Community-based participatory research to improve life quality and clinical outcomes of breast cancer patients (DianaWeb in Umbria pilot study)

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Community-based participatory research to improve life quality and clinical outcomes of breast cancer patients (DianaWeb in Umbria pilot study)

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Keywords: Breast cancer; Prevention; Community-based participatory research; Life-style prescriptions.
Abstract

Introduction: Breast cancer (BC) is the most frequent cancer in Europe and the International Agency for Research on Cancer (IARC) has estimated a number of 464,000 incident cases per year. Survival among BC patients has increased in the last decades and the estimated 5-year relative survival rate is 82% for patients diagnosed in 2000-2007. There is growing evidence that lifestyle (such as a diet based on Mediterranean principles associated with moderate physical activity) may influence prognosis of BC, but only a few epidemiological studies have investigated the role of diet in BC recurrence and metastasis. Furthermore, these information are not currently available to patients and are not yet included in oncology protocols.

Methods and analysis: DianaWeb is a community-based participatory research dedicated to BC patients and represents a collaborative effort between participants and research institutions to determine if a specified change in lifestyle would result in improved outcomes in terms of quality of life or survival. The aim of the study is to recruit a large number of participants, to monitor their life-style and health status over time, to provide them tips to encourage sustainable changes, analyze clinical outcomes as a function of baseline risk factors and subsequent changes, and to share with patients methodologies and results. DianaWeb utilizes a specific interactive website (http://www.dianaweb.org/). In this paper we describe the pilot study, namely DianaWeb in Umbria.

Ethics and dissemination: DianaWeb does not interfere with prescribed oncological treatments, on the contrary, it recommends participants to follow the prescriptions that they have received. The results obtained will be used to plan guidelines for nutrition and physical activity for BC patients. The pilot study was approved by the local Ethics Committee of the University of Perugia, ref. number: 2015-002, and is supported by Fondazione Cassa di Risparmio di Perugia, grant number: 2013.0185 021.
Strengths and limitations of this study:

Strengths

- DianaWeb in Umbria study will be the first community-based participatory research offered to breast cancer patients, whatever the clinical stage of their disease.
- This study represents a collaborative effort between participants and research institutions, to determine if a specified change, e.g. in lifestyle, would result in improved outcome, e.g. quality of life or survival.
- DianaWeb utilizes a specific interactive website (http://www.dianaweb.org/), and, with very few exceptions, all the communications are done through the web.
- This study will be coordinated by a research centre with experience in conducting preventive trials.

Limitations

- Study participants could be influenced from their ability in manage internet; this might reduce the participation of older patients.
- The sample size of DianaWeb in Umbria pilot study (500 women with breast cancer) is small, but it is sufficient to test procedure adequacy for formalizing the design of a definitive trial: the full study is intended to recruit over 50,000 patients in Italy.
INTRODUCTION

Breast cancer (BC) is the most frequent cancer among the European population. The International Agency for Research on Cancer (IARC) estimated a number of 464,000 incident cases per year in Europe, more than colorectal cancer (447,000), prostate cancer (417,000) and lung cancer (410,000). In Italy the annual age-standardized BC incidence is 118/100,000 and it is still increasing [1].

Patients’ survival increased in the last decades and the prevalence of women with previous BC experience is rocketing, being presently of the order of 4 millions in Europe and 500 thousand in Italy. The EUROCARE-5 project estimated that European BC patients’ 5-year relative survival (i.e. survival in absence of non-BC deaths) was 82% for patients diagnosed in 2000-2007 [2].

Investigating whether lifestyle factors affect BC patients’ survival is a relatively new area of research, but there is growing evidence that the effect of lifestyle may be of the same order of magnitude than the effect of the usual clinical-pathological risk factors (TNM classification, hormonal receptors expression, Ki67). In fact, epidemiological studies have shown that the occurrence and prognosis of BC are affected by modifiable lifestyle factors and biomarkers like obesity, metabolic syndrome (conventionally defined by the presence of three or more of the following risk factors: abdominal obesity, hypertension, hyperglycemia, high triglycerides or low HDL cholesterol), sedentary lifestyle, high fat intake, alcohol consumption, high fasting glucose plasma levels, subclinical chronic inflammation, high plasma insulin and sex hormone levels, low sex hormone-binding protein [3 4].

Obesity is an independent risk factor for postmenopausal BC and, in particular, for estrogen receptor (ER)-positive/progesterone receptor (PR)-positive BC. Moreover, obesity is associated with worse prognosis, both before and after menopause [5]. The obesity is also related to poor quality of life and increased risk of developing comorbid conditions [6]. Both chemotherapy and, to a lesser extent, tamoxifen and nonsteroidal aromatase inhibitors have been associated with weight gain [7]. Moreover, weight gain during and after cancer treatment has been reported to increases the risk of recurrences [8].

Among the potential mechanisms behind the association between weight gain, obesity, and recurrence and mortality of breast cancer, there is an increased conversion of androgens to estrogens in peripheral adipose tissue and increased circulating levels of insulin, insulin-like growth factors (IGFs), and leptins, that promote tumor cell proliferation [9].

It has been shown that high fasting glycaemia, even within the normal range, is associated with a significantly increased risk of BC [10 11] and more recently that, in BC patients, high glycemic levels are associated with higher incidence of recurrences [12 13].
Also metabolic syndrome is associated with increased risk of BC in postmenopausal women [14], and with BC recurrences in patients diagnosed both before and after menopause [15]. After adjustment for tumor stage and hormonal receptors expression, BC patients with metabolic syndrome have a 2.2-fold higher risk of developing distant metastasis than patients without any metabolic syndrome trait. Metabolic 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 high plasma testosterone levels are associated with BC incidence [16] and that BC patients with high testosterone levels have worst prognosis [17-18]. Insulin stimulates the synthesis of testosterone in the ovary, and high plasma insulin levels are associated with both increased BC incidence [19] and increased risk of recurrences [20]. 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 IGFBP1 and IGFBP2), and bioavailable IGF-1 is associated with both BC incidence [21] and prognosis [22]. Also high plasma levels of C-reactive protein, even within the normal range, are associated with increased incidence [23], increased risk of recurrence [24-26], and shorter survival [27] in patients with advanced BC.

All these factors can be modified favorably through adopting a diet inspired to the traditional Mediterranean Diet and to the European Code Against Cancer (ECAC), the latter including recommendations on diet and on physical exercise of moderate intensity. The ECAC recommends to eat plenty of whole grain cereals, pulses, vegetables and fruit, to avoid sugared drinks and processed meat, to limit red meat, alcoholic beverages and calorie dense food, which is basically the traditional Mediterranean Diet. The analysis of prospective cohort studies suggested that a high score of adherence to the ECAC is associated with 30-50% lower incidence of BC [28-29], and several studies have suggested a decrease of BC recurrence and death in patients who exercise at least 30 min /day [30-32].

These information are not currently available to patients and are not yet included in oncology protocols. With a few exceptions, too physicians are not aware of these scientific results and are not yet culturally prepared for life-style prescriptions.

DianaWeb is a community-based participatory research (CBPR) offered to BC patients, whatever the clinical stage of their disease. There is increasing interest in the CBPR defined by Minkler and Wallerstein [33] as “a process that involves community members or recipients of interventions in all phases of the research process”. Therefore, DianaWeb represents a collaborative effort between participants and research institutions to determine if a specified change, e.g. in lifestyle, would result in improved outcome, e.g. quality of life or survival.
The basic scientific strategy in the DianaWeb study is to recruit a large number of participants, to monitor participants’ life-style and health status over time, to provide them with evidence based recommendations and tips for sustainable changes, to analyze clinical outcomes as a function of baseline risk factors and subsequent changes, and to share with them methodologies and results.

DianaWeb will utilize a specific interactive website, and, with very few exceptions, all the communications between participants, and between participants and the research team, will be through the web.

In this paper we describe the pilot study (namely DianaWeb in Umbria), aimed at recruiting at least 500 patients in Central Italy (Umbria and bordering Regions). The full study is intended to recruit over 50,000 patients in Italy.

**METHODS**

**Study hypothesis and aims**

We hypothesize that an interactive CBPR may increase patients’ compliance with lifestyle recommendations (with respect to usual face to face or leaflet based recommendations) and significantly decrease BC recurrence risk factors and BC mortality.

Prevention of BC recurrences with low cost technologies, easily available to everybody, is a priority for both public health and public finances. Informing about the major modifiable risk factors effecting the progression of BC and metastatic diffusion, and about how to reduce their impact, may improve prognosis and prolong life also in women with advanced disease.

Offering high-quality evidence-based preventive information to BC patients we will avoid the risk that they become prey of “alternative” medicines that may induce them to decline evidence based treatments.

The DianaWeb aims are: (1) to build a cohort of women with a previous diagnosis of BC, and willing to actively participate in the project; (2) to propose a nutritional switch towards a diet that is poor in refined carbohydrates, fats and animal proteins, and rich in unrefined cereals, pulses and other vegetable foods, according to the ECAC guidelines; (3) to promote regular physical activity of moderate intensity; (4) to monitor the change over time of dietary habits, exercise, body weight, and the prevalence of metabolic syndrome parameters (including markers of chronic inflammation and of insulin resistance); (5) to monitor the occurrence of new BC related to clinical events, and quality of life of the study participants; (6) to test the hypothesis that the participants who succeed to
improve their pattern of risk factors, can reduce the incidence of cancer recurrences (local, remote, or new BC), and increase survival if already affected by metastasis.

**Experimental design**

DianaWeb is a CBPR for the prevention of BC recurrences and the improvement of prognosis through lifestyle modifications.

In the DianaWeb in Umbria pilot project about 500 Italian women with a diagnosis of BC agreed to participate. The women could be with or without metastasis, local recurrence or second cancers; with *in situ* or invasive cancer, whatever the disease stage at diagnosis; whatever histological diagnosis; whatever the time elapsed since diagnosis. All the above traits will be taken into account as confounders in the statistical analysis.

The basic scientific strategy is to register the clinical history of the patients, provide them with evidence-based recommendations and tips for sustainable life-style changes, monitor participants’ changes, and analyze their effects on clinical outcome.

Participants will be requested to provide clinical and pathological information on their disease at the time of diagnosis and at periodic clinical follow-ups. Enrolled women will be provided with up-to-date evidence-based scientific information about the life-style that may prevent recurrences and cancer progression. Every few months they will receive short questionnaires on their life-style, health status and treatments.

The scientific analysis will focus on the association of baseline dietary habits, physical exercise, biomarkers and anthropometric data, and of their changes over time, with clinical outcomes.

Women will have access to their individual row data and to anonymized data on the whole group of participants. In the DIANA-website individual information are protected but elaborated information (e.g., descriptive statistics, case-control and cohort analyses) are open to all participants.

DianaWeb requires the following steps:

1. setting up a special interactive Web site for keeping in contact with recruited women (http://www.dianaweb.org/);
2. dissemination of the project to the public (press releases, public conferences, flyers to be distributed through pharmacies, doctors, cancer centers, charities, etc.). On the basis of previous experience, word of mouth among patients who meet during clinical controls is expected to be the most effective recruitment strategy;
3. recruitment: patients will be enrolled on a voluntary basis, will sign an informed consent form, will fill in a questionnaire on lifestyle, nutrition and medical history, and will provide
anthropometric data (weight, height, waist circumference, blood pressure), results of routine biochemical analysis, and clinical information (histology report and hospital discharge letters, any other subsequent diagnosis); 4. intervention to promote improved nutrition and physical activity through videos and lectures available on the web-site (theoretical lectures on preventive strategies, and practical videos on cooking techniques and specific physical exercises), and applications for smartphone; we will develop specific recommendations for women with different characteristics (lean, overweight, obese, active/sedentary lifestyle, dismetabolic patients, patients with BRCA mutation, patients under chemotherapy, hormonal therapy or radiotherapy, patients suffering from joint pain, osteoporosis, menopausal symptoms, cardiovascular toxicity and other complaints related to the side effects of treatments); 5. monitoring of lifestyle changes, health changes, and quality of life though periodic questionnaires.

The scientific method of the DianaWeb study includes three phases. The first phase started on January 2015 and closed in June 2015. During the first phase we created an interactive web site. The home page contains a summary of the project in plain language and instructions on how to participate to the phase II of the project. During the phase II we will ask to the patients interested in joining the project to fill in a personal data sheet with valid email address and a mobile phone number. In this phase we will send by email to all participating patients an Information Consent (IC) form and detailed explanation about the project. Once the signed IC (by mail or certified e-mail) with a copy of the identity card, hospital discharge letter reporting the diagnosis of BC and the histology report are received, we will send back to the patient, in order to allow her to access the project, credentials for login [i.e. identification (ID) and password (PW)]. Once the patient accesses with her ID and PW, an identification number is assigned, this personal code will be automatically reported in all forms. The pdf file of the signed IC will be stored in a protected folder, whereas the paper sheets are stored in a locked cabinet. Clinical data [TMN, grading, receptor (ER, PGR, ErbB2), p53, Ki67, date of the first surgery, type of treatment, date and type of recurrences] will be entered into the database. In the phase III, once completed the previous steps, the patient will be notified that she is in the project and invited to open her personal information section of the web site. The patient can read the acknowledgment for joining the study. After the women can access a menu with the datasheets to fill in: (i) anthropometry form (with instructions on how to make the measurements at home of height, weight, waist circumference, blood pressure), (ii) medical history questionnaire, (iii) short dietary habits questionnaire, (iv) results of the last routine blood tests (glycaemia, cholesterol tot, C-HDL, C-LDL, triglycerides, CRP, liver tests, plasma albumin,
vitamin D). Participants are suggested to require, in subsequent routine blood examinations, also insulin and testosterone. The forms have to be completed within the first month since recruitment. From the second month onwards, participants will be asked to post regularly, every 3 months, a 24h recall on food frequency and physical exercise. Periodically, every 12 months, to all women enrolled in the study we will send 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 or certified e-mail the documentation on the diagnosis. Each year, the patient will receive an email asking her to update anthropometry (with attached instruction to make the measurements at home of height, weight, waist circumference, BP) and new chemical chemistry data (if any). 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. Every month the system will email the patient with kitchen recipes, prevention tips, or reminders on physical activity.

To allow the patient to contact us, a section for questions and proposals has been created with 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 is 500. FAQ (frequently asked question) section has been created in the home page, to be progressively implemented. When the patient will complete all the steps, she will receive a free phone number for emergencies, active 2 hours a day for 5 days a week.

During this phase, we will encourage DianaWeb participants to organize meetings, conferences, kitchen classes, walking groups, exchange of information on recipes and on their strategy to comply with the recommendations. The DianaWeb staff will participate in these activities.

The basic life-style recommendations are those in the ECAC [34-37]. For overweigh patients we will stress the evidence based recommendations for losing weight: reduce protein intake [38], avoid chips, potatoes, processed meat, red meat, sugared beverages, white bread, commercial pastries, refined flour [39]. We will teach how to cook whole grain cereals, legumes, seeds, vegetables and low glycemic-index desserts, which have proven to help losing weight [40]. Specific dietary and exercise counseling will be offered to patients with hypertension, hyperglycaemia, diabetes, dyslipidemia, heart diseases, osteoporosis, liver steatosis, chronic inflammation [41-43].

**Feasibility**

The primary purposes of the DianaWeb in Umbria pilot study are to guarantee that the study implementation is practical and to reduce threats to the validity of the study’s outcomes. The aspects of feasibility that will be examined with the DianaWeb in Umbria pilot study are: (1) number of enrolled patients; (2) refusal rates for participation after recruitment, retention and
follow-up rates as the participants move through the study; (3) adherence rates to study procedures, intervention attendance, and engagement. We will also evaluate if eligibility criteria are clear, if the participants are able to understand the questions and the data collection methods, if they respond with missing or unusable data. Regarding data collection, we will assess if the participants have enough time and are able to complete data collection procedures and if the overall data collection plan involve a reasonable amount of time, or if creates a burden for the participants. Furthermore, we will estimate relevance and affordability of the intervention to obtain significant change.

Study participants could be influenced from their ability in manage internet. This may reduce the participation of older patients, but there is no reason to think that this aspect will bias the results on those who can participate.

The statistical power of the pilot study to monitor changes in anthropometric and metabolic parameters will be very high, above 95% for changes of the order of 10%. In the full-scale study we expect to reach a sufficient number of patients to eventually test the prognostic effect of lifestyle and modification of life-style in both early and advanced stage of disease, and in relevant subgroups of 1-2,000 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. Considering that, the target sample size of 500 women is relatively large for a pilot study, we anticipate to have sufficient power to detect significant differences in anthropometric and metabolic parameters in relation to changes in compliance with recommendations also in the DianaWeb in Umbria pilot study.

**Ethics**

DianaWeb does not interfere with prescribed oncological treatments, on the contrary it recommends participants to follow the prescriptions that they have received. The participant themselves, however, may exchange information on the treatment that they have received, and this may stimulate patients to become more critically aware of their health decisions and to request a second opinion.

The DianaWeb in Umbria study has received ethical approval from the local ethics committee of the University of Perugia (Comitato Universitario di Bioetica), Reference Number: 2015-002.

**CONCLUSIONS**

At most the institutional studies on BC prognosis in relation to lifestyle have recruited about 2,000 women. The DianaWeb study is aimed at following a greater population. A collaborative effort
between patients and research institutions to engage in researches that benefit community is a central tenet of CBPR. The aim of DianaWeb study is to improve (both in patients and in researchers) the framework of knowledge about risk factors associated with BC recurrence and survival using a specific interactive website. In particular, we intend to verify whether sustainable lifestyle changes related to nutrition and physical activity can significantly reduce important risk factors for recurrence (such as the factors characterizing the metabolic syndrome) and ultimately the incidence of recurrence of BC and second cancers. The results obtained will be used to plan guidelines for nutrition and physical activity for BC patients.

The cost profiles of cancer patients in Italy, based on individual patterns of care, was about € 7.5 billion in 2009, thus representing 6.7% of total health expenditure and appears to be increased. Every year in Italy more than 10,000 patients develop recurrence or metastasis, about 39,500 women develop breast cancer; 43,000 news cases of breast cancer will be estimated to occur in 2020, with increased costs of 8.7% compared to the total expenditure in 2009 in Italy. A prevention approach using web-easy and low cost technology is an achievable social challenge, significant not only for public health but also for our economy.

Acknowledgements

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Contributors

AV, FB and MV conceived the project and procured the project funding; AV is leading the coordination of the trial; MV is the coordinator of the pilot study. CL, DN, VG, TM, GG and MM assisted with protocol design. TM, CL, DN, VG, AB, EB and GG are managing the trial including data collection. MV and AV drafted the manuscript. MM and FB helped to draft and extensively
revise the manuscript. All authors have approved the final manuscript and are willing to take responsibility for appropriate portions of the content.

Competing interests
No, there are no competing interests.

References


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Obesity is an independent risk factor for postmenopausal BC and, in particular, for estrogen receptor (ER)-positive/progesterone receptor (PR)-positive BC. Moreover, obesity is associated with worse prognosis, both before and after menopause [5]. The obesity is also related to poor quality of life and increased risk of developing comorbid conditions [6]. Both chemotherapy and, to a lesser extent, tamoxifen and nonsteroidal aromatase inhibitors have been associated with weight gain [7]. Moreover, weight gain during and after cancer treatment has been reported to increases the risk of recurrences [8].

Among the potential mechanisms behind the association between weight gain, obesity, and recurrence and mortality of breast cancer, there is an increased conversion of androgens to estrogens in peripheral adipose tissue and increased circulating levels of insulin, insulin-like growth factors (IGFs), and leptins, that promote tumor cell proliferation [9].

It has been shown that high fasting glycemia, even within the normal range, is associated with a significantly increased risk of BC [10 11] and more recently that, in BC patients, high glycemic levels are associated with higher incidence of recurrences [12 13].
Also metabolic syndrome is associated with increased risk of BC in postmenopausal women [14], and with BC recurrences in patients diagnosed both before and after menopause [15]. After adjustment for tumor stage and hormonal receptors expression, BC patients with metabolic syndrome have a 2.2-fold higher risk of developing distant metastasis than patients without any metabolic syndrome trait. Metabolic 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 high plasma testosterone levels are associated with BC incidence [16] and that BC patients with high testosterone levels have worst prognosis [17-18]. Insulin stimulates the synthesis of testosterone in the ovary, and high plasma insulin levels are associated with both increased BC incidence [19] and increased risk of recurrences [20]. 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 IGFBP1 and IGFBP2), and bioavailable IGF-1 is associated with both BC incidence [21] and prognosis [22]. Also high plasma levels of C-reactive protein, even within the normal range, are associated with increased incidence [23], increased risk of recurrence [24-26], and shorter survival [27] in patients with advanced BC.

All these factors can be modified favorably through adopting a diet inspired to the traditional Mediterranean Diet and to the European Code Against Cancer (ECAC; http://cancer-code-europe.iarc.fr), the latter including recommendations on diet and on physical exercise of moderate intensity. The ECAC recommends to eat plenty of whole grain cereals, pulses, vegetables and fruit, to avoid sugared drinks and processed meat, to limit red meat, alcoholic beverages and calorie dense food, which is basically the traditional Mediterranean Diet. The analysis of prospective cohort studies suggested that a high score of adherence to the ECAC is associated with 30-50% lower incidence of BC [28-29], and several studies have suggested a decrease of BC recurrence and death in patients who exercise at least 30 min /day [30-32].

These information are not currently available to patients and are not yet included in oncology protocols. With a few exceptions, too physicians are not aware of these scientific results and are not yet culturally prepared for life-style prescriptions.

DianaWeb is a community-based participatory research (CBPR) offered to BC patients, whatever the clinical stage of their disease. There is increasing interest in the CBPR defined by Minkler and Wallerstein [33] as “a process that involves community members or recipients of interventions in all phases of the research process”. Therefore, DianaWeb represents a collaborative effort between participants and research institutions to determine if a specified change, e.g. in lifestyle, would result in improved outcome, e.g. quality of life or survival.
The basic scientific strategy in the DianaWeb study is to recruit a large number of participants, to monitor participants’ life-style and health status over time, to provide them with evidence based recommendations and tips for sustainable changes, to analyze clinical outcomes as a function of baseline risk factors and subsequent changes, and to share with them methodologies and results. DianaWeb will utilize a specific interactive website, and, with very few exceptions, all the communications between participants, and between participants and the research team, will be through the web.

In this paper we describe the pilot study (namely DianaWeb in Umbria), aimed at recruiting at least 500 patients in Central Italy (Umbria and bordering Regions). The full study is intended to recruit over 50,000 patients in Italy.

METHODS

Study hypothesis and aims

We hypothesize that an interactive CBPR may increase patients’ compliance with lifestyle recommendations (with respect to usual face to face or leaflet based recommendations) and significantly decrease BC recurrence risk factors and BC mortality.

Prevention of BC recurrences with low cost technologies, easily available to everybody, is a priority for both public health and public finances. Informing about the major modifiable risk factors effecting the progression of BC and metastatic diffusion, and about how to reduce their impact, may improve prognosis and prolong life also in women with advanced disease.

Offering high-quality evidence-based preventive information to BC patients we will avoid the risk that they become prey of “alternative” medicines that may induce them to decline evidence based treatments.

The DianaWeb aims are: (1) to build a cohort of women with a previous diagnosis of BC, and willing to actively participate in the project; (2) to propose a nutritional switch towards a diet that is poor in refined carbohydrates, fats and animal proteins, and rich in unrefined cereals, pulses and other vegetable foods, according to the ECAC guidelines; (3) to promote regular physical activity of moderate intensity; (4) to monitor the change over time of dietary habits, exercise, body weight, and the prevalence of metabolic syndrome parameters (including markers of chronic inflammation and of insulin resistance); (5) to monitor the occurrence of new BC related clinical events, and quality of life of the study participants; (6) to test the hypothesis that the participants who succeed to
improve their pattern of risk factors, can reduce the incidence of cancer recurrences (local, remote, or new BC), and increase survival if already affected by metastasis.

Experimental design

DianaWeb is a CBPR for the prevention of BC recurrences and the improvement of prognosis through lifestyle modifications.

DianaWeb has a prospective, before–after study design. As the association of metabolic syndrome or its components with cancer development and cancer-related mortality is always more frequently highlighted in the literature [34], the primary outcome of DianaWeb in Umbria pilot study is the decrease of metabolic syndrome status, secondary outcomes in the full-scale DianaWeb study includes recurrences and mortality.

In the DianaWeb in Umbria pilot project about 500 Italian women with a diagnosis of BC agreed to participate. The women could be with or without metastasis, local recurrence or second cancers; with *in situ* or invasive cancer, whatever the disease stage at diagnosis; whatever histological diagnosis; whatever the time elapsed since diagnosis. All the above traits will be taken into account as confounders in the statistical analysis.

The basic scientific strategy is to register the clinical history of the patients, provide them with evidence-based recommendations and tips for sustainable life-style changes, monitor participants’ changes, and analyze their effects on clinical outcome.

Participants will be requested to provide clinical and pathological information on their disease at the time of diagnosis and at periodic clinical follow-ups. Enrolled women will be provided with up-to-date evidence-based scientific information about the life-style that may prevent recurrences and cancer progression. Every few months they will receive short questionnaires on their life-style, health status and treatments.

The scientific analysis will focus on the association of baseline dietary habits, physical exercise, biomarkers and anthropometric data, and of their changes over time, with clinical outcomes.

Women will have access to their individual row data and to anonymized data on the whole group of participants. In the DIANA-website individual information are protected but elaborated information (e.g., descriptive statistics, case-control and cohort analyses) are open to all participants.

DianaWeb requires the following steps:

1. setting up a special interactive Web site for keeping in contact with recruited women;
2. dissemination of the project to the public (press releases, public conferences, flyers to be distributed through pharmacies, doctors, cancer centers, charities, etc.). On the basis of previous
experience, word of mouth among patients who meet during clinical controls is expected to be the most effective recruitment strategy;

3. recruitment: patients will be enrolled on a voluntary basis, will sign an informed consent form, will fill in a questionnaire on lifestyle, nutrition and medical history, and will provide anthropometric data (weight, height, waist circumference, blood pressure), results of routine biochemical analysis, and clinical information (histology report and hospital discharge letters, any other subsequent diagnosis);

4. intervention to promote improved nutrition and physical activity through videos and lectures available on the web-site (theoretical lectures on preventive strategies, and practical videos on cooking techniques and specific physical exercises), and applications for smartphone; we will develop specific recommendations for women with different characteristics (lean, overweight, obese, active/sedentary lifestyle, dismetabolic patients, patients with BRCA mutation, patients under chemotherapy, hormonal therapy or radiotherapy, patients suffering from joint pain, osteoporosis, menopausal symptoms, cardiovascular toxicity and other complaints related to the side effects of treatments);

5. monitoring of life-style changes, health changes, and quality of life though periodic questionnaires; the pilot study will be completed in late 2016.

The scientific method of the DianaWeb study includes three phases. The first phase started on January 2015 and closed in June 2015. During the first phase we created an interactive web site. The home page contains a summary of the project in plain language and instructions on how to participate to the phase II of the project. During the phase II we will ask to the patients interested in joining the project to fill in a personal data sheet with valid email address and a mobile phone number. In this phase we will send by email to all participating patients an Information Consent (IC) form and detailed explanation about the project. Once the signed IC (by mail or certified e-mail) with a copy of the identity card, hospital discharge letter reporting the diagnosis of BC and the histology report are received, we will send back to the patient, in order to allow her to access the project, credentials for login [i.e. identification (ID) and password (PW)]. Once the patient accesses with her ID and PW, an identification number is assigned, this personal code will be automatically reported in all forms. The pdf file of the signed IC will be stored in a protected folder, whereas the paper sheets are stored in a locked cabinet. Clinical data [TMN, grading, receptor (ER, PGR, ErbB2), p53, Ki67, date of the first surgery, type of treatment, date and type of recurrences] will be entered into the database. In the phase III, once completed the previous steps, the patient will be notified that she is in the project and invited to open her personal information section of the web site. The patient can read the acknowledgment for joining the study. After the women can access a
menu with the datasheets to fill in: (i) anthropometry form (with instructions on how to make the measurements at home of height, weight, waist circumference, blood pressure), (ii) medical history questionnaire, (iii) 24-hours recall on food intake and physical activity, (iv) short questionnaire on Mediterranean diet, (v) results of the last routine blood tests (glycaemia, cholesterol tot, C-HDL, C-LDL, triglycerides, CRP, liver tests, plasma albumin, vitamin D). Participants are suggested to require, in subsequent routine blood examinations, also insulin and testosterone. The forms have to be completed within the first month since recruitment.

24-Hours recall sheet contains a list of 65 food items, without referring on portion size or weight, nor on recipes. The recall also contains five questions about the time spent on physical exercise on the day before the interview and enquiring on work and recreational physical activity duration (hours/minutes) and intensity (moderate, vigorous). The 24-hours recall sheet was developed to assess dietary habits in the Diana-5 trial and was used to calculate a score of adherence to the WCRF/AICR recommendations. Analysis of data obtained with 24-hours recall in the Diana-5 study have suggested that compliance with the WCRF/AICR recommendations may reduce the risk of cancer and other chronic diseases through the reduction of metabolic syndrome [35 36].

A 24-point food-items questionnaire, an adaptation of the previously validated MEDAS (a 14-points Mediterranean Diet Adherence Screener) [37], is aimed at assessing adherence to the traditional Mediterranean diet. The 24-items screener includes 12 additional items that are critical to evaluate the intake of whole grains and/or legumes, non-starchy vegetables, processed meat, milk and dairy products.

From the second month onwards, participants will be asked to post regularly, every 3 months, a 24h recall on food frequency and physical exercise. Periodically, every 12 months, to all women enrolled in the study we will send 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 or certified e-mail the documentation on the diagnosis. Each year, the patient will receive an email asking her to update anthropometry (with attached instruction to make the measurements at home of height, weight, waist circumference, BP) and new chemical chemistry data (if any). 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. Every month the system will email the patient with kitchen recipes, prevention tips, or reminders on physical activity.

To allow the patient to contact us, a section for questions and proposals has been created with 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 is 500. FAQ (frequently asked question) section has been created in the home
page, to be progressively implemented. When the patient will complete all the steps, she will receive a free phone number for emergencies, active 2 hours a day for 5 days a week. During this phase, we will encourage DianaWeb participants to organize meetings, conferences, kitchen classes, walking groups, exchange of information on recipes and on their strategy to comply with the recommendations. The DianaWeb staff will participate in these activities.

The basic life-style recommendations are those in the ECAC [38-41]. For overweigh patients we will stress the evidence based recommendations for losing weight: reduce protein intake [42], avoid chips, potatoes, processed meat, red meat, sugared beverages, white bread, commercial pastries, refined flour [43]. We will teach how to cook whole grain cereals, legumes, seeds, vegetables and low glycemic-index desserts, which have proven to help losing weight [44]. Specific dietary and exercise counseling will be offered to patients with hypertension, hyperglycaemia, diabetes, dyslipidemia, heart diseases, osteoporosis, liver steatosis, chronic inflammation [45-47].

Feasibility

The primary purposes of the DianaWeb in Umbria pilot study are to guarantee that the study implementation is practical and to reduce threats to the validity of the study’s outcomes. The aspects of feasibility that will be examined with the DianaWeb in Umbria pilot study are: (1) number of enrolled patients; (2) refusal rates for participation after recruitment, retention and follow-up rates as the participants move through the study; (3) adherence rates to study procedures, intervention attendance, and engagement. We will also evaluate if eligibility criteria are clear, if the participants are able to understand the questions and the data collection methods, if they respond with missing or unusable data. Regarding data collection, we will assess if the participants have enough time and are able to complete data collection procedures and if the overall data collection plan involve a reasonable amount of time, or if creates a burden for the participants. Furthermore, we will estimate relevance and affordability of the intervention to obtain significant change.

Statistical power

In the ongoing Diana-5 study, a randomized controlled trial aimed at evaluating the effectiveness of diet modification in reducing BC recurrences [36], we have observed a marked improvement in metabolic parameters associated with cancer progression in the intervention group (i.e., patients who participated monthly in kitchen classes and physical exercise sessions). Moreover, we have also observed a significant reduction in several metabolic syndrome parameters (i.e., body weight, waist circumference, serum cholesterol and triglycerides) in patients enrolled in the control group who have received only written lifestyle recommendations (unpublished data), the same that we are
proposing in the DianaWeb study. On these basis, we have estimated that in the DianaWeb in Umbria pilot study we would have over 90% power of obtaining significant differences in the considered metabolic parameters between compliant and non-compliant women, with a target sample of 500 patients.

In the full-scale study we expect to reach a sufficient number of patients to eventually test the prognostic effect of lifestyle and modification of life-style in both early and advanced stage of disease, and in relevant subgroups of 1-2,000 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.

**Ethics**

DianaWeb does not interfere with prescribed oncological treatments, on the contrary it recommends participants to follow the prescriptions that they have received. The participant themselves, however, may exchange information on the treatment that they have received, and this may stimulate patients to become more critically aware of their health decisions and to request a second opinion.

The DianaWeb in Umbria study has received ethical approval from the local ethics committee of the University of Perugia (Comitato Universitario di Bioetica), Reference Number: 2015-002.

**Potential biases and limits**

Given that in the DianaWeb study the greater part of the contact with patients will be through the web site, the study design could be prone to high dropout rates of participants.

Another limitation is that we will use a food and physical activity 24-hours recall that depends on the respondent’s full co-operation. 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, because participation is limited to women that have an email address, our findings may not necessarily reflect the overall situation of breast cancer survivors. In fact, the ability in managing internet might reduce the participation of older patients. However, there is no reason to suppose that this aspect could bias the results on those women who will be able to participate.

**CONCLUSIONS**

At most the institutional studies on BC prognosis in relation to lifestyle have recruited about 2,000 women. The DianaWeb study is aimed at following a greater population. A collaborative effort
between patients and research institutions to engage in researches that benefit community is a central tenet of CBPR.

The aim of DianaWeb study is to improve (both in patients and in researchers) the framework of knowledge about risk factors associated with BC recurrence and survival using a specific interactive website. In particular, we intend to verify whether sustainable lifestyle changes related to nutrition and physical activity can significantly reduce important risk factors for recurrence (such as the factors characterizing the metabolic syndrome) and ultimately the incidence of recurrence of BC and second cancers. The results obtained will be used to plan guidelines for nutrition and physical activity for BC patients.

The cost profiles of cancer patients in Italy, based on individual patterns of care, was about € 7.5 billion in 2009, thus representing 6.7% of total health expenditure and appears to be increased. Every year in Italy more than 10,000 patients develop recurrence or metastasis, about 39,500 women develop breast cancer; 43,000 news cases of breast cancer will be estimated to occur in 2020, with increased costs of 8.7% compared to the total expenditure in 2009 in Italy.

A prevention approach using web-easy and low cost technology is an achievable social challenge, significant not only for public health but also for our economy.

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Contributors

AV, FB and MV conceived the project and procured the project funding; AV is leading the coordination of the trial; MV is the coordinator of the pilot study. CL, DN, VG, TM, GG and MM assisted with protocol design. TM, CL, DN, VG, AB, EB and GG are managing the trial including data collection. MV and AV drafted the manuscript. MM and FB helped to draft and extensively...
revise the manuscript. All authors have approved the final manuscript and are willing to take responsibility for appropriate portions of the content.

**Competing interests:** none.
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Community-based participatory research to improve life quality and clinical outcomes of patients with breast cancer (DianaWeb in Umbria pilot study)

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