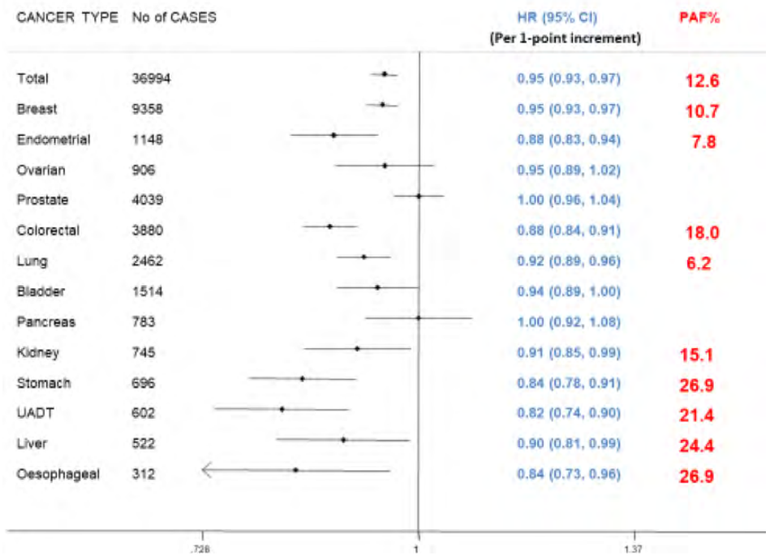
Is concordance with World Cancer Research Fund/American Institute for Cancer Research guidelines for cancer prevention related to subsequent risk of cancer? Results from the EPIC study



Final sample (after exclusions): 386,355 participants - 11.0 y fu - 36,994 incident cancer cases

Cox regression model stratified by centre and age, and adjusted by energy intake, level of school, smoking status, presence of chronic diseases at baseline, ever use of contraceptive pills, ever use of HRT, age at first menarche, age at first pregnancy, and menopausal status

The WCRF/AICR score and cancer subtypes: EPIC



Adapted to WCRF/AICR score 2007 Romaguera *et al.*, *AJCN* 2012.

Based upon the score developed in EPIC, a systematic review and meta-analysis was performed, which included data from seven prospective cohorts and one case-control study. It determined that, for each additional point of adherence to the recommendation, there was a 9%- decrease risk for breast cancer.

Likewise, and by using the multiple-case control study (MCC) in Spain, IS Global applied 6 of the recommendations used in the EPIC analysis. A very strong inverse association was found between adherence to the recommendations and the risk of colorectal cancer. For breast cancer, there was an inverse association but it was only statistically significant in postmenopausal breast cancer cases.

This work is still ongoing. Our research group basically aims to develop improved scores, based on previous research, to operationalize the new recommendations released in the 2018 report. It is a challenging task, for recommendations were not formulated so that they could easily be operationalized by epidemiologists, but rather for the end-user. In the future we will try to integrate new definitions and categories to better define fast- and ultra-processed foods. And the final goal will remain the same: to continue to generate useful literature on how nutritional factors can help in cancer prevention.

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NUTRITIONAL QUALITY AS REPRESENTED BY THE NUTRI-SCORE LABEL AND CANCER RISK IN EUROPE

Antonio Agudo

Head of the Unit of Nutrition and Cancer. Catalan Institute of Oncology (ICO). ICO Coordinator for Onconet.

According to the World Health Organization (WHO), nutrient profiling is "the science of classifying or ranking foods according to their nutritional composition for reasons related to preventing disease and promoting health." It has been recognized by the WHO as a useful tool for a variety of applications and is considered to be a critical tool for the implementation of restrictions on the marketing of foods. The rationale behind it is that helping consumers make healthier food choices is a key challenge for the prevention of cancer and other chronic diseases. This is why in many countries; political authorities are considering the implementation of a simplified labelling system to reflect the nutritional quality of food products.

In Europe, front-of-pack labelling was initially introduced in the 1980s, by Sweden and Denmark (Green Keyhole) and in the 2000s in the Netherlands (Choices) and the United Kingdom (Multiple Traffic Lights). In 2014, New Zealand and Australia introduced the Health Star Rating System. Finally, in 2016, Chile adopted warning symbols for any foods in which a given nutrient could be considered too high. In the European Union (EU), regulations on food information to consumers determine the contours of front-of-pack nutrition labelling. Nevertheless, within this legal framework only voluntary schemes are currently possible.

France launched a public health nutrition policy in the year 2001, called the *Programme National Nutrition Santé* (PNNS). Among the 15 new proposals by the PNNS, one included the introduction of a front-of-pack nutrition label: the five-color nutrition label (5-CNL). A law was discussed in 2015, voted in Parliament in December 2016 and enacted in January 2017. The *Nutri-Score* (graphical version of the 5-CNL) was finally selected and was announced by the Minister of Health in March 2017 as the official front-of-pack nutrition label for France.

The Nutri-Score five-color labelling system uses a modified version of the *British Food Standards Agency Nutrient Profiling System* (FSAm-NPS). The latter allocates a score to a given food or beverage from its content per 100 g of energy, sugar, saturated fatty acids, sodium, dietary fibers, proteins, and percentage of fruit/vegetables/legumes/nuts. The FSAm-NPS score for each food/beverage is therefore based on a unique discrete continuous scale, theoretically ranging from −15 (most healthy) to +40 (least healthy). Based upon this score, five categories of nutritional quality are possible, from green to red.

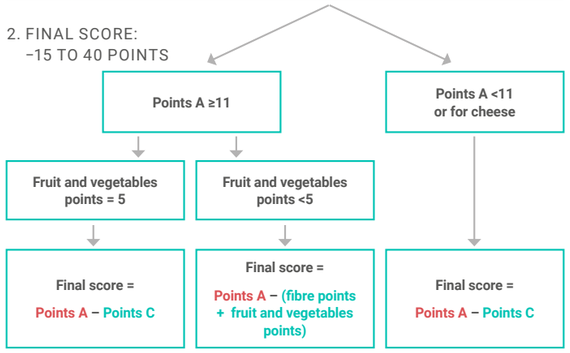
Detailed computation of the Nutri-Score/5-CNL Label

1. ATTRIBUTION OF POINTS, BASED ON THE CONTENT OF NUTRIENTS AND OTHER ELEMENTS PER 100 G OF A FOOD/BEVERAGE

Points A			Specific cut-offs: **beverages**			Specific cut-offs: **fats**	
Points	Energy (kJ)	Sugars (g)	Energy (kJ)	Sugars (g)	Saturated fat (g)	Saturated fat/lipids (%)	Sodium (mg)
0	<335	<4.5	≤0	≤0	<1	<10	<90
1	>335	>4.5	≤30	≤1.5	>1	<16	>90
2	>670	9	≤60	≤3	>2	<22	>180
3	>1005	>13.5	≤90	≤4.5	>3	<28	>270
4	>1340	>18	≤120	≤6	>4	<34	>360
5	>1675	>22.5	≤150	≤7.5	>5	<40	>450
6	>2010	>27	≤180	≤9	>6	<46	>540
7	>2345	>31	≤210	≤10.5	>7	<52	>630
8	>2680	>36	≤240	≤12	>8	<58	>720
9	>3015	>40	≤270	≤13.5	>9	<64	>810
10	>3350	>45	>270	>13.5	>10	≥64	>900
	0–10 (a)	**0–10 (b)**	**0–10 (a)**	**0–10 (b)**	**0–10 (c)**	**0–10 (c)**	**0–10 (d)**
Total	**Points A = (a) + (b) + (c) + (d) [0–40]**						

		Specific cut-offs: **beverages**	Points C	
Points	Fruit, vegetables (%)	Fruit, vegetables (%)	Fibre (g)	Protein (g)
0	<40	<40	<0.7	<1.6
1	>40	–	>0.7	>1.6
2	>60	>40	>1.4	>3.2
3	–	–	>2.1	>4.8
4	–	>60	>2.8	>6.4
5	>80	–	>3.5	>8.0
6	–	–	–	–
7	–	–	–	–
8	–	–	–	–
9	–	–	–	–
10	–	>80	–	–
	0–5 (a)	**0–10 (a)**	**0–5 (b)**	**0–5 (c)**
Total	**Points C = (a) + (b) + (c) [0–15]**			

2. FINAL SCORE: −15 TO 40 POINTS



3. ATTRIBUTION OF COLOURS:

Foods (points)	Beverages (points)	Colour
Min to −1	Water	Dark Green
0 to 2	Min to 1	Light Green
3 to 10	2 to 5	Yellow
11 to 18	6 to 9	Light Orange
19 to max	10 to max	Dark Orange

Dark Green: highest quality Dark Orange: lowest quality

Source: Julia C, Etilé F *et al.*, *Lancet Public Health* 2018;3:e164.

Therefore, the analysis of population data of dietary information based upon the FSAm-NPS score is essentially an assessment of the performance of the Nutri-Score. Several studies support the scientific relevance and the potential impact on public health of using the FSAm-NPS as a basis for nutrition policies. In particular, studies performed in the SU.VI.MAX and NutriNet-Santé cohorts have shown that a diet consisting of food products with better FSAm-NPS scores would lead to more favorable health outcomes in regard to weight gain, metabolic syndrome, cardiovascular diseases, and cancer risk.

These results were promising albeit restricted to French populations and based on a relatively limited number of cases (especially to perform robust analyses by cancer sites). So far, scientific evidence regarding the relevance of the Nutri-Score (and the underlying FSAm-NPS score) has been obtained at national/regional level. Expanding investigations to a European level is, therefore, of importance, for instance within the framework of the European Prospective Investigation into Cancer and Nutrition (EPIC).

The EPIC study

EPIC (European Prospective Investigation into Cancer and Nutrition) is a multicenter prospective cohort study investigating metabolic, dietary, lifestyle and environmental factors in relation to cancer and other chronic diseases. Between 1992 and 2000, more than 500,000 volunteers (ages 25-70) were recruited from 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the UK). Of the 521,324 enrolled participants, 471,495 meet the criteria to be included in this analysis, among which 49,794 incident invasive cancer cases were identified during a median follow-up time of 15.3 years.

Usual food intakes of EPIC participants were assessed with standardized country-specific diet assessment methods. The FSAm-NPS was calculated for each food/beverage using their 100-g content in energy, sugar, saturated fatty acids, sodium, fibers, proteins, and fruits/vegetables/legumes/nuts. In a second step, the FSAm-NPS dietary index (DI) was computed at the individual level as an energy-weighted mean of the FSAm-NPS scores of all foods and beverages consumed. This (FSAm-NPS DI) score was then used as an exposure variable, in order to assess its association with cancer risk.

The values of the FSAm-NPS DI were consistent with dietary consumption of foods -or groups of foods- related to the nutrients or components used to calculate the score. Participants with a higher FSAm-NPS DI score, which indicates a diet of lower nutritional quality, were consistently more likely to have unhealthy dietary intakes, e.g., higher intakes of alcohol, energy and red and processed meat, or lower intakes of dietary fibers, vegetables, fruit and fish.

The association with cancer risk was assessed by means of the Hazard Ratio (HR), an estimate of the relative risk. A HR value of 1 is interpreted as meaning no association, while values above 1 indicate increased risk and values below 1 indicate protection. In this analysis, subjects ranked according to their FSAm-NPS DI value and were divided into five groups of equal size (quintiles). The risk of cancer for subjects in the highest quintile was compared with the risk of those from the lowest quintile. Alternatively, the increase in risk associated with each 2-point increment in the score was also calculated.

Association with cancer

The 20% of participants who obtained the highest values to the score (those in the 5th quintile) had a significant 7% increase of cancer risk, compared to those in the lowest quintile. Each 2-point increase in the score was associated with a 2% increase in risk (also statistically significant). This pattern remained the same when estimates for men and women were performed separately.

Association between FSAm-NPS and cancer risk. EPIC study

	Hazard ratio (95% CI)		*p*-value for trend
	Per 2-point increment	Q_5 vesus Q_1	
Men	1.03 (1.01 -1.04)	1.07 (1.02 -1.13)	*0.001*
Women	1.02 (1.02 - 1.03)	1.07 (1.03 -1.11)	*0.001*
All	1.02 (1.01 -1.03)	1.07 (1.03 - 1.10)	*<0.001*

When looking at specific tumor sites, the analyses restricted to common cancers with sufficient number of cases showed a significant increase in risk for colorectal, kidney, stomach, prostate and breast cancers. For each 2-point increase of the score, the increase in risk ranged from 2% for colorectal and breast cancer, up to 10% for cancer of the stomach. No significant associations were found with cancers of the urinary bladder, upper aero-digestive tract, pancreas, liver, lung, endometrium, cervix uteri or ovary.

Association between FSAm-NPS and cancer risk. EPIC study

	Hazard ratio (95% CI)		*p*-value for trend
	Per 2-point increment	Q_5 vesus Q_1	
Colorectal	1.02 (1.01 -1.03)	1.07 (1.03 - 1.10)	*<0.001*
Kidney	1.07 (1.00 - 1.15)	1.17 (0.93 - 1.46)	*0.04*
Stomach	1.10 (1.02 - 1.18)	1.25 (0.99 -1.58)	*0.1*
Prostate	1.03 (1.00 - 1.06)	1.07 (0.98 - 1.17)	*0.04*
Breast	1.02 (1.00 - 1.04)	1.06 (0.99 - 1.14)	*0.05*

Number of cases: colorectal, 5806; kidney, 926; Stomach, 963; Prostate, 6745; Breast, 12063.

Multivariate models stratified for centre and age at recruitment (1-y intervals) and adjusted for: sex, BMI, height, alcohol intake (g/d), physical activity, smoking status and intensity of smoking, family history of breast or colorectal cancer, educational level, and baseline energy intake (kcal/d). Women: further adjustment for menopausal status, ever use of oral contraception, ever use of hormonal treatment for menopause.

No significant associations with cancers of the *Urinary Bladder, Upper aero-digestive tract, Pancreas, Liver, Lung, Endometrium, Cervix uteri, Ovary*.

Further analyses to the most common tumors revealed that the risk of colorectal cancer was slightly higher in women than in men and that the increased risk for breast cancer was restricted to post-menopausal cases.

Summary and overall conclusions

The consumption of a diet with higher FSAm-NPS scores –which reflects lower nutritional quality– was associated with an increased risk of developing cancer (overall and for several specific cancer sites). Stronger associations were observed in women for colorectal cancer and post-menopausal breast cancer. Consistent with these results, previous studies performed in the SU.VI.MAX and NutriNet-Santé cohorts reported higher risks for total and breast cancers in patients whose diet had higher FSAm-NPS DI scores. However, these studies exhibited limited statistical power to investigate the relationships for other specific cancer types. In the Nurses' Health Study and the Health Professionals Follow-up Study, a higher ONQI-f (Overall Nutritional Quality Index) –reflecting a higher overall nutritional quality of the diet– was associated with lower risk of mortality, cardiovascular disease, and diabetes, but was not associated with cancer risk.

The results of this work come from a study with remarkable strengths, including a prospective design, a large sample size, the fact that participants were from different European countries, and the availability of standardized data collection for diet. However, some limitations and drawbacks must also be taken into account: the results cannot be directly applicable to the entire European population; unhealthy dietary behaviors may have been underrepresented, which may have weakened the observed associations; the study used a single assessment of dietary intakes at baseline, but diet may change over time. Finally, dietary measurement instruments are built to capture the usual dietary intakes of an individual but are still subject to imprecision and inaccuracy.

Overall, the findings of this work add support to the relevance of using the FSAm-NPS in order to grade the nutritional quality of food products as a basis for prevention strategies for cancer.

Beyond the specific results of this research, the following criticisms and advantages have often been considered for the Nutri-Score.

Criticisms

- **Controversial classification for some foods: olive oil (D), breakfast cereals (C). However, the Nutri-Score system is flexible enough to allow for exceptions.**
- **It does not provide information on specific nutrients responsible for the final score.**
- **Labelling only includes macronutrients, without considering micronutrients, additives, or enrichment and processing techniques.**

Advantages

- **Improved information on the nutritional quality of foods, easily and quickly.**
- **Easier interpretation than other models of front-of-pack labelling.**
- **Allows for intermediate categories (not just bad or good).**
- **Flexible model giving room for exceptions, according to scientific evidence.**
- **Allows comparing foods of different formats and categories (the algorithm is based upon 100 g of the product).**
- **It encourages the food industry to reformulate its products, so as to make them healthier. And it promotes the competition of companies for this purpose.**

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MEDITERRANEAN DIET: A TECHNICAL REVIEW OF ITS DEFINITION AND THE IMPLICATION ON CANCER RISK

Cecilia Galbete

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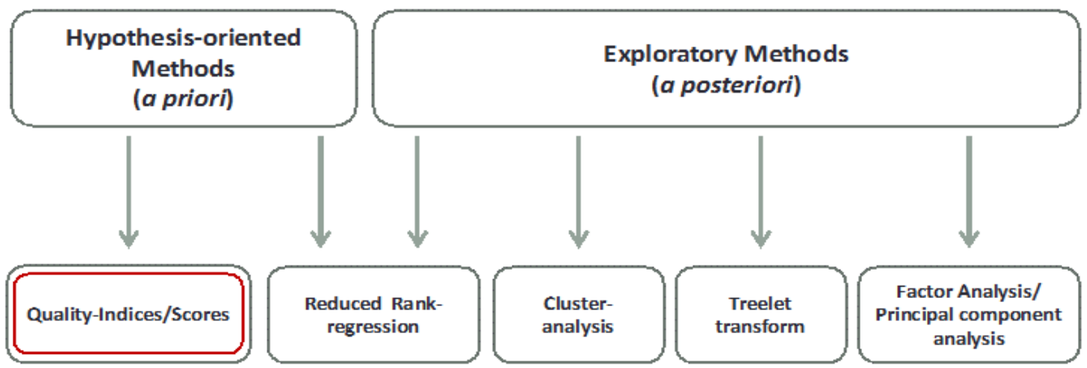
In the last years, the study of dietary patterns has become increasingly relevant within the field of Nutritional Epidemiology. The study of patterns constitutes a complementary tool, enabling researchers to capture the complexity of overall diet. By doing so, it becomes possible to understand the effects of potential interactions within the foods and nutrients. These interactions can be synergetic, antagonistic, additive, among others. Moreover, dietary patterns are a useful tool to control for over-all diet when our primary aim is another exposure variable, such as for example, physical activity.

In order to work with dietary patterns, several methods have been developed. The latter can be grouped into two main categories: exploratory methods, where nothing is pre-stablished; and *a-priori* methods, where current knowledge about a given diet (e.g. Mediterranean diet) is used as a basis, in order to create an adherence score or index.

The figure below shows the most common methods to identify and work with dietary patterns.

BACKGROUND - Methods of dietary pattern analyses



Mediterranean Diet

The Mediterranean diet was first studied in the 70's, when studies by Ancel Keys were published. In the *Seven Countries Study*, he observed lower incidences of coronary cardiopathies associated with the "good Mediterranean diet". The most relevant publications at that time identified that this diet was mainly vegetarian, low in meat and dairy products, rich in fish, vegetables and olive oil, and used fruit as a dessert.

From that time, a countless number of studies on the Mediterranean Diet and different chronic diseases have been published. Moreover, researchers have tried to summarize all that information in several meta-analyses. One of the most relevant meta-analyses on the Mediterranean Diet and cancer was published in 2017, by Schwingshackl *et al.* In their systematic review, titled *Adherence to Mediterranean Diet and Risk of Cancer*, they analyzed the adherence to the Mediterranean diet and its effect on risk of overall cancer mortality, risk of different types of cancer, cancer mortality and recurrence risk in cancer survivors. The updated review process showed 27 studies that were not included in the previous meta-analysis (2013), with a total of 83 studies evaluated and involving 2,130,753 subjects. In this piece of work, it was observed that high adherence scores to a Mediterranean diet were inversely associated with risk of cancer mortality, as well as with risk of certain types of cancer (colorectal, breast, gastric, liver, head and neck and prostate cancer). Nevertheless, the association between adherence to the Mediterranean Diet and risk of cancer mortality and cancer recurrence, was not statistically significant among cancer survivors. Pooled analyses of individual components of the Mediterranean diet revealed that the protective effects appear to be most attributable to fruits, vegetables, and whole grains. Extra virgin olive oil is one of the most important components of this diet. Its richness in phenolic compounds gives confers it antioxidant, anti-inflammatory, and antibacterial properties. In spite of that, it should be born in mind that high caloric intake has been associated with the development of cancerous tumors.

Risk ratio/odds ratio for the association between with the highest *vs.* lowest adherence to Mediterranean dietary pattern with cancer risk

Outcome	N° studies	Study type	RR/OR	95% CI	I^2%
Cancer mortality	14	Observational	0.86	0.81-0.96	82%
Colorectal cancer	11	Observational	0.82	0.75-0.88	73%
Breast cancer	1	RCT	0.43	0.21-0.88	NA
Breast cancer	16	Observational	0.92	0.87-0.96	22%
Gastric cancer	4	Observational	0.72	0.60-0.86	55%
Liver cancer	2	Observational	0.58	0.46-0.73	0%
Head and neck cancer	7	Observational	0.49	0.37-0.66	87%
Prostate cancer	6	Observational	0.96	0.92-1.00	0%

Source: Lukas Schwingshackl, *Nutrients* 2017, 9, 1063; doi:10.3390/nu9101063.

Research has shown that greater adherence to the Mediterranean diet is associated with a reduced risk of suffering major chronic diseases. For instance, cancer, as shown in the study by Schwingshackl *et al.* However, the existing literature still leads to areas of debate. Some examples of this would be the actual measuring of adherence to the Mediterranean diet, the use of a wide variety of dietary indices with various food components and the large heterogeneity across the studies. In order to summarize the evidence and evaluate the validity of the association between the adherence to the Mediterranean diet and major chronic diseases, Galbete *et al.* worked on an umbrella review of the evidence across meta-analyses of longitudinal cohort studies. It was called *Mediterranean diet and multiple health outcomes* (T2D, overall cancer, CVD and cognitive-related disorders). This study gathered 27 meta-analyses; T2D: 4 meta-analyses, CVD: 13 meta-analyses; overall cancer incidence and/or mortality: 4 meta-analyses, cognitive disorders: 6 meta-analyses. All and all, 70 primary studies were identified and 34 different scores aiming to reflect adherence to the Mediterranean diet were found.

	Vegetables	Legumes	Fruits/nuts	Cereals	Fish	Meat	Dairy products	Alcohol	Fat intake	Extras	Cited
MedDiet	1	1	2	3	-	1	1	n.d.	1	-	[2]
tMedDiet	1	1	1	1	1	1	1	1	1	-	[7, 25, 39-50]
tMedDiet 1	1	1	1	1	1	1	1	1	4	-	[51-53]
tMedDiet 2	1	1	2	1	1	1	1	3	1	-	[54]
tMedDiet 3	1	1	1	1	1	1	1	4	1	-	[55]
tMedDiet 4	1	1	1	1	1	1	1	1	2	-	[11, 56-59]
tMedDiet 5	1	1	1	1	1	1	1	-	2	-	[60]
tMedDiet 6	1	1	2	1	1	1	1	16	1	-	[61-63]
tMedDiet 7	1	1	2	1	1	1	1	14	1	-	[64]
tMedDiet 8	1	1	2	1	1	1	1	17	1	-	[65]
tMedDiet 9	1	1	2	1	1	1	1	1	1		[66]
aMedDiet	1	1	2,3	2	1	2	-	5	1	-	[67-75]
aMedDiet 1	1	1	2,3	2	1	2	-	15	1	-	[76]
aMedDiet 2	1	1	2,3	2	1	2	-	6	1	-	[77]
aMedDiet 3	1	1	2,3	2	1	2	-	7	1	-	[78, 79]
aMedDiet 4	1	1	2,3	2	1	2	2	6	1	-	[80]
MedDiet 1	2,3	-	2	2	1	-	-	-	2	-	[81]
MedDiet 2	1,4	-	2	2	1	3	3	8	3	-	[82]
MedDiet 3	1	2	2	1	1	1	1	13	4	-	[83, 84]
MedDiet 4	5*	*	2	3	1	1	1	1	6	-	[85, 86]
MedDiet 5	1	-	2	1	1	4	1	2	4	-	[87]
MedDiet 6	1	2	2	2	1	2,5	2	14	5	-	[88]
MedDiet 7	8**	2	**	2	1	2	11	5	11	-	[89, 90]
MedDiet 8	1,8	2,3	1	2	1	3,6,9,10	3	-	2	2,5-10	[91]
MedDiet 9	1	-	2,3	9	1	2,3	12	5	1	4	[92]
MedDiet 10	1	1	2	2	1	2,5	2	18	2	3	[93]
mMedDiet	6	3	-	1	1	1	1	-	1	-	[94]
iMedDiet	7	1	2	4	1	6	4	9	2	1, 2	[39, 95]
CA	1	-	2	5, 6	-	-	5, 6	8, 10	-	-	[96]
FA	1	-	-	4, 7	1	-	-	-	7	3	[97]
rmMedDiet	6	-	4	2	1	1	1	2	4	-	[98]
AHEI	1	2	5	2	-	2	-	11	8-10	2, 4	[99, 100]
sMedDiet	1	1	1	2	1	2, 5, 7	2, 7	12	2	3	[101, 102]
MAI	1	1	2	1	1	1, 7	8-10	8	2	2, 3, 5	[103]

Fruits/nuts (+); 1: fruits + nuts; 2: fruits; 3: nuts; 4; fruits + juices; 5: fresh fruit only

Fats; 1: MUFA:SFA ratio; 2: Olive oil; 3: MUFA; 4: (MUFA+PUFA):SFA ratio; 5: PUFA+MUFA; 6: PUFA:SFA ratio; 7: Oils; 8: trans fatty acids; 9: EPA+DHA fatty acids; 10: PUFA; 11: olive oil and/or rapeseed oil as main sources of fat

Alcohol; 1:max. score=women 5-25 g/d, men 10-50 g/d; 2: mas score ≥ sex-specific median; 3: max. score > 0 drinks/wk ≤ 2 drinks/d; 4: max. score=women ≤ 1drink/d, men ≤ 2 drinks/d; 5: max. score=women 5-15 g/d, men 10-25 g/d; 6: max score=5-15 g/d; 7: max. score=women 5-15 g/d, men 10-15 g/d; 8: wine; 9: max. score=> 0 to 12 g/d; 10: beer (CA); 11: max. score= women 0.5-1.5 drinks/d, men 0.5-2.0 drinks/d; 12: max. score <3 glasses/d = 5 points and min. score > 7 glasses/d or none = 0 points; 13: max. score ≥ 1 drink/month; 14: max. score to those in the second quintile of alcohol intake; 15: max. score = 5-25 g/day for everybody; 16: max. sore = > 0 – 30 g/d; 17: max.score = women 1-7 drinks/wk, men 1-14 drinks/wk; 18: max. score 1-300 ml/d max. score > 0 drinks/wk

The application of the AMSTARM showed that all the investigated meta-analyses achieved a medium-to-high quality score, suggesting that current meta-analyses evaluating the effects of the Mediterranean diet on health status comply, either partially or almost fully, with methodologic quality standards.

Two main Mediterranean diet scores were identified as most commonly used. These were the so-called traditional Mediterranean diet (tMedDiet) and the alternative Mediterranean Diet (aMedDiet). The two scores present some differences: the tMedDiet includes fruits and nuts together, whereas the aMedDiet includes fruits and nuts, but separately. The aMedDiet only takes red meat and processed meat, while the tMedDiet considers every kind of meat. Finally, the aMedDiet does not consider dairy products as detrimental. According to the available scientific evidence, the aMedDiet can be considered an improved version of the tMedDiet.

In this work, the authors re-conducted the analysis by putting together only those studies which were using a common (the same) definition. Regarding the re-analyses for cancer, stronger inverse associations were observed for the aMedDiet, in comparison to the tMedDiet.

Following are some conclusions and reflections derived from the study

- **A large variability in the use of scores reflecting the Mediterranean diet were observed.**
- **Apart from the two main definitions (tMedDiet & aMedDiet), 19 other definitions were found and used in 24 studies.**
- **A stronger association with cancer was observed for the aMedDiet, probably due to the selection of healthier items. I have to mention that these analyses were limited to those performed by the authors of the meta-analyses, for example a combination of different end points. Other sources of heterogeneity -due to the construction of the scores, are not reflected here. Different nutritional assessment tools (FFQ, 24-HDRs…), could have been used and we are aware that the different tools and methods imply different biases. Furthermore, this work is limited to prospective cohort studies.**

To conclude, I would like to encourage researchers to be consistent with the definitions of the Mediterranean diet, in order not to hamper comparability. Regarding its association with cancer, the Mediterranean diet has been inversely associated with overall cancer incidence and cancer mortality and with some specific types of cancer. The re-analyses of the association observed better results for the aMedDiet score.

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LIPID METABOLISM IN COLORECTAL CANCER

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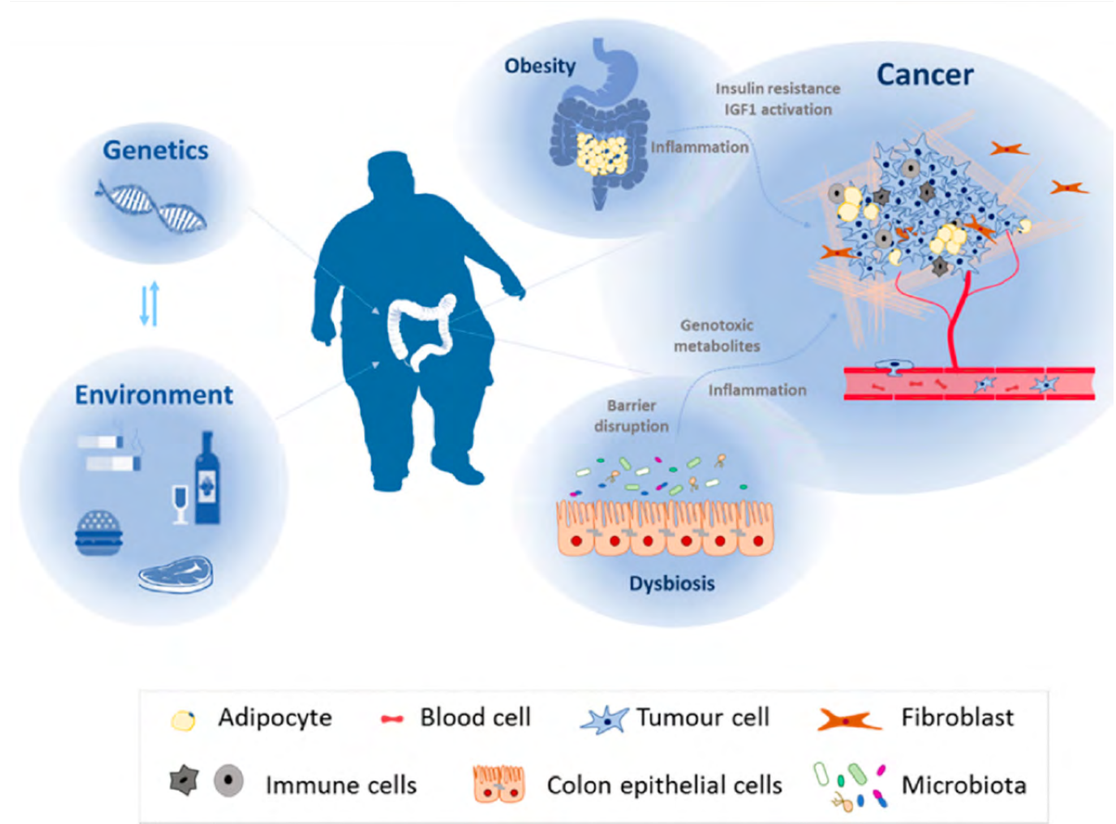
Cancer is a multifactorial condition with genetic and environmental factors modulating tumorogenesis and disease progression. It is, nonetheless, preventable, as some of the risk factors involved -diet among them- are modifiable. In regard to colorectal cancer (CRC), several nutrients can directly affect fundamental cellular processes and are considered among the most important risk factors. Some of the best-known diet components which interact with colorectal cancer susceptibility include red and processed meat, fiber, and folate. In addition, the direct association between unhealthy diets and both obesity and dysbiosis opens new routes in the understanding of how diet could influence cancer prognosis. On the other hand, genomic and transcriptomic studies have also been extensively used in relation with CRC risk and progression. The relationship between CRC carcinogenesis and nutrition factors is more complex than originally expected, although it is widely accepted that several genetic variants in diet-nutrition-related genes are clearly associated with CRC, the most representative example being the role of variants in genes related to folate synthesis. Folate is involved in the synthesis of nucleic acids and DNA methylation; genetic polymorphisms in methylenetetrahydrofolate reductase (MTHFR) enzyme are modulating their own activity, and SNPs in MTHFR and levels of folate intake combine to regulate CRC risk. Particularly, minor homozygous allele TT of Cys677Thr polymorphism in MTHFR gene reduces in vitro MTHFR enzymatic activity to 30%, and the T genotype is associated with CRC risk in the context of low folate intake, whereas it is protective for CRC when high intake of folate occurs.

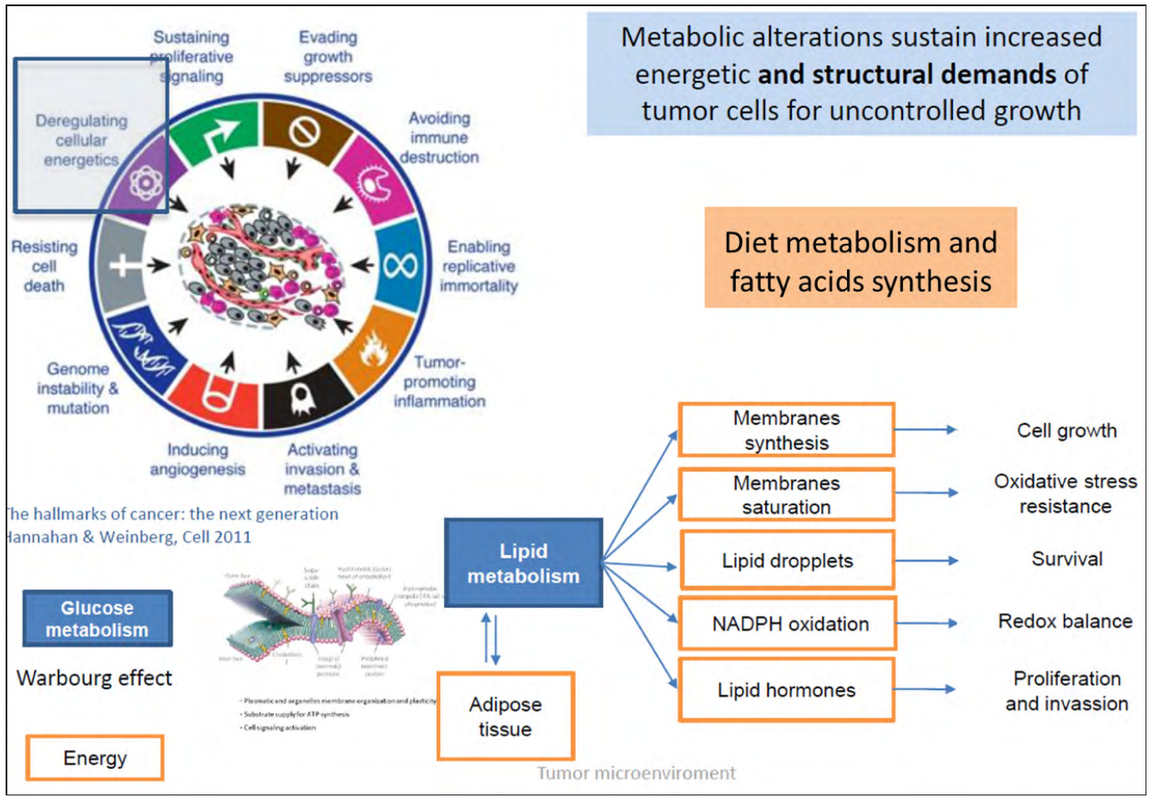
Colorectal cancer: genetic and environmental factors and their interaction



Source: *Nutrients* 2017;9:1076.

In the "omics" era, traditional nutrition has evolved to precision nutrition where technical developments have contributed to a more accurate discipline. Instead of aiming at general recommendations to the population, precision nutrition aims to set targeted nutritional strategies based on molecular effects. Recently, altered metabolism has been added to the list of core hallmarks of cancer. The Warburg effect, by which cancer cells preferentially drive glucose metabolism to lactate production under aerobic conditions, is well known. However, in addition to carbohydrate metabolism, other metabolic pathways have been found to be altered in cancer. There is increasing evidence that cancer cells show specific alterations in different aspects of lipid metabolism. Changes in lipid metabolism can affect numerous cellular processes, including cell growth, proliferation, differentiation and motility. Fatty acids, as major building blocks for the synthesis of triacylglycerides (which are mainly used for energy storage), may play a key role in the relationship between lipid metabolism and cancer.

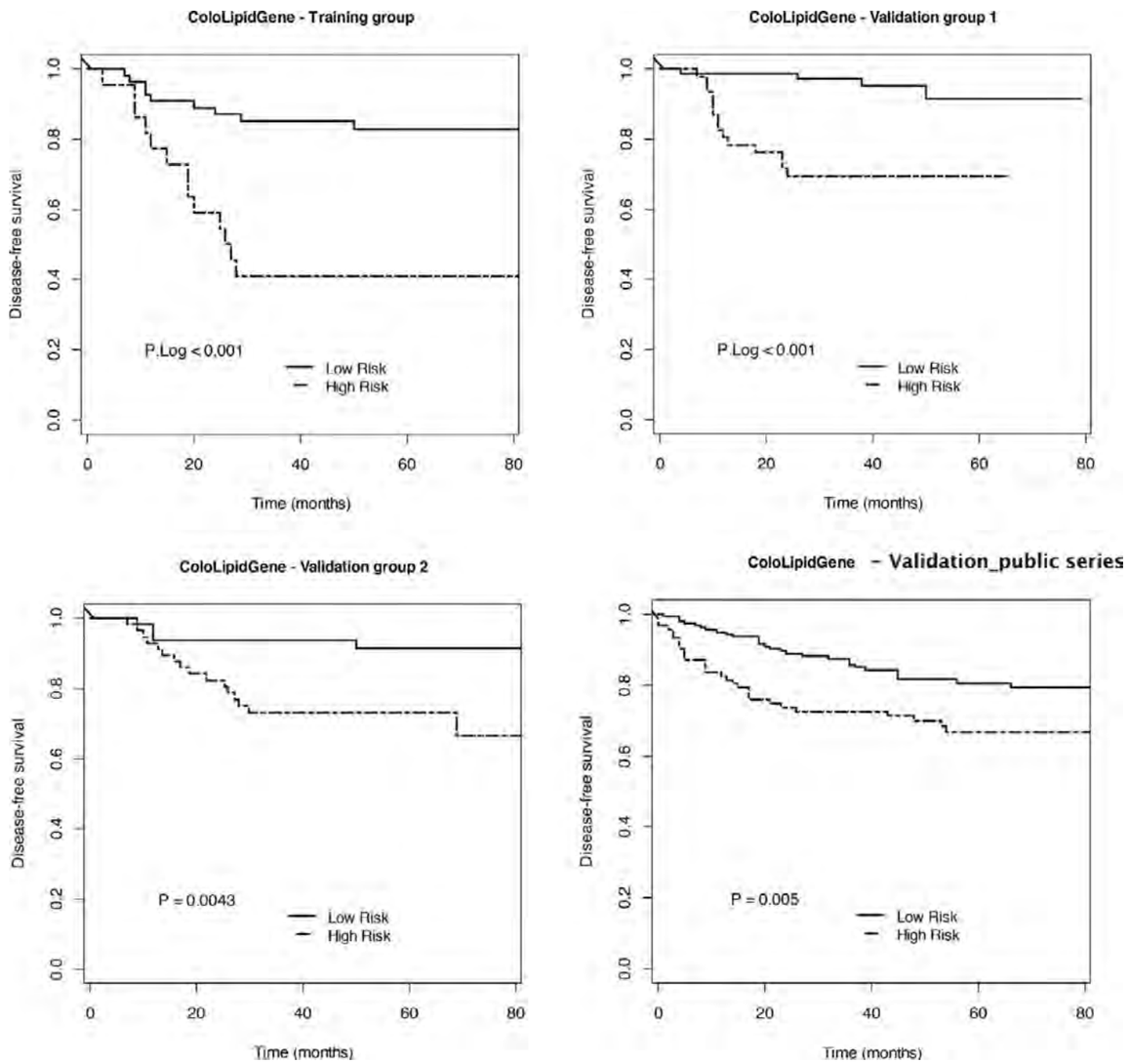
Lipid metabolism in cancer



Adapted from FEBS J 2012;279:2610-23 .

Lipid metabolisms and lipidomics research on colorectal cancer is one of the main research lines in our institution. Together with classical diet-nutrition-related genes, nowadays, lipid-metabolism-related genes have acquired relevant interest in precision nutrition studies –one of our major topics of interest. Overexpression of lipogenic enzymes has been reported as a common characteristic of many cancers; key enzymes involved in lipid-metabolic pathways are differentially expressed in normal and tumor tissues, and some of them have been individually proposed as prognosis markers in cancer. One of our projects investigated the association between expression of lipid metabolism-related genes and clinical outcome, in intermediate-stage colon cancer patients with the aim of identifying a metabolic profile associated with greater malignancy and increased risk of relapse. Expression profile of 70 lipid metabolism-related genes was determined in 77 patients with stage II colon cancer, with the purpose of identifying a metabolic-related signature associated to prognosis. The metabolic signature was further confirmed in two independent validation sets of 120 patients and, additionally, in a group of 264 patients from a public database. The combined analysis of four genes (ABCA1, ACSL1, AGPAT1 and SCD) constitutes a metabolic-signature (ColoLipidGene) able to accurately stratify stage II colon cancer patients with 5-fold higher risk of relapse with strong statistical power, in the four independent groups of patients. ABCA1 is involved in cholesterol transport, ACSL1 codifies an isoenzyme of the Acyl-CoA synthetase family, AGPAT1 is involved in triacylglycerol metabolism and SCD in fatty acids biosynthesis. The identification of a group of genes that predicts survival in intermediate-stage colon cancer patients enables us to delineate a high-risk group that may benefit from adjuvant therapy, and avoids the toxic and unnecessary chemotherapy in low-risk patients.

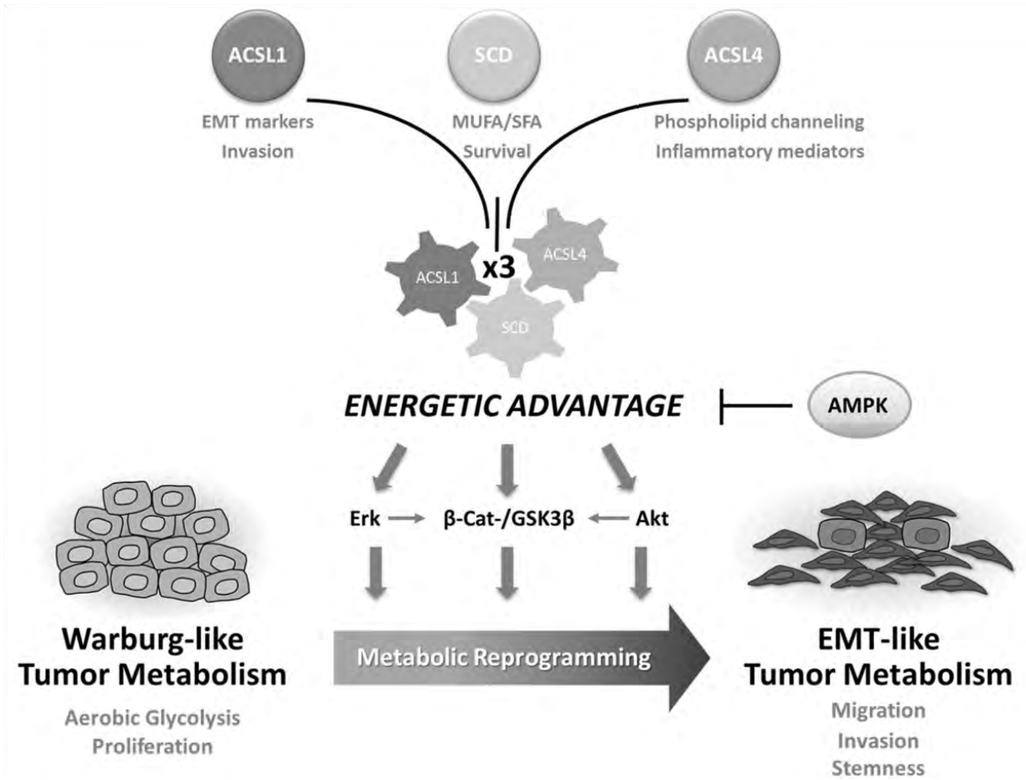
Gene expression signature to predict disease-free survival in early-stage CRC patients



Source: *Oncotarget* 2015;6:7348-63.

Further research of our group tried to characterize the molecular mechanisms of the identified genes in colorectal carcinogenesis and progression. The acyl-CoA synthetase/stearoyl-CoA desaturase ACSL/SCD network is a metabolic pathway involved in malignant progression, causing epithelial-mesenchymal transition (EMT). Epithelial-mesenchymal transition is a conserved morphogenetic program that is characterized by the loss of epithelial phenotype and the gain of mesenchymal features. These properties promote migration and invasion of colon cancer cells. The mesenchymal phenotype produced upon overexpression of these enzymes is reverted through the reactivation of AMPK signaling. Furthermore, this network expression correlates with poorer clinical outcome of stage-II colon cancer patients. Combined treatment with chemical inhibitors of ACSL/SCD selectively decreases cancer cell viability without reducing normal cells viability. Thus, the ACSL/SCD network stimulates colon cancer progression through conferring increased energetic capacity, as well as invasive and migratory properties to cancer cells, and might represent a new therapeutic opportunity for colon cancer treatment. This fatty acid metabolism switch that acts through an EMT program is thus an example of how different types of metabolic reprogramming can be used by tumors to increase their malignity, depending on the needs and the environment.

ACSL/SCD-mediated tumor metabolic reprogramming

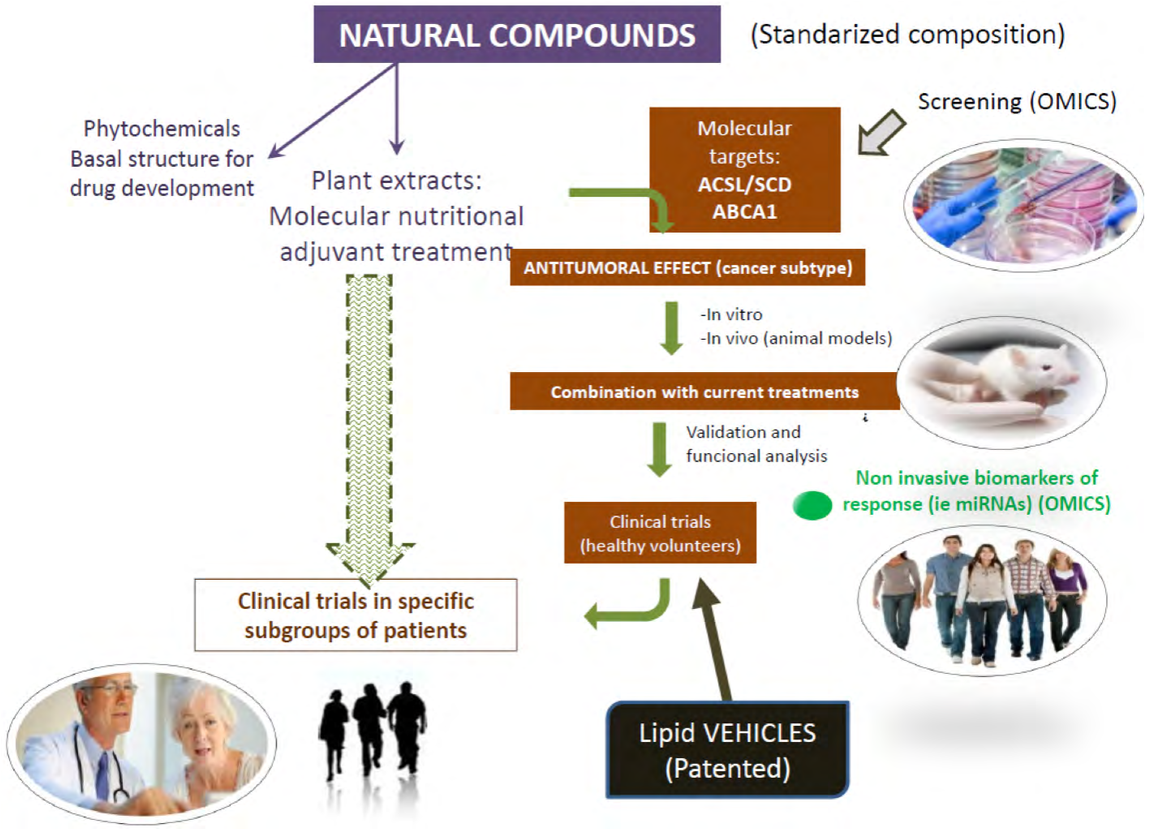


Source: *Oncotarget* 2015;6:38719-36.

In order to improve the knowledge of function, regulation and roles of the lipid metabolism genes involved in CRC, a transcriptomic meta-analysis in more than one thousand CRC individuals was performed. It aimed to thoroughly explore the transcriptomic and genomic scenarios of ABCA1, ACSL1, AGPAT1 and SCD genes. On top of that, the genomic coding sequence in 95 patients was also analyzed. The genetic variant rs3071, located on SCD gene, defines a 9.77% of stage II CRC patients with high risk of death. Moreover, individuals with upregulation of ABCA1 and AGPAT1 expression have an increased risk of CRC recurrence, independently of tumor stage. ABCA1 emerges as one of the main contributors to signature's prognostic effect: both high ABCA1 expression and presence of genetic variants located in an ABCA1 coding region seem to be associated with higher CRC risk of death.

Finally, another important line of research in precision nutrition in our group is the search for new therapeutic approaches using bioactive compounds, mostly phytochemicals. Within this field, Rosemary (*Rosmarinus officinalis L.*) extracts and its components have been reported as natural potent anti-proliferative agents against cancer cells. However, the molecular mechanism responsible for its antitumor effects is not completely understood, yet. In order to properly apply rosemary as a nutritional supplement for cancer therapy, additional information ~~in~~ regard to the most effective composition, its *in vivo* antitumor effects and its main molecular mediators ~~is~~ is needed. In one of our works, five carnosic acid-rich supercritical rosemary extracts (RE) with different chemical compositions have been assayed for their antitumor activity, both *in vivo* (in nude mice) and *in vitro,* against colon and pancreatic cancer cells. The antitumor effect of carnosic acid together with carnosol was higher than the sum of their effects separately, which supports the use of the rosemary extract as a whole. In addition, gene and microRNA expression analyses revealed that up-regulation of the metabolic-related gene GCNT3 and down-regulation of its potential epigenetic modulator miR-15b correlated with the antitumor effect of rosemary. GCNT3 has been previously reported to possess tumor suppressor activities in colon cancer, and it is up-regulated by several chemotherapeutic drugs. These results indicate that RE exerts antitumor activity on both colon and pancreatic cancers, probably through the up-regulation of GCNT3 and the down-regulation of miR-15b. For the stated reasons, rosemary extract constitutes a promising therapeutic tool.

Use of bioactive compounds in precision nutrition



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MIS-TIMED EATING PATTERNS AND CANCER RISK

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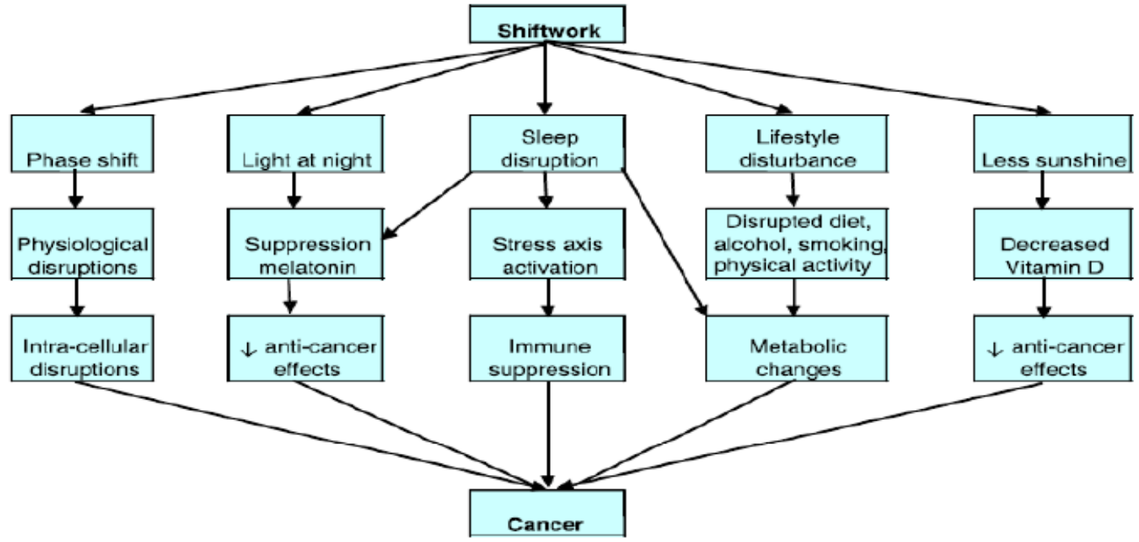
In 2007, the IARC classified shift work involving circadian disruption as probably carcinogenic to humans (group 2A). This was based on sufficient evidence on animal studies and limited evidence on epidemiological studies. Studies on humans were mainly based on the metanalysis of female workers. A moderately and significantly elevated breast cancer risk was found, among both female airline cabin crew and among female night-shift workers. Overall, the combined estimate for all 13 studies was 1.48 (95% CI, 1.36–1.61).

After this evaluation, questions arose in regard to different aspects:

- Does this apply to breast cancer only? -In the multicase-control (MCC-Spain) study, we found elevated risks for other cancer sites, such as prostate or colorectal.
- What are the mechanisms? -There are several, and the main that has been explored is related to the exposure to artificial light at night, which reduces melatonin production and, in turn, has been hypothesized to have anti-cancer effects. There are other mechanisms that need to be considered, such as the changes in reproductive hormone levels, attributable to light at night exposure, thereby inducing hormone sensitive tumors.
- Does it only influence cancer? -Some studies showed an increased weight in mice which were fed during day-time, compared to night time (it should be noted that mice are nocturnal animals and are therefore metabolically active during the night).
- Does it affect the general population? -It does! Nights used to be completely dark in most latitudes, before electricity was invented. Nowadays, most places have light during the night, so we are all exposed to light.

Theoretical framework of possible mechanisms by which shiftwork might cause breast cancer



Source: L Fritschi *et al.*, *Medical Hypotheses*, 2011.

Within the human body, where are our clocks located? -The main central clock is in the pineal gland. The pineal gland produces melatonin and the latter is one of the main molecules that control the circadian rhythm. However, it is not the only clock in our system. We know of several peripheral clocks in human bodies. These peripheral clocks have been associated with different end points, such as fat accumulation, food absorption, immunity, etc. From an evolutionary perspective, Humans have mostly had intermittent eating patterns. This implies that there were periods of fasting and there were other periods when food was mostly consumed during the day, and night-time constituted a long period of fasting. Needless to say, those are not the current patterns in society. Nowadays, patterns can be of several types. We can, for instance, have patterns with three main meals (i.e. two during daylight and one during night) plus two small snacks. This might be somehow similar to current uses of the Spanish population. Several other patterns are, nonetheless, present: an individual could fast completely, they could have three small snacks or three small meals during daylight only. This clearly exemplifies how our society has many different patterns. This we know from the MCC study, where we collected data on the timing of eating.

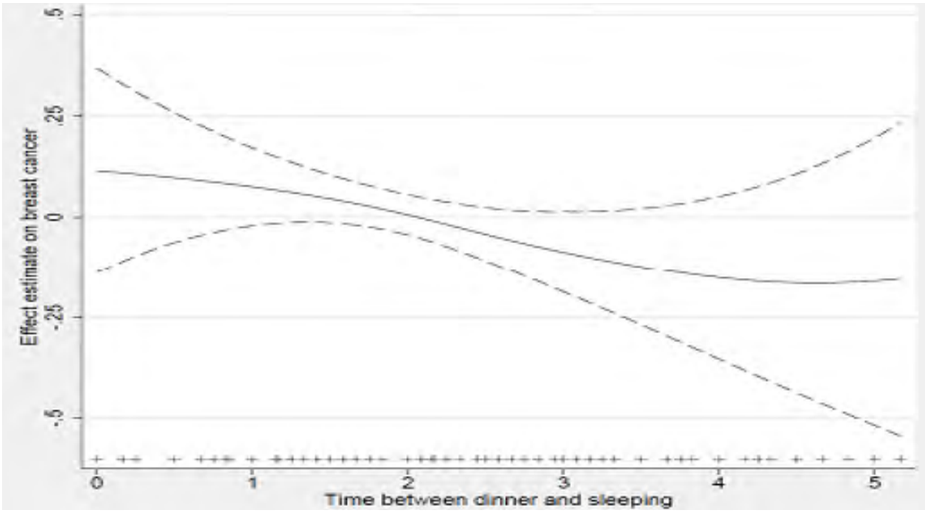
Launched in 2017, the MCC Spain study (Castaño-Vinyals *et al.*, 2015) aimed to evaluate the influence of environmental exposures and their interaction with genetic factors in five common tumors (prostate, female breast, colorectal, stomach and chronic lymphocytic leukemia). MCC-Spain is a population-based multicase-control study carried out between September 2008 and December 2013, in 12 Spanish provinces (Asturias, Barcelona, Cantabria, Girona, Granada, Gipuzkoa, Huelva, León, Madrid, Murcia, Navarra and Valencia). Recruitment of cases and controls was performed simultaneously: study personnel

contacted newly diagnosed cancer cases in the 23 collaborating hospitals, as well as population controls from the primary level health centers. The study recruited a total of 10,183 subjects.

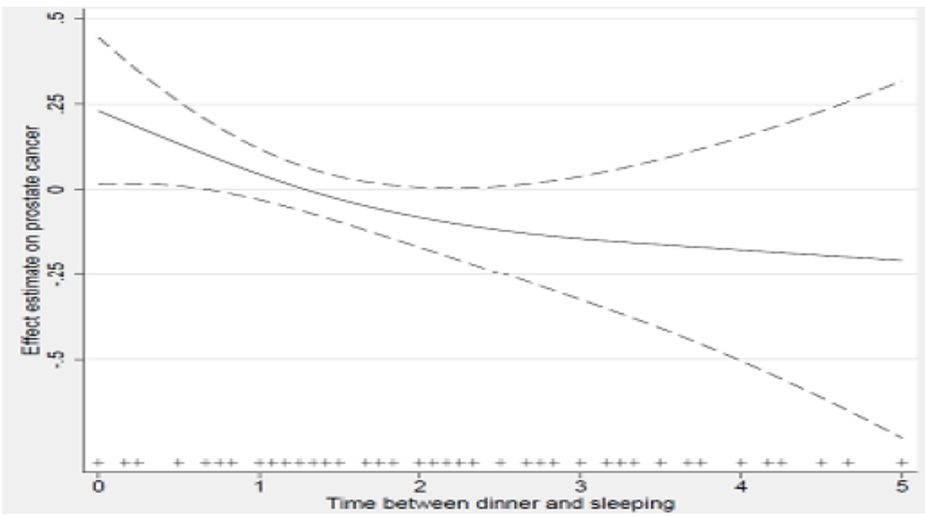
We analyzed the association between the time individuals had their dinner and their start time of nocturnal sleep, observing a decrease in the risk of breast cancer and prostate cancer, with an increase in the time interval between dinner and sleep. That is to say, a decrease in these types of cancer, the greater the time lapse in between dinner and bed time.

General additive models truncated at 5 hr showing the association (smooth function) of timing of supper and sleep interval and risk of breast and prostate cancer. Estimates are adjusted for age, center, educational level and menopausal status (breast cancer only)

Breast



Prostate



Source: Kogevinas *et al.*, *Int. J. Cancer*: 143, 2380–2389 (2018) © 2018 UICC.

A similar decrease in cancer risk was observed when we analyzed time of dinner, observing an 18% decrease risk for those subjects who ate dinner before 21.00h, compared to those who took it at 22.00h or later. We only managed to analyze the results for these two tumor sights because we didn't have information on the other tumor sights.

Association of timing of dinner and sleep interval on risk of breast and prostate cancer

	Breast cancer OR (95%CI)	Prostate cancer OR (95%CI)	Combined breast and prostate cancer OR (95%CI)
Dinner/sleep interval			
1 hour or less (ref)			
>1 to ≤2 hours	0.99 (0.79,1.24)	0.79 (0.62,1.02)	0.89 (0.72,1.11)
More than 2 hours	0.84 (0.67,1.06)	0.74 (0.55,0.99)	0.80 (0.67,0.96)
Time of dinner			
22:00 o later (ref)			
21:00 to <22:00	0.86 (0.70,1.05)	0.88 (0.69,1.12)	0.86 (0.74,1.01)
Before 21:00	0.85 (0.66,1.09)	0.75 (0.53,1.07)	0.82 (0.67,1.00)

Adaptation of table 4 in MCC-Spain Study. Kogevinas *et al.*, *Int. J. Cancer*, 2018.

Distribution of potential risk factors for breast and prostate cancer by time interval between supper and sleeping (more or less than two hours) among controls

	Female		Male	
	<2h N=727	>=2h N=530	<2h N=625	>=2h N=210
Educational level				
Less than primary	14%	12%	15%	9%
Primary	31%	32%	30%	26%
Secondary	33%	36%	32%	27%
University	22%	21%	22%	38%
Chronotype				
Morning	41%	34%	52%	46%
Intermediate	38%	44%	36%	39%
Night	21%	22%	12%	15%
WCRF/AICR				
Tertile 1 (low)	40%	40%	40%	40%
Tertile 2	30%	28%	34%	36%
Tertile 3 (high)	30%	32%	25%	24%

Adapted from table 5 in MCC-Spain Study. Kogevinas *et al.*, *Int. J. Cancer*, (2018).

When we stratified our analyses of timing of dinner and sleep by chronotype, we saw a higher decrease in risk for the morning chronotypes.

Combined breast and prostate cancer by chronotype

	< 2h (OR 95%CI)	>2h (OR 95%CI)
Chronotype		
Morning type	0.80 (0.61-1.66)	0.66 (0.49-0.90)
Intermediate	0.85 (0.51-1.43)	0.85 (0.62-1.16)
Evening type	1.03 (0.76-1.40)	0.86 (0.57-1.30)

Adapted from Table 6 in MCC Spain study. Kogevinas, UC, 2018.

To summarize, it can be stated that adherence to a more diurnal eating pattern specifically, where dinner is taken early and there is a long interval between the last meal and sleep are associated with a lower breast and prostate cancer risk. Our hypothesis is supported by experimental evidence and our findings stress the importance of evaluating circadian rhythms and sleep in studies on diet and cancer, as well as the development of recommendations, not merely on food quantity and type of food, but maybe also on timing.

As to my knowledge, only these two studies that I showed are available to date. It will be interesting to discover how other populations behave. This is especially relevant due to the rather late-time habits of Spaniards, as compared to other European citizens. Other populations might be taking bigger dinners at earlier times (around 18h-19h) and then go to bed. Or they may as well have a snack between dinner and bed time. Apart from this, we are also now analyzing the effects of physical activity at different times of the day. We hope to be able to show results in the near future. As a take-home message I would like to stress that timing could be a factor that potentially would need to be added to cancer prevention recommendations.

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DISCUSSION I

Diet and cancer prevention

Chair: Paula Jakszyn

Participants Dora Romaguera, Antonio Agudo, Cecilia Galbete, Ana Ramírez De Molina, Gemma Castaño-Vinyals

Questions, comments or concerns

Jakszyn - **It is sometimes stated that chrono types may be related to genetic factors. Do you have any information to this regard?**

Castaño - In the questionnaires that we have been using, genetics have not been taken into account. We do have some genotypes that seem to be correlated to our circadian rythms. It will be difficult to obtain high statistical power from this analysis. However, we hope to be able to analyze some of the circadian genes regulation, relative to shift work and sleep timing, in the future.

Jakszyn - **I notice most of the results presented by Dr. Castaño dealt around breast and prostate cancer. Is there a specific reason for this?**

Castaño - We decided to focus on breast and prostate cancer, for we knew that the circadian rhythm mainly has effects on hormonal tumors. We had previously worked on another study, on shift workers, where urine and blood tests were performed. Our results from that study showed that whenever an individual's circadian rhythm is altered (for example by being exposed to light at night), it is not only melatonin that becomes affected but also some endogenous hormones. And that reinforced our intention to further study breast and prostate cancer patients.

Romaguera - **The seems to be incipient evidence also that it is preferable to eat dinner when there is still sunlight or at least, not too close to bed time. And what would be really interesting to determine is whether pre-determined sleep patterns can or cannot be modified.**

Castaño - Our studies already make it clear that people are able to somewhat adapt. In our shift-work-study, we noticed that some night workers postponed their melatonin production to the time when they actually got their sleep (in the morning). That proofs that there is adaptation. However, shift workers produced lower overall quantities, so the adaptations achieved do not completely counteract the negative effects.

Romaguera - Apparently, some research has tried to determine if chrono type can be altered by means of a specialized plan. Apparently, a continuous action plan can lead to some changes but any divergence from the initial plan (i.e. if you skip the plan for as short as 1 day), all previous achievements are lost.

Agudo - **In the 1040s, Dr. Tannenbaum started to determine a correlation between diet and cancer. In his studies, he proved that mice who had lower energy intake were less prone to developing cancer, for equal doses of carcinogens. That study also concluded that mice which obtained their energy mainly through fat intake were more prone to develop cancer. How does your research relate to that?**

Ramírez - I agree that epidemiological studies about fat and high-fat diets have not yet answered its relationship to cancer. However, molecular experiments each day provide a growing body of evidence. In regard to our clinical trial, it was meant to be a phase one trial. Subjects were administered the compound between diagnosis and the time of surgery. This design doesn't allow for correct observation of results. But now we know the role or markers and we have results from healthy volunteers. So it is only a matter of time until we get approval for a longer trial. Then we will take a look not only at survival but also at relapse.

Agudo - **In addition to colorectal cancer, what do you reckon will be the next target or candidates to be studied?**

Ramírez - We are focusing our research on breast cancer patients because they often also gain weight and sometimes develop metabolic syndrome. So their metabolism of lipids becomes highly relevant. On top of that, we chose breast cancer because rosemary extract has an effect on estrogens, which could also lead to therapeutic effects. Our animal model experiments showed greater effects in breast cancer sonograms than in colon cancer sonograms. Our idea is to research on both of these cancer sites in the near future.

Jakszyn - **Dr. Galbete, are you aware of any research which may have performed sensitive analysis on wine, use instead of total alcohol intake?**

Galbete - I cannot think of any study that has. My impression is that analyses are most frequently done with the data that is available. For Mediterranean diet, that is usually total alcohol intake. Maybe some questions would need to be redefined and adjusted to current times and locations. And it would also be advisable to place more emphasis on sensitivity analysis.

Ramírez - Prior to this conference I was not aware of the existence of epidemiological studies on food labeling. I had only received information via mass media (television) and, from that, I got the impression that new food labeling systems were not reliable. It has been explained here, for example, that olive oil had been classified as D, while less healthy foods were marked as B or C. I am afraid the general population may be somewhat dubious. Do you think they trust these labels?

Agudo - There are several aspects to this. One of them is that mass media is not always a reliable source of information. Food labeling was intended as a useful way to help people in making healthier nutritional choices. I must say I don't blame the population for not trusting it. Still, I find it a useful informational tool that can help society make sound decisions. And, additionally, it may help to prevent 3-4% of cancers. Both of these factors could constitute argument in favor or promoting adequate labeling.

Romaguera - **I am afraid these kinds of indexes were designed by focusing mainly on the effects of food on obesity and type II diabetes. That explains, for example, why they qualify total protein but they do not make a distinction between animal or plant sources. The latter would be relevant for cancer. In the future, it might be advisable to broaden the spectrum. And specific modifications would need to be included. For instance with wine, which can have different effects on health, depending on which condition or disease is being considered.**

Agudo - Even the authors to this code system acknowledge that it is not perfect. However, the algorithm that was used allows for some modifications. It is challenging to provide people with information that is sufficient but not overwhelming. We may have been too exhaustive and failed to deliver useful information. Educating end-users seems challenging if our labeling systems are not standardized. Efforts should probably be targeted towards one single labeling code, that is easy to interpret and of high quality.

Romaguera - **Is application of the Nutri-Score voluntary for companies? And is it appliccable to both processed and fresh foods (e.g. apples)?**

Agudo - According to current EU regulations, application of this system is voluntary for companies. And yes, it is often applied to fresh produce, also. Dr. Romaguera could maybe provide us with some further insight as to whether the inclusion of mechanistic data within the label would be convenient. Do you think this will be implemented?

Romaguera - I know that the recommendations are mainly based on the meta-analysis of epidemiological studies. As far as implementation of mechanistic labelling policies, I am afraid I don't have any useful information.

Jakszyn - **Is the public's opinion on this labeling system known? Do patients believe nutrients, as from the labels, can impact their health?**

Agudo - As far as I know, the system has not been implemented in Spain, yet. So it is uncertain how the general public will react to it once -and if- it becomes implemented. It was meant as a mere guideline and provides relevant information, which can be used by some in their decision-making process.

Jakszyn - **In regard to the Mediterranean diet. Have you seen or even taken into consideration the effort made by SOFI to create a score with thresholds that are based on their previous meta-analyses? Has someone already applied it?**

Galbete - I am acquainted with the project and I reckon they made considerable effort. It may be feasible to implement it in countries which are close to following a Mediterranean diet. But I doubt that it could be successful elsewhere. Some of the proposed aims seem so high that are likely to be discouraging for users.

Agudo - **There seems to be a variety of definitions to the Mediterranean diet. However, as far as determining the relationships of diet to specific outcomes, this multiplicity of definitions is not so relevant, for most scores are relative. Results will be relative to the specific population being studied. In Sweden, for instance, it has been determined that the individuals who adhere to the Mediterranean diet have lower risk of developing breast cancer.**

Romaguera - Yes, I agree. We did many modifications using different thresholds for different countries when I was working on EPIC. In the end, I agree that a simple score, such as that by Trichopolou, could work well and be easier to apply.

Galbete - Back in the days, the head of EPIC Postdam critized this score for only including known "healthy" items.

Romaguera - I am an advocate of the Mediterranean diet but I think it reflects the way people used to eat 50 years ago.

Jakszyn - **About the Nova classification, are you planning on using its fourth category as a proxy for fast food consumption? Or will you also include the third?**

Romaguera - No, I think our conclusion is only to use the fourth category. Thus, the Nova classification categorizes the foods according to the degree of processing involved. It does not consider whether the food is healthy or not, it is only a degree of processing. The fourth group is where the most processed foods are. Group one is for unprocessed foods, group two refers to ingredients, and the third group is processed medium, such as canned peas; the ultra-processed foods will go to the fourth group, due to industrialization. If we ask for example to what category a yoghurt belongs to, we would say that in the fourth, if it has sugar, fruits, cereals or any other component, only natural yogurt could be in 3. Therefore, there are ultra-processed foods that are healthy, for example, the cereals that we consume at breakfast are usually high in sugars and other additives.

Romaguera - We plan on only using the fourth category, which indicates industrial processing. The Nova classification groups foods according to the degree of processing, regardless of how healthy or unhealthy those processes may be. Both its third and fourth categories indicate processing. However, the third category could include processes as small as putting a food into a can. That is why we have decided to stick with the fourth category, which involves ultra-processing. In spite of that, some questions did arise, for example with yoghurt. Yoghourt belongs in the fourth (ultra-processed) category, at least in cases where it contains added sugar. But food frequency questionnaires do not specify this. So, this exemplifies how some foods in the fourth category may actually be considered healthy, in spite of being considered ultra-processed. And a similar situation is found with breakfast cereal. They may or may not contain added sugar, but they will be found in the ultra-processed category, nevertheless.

Jakszyn - **Some questionnaires were designed 20 years ago. Much has changed relative to food consumption since then. Even the concept of ultra-processed is now considerably different. Do you believe those questionnaires are able to properly classify diet, in present times?**

Agudo - It is true that they were made many years ago, but they can be modified and adapted. New or adapted questionnaires can be developed and previously collected data can still be used, under different research hypotheses. In regard to the Nova classification, I understand it is far from being perfect, but it can be worthy if we consider the strict nutritional definition, not extracting any conclusions as to how they affect health. In my opinion, what is important is working under a solid definition –whether good or bad- and only then look for effects. And this is applicable, also to dietary patterns, such as the Mediterranean diet.

Galbete - Regarding the NOVA classification, I am sure you know the published article that observed that these ultra-processed foods were associated with cancer risk. Certainly, we cannot ensure that ultra-processing is responsible for the development of cancer, but there is a relationship, especially when it comes to fast food.

Jakszyn - **Thank you very much to all attendees for being here and thank you to all speakers for bringing some light onto these topics.**

Session II

Physical activity, sedentary behavior and cancer

THE ROLE OF PHYSICAL ACTIVITY BEFORE AND AFTER CANCER DIAGNOSIS: CURRENT EVIDENCE

Anne M. May

University Medical Center Utrecht, Julius Center. Utrecht, The Netherlands.

This session on the role of physical activity on cancer consisted of two parts. Dr. May focused initially on physical activity before diagnosis, or in other words, on whether there physical activity can have a protective effect against the occurrence of cancer. The second part dealt around the effects of physical activity and exercise on health after a cancer diagnosis. This would additionally address the question of whether physical activity may have a role as a prognostic factor. Both parts to this conference include results of intervention studies carried out by Dr. May's research group in Utrecht. This will help us to understand these relationships and offer insights on what should be done in clinical practice. The World Cancer Research Fund (WCRF) in the continuous update project has recently assessed the relationship between physical activity and cancer risk. They concluded that there is a convincing evidence of a protective role of physical activity against colorectal cancer and probably protects also against breast cancer. They also reported a limited evidence for other types of tumors. Other authors have assessed the potential association in a quantitative way, showing the relative risk of developing several various types of cancers in patients with high physical activity, as compared to those with low levels of physical activity. As an example, a 25% risk reduction was estimated for colorectal cancer.

Association between high versus low physical activity levels & incidence of specific cancers

Cancer Type	Number of Studies	Relative Risk
Substantial Evidence		
Colon	21	0,74 (0.68-0,80)
Endometrial	20	0,82 (0.75-0,90)
Breast	31	0,88 (0,85-0,91)
Weak on moderate evidence		
Prostate	24	0,94 (0,91-0,98)
Stomach	18	0,90 (0,76-1,06)
Ovary	09	0,89 (0,79-1,01)
Kidney	19	0,89 (0,80-0,99)
Lung	14	0,77 (0,75-0,81(
Pancreas	05	0,72 (0,75-0,81)

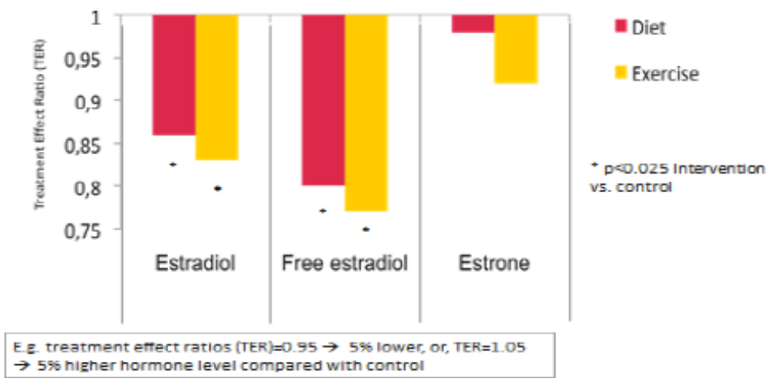
Risk reductions of 26% - 12%

Adapted from Leitzmann *et al.* European Code against Cancer 4th Edition: Physical activity and cancer. *Cancer Epidemiol.* 2015 Dec;39 Suppl 1:S46-55".

In view of these results, it is necessary to identify a mechanism that could satisfactorily explain how physical activity is able to generate this protection. It is widely accepted that the metabolic pathway of insulin and its effect on glucose levels and inflammation, as well as its relationship with hormone levels in blood, are key components of this effect, maybe together with and indirect effect of physical activity in the reduction of adiposity.

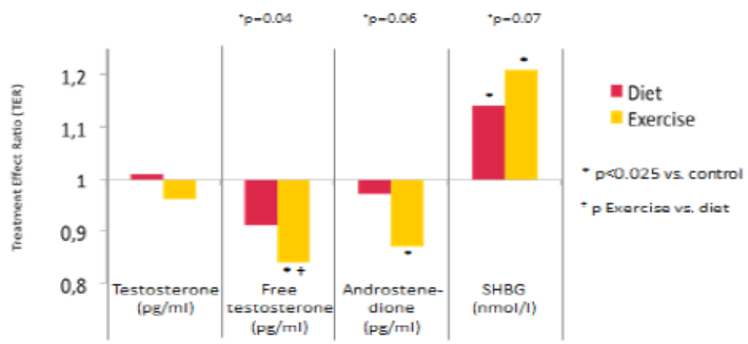
The knowledge about such mechanisms and pathways has often been used in intervention studies. For instance, our group in Utrecht conducted the study called SHAPE-1. Overall, a one-year exercise intervention showed no effect in sex hormone levels in post-menopausal women. However, there was a significant decrease in estrogen levels among those who lost 2% of body fat. A similar effect had been also found in other studies, and this led us to wonder whether physical activity and exercise may have beneficial effects that go beyond the effects on weight and body composition. Taking this into consideration, for SHAPE-2 the research question was to assess the effect of equivalent weight loss with or without exercise on sex hormone levels and inflammatory markers. This study assessed postmenopausal women with BMI>25, for 16 weeks, and had three arms: one group received an exercise program with a very small caloric restriction; another group received only a dietary program, and the third one was the control group. Women in the exercise program came in twice per week for a supervised group training that included endurance and resistance exercises. They also performed two one-hour Nordic walking sessions. Subjects in the diet program received a series of individual consults with a trained dietician and five group sessions. They were also motivated by weekly telephone consults. The main measurements consisted of anthropometric measurements, body composition by means of DEXA, physical fitness and physical assessment by means of questionnaire and accelerometer. Both of the groups that followed an intervention achieved the target of 5 kg weight loss. In regard to body composition, there was a significant loss of muscle mass in the group subject to the diet plan only, while the group in the exercise program, inspite of also being subject to a calorie restriction, compensated the weight of the muscle mass through the physical activity. The physical condition of the group that followed the exercise program increased significantly. Regarding the primary outcomes of the study (sex hormones), estradiol levels were significantly decreased in the two intervention groups compared with the controls, but there were no differences between the two intervention groups. A similar pattern was found for testosterone and androstenedione, but only for free testosterone the exercise group showed a higher and significant decrease compared to the diet only group. However, when the same comparisons were made adjusting for the proportion of fat loss, all significant effects disappeared. This shows that the effects observed on sex hormones are mediated by loss of fat. In a similar way, no significant results were observed in inflammatory markers after adjusting for change in the percentage of fat.

Results. Effects on sex hormones: Estrogens



Adapted from van Gemert *et al.* Effect of weight loss, with or without exercise, on body composition and sex hormones in postmenopausal women: the SHAPE-2 trial. *Breast Cancer Res.* 2015 Sep 2; 17:120.

Results. Androgens & SHBG



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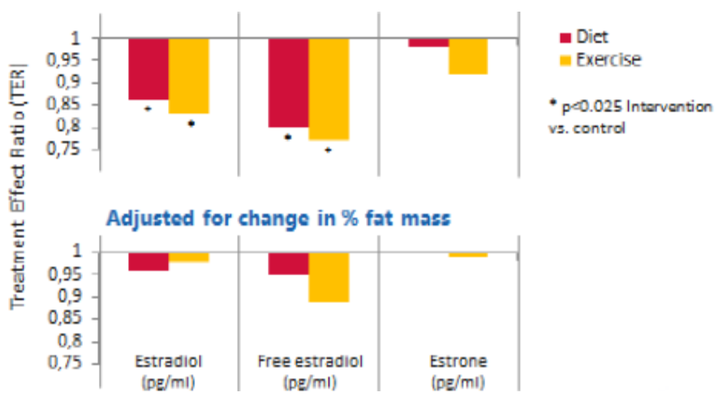

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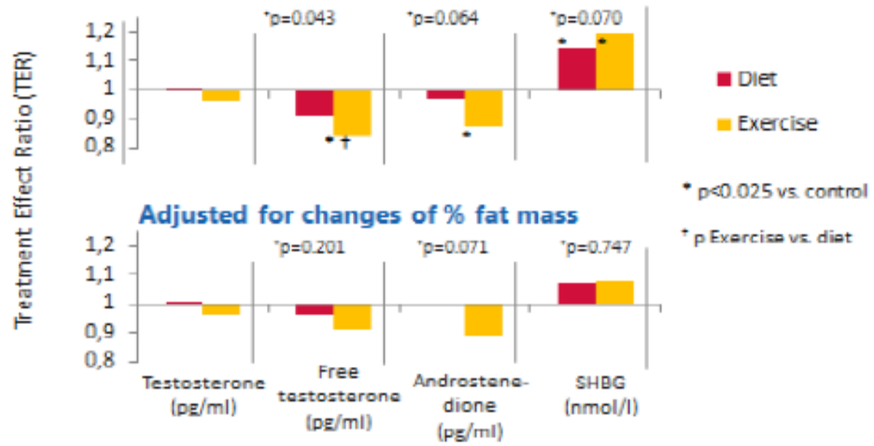
Results. Effects on sex hormones: Androgens & SHBG



Adapted from van Gemert *et al.* Effect of weight loss, with or without exercise, on body composition and sex hormones in postmenopausal women: the SHAPE-2 trial. *Breast Cancer Res.* 2015 Sep 2; 17:120.

To conclude, both interventions showed favorable effects on sex hormones and some inflammatory markers, compared to control. Compared with diet induced weight loss, equivalent weight loss by mainly exercise has more beneficial effects on body composition and physical fitness. There is also an indication for more beneficial effects of exercise in serum androgens. However, fat mass is an important mediator in the effects of exercise on biomarkers related with breast cancer risk. Therefore, it seems that exercise (combined with caloric restriction) is the preferred measure in order to decrease breast cancer risk in overweight or obese postmenopausal women.

After reviewing the potential effect of physical activity before a diagnosis of cancer, we are now moving to the moment when the disease has already been diagnosed. Now the question is whether or not physical activity is associated to an improved cancer prognosis.

The first studies trying to provide an answer to such question emerged in 2005-06, and they found that higher levels of physical activity were associated to longer survival rates after both breast and colorectal cancer. So the simple answer to the question of whether physical activity is associated to an improved cancer prognosis could be answered by saying yes. There is however, a big 'but': the existing evidence is based upon observational studies. Consequently, it cannot be ruled out that there are other factors which may at least in part explain the results. A definitive answer should preferably come from randomized controlled trials (RCTs). Unfortunately, carrying out RCTs in practice is quite challenging. Patients must be asked to be involved after diagnosis and would have to be randomized to either a physical exercise program or a control. Furthermore, we must assume that controls do not exercise. Of course, we know that observational studies now indicate a positive effect on prognosis.

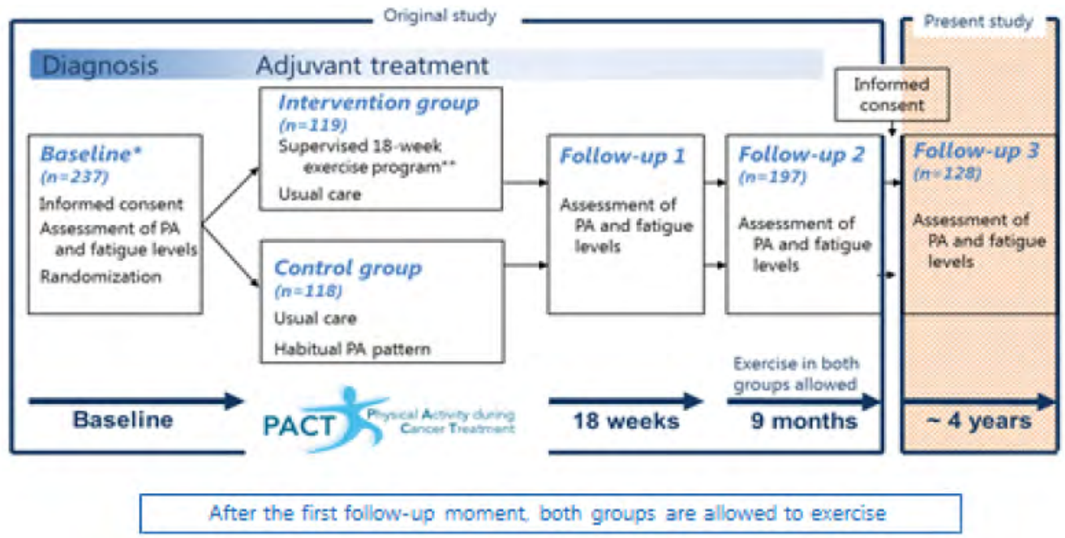
Nevertheless, there's also a lot of work going on investigating the effects of various exercise interventions. Many work teams have been investigating for more than 20 years the effects of interventions with exercise programs on cancer patients. Their constant intent is to identify how physical activity influences some side effects related to oncological therapy (e.g. fatigue, nausea and pain). Some small studies have been published, highlighting the positive results on the control of nausea, body composition and physical performance, in patients under oncological treatment, which have been accompanied by a team of nurses, to ensure the compliance of the exercise program. The first recommendations about exercise for people with cancer were published in 2003, by the American Cancer Society.

Even though there is no standard program of supervised exercises, publications in Europe and the United States agree that physical activity should be carried out 2 to 3 times a week, with an approximate duration of one hour (depending on the type of exercise) and combining aerobic with resistance activities. Also non-supervised (home-based) exercise programs were investigated consisting mostly of walking a minimum of 30 uninterrupted minutes, 5 times a week. Some programs reported in the Netherlands combine a program of moderate-to-high intensity exercises, twice a week, supervised by a physiotherapist, with a home program, by which they must walk 30 minutes, daily. The purpose of the studies was to determine the impact of the exercise program during treatment in the prevention of therapy-induced side effects, and after treatment. The results from these interventions have been able to demonstrate the improvement of the patient's physical condition and muscular strength, with a positive impact on the control of fatigue, sleep and depression.

Future studies should focus on effects of exercise on tolerance to chemotherapy and understudied types of cancers, and assess the impact of an exercise program on progression and survival in cancer, as well as the relationship of oncological therapy with other side effects, such as cognitive decline and the development of osteoporosis. We will now review more in depth one of our past studies.

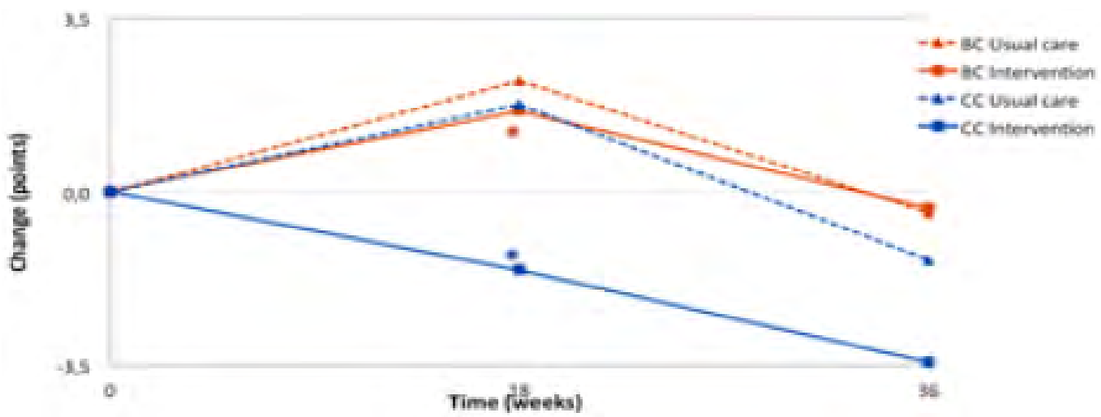
The PACT (Physical Activity during Cancer Treatment) study had as its main objective to assess the impact on fatigue of a supervised exercise program for eight weeks, with a nine-month follow-up, which was then extended to 4 years (to assess the long-term effects), in patients treated with chemotherapy for breast cancer and colon cancer. The results of the evaluation of the exercise program at week eight showed a highly significant beneficial effect on symptom control in those patients who belonged to the exercise group. This lead the group of researchers to incorporate all patients in the control group into the exercise program, customized according to their physical condition. The exercise program included supervised sessions of high intensity aerobic exercise 2 times a week, and 3 weekly unsupervised walking sessions, of 30 minutes each.

PACT study design



The recruitment of patients was much more successful for breast than for colon cancer patients, maybe owing to the many publications on the potential effects of exercise on breast cancer. Regarding the major outcome, fatigue, when compared to the control group, fatigue decreased for both types of patients. Even though the colon cancer group was smaller than the one for breast cancer, results were in either case statistically significant.

MFI physical fatigue in BC & CC patients



Adapted from May AM *et al.* Cost-effectiveness analysis of a 18-week exercise programme for patients with breast and colon cancer undergoing adjuvant chemotherapy: the randomised PACT study. *BMJ Open.* 2017 Mar 6;7(3): e012187.

After examining these results, there is an important question which is often neglected: were our patients really able to follow our protocol or was the intended intensity so high that maybe no one did it? – In order to check on this, we analyzed all training logs. And the answer was mostly yes. There was an attendance of 80% and adherence to the program can consequently be considered good. When looking at compliance rates, we discovered that they were very capable of executing the 20 minutes of cycle ergometer program, although they did reduce the intensity. And apart from that, they also carried out the resistance exercise program well, and complied with 60% of the three weekly days of home based exercise, for the eight weeks.

We will now take a look at the results at 4 years post-intervention. The reader should take into account that colon patient number was low and we therefore combined patients with breast and colon cancer. It was found that the exercise intervention group reported significant higher physical activity levels four years later, when compared to the control group. Regarding fatigue, the exercise group was less fatigued compared to the usual care group, but this was not statistically significant. At four years, the effect size had remained the same as that right at the end of the intervention. These are relevant and very promising results which show that physical exercise during treatment can also have long term effects on fatigue levels.

According to this study, and to others that have been performed in other countries on patients with breast cancer, doing physical exercise during chemotherapy has beneficial effects on fatigue, physical fitness and physical activity behavior in the long term. With these results in mind, physical exercise during cancer treatment should be encouraged and is expected to render positive effects. And this, I believe, most probably doesn't only apply to breast cancer.

To put all these results into context, it must be recalled that The American College of Sports Medicine (ACSM) issued in 2010 their guidelines on physical activity as a common clinical practice. In it, experts insist that inactivity should be avoided in all people with a cancer diagnosis. Even after surgery, patients should be encouraged to return to their activities of daily life as soon as possible. These recommendations coincide with the guidelines in Spain, where 150 minutes of weekly physical activity are indicated, performed at a moderate-to-high intensity. Updated ACSM recommendations will be published in 2019.

To conclude, it seems that lifestyle factors such as physical activity and overweight play an important role in the development and progression of cancer. In addition, the effectiveness of exercise seems to depend on the characteristics of the tumor. Exercise interventions during and after cancer treatment are beneficial to reduce treatment-related side effects or to improve it. These beneficial effects seem to be maintained once the study is finished.

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PHYSICAL ACTIVITY INTERVENTIONS IN PATIENTS WITH CHRONIC CONDITIONS

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Dr. Oviedo's presentation dealt about the concepts of sedentarism and physical activity. It highlighted the differences in meaning and, consequently, in the means by which they can be assessed. Clinical data was presented, based on studies carried out at the Physiology Unit of the University of Barcelona.

Sedentary behavior

Movement can be considered a continuum. In it, sleep would constitute the lowest end, whereas intense exercise would be placed at the highest end of the continuum. In the intermediate points of such a model, we could find sedentary behavior, light and moderate physical activity.

The upper end of the continuum –that which corresponds to exercise physiology- has been much more extensively researched. Not so much is known about sedentary physiology even though it could be equally important.

Sedentary behavior was first defined in 2012, in a letter to the editor of the Applied Physiology Journal. It was described as "any waking behavior characterized by an energy expenditure ≤1.5 METs while in a sitting or reclining posture". Sedentary time is any time spent, regardless of its duration or context, in sedentary behaviors. This has been a field of study for as short as 10 to 15 years and we are only now realizing that an important factor may be the ratio between sedentary bouts (i.e. periods of uninterrupted sedentary time) to sedentary interruptions or breaks (i.e. non-sedentary bouts in between two sedentary bouts). Our lab is interested in sedentary behavior patterns. Thanks to the use of accelerometers, we have been analyzing the timing, duration and frequency of those patterns. We observe the number of times a person breaks sedentary behavior throughout the day, how long are the bouts and the breaks, how intense is the activity performed during the breaks and in which ways those variables may affect the health of the individual. Literature from the year 2008 and on, indicates that, for any given sedentary time, people who take the most breaks have lower average waist circumference, body mass index, triglycerides and 2-hr plasma glucose.

All of the previous information should lead researchers to not merely be interested in improving subjects' physical activity and cardio respiratory fitness, but to also aim to reduce their sedentary behavior. Clinical guidelines by the Canadian Society for Exercise Physiology on sedentary behavior are readily available, but only relative to children (from 0 to 17 years of age). A version for adults is sure to come. And maybe in the future, the World Health Organization (WHO) will be issuing guidelines for sedentarism, just like they currently are issuing guidelines on physical activity.

Guidelines for children can be accessed via https://csepguidelines.ca/

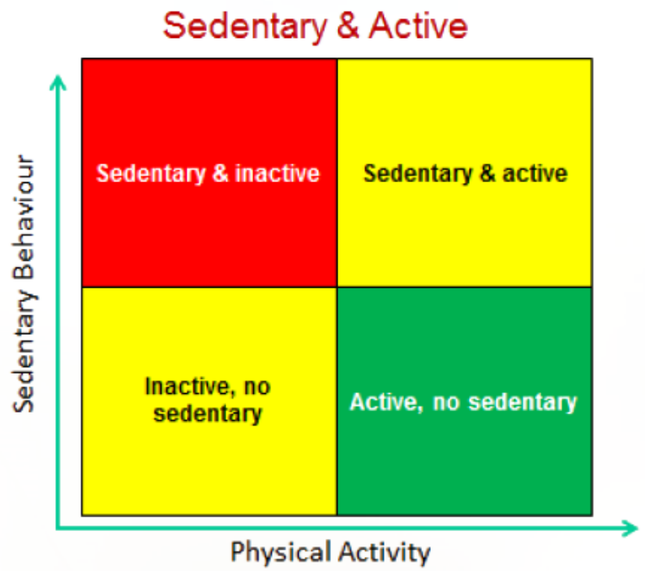
It should be noted that being sedentary does not imply being physically inactive. This will be further explained in the following lines.

Physical inactivity

Individuals can be categorized into active or inactive, depending on whether they fulfil the physical activity recommendations by the WHO. The latter indicates that adults should spend a minimum of 150 minutes per week doing moderate intensity (3-5.99 METS) physical activity or 75 minutes of intensive (6+METS) activity, per week. Any person not meeting those requirements is to be considered inactive.

Knowing that sedentarism and physical inactivity are two different parameters, it is only logical that any combination of these two behaviors may exist.

Not all behaviours are mutually exclusive



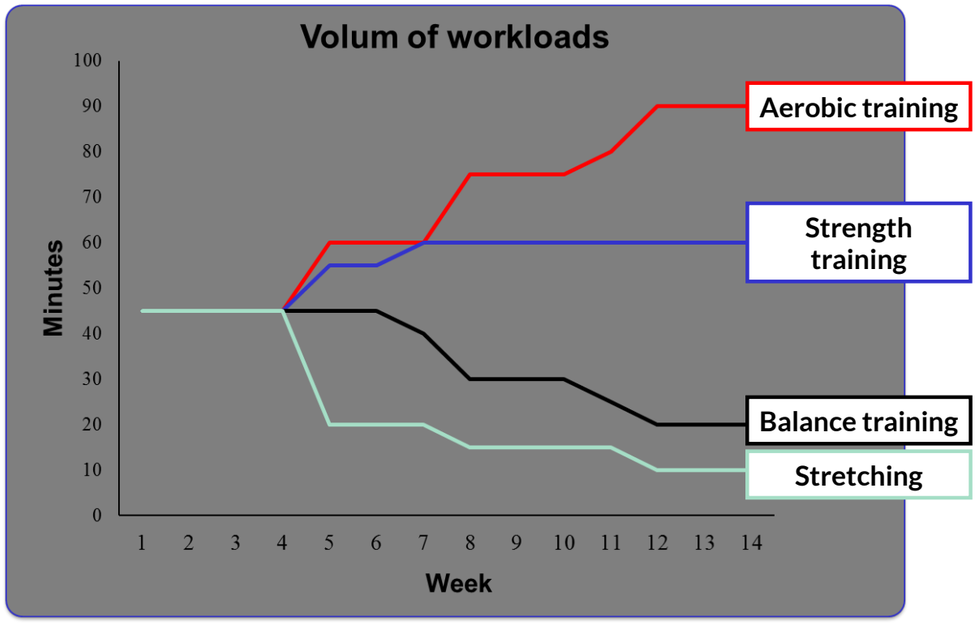
Source: https://www.sedentarybehaviour.org/.

A person who meets the WHO's recommendations for physical activity is active but can, nevertheless be sedentary (if they spend most of their day sitting and for instance, just go to the gym to exercise two times a week) or non-sedentary (if apart from being active, spends most of their time standing or walking). Inactive individuals, on the other hand, are those who do not meet the WHO's recommendations for activity, but they may or may not spend much time sitting or lying.

Research in our lab

Our lab focuses on the analysis of all four pillars of physical fitness: aerobic capacity, body composition, muscular strength & endurance, flexibility & balance. We follow the American College of Sports Medicine's (ACSM) Guidelines for Exercise Testing and Prescription (2017) and try to adjust our protocols to fit every participant. To this regard we determine specific values for frequency, intensity, time, type and volume. But we also aim for a correct pattern –i.e. the order in which exercises will be performed-, and progression –i.e. increased challenge over time.

In the past few years, we have carried out research in people with spinal cord injuries, multiple sclerosis and intellectual disability, among others. Below is a graph showing how we pursued our goal of increasing the aerobic capacity in individuals with intellectual disability. Interestingly, apart from measuring the usual variables, we also analyzed arterial stiffness by measuring carotid and femoral pulse wave velocities, as well as the past waves, which clearly correlates with health conditions.



Source: Effects of aerobic resistance and balance training in adults with intellectual disabilities. Oviedo *et al.*, *Research in Developmental disabilities*, 2014.

Next, I would like to introduce a study we conducted on 29 patients with remittent multiple sclerosis, who were fully ambulatory and minimally disabled. The study consisted of 3 groups: one which we called combined face-to-face group. Participants in this group followed a supervised high intensity interval training plus home exercises. Another group we called home-based exercises group and people in this group received their programs via e-mail. And we had one last, control group, where participants did not train at all. Analysis of our data showed quite similar results between the two intervention groups. However, the supervised exercise group was better able to retain participants and facilitate high-intensity exercises. This seems to be a positive characteristic for therapeutic exercise interventions. Another interesting aspect is that we did not base our programming on initial assessment for peak intensity, but instead we performed regular testing at 12-13 points on the Borg scale, so as to better adjust the target training the next mesocycle's training plan.

Training Period 1								Training Period 2								Training Period 3			
Mesocycle 1				Mesocycle 2				Mesocycle 3				Mesocycle 4				Mesocycle 5			
W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12	W 13	W 14	W 15	W 16	W 17	W 18	W 19	W 20
			T1				T2				T3				T4				T5
Borg's scale 12 – 13								Borg's scale 13 – 14											

Warm-up: Balance training. Low intensity exercise: walking, joint mobility exercise.
Main part: High intensity interval training (HIIT). Strength training. Core training or aerobic training.
Cool-down: Stretching and body awareness work.

Endurance training Ss – 30 min cycling Hs – 45 min walking	**Endurance training** Ss – HIIT 3' x 3sets (rec 3') 3' (30" TR + 30%TR – 30" rec) – Cycling Hs – 60 min walking	**Endurance training** Ss – HIIT 4' x 3sets (rec 3') 4' (30" TR + 30%TR – 30" rec) – Cycling Hs – 75 min walking	**Endurance training** Ss – HIIT 5' x 3sets (rec 3') 5' (30" TR + 30%TR – 30" rec) – Cycling Hs – 85 min walking	**Endurance training** Ss – HIIT 5' x 3sets (rec 3') 5' (30" TR + 30%TR – 30" TR – 20%TR) – Cycling Hs – 90 min walking
Strength training 12 – 15 rep x 2 sets Load was increased when participants demonstrated the ability to perform 2 repetitions more than the target for the session.	**Strength training** 10 – 15 rep x 3 sets Load was increased when participants demonstrated the ability to perform 2 repetitions more than the target for the session.	**Strength training** 10 rep x 4 – 5 sets Load was increased when participants demonstrated the ability to perform 2 repetitions more than the target for the session.	**Strength training** 10 rep x 4 – 5 sets Load was increased when participants demonstrated the ability to perform 2 repetitions more than the target for the session.	**Strength training** 10 rep x 5 sets Load was increased when participants demonstrated the ability to perform 2 repetitions more than the target for the session.

Propioception training
Balance training is present during all the program in de Ss. Body awareness work this kind of training appears in some Ss and in a weekly Hs.

Flexibility training
Stretching is present in all the Ss and Hs. Joint mobility is present along the program but the volume of this kind of training decrease along the program.

Training period 1				Training period 2				Training period 3				Training period 4				Training period 5			
Mesocycle 1				Mesocycle 2				Mesocycle 3				Mesocycle 4				Mesocycle 5			
W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12	W 13	W 14	W 15	W 16	W 17	W 18	W 19	W 20
Int 50-60	Int 50-60	Int 55-65	Int 55-65	Int 60-70	Int 60-70	Int 65-75	Int 65-75	Int 70-80	Int 70-80	Int 75-85	Int 75-85	Int 75-85	Int 75-85	Int 75-85	Int 75-85	Int 75-85	Int 75-85	Int 75-85	Int 75-85

Warm-up: mobility; walking at different intensities; low intensities exercises (5-15min).
Strength training: calisthenics exercises; resistance exercises with elastic bands. We focused on large muscle groups and antigravity muscle groups (2-3 sets of 8-15 repetitions; 10-20min).
Endurance training: jogging, running, stepping, fit ball exercise (10-60 min).
Propioception training: movements in diverse directions and on different surfaces; comparison eyes open/eyes close; single leg static balance, tandem and semi tandem positions (10-30 min)
Cool-down: Stretching, joint mobility and body awareness work (5-15 min)

Charts sourced from: Guillamó E, Cobo-Calvo Á, Oviedo GR, Travier N, Álamo J, Niño-Mendez OA, Martínez-Yelamos A, *et al.* Feasibility and Effects of Structured Physical Exercise Interventions in Adults with Relapsing-Remitting Multiple Sclerosis: A Pilot Study. *J Sports Sci Med.* 2018 Aug 14;17(3):426-436.

And to finish with, I'd just like to introduce you to our latest research, by which we are analyzing the effects of sprint all out interval training, that is training where participants exert their maximum effort for brief periods of time (5-30 seconds, approximately), followed by some (ca.40) of recovery, for a total duration of 6 months. We hope to have results soon and to be able to share them with the scientific community soon. Thank you very much.

REGULAR EXERCISE INTERVENTIONS IN CANCER PATIENTS

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Exercise training has been established as a feasible and safe intervention during or after neoplastic treatment in several types of cancer. Numerous studies have shown that exercise can prevent and control various treatment-related side effects, including functional limitations, physical capacity, anxiety, and sleep disturbance. In the longer term, an active lifestyle has been demonstrated to increase survival in women with breast cancer, who maintain a moderate level of activity; 30-75 minutes of brisk walking 5 days a week. Specifically, physically active breast cancer survivors have a 51% to 85% lower cancer-specific mortality and 33% to 82% lower all-cause mortality. Over the last few years, numerous evidences have been published that demonstrate the importance of intervention of exercise in cancer patients. Next, we shall take a look at some of their main conclusions.

Effects of exercise on leisure-time activity

A study by the Universidad Politécnica de Madrid (UPM) and Asociación de Cáncer de Mama de Madrid (ASCAMMA) showed increased leisure time activity that was maintained up to a 12-weeks follow up, for a group-based exercise intervention, together with an educational program. Moreover, subjects also showed improvements related to aerobic capacity, strength and mental well-being (Casla *et al.*, *Integrative Cancer Therapies*, 2014).

There is a study with a very large sample size (n= 1.44 million adults), which aimed to prospectively analyze leisure-time activity in relation to risk of 26 different cancer types. Results adjusted for body mass index showed statistically significant inverse associations of leisure-time physical activity and risk for 13 types of cancer. Leisure-time physical activity was associated with higher risks of malignant melanoma (probably due to insufficient sun block protection) and prostate cancer (Moore *et al.*, *JAMA Intern Med*. 2016).

Physiopathology of tumor cells. Effects of exercise on animal models

In animal studies, regular exercise inhibits tumor onset and progression across a wide range of tumor models and anatomical locations. The usual schedule in animal models showing inhibition of cancer progression is regular exercise on most days of the week (up to 60 min/session) for several weeks (4–32 weeks, which translates into human 'years') using, typically, voluntary wheel running, but also forced treadmill running or swimming. A wealth of evidence supports an association between regular physical activity (PA) and decreased risk for cancer and cancer mortality.

To name some of the benefits of exercise we know that the latter may help prevent cancer by reducing the circulating levels of multiple hormones (e.g. IGF-1) and evading growth suppressors (e.g. exercise can increase p53 activation, one of the most important oncogenes promoting apoptosis of cancer cells). It can also reduce tumor cell proliferation (e.g. by stimulating AMPK and raptor-phosphorylation), while upregulating the tumor suppressor PDCD4 (Ruiz-Casado *et al. Trends in Cancer*,2017).

Cancer progression, mortality and recurrence

Together, clinical studies on animals and humans show data that could lead to a novel hypothesis that changes in circulating factors in the host may, in turn, influence release of secondary factors from other organ sites such as the bone marrow, skeletal muscle, or liver with the end result of altering ligand availability in the primary tumor microenvironment and/or distant ectopic sites to influence tumorigenesis and metastasis, respectively (Betof *et al.*, Brain Behav Immun. 2013).

We know from a review of 100 studies that, compared with patients who performed no/less exercise, patients who exercised following a diagnosis of cancer were observed to have a lower relative risk ofcancer mortality and recurrence and experienced fewer/less severe adverse effects So it all leads us to thinking that exercise in an important adjunct therapy, as well (Cormie *et al.*, *Epidemiol Rev* 2017).

Exercise, Cancer Biomarkers: Sex Hormones

The Women's Health Initiative Dietary Modification Trial included 267 postmenopausal women. BMI was found to be positively associated with estrone, free estradiol, free testosterone and prolactin and negatively associated with SHBG. Total physical activity (metabolic equivalent tasks per week) was negatively associated with concentrations of estrone, estradiol, and androstenedione, respectively. Using a composite variable of BMI and physical activity dichotomized by median values, women with high BMI/low physical activity had a mean estrone

concentration of 28.8 pg/ mL, compared with 24.1, 19.9, and 18.4 pg/mL for women with high BMI/high physical activity, low BMI/low physical activity, and low BMI/high physical activity, respectively. Similar trends were observed for estradiol and free estradiol and, in inverse, for SHBG. These associations may, in part, explain the positive associations between overweight/ obesity and a sedentary lifestyle on breast cancer risk (Tierman *et al.*, *Obesity*, 2006).

The American Society of Clinical Oncology found something slightly different. When comparing breast cancer survivors who did aerobic exercise (225 min/week. Duration 1 year) with controls, no significant differences in estrone, androstenedione, and testosterone levels were observed between exercisers and controls at 12 months. However, statistically significant reductions in estradiol and free estradiol and increases in SHBG were observed in the exercise group compared with the control group, which is consistent with a lower risk for postmenopausal breast cancer (Friedenreich *et al.*, *J Clin Oncol*,2010).

In postmenopausal women, estrone, estradiol, free estradiol, SHBG and free testosterone seemed to decrease most significantly when combining diet and exercise (usually followed by diet only, and then exercise only) and effects were stronger the greater the weight loss (Campbell *et al.*, *J Clin Oncol*,2012).

Exercise, Cancer Biomarkers: Insulin, Insuline-like growth factor 1 (IGF1), IFG binding protein 3 (IGFBP3)

The positive association between obesity and postmenopausal breast cancer has been attributed, in part, to the fact that estrogen, a risk factor for breast cancer, is synthesized in adipose tissue. Obesity is also associated with high levels of insulin, a known mitogen. This is consistent with the results of a prospective cohort study with 93,676 postmenopausal women which also suggested that hyperinsulinemia is an independent risk factor for breast cancer and may have a substantial role in explaining the obesity – breast cancer relationship (Gunter *et al.*, *J Nat Cancer Inst*,2009).

Circulating IGF1 seems to be positively associated with breast-cancer risk. IGF1 concentrations seem to be positively associated with height and age at first pregnancy, inversely associated with age at menarche and years since menopause and higher in moderately overweight women and moderate alcohol consumers than in other women. The association is not substantially modified by IGFBP3, and does not differ markedly by menopausal status, but seems to be confined to estrogen-receptor-positive tumors (Timothy J Key *et al.*, *The Lancet Oncology* 2010).

High insulin and IGF-I levels may therefore be associated with an increased breast cancer risk and/or death. We know from a Yale Exercise and Survivorship Study which was performed with postmenopausal breast cancer survivors, that >150 min/wk of moderate-intensity aerobic exercise can decrease insulin, IGF-1 and IGFBP-3. These exercise-induced decreases in IGFs may mediate the observed association between higher levels of physical activity and improved survival in women diagnosed with breast cancer (Melinda Irwing *et al.*, *Cancer Epidemiol Biomarkers Prev*. 2009).

Exercise and Cancer Biomarkers: Inflammation

In patients with curatively-treated colorectal cancer, a prospective trial on 23 subjects demonstrated that a short-term (2 weeks) rehabilitation program with moderate-intensity (0.55-0.65% of maximal aerobic capacity, and not less) exercise leads to a to a decreased LPS-induced antagonist response with a shift to a more pro-inflammatory state (decreased antagonist / cytokine ratio). Whether this change of the phasic immune response to moderate exercise may be clinically beneficial (decreased rates of infection, relapses and/or second tumors) is possible, but has to be investigated in long-term studies (Allgayer *et al.*, *Cancer Detect Prev*. 2004).

Regular exercise can have an anti-inflammatory effect, maybe due to alterations in immunological and inflammatory mechanisms. Mechanisms could include increased release of cortisol and adrenaline from the adrenal glands; increased production and release of IL-6 and other myokines from working skeletal muscle; reduced expression of TLRs on monocytes and macrophages; inhibition of adipose tissue infiltration by monocytes and macrophages; phenotypic switching of macrophages within adipose tissue; a reduction in the circulating numbers of pro-inflammatory monocytes; and an increase in the circulating numbers of TReg cells. Although there is a consensus that exercise training protects against some types of cancer, it is likely that effects will depend on the mode, frequency, intensity and duration of the exercise performed (Gleeson *et al.*, *Nat Rev Immunol.* 2011).

Adipose tissue undergoes important changes in obesity due to excess storage of lipids, leading to adipocyte cell death and the recruitment of macrophages. The resultant state of chronic low-grade inflammation is associated with the activation of NFkB signaling and elevated levels of aromatase, the rate-limiting enzyme in estrogen biosynthesis. This occurs not only in the visceral and subcutaneous fat, but also in the breast fat. In breast cancer patients, interventions aimed at modifying weight, including diet and exercise, are associated with changes in adipose tissue inflammation and estrogen production that are likely to impact breast cancer risk (Zahid *et al.*, *Curr Opin Pharmacol.* 2016).

Exercise and Cancer Biomarkers: Immune System

Training on cycloergometers, three times a week, for 15 weeks proved to increase natural killer cell cytotoxic activity and unstimulated [3H]thymidine uptake by peripheral blood lymphocytes in postmenopausal breast cancer survivors' Natural killers are collected by epinephrine and it would be interesting to study if this leads to better prognosis. It also opens a window to investigate what would the results be of combining treatment with immune therapies (Fairey *et al.*, *J Appl Physiol* 1985-2005).

Yet, another study, this one examining the effects of a 3-day per week resistance training program in breast cancer survivors, proved that resistance training has a beneficial effect on the NK and NKT cell expression of TNF-α indicating that RT may be beneficial in improving the inflammatory pro-

file in breast cancer survivors (Hagstrom *et al.*, *Breast Cancer Res Treat.* 2016).

A study consisting of an exercise intervention (resistance and aerobic activity at 60-75% functional capacity, 3 times per week, for 6 months) showed that exercise may improve immune function by increasing lymphocyte activation in patients with breast cancer following chemotherapy for breast cancer. When compared to a non-exercise group, the exercising patients showed a greater percentage of CD4(+)CD69(+) cells and a greater level of tritiated thymidine incorporation (DNA synthesis) when stimulated with ConA, PHA, and PWM at the end of the intervention. Plasma and mitogen-stimulated IL-6 and IFN-gamma production were similar in both groups (Hutnick *et al.*, *Med Sci Sports Exerc.* 2005).

The published trials combine supervised interventions, with a combined plan of cardiovascular exercise, resistance exercise and anaerobic exercise, with an intensity between 60-85% of the maximum heart rate, with a frequency of 2-5 days per week, with a time minimum that goes from 1-4 weeks before the surgery. Likewise, for the patient receiving adjuvant therapy the program includes aerobic exercises, with a frequency of 3 days per week, and follow-up of 6 to 12 weeks, supervised or unsupervised, in these cases, the effects are manifested with a better tolerance to chemotherapy and a decrease in side effects (Goh *et al.*, *Exerc Immunol Rev.* 2012).

Prehabilitation

Much of the existing literature on prehabilitation has to do with patients with lung cancer, since they commonly require improvement of their maximum VO2 before undergoing surgery.

Authors of a meta-analysis reached the conclusion that preoperative exercise (interventions ranged from 60%-85% of maximal heart rate; frequency ranged from 2 to 5 days per week; and duration 1-4 weeks) training may shorten length of hospital stay, decrease postoperative complications and increase the 6-minute walking distance (6MWD) test. Postoperative exercise training can also effectively improve both the 6MWD and quality of life in surgical patients with non-small cell lung cancer but requiring a longer training period (Ni HJ, Pudasaini B *et al.*, *Integr Cancer Ther.* 2017).

Keys to putting an exercise plan together

There is no consensus on what the most appropriate type of dosage of exercise may be. Breast cancer is, undoubtedly, the type of cancer that has been most widely studied to date. A 2016 Cochrane Systematic Review by Furmaniak *et al.* showed that, for breast cancer, a variety of protocols have been researched. This include both supervised and unsupervised modalities, interventions most commonly included a combination of exercise modes, aerobic capacities were trained in ranges from 40 to 60% of VO2Max, using heart rate as a reference (60-80% HR Max). In spite of this, it is resistance training that has proven to be most beneficial, with loads between 60 and 80% of 1RM. Training frequencies that have been studied range from 2 to 5 days per week, with durations from 12 to 27 weeks in total.

Another reference that may proof useful to clinicians is the Cosa Position Statement on Exercise in Cancer Care, by the Clinical Oncology Society of Australia. In it, they recommend the use of personalized program including combined exercise types, with intensities that are superior to 70% of maximum heart rate, performed 3 to 5 days per week, for a total of 150 minutes/week.

Next is an outline of how we, at Asociación Española Contra el Cáncer, approach exercise programming. First of all, patients are assessed for VO2Max, body composition and strength. This provides us with information that will allow for personalization of exercise type and intensity. We offer 12-week programs with a combination of strength and aerobic training. Once the intervention is over, they are assessed one more time and receive instruction so as to what their future practice should be like. After one year, they are called for a follow-up. All of this we plan in multidisciplinary teams, including oncologists.

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MEASURING PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOUR IN FREE-LIVING ENVIRONMENTS

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Defining key concepts: physical activity and sedentary behavior

Physical Activity

Physical activity is defined as any bodily movement produced by skeletal muscles that requires energy expenditure above the resting metabolic rate. It includes many activities that are undertaken in different daily living domains, which include vocation, transportation, household work and leisure time. Although physical activity is closely related to exercise and physical fitness constructs, the latter have different meanings. When physical activity is planned, structured, repetitive and usually performed to improve or maintain physical fitness, the appropriate term is exercise. The term "physical fitness" is used to describe a set of attributes that people have or achieve. Examples of health-related components of physical fitness include cardiorespiratory endurance, body composition and muscular strength. In the context of epidemiology and health, five components of physical activity are usually considered: duration (total time per day or per week engaged in the activity); frequency (how often physical activity is undertaken over time (e.g. daily, weekly, monthly), type (e.g. cardiovascular, strengthening, stretching), setting where the activity is performed (e.g. leisure-time, vocation, commuting,) and intensity (magnitude of the effort required to perform a given activity).

Classification of objectively measured physical activity intensities

	METS	$\%HR_{max}$	%HRR	VO_{2max}
Very light PA	<2	<57	<30	<37
LIPA	2.0-2.9	57-63	30-39	37-45
MPA	3.0-5.9	64-76	40-59	46-63
VPA	6.0-8.2	77-95	60-89	64-90
Near maximal to maximal PA	≥8.8	≥96	≥90	≥91

Table adapted from the American College of Sports Medicine (2013) and Garber *et al.*, 2011. PA= physical activity, LIPA= light physical activity, MPA= moderate physical activity, VPA= vigorous physical activity, $\%HR_{max}$ = maximal heart rate, %HRR= heart rate reserve, VO_{2max}= maximal oxygen uptake.

Sedentary Behavior

Sedentary behavior refers to those waking activities characterized by an energy expenditure of ≤1.5 METs while in a sitting or reclining posture. Sedentary behaviors occur within different contexts of our daily-living, which can include sitting during commuting, at the workplace and during leisure time. Sedentary behaviors are not merely the absence of physical activity. In fact, sedentary behavior and low levels of physical activity represent complementary aspects of human behavior that may entail a variety of physiological effects.

Measuring physical activity and sedentary behavior in free-living conditions

Given the importance of sedentary behaviors and physical activity as health-related behaviors, their precise measurement in free-living environments is critical to surveillance and epidemiological studies. Physical activity and sedentary behaviors can be assessed through different techniques, that can mainly be categorized into subjective and objective measures.

Self-reported measures of physical activity and sedentary behaviors

Self-reported measures, which include self/interviewed administered questionnaires and activity diaries, are considered subjective measures, for they measure a persons' ability to recall their behavior either from a specified time-frame (e.g. past day, past 7 days, past month, past year), throughout the day or about typical patterns of behavior.

Recall questionnaires are the most common form of assessing self-reported physical activity and sedentary behavior. This is so because they can be implemented on a large scale, they are relatively inexpensive, they do not alter the behavior under study, and they provide additional information about the context/domain where the behavior takes place (objective measures fail to obtain this data). However, self-reported instruments present some limitations. Questionnaires are susceptible to random and systematic reporting errors, as recalling behaviors that are sporadic or intermittent in nature may be challenging for the individual, who may also be exposed to social desirability bias. Moreover, and specifically in the reporting of physical activity, confusions may appear when categorizing time spent in moderate physical activity and vigorous physical activity as these terms may be ambiguous, and categorization is based on subjective perceptions that are influenced by participants' physical fitness and duration of the activity. For this reason, validity and reliability of questionnaires to assess physical activity and sedentary behavior remains questioned and further efforts should be directed towards the development of more accurate methods for obtaining the highest quality of information.

Objective monitoring of physical activity and sedentary behaviors: Motion sensors

Objective monitors —such as pedometers and accelerometers, offer greater validity and reliability, compared to self-reported data, as they can provide more accurate assessments.

Measuring physical activity via accelerometry

Accelerometery-based monitors have been widely used in order to measure physical activity in free-living environments, both in observational and interventional studies.

Accelerometers (e.g. ActiGraph GT3X, GENEA) measure body accelerations. Through proprietary algorithms, these accelerations are converted into activity counts occurring within a given time interval, which is referred to as an epoch. The analysis of these counts allows researchers to estimate parameters of physical activity such as intensity, with greater accelerations providing more counts, frequency and duration.

Although the use of accelerometers provides valid and objective estimates of individuals' physical activity in free-living conditions, they are nonetheless subject to limitations. Several variables —in terms of monitors' calibration, data collection and data processing criteria— must be considered carefully considered when interpreting resulting data. In addition, although accelerometers are accurate for measuring locomotor movement (which accounts for a great amount of adults' daily physical activity), these monitors are not able to measure all types of physical activities. In particular, they cannot account for upper body movements (mostly because the instrument is commonly positioned at the waist), they are unable to capture load-carrying activities, (since the latter do not require changes in acceleration patterns), and they also fail to measure cyclic movements or water-based activities. Yet, another limitation of physical activity monitors is that there is little consensus about the number of days of monitoring that are required, in order to reflect a valid measurement of usual physical activity. In addition, short periods of recording may also be biased by response to activity measurement, weekly or seasonal changes. Lastly, while objective measurements provide more accurate measures of physical activity, compared to structured questionnaires, they cannot gather domain-specific information. This, however, would be important for public health surveillance as well as for context-specific interventional studies.

Measuring sedentary behavior via accelerometry

Accelerometers can be broadly classified into those that mainly provide an approximation of energy expenditure (e.g. Actigraph) and those which primarily aim to classify posture (e.g. activPAL). While energy-expenditure devices provide accurate measurements for physical activity, their ability to capture static behaviors has been questioned.

Energy-expenditure devices categorize sedentary behavior based on periods of inactivity. A <100 counts per minute criteria has been widely used as a cut-off threshold for sedentary behavior. However, this criterion has not been selected from empirical studies and conclusions of sitting time using such thresholds must be interpreted cautiously.

Some studies reported overestimations of <100 accelerometer cut-point for estimating total sitting time in free-living conditions, while others reported underestimations of sitting time using <100 threshold. It has been suggested that a threshold of <150 counts per minute could be more appropriate, in order to accurately measure sitting time. More importantly, energy-expenditure devices are not sufficiently sensitive to distinguish between sitting/lying and standing time, as both behaviors produce <100 counts per minute. This constitutes a remarkable limitation, for standing itself is not considered a sedentary behavior. Monitoring devices, such as the activPAL™, use accelerations and body inclinations to accurately capture body positions and are currently considered the gold standard for detailed measurement of sedentary behaviors. As a matter of fact, recent (2017) evidence indicates that activPAL™ is more accurate than waist- and wrist-worn accelerometers in objectively measuring sitting and standing activities. Moreover, it is important to not only examine total accumulated sedentary time, as it may not provide all features of sedentary behavior. In that sense, the activPAL also captures data on sedentary breaks and bouts, both of which have been found to influence health outcomes.

Apart from SB, the activPAL also provides accurate estimated times of free-living physical activity intensity categories in adults and adolescents.

Despite these significant improvements in sedentary behavior measurements, there is still a lack of consensus regarding the wear period – in terms of number of days necessary to estimate habitual sedentary patterns and wearing hours – and protocols for data processing. In addition, posture-based devices are usually worn for 24 hours, which is why differentiating between sleep and wakeful lying/sitting is important. Yet, this is out of the scope of accelerometers' algorithms and the truth is empirical accepted waking time identification protocols have not yet been developed. Despite these limitations, there is no doubt that accelerometer devices constitute a valuable tool to measure health-related behaviors in free-living conditions.

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DISCUSSION II

Physical activity, sedentary behavior and cancer

Chair: Antonio Agudo

Participants Anne M. May
Guillermo R. Oviedo
Soraya Casla
Mireia Félez

Questions, comments or concerns

Agudo - **How often did the monitoring devices that you used report data?**

Oviedo - We used Polar brand bracelets, which had to be worn by subjects while they exercised. The bracelet sent information directly to the individual's phone. Once we received the data, we proceeded to its analysis. We, moreover, contacted participants every two to three weeks and gave them feedback on their progress.

Agudo - **What were the results?**

Oviedo - We found no statistically significant improvements in aerobic capacity. The intervention groups maintained balance and improved aerobic capacity a little, whereas the control group decreased balance. We estimate that this may be due to the fact that for the last two weeks of the program, subjects were supposed to follow a home-based program. And they failed –to various degrees- to exercise 6 times a week.

Agudo - **You mentioned it is advisable to break up sitting time. Can accelerometers adequately calculate this, even for very low activity levels?**

Oviedo - Low intensity physical does not necessarily involve sitting. Having accelerometer data of very low activity should not lead us to assume that the individual is sedentary. In order to determine that, we would need extra information.

Agudo - **In spite of that, could we still try to model and assume that they are sedentary if accelerometer records show very low levels of activity?**

Oviedo - If we had been using hip accelerometers, data would have probably been more reliable. However, for our study, subjects were wearing the accelerometer at the wrist. There are, however, other devices, like Active Pal, which we are using for other studies. Measurements are more reliable, since the device is worn attached to the thigh. This constitutes a better approach, for it allows us to know the exact position of the thigh and the number of times that the subject breaks their sedentary time. [Note: the speaker holds no commercial interest with any of the brands named.]

Agudo - **In the past, we have been focusing on recommending physical activity for general health and cancer prevention. It was widely accepted that the recommendations on physical activity were to be met or even exceeded. In all, we don't seem to be operationalizing sedentary behavior. Little has been published and we lack thresholds. Should we aim to incorporate this concept for cancer treatment and prevention?**

Félez - Evidence as to how much sedentary behavior could be detrimental to health is still controversial. The scientific world is not ready yet to precisely determine the threshold. We hope to be able to provide more clear answers in the future but right now, all we can say is "try to minimize the time you spend sitting".

May - I agree with Dr. Félez. We, in the committee for the Dutch guidelines on physical activity, carried out a thorough literature search and could not establish thresholds, either.

Agudo - **How do cancer prevention guidelines differ in Spain, when compared to The Netherlands. What types of programs are individuals offered in Spain and what is it like in The Netherlands?**

Casla - We, at the expert unit at Madrid's Spanish Association against Cancer accept all patients for our free exercise sessions, whatever stage of disease they may be in. There are very few criteria for exclusion. Only patients with specific ecosonogram results, those who cannot walk or remain standing, as well as those with active bone metastases are initially rejected from our program. Of course, they could possibly be exercising under different parameters to ours.

May - In The Netherlands, exercise interventions and access to them greatly differs for the various hospitals. In fact, some offer this service, while others don't. There are in fact many Pphysical therapists who provide this type of programs, but whether patients can o cannot participate usually depends on their medical insurance coverage.

Agudo - **The Clinical Oncology journal established that there is a large base of observational evidence stating that weight control is good for the prognosis of breast cancer. However, there seem to lack randomized controlled trials (RCT). The same is probably true for physical activity and for other types of cancer. Dr. May, do you agree there is a need to invest in RCTs to determine a gold standard?**

May - I know it can be costly but yes, I think oncologists will only be willing to rely on randomized controlled trials. Unfortunately, some of the tests that have been used in observational studies won't be able to be replicated in large studies but, still, RCTs are needed.

Agudo - **What considerations need to be made when designing exercise interventions for non-metastatic or metastatic cancer?**

May - There probably isn't much information yet on metastasis. Focus would probably have to be placed in adjusting intensities and intervention duration, mainly depending on whether the individual is undergoing treatment at that precise time or they are not. The reason for this is that, for most cancers –all except those that are hormonal- patients go from a fixed time of treatment, to a stage without treatment.

Casla - **What are the technical and ethical concerns with regard to control groups which do not receive exercise interventions?**

May - Having control groups which do not receive exercise intervention is a big challenge. Patients tend to enroll in hopes that they will be assigned to the exercise intervention group. But when they don't, they often decide to drop out. Yet another difficulty we face is that those subjects allocated to the control group may start to be active on their own. This has led to us having very high contamination rates in some of our studies. If we turn this into conclusions, it would probably mean that the positive results that we observed in our studies are probably underestimations. In order to avoid this, we are now carrying out a piece of research with a cohort design where people in the control group do not know that they are control. The results we are observing are very interesting, and this time contamination has been dodged.

May - When we —in the Ethics Committee, are evaluating a study protocol, we expect the control group to receive, at least, the program that is being implemented in that particular institution at that particular time, i.e. their usual clinical practice. And we also carefully assess if the research questions is innovative, and to what extent.

Agudo - **What impact does exercise have on lymphocytosis?**

May - What we know is that studies which focused primarily on lymphedema did not show exacerbations of it while subjects were exercising. It should all be monitorized but women are able to do resistance training with no increased risk.

Agudo - **Thank you very much.**

PANEL OF EXPERTS

Antonio Agudo

Head of the Unit of Nutrition and Cancer. Catalan Institute of Oncology (ICO). ICO Coordinator for Onconet.

Antonio Agudo is a physician, with an expertise inn preventive medicine and public health. He graduated in Medicine (MD) at the University of Barcelona (UB), and has a Master of Sciences (MSc) degree in Clinical Epidemiology from the Erasmus University of Rotterdam (The Netherlands). He completed his doctoral training at the Autonomous University of Barcelona (UAB), where he obtained a PhD in Public Health and Methodology of Biomedical Research.

Dr. Agudo started to work in cancer epidemiology conducting case-control studies on lung cancer, mesothelioma, and head and neck cancer. He was involved in the design of and recruitment for the European Investigation into Cancer and Nutrition (EPIC) program, a large multicentric cohort study which was carried out in ten European countries. Since 1999, he is employed at the Catalan Institute of Oncology (ICO), where he currently holds a position as Head of the Unit of Nutrition and Cancer. He is also the coordinator of the EPIC cohort in Spain and the representative of EPIC-Spain at the EPIC Steering Committee, as well as a member of several working groups of EPIC-Europe.

His main research lines include the relationship between environmental carcinogens and genetic susceptibility in gastrointestinal cancers and lung cancer; the role of diet, body composition and physical activity in breast cancer and other hormone-related tumours; and the role of chemical compounds and related biomarkers in the carcinogenic process.

He has collaborated with the International Agency for Research on Cancer (IARC) in the IARC Monographs on the Evaluation of Carcinogenic Risk to Humans, and the IARC Handbooks of Cancer Prevention. He also has served as a WHO Temporary Adviser for the Joint FAO/WHO Expert Committee on Food Additives and Contaminants.

Soraya Casla

Responsible for the Oncologic Physical Exercise Unit. Spanish Association Against Cancer (AECC).

Soraya Casla is Ph.D. in Exercise-Oncology by Technical University of Madrid and she complemented her qualification in research, exercise and physical therapy, cancer biomarkers and exercise and all type of cancer strength protocols around world, respectively in Duke University (USA), University of Alberta (Canada), Rig Hospitalet (Denmark) and Edith Cowan University (Australia).

After that, Soraya was working as Coordinator of exercise programs in oncology in Spanish Breast Cancer Group (GEICAM) until a new challenge was proposed as Exercise-oncology responsible of AECC Madrid. At this moment, Soraya and her team are building and testing the exercise protocols and procedures to spread the exercise oncology to other AECC sites.

Gemma Castaño-Vinyals

Project Manager. Barcelona Institute for Global Health (ISGlobal).

Gemma Castaño Vinyals got a bachelor in Environmental Sciences (2000) from the Universitat Autònoma de Barcelona and did her PhD (2007) at the Universitat Pompeu Fabra within the programme of Health and Life Sciences. During her predoctoral studies, she spent some periods abroad in the University of California San Francisco, University of Cincinnati and at the Institute for Risk Assessment Sciences from Utrecht University.

Her doctoral thesis was based on the association between air pollutants and bladder cancer risk, including studies in molecular epidemiology. She is involved in several projects regarding non-communicable diseases and environmental exposure, specifically working in the multicase-control study including high incidence tumours in Spain (MCC-Spain), in studies on circadian disruption (HORMONIT) and studies on occupational health (OMEGA-NET). In the radiation programme, she is the scientific coordinator of the Mobi-kids study, an international case-control study to examine the potential associations between use of communication devices and other environmental factors and risk of brain tumours; and GERoNiMo project, aiming to close gaps in knowledge on EMF and health and reduce exposures.

Mireia Félez Nóbrega

Research, Innovation and Teaching Unit. Parc Sanitari Sant Joan de Déu-CIBERSAM.

Mireia Felez-Nobrega, PhD, M.Sc, has a Master degree in Neuroscience and a PhD in Cognitive Psychology and Exercise Science. She was a visiting PhD student at Center for Cognitive and Brain Health (Department of Psychology, Northeastern University, USA). She currently works as a postdoctoral researcher at PSJJD. Her main areas on interest are related to lifestyle behaviors (physical activity and sedentary behavior) and their impact on cognitive abilities and overall brain health, health promotion, cognitive neuroscience, and prevention of mental disorders.

Cecilia Galbete

Communication Director. MG Nutrición 3G, S.L.

After her PhD in Biological Sciences at the University of Navarra, Dr. Galbete did a postdoctoral stay for almost five years at the German Institute of Human Nutrition (DIfE, by its acronym in German). During this 10-year working in research she has focus her investigations in the area of Nutritional Epidemiology, putting a special emphasis in the Mediterranean diet and its plausible benefits for health.

PANEL OF EXPERTS

Paula Jakszyn

Researcher atUnit of Nutrition and Cancer. Catalan Institute of Oncology (ICO). WP 1.1 Coordinator for Onconet.

Paula Jakszyn received her Nutrition Degree from Buenos Aires University, Argentina in 1999. In 2002, she moved to Barcelona and joined the Unit of Nutrition and Cancer (UNAC) at the Catalan Institute of Oncology (ICO) to work in the EPIC (European Prospective Investigation into Cancer and Nutrition) study. While working at ICO, she obtained a Masters in Public Health and a PhD from the Pompeu Fabra University. Since then, she has been working at the UNAC as senior investigator, leading different projects in the field of nutritional and cancer epidemiology. Moreover, she is an Associate Professor at the Blanquerna Faculty of Health Sciences (Ramon Llull University), as well as at Pormpeu Fabra University.

Anne M. May

Department of Epidemiology. Julius Center for Health Sciences and Primary Care.

Anne May obtained her Master's degree in Sciences of Human Movement (with distinction) at the Free University in Amsterdam in 2001. From June 2001 to December 2002 she worked as a (Sport-)Nutrition Scientist at Numico Research BV in Wageningen. From 2003 till 2007 she conducted her PhD research on the effects of rehabilitation in cancer patients at the University Medical Center Utrecht, Julius Center for Health Sciences and Primary Care. She obtained her Master of Science degree in Epidemiology at the Netherlands Institute of Health Sciences, Erasmus Medical Center Rotterdam in August 2006.

After completing her PhD, she continued working at the Julius Center. She is currently head of the department of epidemiology and works as an Associate Professor conducting research on physical activity, exercise, obesity and cancer. She is the PI of several ongoing multi-center exercise-oncology RCTs (PACT, PERFECT, UMBRELLA-FIT and PAM). As of 2019, she leads the H2020 funded PREFERABLE project investigating the effects of exercise in patients with metastatic breast cancer.

Guillermo R. Oviedo.

Faculty of Psychology, Education and Sports Sciences. Ramon Llull University.

Guillermo Oviedo graduated with an Education and Sports Sciences degree in Tucumán Argentina (2007). Became a physical education teacher and obtained a Sport and Psycology master degree in the Catholic University del Sacro Cuore (Italy). In 2014 he completed his doctorate in the Ramon Llull University where he is an associate professor. He has published some articles during his career. Research Group on Health, Physical Activity & Sports.

Ana Ramírez de Molina

Deputy Director and Director of the precision nutrition program for cancer. IMDEA Food Institute.

PhD in Molecular Biology by Autonoma University of Madrid (2002, extraordinary recognition), Dr. Ana Ramírez de Molina has developed her scientific career in the field of lipid metabolism, nutrition and cancer. She has worked as an associated researcher in the Translational Oncology Unit CSIC-UAM-La Paz Hospital (Madrid), with long postdoctoral stays at Cancer Research UK Centre for Therapeutics (Royal Marsden Hospital, London) and the Molecular Pathology Division of the Sloan Kettering Cancer Center (New York). She has published more than 60 scientific articles in her research field and is co-inventor of 6 licensed patents in different phases of exploitation. One of her patents promoted the creation of a spin-off company from CSIC in which she was former Director of R&D for more than 3 years, conducting a "first in class" drug to clinical trials for cancer patients. She joined IMDEA Food Institute in 2010, where she leads the Program of Precision Nutrition for Cancer and the Molecular Oncology Group. From 2014 she is the Deputy Director of the Institute, being also the co-director of the Innovation Unit. She has supervised 7 PhD thesis and participated in numerous courses and scientific evaluation panels. In 2002 she was awarded with the prize Young Researchers MSD, in 2017 the International John Kinney Award for her work in molecular nutrition and metabolism, and in 2016 the 8th March distinction from the Community of Madrid as an outstanding woman in Science.

Dora Romaguera

Barcelona Institute for Global Health (ISGlobal); Institut d'Investigació Sanitària Illes Balears (IdISBa); Spanish Biomedical Centre in Physiopathology of Obesity and Nutrition (CIBEROBN).

Dora Romaguera has a Degree in Pharmacy (University of Barcelona), Master in Public Health Nutrition (London School of Hygiene and Tropical Medicine) and a PhD in Human Nutrition (University of the Balearic Islands). She was a postdoctoral researcher at Imperial College London (2007-2011) and in 2012 she returned to the Balearic Islands (IdISBa) with a Ramón y Cajal research contract. Currently she is principal Investigator of the PREDIMED-PLUS project in the Balearic Islands and co-PI of the CIBER Physiopathology of Obesity and Nutrition (CIBER-OBN). She is also a collaborating researcher at Imperial College London (United Kingdom) and at ISGlobal (Barcelona). Her research line is focused on the study of dietary patterns as determinants of occurrence of chronic diseases (obesity, diabetes, cancer, cardiovascular disease) in various epidemiological studies.

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