Title:

DianaWeb: before and after study online based participatory research to test whether lifestyle and diet are able to reduce the incidence of recurrences (local, remote) or secondary cancers, improve prognosis and survival of breast cancer

NCT:

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ABSTRACT
DianaWeb is a community-based participatory research (BPCR) offered to Italian breast cancer patients. The aim of the study is the evaluation of effectiveness of a lifestyle and nutrition intervention to improve the prognosis. DianaWeb study utilizes an interactive website (http://www.dianaweb.org/) to monitor patient life-style, and to obtain clinical, pathological and anthropometric data (height, body weight, waist circumference and blood pressure). Detailed instructions were provided for measuring at home. The website contains theoretical and practical advice to encourage women to follow healthy lifestyles and nutrition, and the indications emerging from research for women diagnosed with breast cancer (BC).
DianaWeb study intends to recruit 50.000 women with BC diagnosis.

Impact
The investigators intend to carry out a participatory research on the influence of lifestyle after cancer diagnosis on the risk of recurrence. The investigators intend wake available to Breast Cancer (BC) patients/survivors' evidence-based information on the effects of lifestyle on quality of life and prognosis and to invite and help them to adopt potentially preventive sustainable lifestyle changes. To improve the prognosis, the investigators will base the recommendations on the European Code Against Cancer (ECAC), on the World Cancer Research Fund (WCRF), Continuous Update Project (CUP) 2018 specific recommendations to BC survivors, and on Mediterranean diet. As for the prevention of side effect of treatments there is no definitive evidence, but the daily exercise seem for reducing menopausal symptoms and osteoporosis, while regular consumption of food with diuretic effect for arthralgia due to aromatase inhibitors(1). The investigators are aware that the path for creating data to implementing evidence in routine practice is long and arduous. The investigators are confident, however, that engaging participants in the research process will enable many of participants to implement evidence-based practices in their everyday life. The investigators, together with computer programmers, have developed an interactive website to build a large cohort of Breast Cancer survivors and to follow up participants about the impact of lifestyles and nutrition on recurrences, incidence of second Breast Cancer, metastasis, other cancers and other chronic diseases. The investigators will also monitor the prevalence of side effects of treatments (the investigators will focus on menopausal symptoms, arthralgia, osteoporosis and bone fractures). Observational epidemiological studies have consistently shown that sedentary lifestyle, overweight, metabolic syndrome, chronic inflammatory status, high glycemia and insulinemia, and a few specific dietary factors (low fibre and high saturated fat) are associated with poor Breast Cancer specific survival. There is ample room for reducing recurrences and cancer progression through lifestyles and nutrition. All these factors are clearly modifiable, but there is uncertainty, however, over whether voluntarily changing these factors after Breast Cancer diagnosis improve prognosis. In a 5 years' time the study after recruitment, the investigators are expected to confirm the prognostic role of this factors**.**

Rationale and feasibility
In Italy every year over 50.000 women develop breast cancer. The country is fairly well equipped with excellent Breast Cancer units and in the second decade of the XXI century 5-year breast cancer net survival reached 88%, a performance similar to the best European countries. (2). Over 750.000 Italian women live with a previous diagnosis of breast cancer (http://www.epicentro.iss.it/temi/tumori/registri.asp). Many of them with some form of cancer treatment and suffer from feeling left alone, fear of cancer recurrence and not receiving enough

information and guidance after treatment: on prognosis, side effects of treatment, lifestyle strategies to help preventing side effects of treatments, recurrences and new primaries.
Many survivors integrate adjuvant treatment with complementary treatments without scientific proof of efficacy, even with folk treatments that might increase the risk of recurrences.

Young women undergoing adjuvant BreastCancer therapy experience a heavy impairment in important quality of life domains (anxiety, depression, loss or sexual desire, weight gain)(3). The great majority of women under hormonal treatment experience an increase in the prevalence of menopausal symptoms (4) and have sexual dysfunction that is distressing and difficult to resolve (5). In postmenopausal survivors with aromatase inhibitor-induced arthralgia the intensity of pain is associated with fear of recurrence (6).
Investigating whether lifestyle factors affect Breast Cancer patients' survival is a relatively new area of research, but there is growing evidence that the effect of modifiable anthropometric and metabolic factors may be of the same order of magnitude than the effect of the usual clinic-pathological risk factors (hormonal receptors expression, Ki67, etc).
Epidemiological evidence, even if based only on observational studies, suggest that lifestyle modification, including physical exercise and dietary habits, might have a strong impact on breast cancer patients overall and specific survival.
Observational cohort studies (https://www.wcrf.org/.../Breast-Cancer-Survivors-2014-Report.p...), for instance, have shown that:
1) overweight and obesity are associated with 10-20% increased risk of recurrences;
2) physical activity after diagnosis is associated with 30-40% reduction of recurrences and mortality;
3) soy food consumption is associated with lower risk
4) saturated fat consumption is associated with higher risk
5) higher consumption of foods containing fibre after diagnosis of primary breast cancer reduces risk of all-cause mortality

Epidemiological studies have shown that modifiable lifestyle factors and biomarkers affecting the occurrence of BC also affect BC prognosis: obesity, metabolic syndrome (conventionally defined by the presence of three or more of the following risk factors: abdominal obesity, high blood pression, hyperglycaemia, hypertriglyceridemia and low HDL cholesterol - *http://www.idf.org/metabolic-syndrome*), sedentary lifestyle, high fat intake, alcohol consumption, high fasting glucose plasma levels (independently of the presence of metabolic syndrome), subclinical chronic inflammation, high plasma insulin and sex hormone levels, low sex hormone-binding protein(7;8).
Obesity is associated with a higher incidence of locally advanced disease, and worse prognosis after diagnosis, both before and after menopause (9-11)
The obesity is also related to poor quality of life and increased risk of developing comorbid conditions(12). Weight gain during and after cancer treatment also increases the risk of recurrence(13;14). Both chemotherapy and, to a lesser extent, tamoxifen and nonsteroidal aromatase inhibitors have been associated with weight gain(15;16). Among the potential mechanisms behind the association between weight gain, obesity, and breast cancer recurrence and mortality there is an increased conversion of androgens to oestrogens in peripheral adipose tissue and increased circulating levels of insulin, insulin-like growth factors (IGFs), and leptins, that promote tumour cell proliferation(12). Current breast cancer treatments can have a negative impact on cardiovascular health (e.g. left ventricular dysfunction, accelerated CVD), and for women with pre-existing CVD, this might influence cancer treatment decisions by both the patient and the

provider. Improvements in early detection and treatment of breast cancer have led to an increasing number of breast cancer survivors who are at risk of long-term cardiac complications from cancer treatments. For older women, CVD poses a greater mortality threat than breast cancer itself. Ideal breast cancer outcomes are reliant on coexisting cardiovascular health along the entire journey of breast cancer treatment. During breast cancer treatment, surveillance, prevention, and secondary management of cardiotoxicity are crucial; thereafter, long-term post-treatment monitoring for late cardiotoxicity and even non–treatment-related development of CVD is essential. Breast cancer and CVD share a number of common risk factors. Cardiovascular clinical care and research have focused on risk factors for >60 years, because it is believed that 80% of CVD can be prevented through risk factor modifications such as promoting a healthy diet, physical activity, and a healthy weight; abstinence from tobacco; blood pressure control; diabetes mellitus management; and a good lipid profile. In women with breast cancer, treatment and the disease itself contribute to weight gain and to decreases in physical activity. Furthermore, it has been reported that cardiopulmonary function in patients with breast cancer improves with exercise, and regular exercise results in an improvement in quality of life. Although the usefulness of exercise to prevent CVD in patients with breast cancer has not been evaluated in randomized trials, it is reasonable to follow the recommendations for physical activity, that is, moderate-intensity aerobic physical activity of ≥30 minutes 5 days each week (47).

High fasting glycaemia, even within the normal range, is associated with higher incidence of recurrences(17;18). Also the metabolic syndrome is associated with increased risk of BC recurrences in patients diagnosed both before and after menopause(19). After adjustment for stage and hormonal receptors expression, BC patients with metabolic syndrome, have 2.2 higher risk of developing distant metastasis than patients without any metabolic syndrome trait. Metabolic syndrome, also called insulin-resistance syndrome, is usually associated with high insulin and testosterone levels, and with subclinical chronic inflammation. Independently of the presence of metabolic syndrome several studies have shown that BC patients with high testosterone levels have worst prognosis(20;21). Insulin stimulates the synthesis of testosterone in the ovary, and high plasma insulin levels are associated with increased risk of recurrences(22). Insulin also increases the bioavailability of IGF-I (through the promotion of its liver synthesis and the inhibition of the synthesis of its binding proteins IGFBP-I) associated with prognosis in women with breast cancer(23). Also high plasma levels of C-Reactive Protein, even within the normal range, are associated with increased risk of recurrence(24-26) and shorter survival in patients with advanced BC(27). It seems reasonable to hypothesize that a comprehensive lifestyle modification, based on AICR/WCRF (report 2007-2018 and report on Diet, nutrition, physical activity and Breast Cancer Survivors) and ECAC (European Code Against Cancer 2014) recommendations, consistent with traditional Mediterranean diet, may reduce the risk of recurrences and improve prognosis. Studies have shown that dietary intervention recommending a modified Mediterranean diet can reduce biological markers of breast cancer risk and recurrences: glycemia, insulinemia, IGF-I bioavailability(28;29) and chronic inflammatory status(30) (*https://www.researchgate.net/publication/264554956_The_Dietary_Inflammatory_Index_A_New_Tool_for_Assessing_Diet_Quality_Based_on_Inflammator*). The Western dietary pattern, high in refined grains, sugars, simple carbohydrates, red meat, and high-fat dairy products, increases the levels of pro-inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6)(31) In contrast, a traditional Mediterranean diet with consumption of whole grains cereals, pulses, vegetables, fruits, fish, nuts and extravergin olive oil is associated with lower levels of pro-inflammatory biomarkers, including endothelial adhesion molecules, CRP, and tumor necrosis-α (TNF-α)(32). Physical exercise also seems to reduce chronic inflammation(33). Furthermore several

studies have suggested a decrease of BC recurrence and death in patients who exercise at least 30 min /day(34-36).
These information's are not currently available to patients and are not yet included in oncology protocols. With a few exceptions, physicians too are not aware of these scientific results and are not yet culturally prepared for life-style prescriptions. DianaWeb does not interfere with prescribed oncological treatments, on the contrary it recommends participants to follow the oncologist's prescriptions, but the study wants avoid the access to non-scientifically correct information that could worsen the prognosis or change the quality of life or their health.
There is increasing interest, in the research community, in the community-based participatory research (CBPR). Its relevance often is relegated to the "right end" (i.e. delivery and dissemination) of the research continuum, but may contribute also to asking the right questions, in particular the more relevant questions for the patients, to improve compliance, and to ensure that basic science research findings affect cancer outcomes in materially important ways especially for large communities that communicate through modern media as websites(37;38).

Long-term DianaWeb aims:
1) decrease the rate of recurrences, the incidence of second breast cancers and improve prognosis through lifestyle changes aiming at reducing body weight and waist circumference in overweight patients, and improving circulating markers of high risk (including chronic inflammation markers, a HOMA index, fasting plasma insulin , glucose and other parameters of metabolic syndrome)
2) improving the compliance AICR/WCRF recommendations for breast cancer patients
Short time DianaWeb aims:
a) improving the quality life of BC patients/survivors
b) test the hypothesis that adherence to ECAC and WCRF recommendations decrease anthropometric and biochemical risk factors for BC recurrence and mortality.
Over the past 20 years or so, cancer patients who choose to become active have focused increasingly on advocacy: campaigning for greater public awareness, lobbying for improvements in patient care, and educating patients about their diseases and treatment options. The investigators will encourage DIANAweb participants to organise meetings, conferences, kitchen classes, walking groups, exchange of information on recipes and on their strategy to comply with the recommendations.
Through continuous information (theoretic and practice) about lifestyles the investigators intend to test if decreased risk factors improve the prognosis.

Experimental design and methodology: We will use a participatory research (CBPR) approach which has been defined as 'a process that involves community members or recipients of interventions in all phases of the research process'(39). Over the past two decades, there has been an increasing presence of community-based research and participatory methods in health research, and involving patients at various stages of the research process has been shown to improve the ethical nature of research and the appropriateness of methods(40). The involvement of cancer patients in conducting cancer research has been discussed as a means of developing the cancer care system to become more responsive to the needs of people living with cancer(41). CBPR is founded on the principles of power sharing, participant voice, respect, reciprocity, and mutual benefit. CBPR does not mean only the involvement of patients/survivors in the data collection process, but also in the fundamental aspects of research question formation, research design, and instrument development and/or selection. By ensuring clarity of the items on questionnaires and web-based instruments, we can reduce the degree of error in survey responses and increase the reliability of the instrumentation.

A few studies have reported on the benefits of including people living with cancer in the selection of domains and to assess the comprehensiveness, ease of understanding, feasibility of items, and survey implementation issues(42). Sharing the ownership of the research process between researchers and participant members also means to allow participants to discuss, challenge, or reject the opinions of investigators and to withdraw their participation if they believe that it was not in the best interest of survivors. Participants will also be given an opportunity to comment on the research findings to confirm or disconfirm their credibility and to discuss the relevance of the key domains that had been obtained from the interview data. This level of active engagement in the research process is an opportunity to regain a sense of control of an otherwise disempowering life trajectory by contributing to research that may benefit others who are diagnosed with BC.

DianaWeb represents a collaborative effort between participants and research institutions to determine if a specified change in lifestyle would result in improved outcome like quality of life or survival using a dedicated website (www.dianaweb.org). We intend to build a large cohort of at least 50.000 women with previous diagnosis of BC (any type and stage) with access to the internet, recruited through social networks and multimedia campaigns, and to monitor participants' lifestyle and health status over time, to provide them with evidence-based recommendations and tips for sustainable changes, to analyse clinical outcomes as a function of baseline risk factors and subsequent changes, and to share with them methodologies and results. Participants will be followed using an online platform connected to their email address. They can change their email address, phone number, or postal address at any time on the DianaWeb website. Newsletters and alerts about new questionnaires will be sent by email. In case of an “undelivered email” problem, participants will be contacted by telephone and then by regular mail. The DianaWeb study is conducted according to the Declaration of Helsinki guidelines and has been approved by the Fondazione IRCCS Istituto Nazionale dei Tumori di Milano ethical committee. Informed consent is obtained by mail from each participant. At inclusion, participants complete a set of questionnaires related to sociodemographic and lifestyle characteristics (date of birth, occupation, educational level, smoking status, sleep disturbances), anthropometry (height, weight, waist circumference, and blood pressure, all measured according specific instructions), validated questionnaires on dietary intakes and physical activity (see below), performance status, medical history before the diagnosis of BC (personal and family history of diseases, drug use including hormonal treatment for menopause, oral contraception, menopausal status, weight change after chemotherapy and cardiovascular health).

Anthropometric measurements and are then repeated every 6 months. Follow-up questionnaire on health status, performance status, drug use and hematochemical values are repeated every year (participants are invited to ask their general practitioner to include metabolic syndrome parameters and CRP at any time they have to do a blood test).

As for diet, participants are invited to complete every six months a modified Mediet (includes 32 items) questionnaire on Mediterranean diet(44) and a series of web based 24 hour recall questionnaires (every 30 days) that are then averaged to describe the usual dietary intake and the dietary changes over time. Participants use the dedicated website interface to declare all food and drinks consumed during a 24 hours period for each of the three main meals (breakfast, lunch, dinner) and any other eating occasion. The present 24h recall includes 46 food items, but, based on indications of the participants we intend to improve the specificity of information with additional short questionnaires, including questions on portion size of relevant items using photographs or usual containers. Furthermore participants are invited to complete every six months a International Physical Activity Questionnaire developed as an instrument for cross-national monitoring of physical activity and inactivity(45). As for clinical and pathological information participants are requested to

mail copy of discharge diagnosis and histological reports of primary BC, of any subsequent BC events and of cardiovascular health.
The intervention consists to provide patients/survivors with evidence-based recommendations and to promote improved nutrition and physical activity through videos and lectures available on the website (theoretical lectures on preventive strategies, and practical videos on cooking techniques and specific physical exercises). To allow the patients/survivors to contact us, a section for questions and proposals has been created with buttons to indicate with whom the patient wants to interact (principal investigator, administrator, medical doctor, nutritionist, biologist, exercise specialist), or the other participating women. The maximum number of characters allowed is 500. The frequently asked questions (FAQs) section has been created in the home page to be progressively implemented. When the participant completes all the steps, she will receive a free phone number for emergencies, active 2 hours a day for 5 days a week. The website contains a section to exchange information on recipes and on strategy to comply with the recommendations, and an agenda to inform on meetings, conferences, kitchen classes, walking groups, organised by the participant themselves.
We are developed specific recommendations for women with different characteristics (lean, overweight, obese, active/sedentary lifestyle, dysmetabolic patients, patients with mutations in breast cancer genes (ie, BRCA1 and BRCA2), patients under chemotherapy, hormonal therapy or radiotherapy, patients suffering from joint pain, osteoporosis, menopausal symptoms, cardiovascular toxicity and other symptoms related to the side effects of treatments. We intend to improve the specificity of information with additional short questionnaires, including questions on portion size of relevant items using photographs or usual container in the kitchen and develop a mHealth applications for smartphone to facilitated a more efficient and timely exchange on information.
Actually participants criticised the request of filling by mail 24h dietary recall forms because they do not access to their computer every day
Waiting to complete the website, the participants have created a chat with "Whatsapp" supervised by the researchers. This allows to collect in real time the needs and expectations that women have placed on the project but also to intervene quickly on any mistakes on understanding the recommendations into practice and to avoid non-scientific information.

Preliminary data: In previous studies we have shown that metabolic syndrome dramatically increases the risk of developing metastasis in women with early stage BC (2,2 higher risk respect to women without any trait of metabolic syndrome(19) and that adherence to AICR/WCRF is associated with significantly lower prevalence of metabolic syndrome (one third in highly adherent women with respect to those with poor adherence(49). Given these preliminary data, our main interest in the present study proposal is to analyse if adherence to AICR/WCRF recommendations will reduce the risk of metastasis**.** To test the feasibility of the project we have launched a pilot DianaWeb study in which we recruited 1024 BC patients/survivors, mainly recruited trough a patients' association and word-of-mouth waiting other 1231 participants have completed registration but have not yet sent the informed consent. Average age was 57 (±8.56), only 5% was older than 69, 42% had been treated with chemotherapy, 65% of whom gained weight during chemotherapy (4,6 kg ±3.7 on average). After exclusion of 138 women diagnosed more than 10 year before recruitment, TNM stage hormonal receptor status, her2, grade, and Ki67 was available for all women. At the baseline average blood tests values were: glycemia 89.0 (±11.31) mg/dl, triglycerides 90.28 (±45.71) mg/dl, total cholesterol 200.0 (±38.86) mg/dl, LDL 118.71 (±41.58) mg/dl, HDL 67.10 (±28.52) mg/dl. All participants have sent self measured anthropometrics data. Average BMI was 23.44 (±7.26), waist circumference was 81.23 (±11.33) cm, systolic blood pressure was 113.79 (± 15.76) and diastolic blood pressure was 72.32 (±10.51).

In the first year we have registered in the website: 26875 accesses to the reserved area, 23106 forms completed and sent, 822643 items answered.
In the pilot phase we carried out anthropometric examination of a convenience sample of 100 women to check the validity of household self-measurements. As expected, home measured blood pressure (BP) was lower than when measured in the ambulatory, according to ESH/ESC guidelines 2013 for the management of arterial hypertension (46). Height and weight were correctly measured. As for waist circumference we discovered that the participants did not properly follow the instructions, which have now been made more clear. We will continue to convene women (about 1000) to monitor the different of home and ambulatory anthropometric measurements, and to check their comprehension of questionnaires.

Statistical analysis:
In the full-scale study, we expect to reach over 50,000 patients to eventually test the prognostic effect of lifestyle and modification of lifestyle both in the early and advanced stages of disease, and in relevant subgroups of 1–2000 patients (e.g. triple negative BC), with statistical power of the order of 85–95% for a 25–33% risk reduction in the upper quintile of compliance (e.g. adherence to ECAC and AICR/WCRF recommendations, adherence to Mediterranean diet, weight and WC reduction of overweight participants, reduction in metabolic syndrome parameters). In 5 years', time we expect to recruit 25,000 women. Assuming an incidence of new breast events (local recurrence or metastases) of the order of 1.5 to 2% each year and an average of three years of follow-up, the hypothesis of a risk reduction of 30% of relapses in top quintile of adhesion to the recommendations with respect to the lowest quintile, we will have a power of 95% to observe a significant difference (P> 0.05). In the Diana-5 study, a randomised controlled trial aimed at evaluating the effectiveness of diet modification in reducing BC recurrences(48), we have observed a marked improvement in metabolic parameters associated with cancer progression in the intervention group (e.g. patients who participated monthly in kitchen classes and physical exercise sessions). Moreover, we have also observed a significant reduction in several metabolic syndrome parameters (e.g. body weight, waist circumference, serum cholesterol and triglycerides) in patients enrolled in the control group who have received only written lifestyle recommendations the same that we are proposing in the DianaWeb study. Meeting five recommendations versus meeting none or only one was significantly associated with a 57% lower MetS prevalence (95% CI 0.35-0.73). Previous trials have shown a 30% reduction of MetS prevalence after a year of recommended Mediterranean diet and a 60% reduction after two years (49). The group of patients/survivors experiencing new BC events during follow-up will be compared with the group of those without relapse with respect to baseline characteristics, to changes in lifestyle score, and to changes in metabolic syndrome after enrolment (e.g. during the first year of observation). Dietary and physical activity exposure will be engineered summing up the information collected through the 24h recalls, and scores of adherence to AIRC/WCRF will be produced with the methodology described in Bruno et al.(49) We will use a Wicoxon rank-sum test for continuous variables and a chi-square test for categorical variables. To estimate the risk of relapse or progression we will use the multivariate Cox proportional hazard model, with time from enrolment to the next relapse as outcome. We will adjust for age, performance status, time interval between BC diagnosis and enrolment, pathological variables (TNM, hormonal receptor status, grade and Ki67), treatment (chemotherapy, hormonal therapy), compliance with adjuvant treatment, and when relevant, BMI, smoking, alcohol consumption and other potential confounders.

Research plan
PHASE I

Creation of an improved interactive web site.
The home page, visible to everyone, contains:

- a summary of the project in plain language and instructions on how to participate
- the project's logo and the logos and the links to other websites (other participating centres and supporters)
- a section dedicated to the European Code against Cancer, WCRF recommendations and other relevant scientific evidence of public interest about lifestyle and cancer
- a calendar of initiatives of interest (e.g. conferences, TV broadcasts, etc.)
- a link to log into the project and to access participants space

The home page, only visible to participants, contains:

- Acknowledgment for joining the study
- A menu with the datasheet to fill in: an anthropometry form (with instructions on how to make the measurements at home of height, weight, waist circumference, blood pressure), a medical history questionnaire (including side effects of treatments and cardiovascular health), a form on results of the last routine blood tests, a 24h food frequency recall, Mediterranean diet (Mediet) and physical exercise questionnaires, forms on other relevant personal and lifestyle information,
- Each year participants will find a query about health status (any changes about your state of health? YES/NO. If the answer is YES, a message will appear asking to the patient to send by mail the documentation on the diagnosis) and performance status.
- A calendar of support activities organized by the project or by participants
- "News" on relevant scientific literature results.
- Kitchen recipes, prevention tips (file and video) and reminders on physical activity
- A phone number for emergencies, active 2 hours a day for 5 days a week

Aspect to be implemented **(Milestone 1):**

- A Frequently Asked Question section
- Chat
- Graphical display of personal anthropometric and metabolic parameters, with alert for values out of the recommended range and specific recommendations
- Alert will remind the patient to complete the forms in case of missing information and a smiling face will appear each time the patient will comply.
- Development of a Health App to facilitate participation and ease timely completion of questionnaires.
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PHASE II, Recruitment

Phase II is dedicated to the recruitment and use different channels: press releases, public lectures, handouts to be distributed through pharmacies, doctors, cancer centres, patients' associations, word of mouth etc.

PHASE III, Participation

- Patients interested in joining the project will be asked to fill in a personal data sheet with valid email address and a mobile phone number.
- An Information Consent (IC) form will be sent by email to the participants together with detailed explanation of the project.
- Once the signed IC is received (by mail or certified email) together with a copy of the identity card, the hospital discharge letter reporting the diagnosis of BC and the histology report, an ID and Password will be sent back to the patient in order to allow her to access the project.

- If the women need more information about the project can write an e-mail to the reference centre or call the phone numbers listed on the and speak with researchers.
- Once the patient will access with her ID and PW, she will be assigned a personal study number and all her forms will automatically report the personal code.
- The PDF of the signed IC will be stored in a protected folder, and the paper sheets will be stored in a locked cabinet. Clinical data will be entered into the database (TMN, GRADING, RECEPTOR-ER, PGR, ErbB2-, p53, Ki67, date of the first surgery, type of treatment, date and type of recurrences). An alert will remind the patient to complete the forms in case of missing information and a smiling face will appear each time the patient will succeed.
- To allow the patient to contact us, a section for questions and proposals will be created.
- There will be buttons to indicate with whom the patient wants to interact (P.I., administrator, medical doctor, nutritionist, biologist, exercise specialist), or the other participating women. The maximum number of characters allowed will be 500.
- Specific dietary and exercise counselling will be offered to patients under chemotherapy, with hypertension, hyperglycaemia, diabetes, dyslipidaemia, heart diseases, osteoporosis, liver steatosis, chronic inflammation.
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PHASE IV, Statistical analysis and Publication

- Study monitoring with yearly descriptive statistics on recruitment and completion of forms and questionnaires.
- Cross-sectional analyses on the relationship between lifestyle factors and anthropometric and metabolic parameters (**Milestone 2**)
- Longitudinal analyses of changes in lifestyle and anthropometric and metabolic parameters changes (**Milestone 3**)
- Longitudinal analyses of the effect of changes in lifestyle, anthropometric and metabolic parameters, on prognosis. (**Milestone 4**)

Mlilestones:

Risk Assessment and contingency plans

DianaWeb does not interfere with prescribed oncological treatments; rather, it recommends participants to follow the prescriptions that they have received.

Given that in the DianaWeb study the greater part of the contact with patients will be through the website, the study design could be prone to high dropout rates of participants. The Pilot phase, however, suggested that participants are willing to continue to receive and provide information.

Another limitation is that we will use a food and physical activity 24 hours recall and Mediet that depends on the respondent's full cooperation. On the advice of the same participants the questionnaires will be administered more often but in shorter form and the 24 hours recall will be visible only one day to avoid that the participants chose to fill after having modified her diet to show that they are compliant.

However, diet and physical activity history will be taken regularly every 3 months and, as such, should give more valid estimates of patients' habits.

Finally, since participation is limited to women who have an email address, our findings may not necessarily reflect the overall situation of BC survivors. In fact, the inability to use internet might reduce the participation of older patients. For this purpose, we intend to increase the number of collaborating centres where to create "help internet points" for web-illiterate women.

GANTT CHART

	Improvement of interactive web site
	Development of a mHhealth App
	Inserting news on relevant scientific literature results, kitchen recipes, prevention tips (file and video) etc.
	Recruitment
	Data collection
	Statistical analysis
	Publications

Q=quarter

1° year				2° year				3° year				4° year				5° year			
1° Q	2° Q	3° Q	4° Q	1° Q	2° Q	3° Q	4° Q	1° Q	2° Q	3° Q	4° Q	1° Q	2° Q	3° Q	4° Q	1° Q	2° Q	3° Q	4° Q

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