STUDY TITLE

NEW INVITED WOMEN TO BREAST CANCER SCREENING: A MULTI-CENTRE, LONGITUDINAL, CONTROLLED, RANDOMISED STUDY ON A DECISION AID TO SUPPORT INFORMED CHOICE.

DONNAINFORMATA-MAMMOGRAFIA.IT

CLINICAL STUDY PROTOCOL

SPONSOR IRCCS Istituto di Ricerche Farmacologiche "Mario Negri"
Via G. La Masa, 19
20136 Milano (Italy)

SUPPORTED BY AIRC - The Italian Association for Cancer Research
Project Number IG2015-17274.

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Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, the host organisation, the members of the regulatory authority and the Ethics Committees, unless authorised to do so.

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PROTOCOL SYNOPSIS

Study title	**New invited women to breast cancer screening: a multi-centre, longitudinal, controlled, randomised study on a decision aid to support informed choice.**
Sponsor	IRCCS Istituto di Ricerche Farmacologiche "Mario Negri" Via La Masa, 19 20156 Milano (Italy)
Supporter	AIRC The Italian Association for Cancer Research Project Number IG2015-17274
Sponsor Representative	Paola Mosconi Laboratory of Medical Research and Consumer Involvement Department of Public Health IRCCS Istituto di Ricerche Farmacologiche "Mario Negri"
Background and rationale	Breast cancer is the most common cancer in women. In Italy, women are invited to a population-based mammography screening programme for the first time at the age of 45 or 50 years. Results from randomised controlled trials, observational studies, and systematic reviews continuously fuel the debate on the balance on benefits (reducing breast cancer mortality) and harms (overdiagnosis, overtreatment) of mammography screening. Physicians, policy makers, as well as laypeople or patient associations agree on the need to inform women about the potential benefits and harms in order to allow an aware decision process. Decision aids are an effective way to support lay people in their decisions about health.
Objectives *Primary*	To assess the effect of an interactive web decision aid on informed choice – measured through knowledge, attitudes and intentions concerning breast cancer screening – comparing the decision aid with a standard information provided via web (web brochure).
Secondary	• To compare the participation rate in breast cancer screening between intervention (web decision aid) and control group (web brochure). • To compare the satisfaction between the intervention (web decision aid) and the control group (web brochure) on information in terms of length, quantity, clarity, balance, helpfulness in making decision and women willingness to recommend it to other women. • To measure the time spent on web pages between the intervention (web decision aid) and the control group (web brochure). Only for the intervention group, to measure number of pages visited, frequency of access, level of information and level of detail reached on the main topics.

	• To compare the decisional conflict process between the intervention and the control group.
Study design	Multi-centre, randomised, controlled study
Number of centers	More than 3
Number of patients	8160 women will be invited in order to reach 816 patients evaluable for primary endpoint.
Target population *Inclusion criteria* *Exclusion criteria*	The women aged 45-69 or 50-69 years new invited to the regional screening programmes of the participant centers . • Women aged 45-69, according to the target age of the screening centres involved; • New invited women in mammography screening programme. None
Assessment schedule	Baseline questionnaire prior to randomization Follow-up questionnaire 7-10 days after the randomization
Endpoints *Primary*	Informed choice, based on the available literature, will be measured according to the three-dimensional framework which covers knowledge, attitude and intention. Knowledge will be measured using a questionnaire structured in thirteen questions with multiple choice answers, with two to four options. Ten questions will be qualitative and 3 will be numerical. A score of 8 out of 13 (about 60%) or higher would be considered "adequate knowledge". Attitude will be measured through a scale consisting of six items with five response options from 1 to 5, with a total score from 6 to 30. For informed choice, we set the threshold for a positive attitude at 24 and consequently the score <24 point a negative attitude. Intention to be screened will be measured using one item with five responses: Definitely will, Likely to, Unsure, Not likely to, Definitely will not. For informed choice, we classified "definitely will" and "likely to" as positive intentions. A woman will be judged to have made an informed choice if she has adequate knowledge and her attitudes and intentions are consistent (both positive or both negative) in the follow-up questionnaire.

Secondary	Participation rate to the breast cancer screening programme will be assessed as a percentage of women who actually participate, both in intervention and in the control group. Satisfaction with the given information will be measured using 8 items with three points scale. The time spent on the pages on the web decision aid and in the web brochure will be assessed trough Pickwick software. Only for the web decision aid, through the same software, the number of pages visited, the frequency of access and level of detail reached will be calculated. Decisional conflict will be assessed using the validated and widely used Decisional Conflict Scale-SURE version, consisted in four-item scale.
Planned study period	15 months (september 2017-december 2018)

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

e-CRF	Electronic Case Report Form
GCP	Good Clinical Practice
GISMA	Italian Group for Mammography Screening
ICH	International Conference of Harmonisation
IEC	Independent Ethics Committee
NHS	National Health Service
ONS	National Centre for Screening Monitoring
RCT	Randomised controlled trial
UK	United Kingdom
US	United States
WMA	World Medical Association

1. BACKGROUND

Breast cancer is the most common cancer in women. Population ageing, impact of early diagnosis and new treatments have changed the epidemiology of the disease in last decades. According with the annual report AIOM/AIRTUM the esteem of the number of new diagnosis of breast cancer in 2016 is 50.000 (1).

Since the end of the eighties, most European western countries have implemented national or regional population-based breast cancer screening programmes. Service screening programmes invite women, mostly in the age 50-69 years, to high quality mammography screening every 2 years according with European Guidelines (2). A recent survey (3) estimated about 26 millions of women received invitation in Europe.

1.1 Evidence and controversy

Screening mammography was first shown to be effective in reducing breast cancer mortality by the Health Insurance Plan randomised controlled trial (RCT) in US in the sixties (4). During the seventies, other 8 RCTs contributed evidence on breast cancer screening efficacy for reducing breast cancer mortality. Wald et al. in 1993 reported an estimate of 20% mortality reduction, based on the RCTs available (5). On that basis, the UK National Health Service (NHS) promoted service screening with invitation of the target population evaluating benefits, harms and costs. Over the nineties, several European countries implemented service screening as public health programmes. In 2003, the European Council Recommendation promoted the implementation of screening programmes in Europe, for breast, bowel and cervical cancer.

Evidence-based demonstration of the breast cancer mortality reduction related to screening mammography is the object of longstanding controversy. Since the beginning, opinions were clashing about the efficacy in younger women. Screening in premenopausal women was less sensitive and evidence of efficacy not shown in RCTs.

In Europe, service screening was restricted to women after 50 years of age, even if some programmes include also women aged 45-50 years. In USA, the National Cancer Institute-NIH Consensus Conference confirmed how sensitive the question of mammography screening in younger women was (6). The UK Age trial, enrolling women at 40-41 years of age, reported positive results, whereas not statistically significant (7).

Over the nineties, the debate continued especially about the study design and potential biases of the Canadian trial with an hot debate (8). In 2001, the publication of Nordic Cochrane systematic review (9), which classified the RCTs on the basis of their quality, and excluded some trials,

demonstrated the absence of efficacy of mammography screening, and re-ignited the controversy in US and Europe. In 2012, the NHS-UK set up an Independent Panel aimed to review the evidence and highlighted the importance of the continuation of the service-screening programme, but asked for changes in the communication and the information about benefits and harms, especially in terms of overdiagnosis of breast cancer (10). In 2012, the Euroscreen working group reviewed the outcome research from the European countries and published a supplement of the Journal of Medical Screening with an estimate of a first European balance sheet of the benefits and harms of service screening (overdiagnosis, overtreatment, and false positive results)(11). Several systematic reviews of the evidence have been published, including the Nordic Cochrane systematic review updates, with substantially different conclusions and data interpretation(12).
The evaluation of screening outcomes and communication to both stakeholders and women was a central issue. Promotion of informed decision making about breast cancer screening balance of benefits and harms was considered responsibility of the public health system.

1.2 Information and Communication

Some studies have shown that women are not aware of the value of mammography screening, thus confounding early diagnosis with prevention (13, 14). Other studies have shown that both leaflets and websites do not provide balanced information to women, most of them highlighting more the benefits than the risks, such as overdiagnosis and overtreatment (15-17). Qualitative studies have discussed how to balance the evidence-based information to enable women to participate in health care decision (18).
Different models of information have been suggested, as well formally tested in RCTs (19, 20). Among these, decision aids are an effective way to assist women to make a decision about mammography screening. According to a recent Cochrane review (21) and a clinical trial (22) on breast cancer screening, decision aid improves patients' knowledge, reduce decisional conflict clarifying their values, and could encourage women to take a more active role in decision making without anxiety.

1.3 Information and Media

Media are not always able to ensure a correct and adequate information about benefits and limits of mammography screening. The British Medical Journal published an update of the Canadian study on mammography screening carried out in early '80s (8). Media coverage was focused on the limits of the screening described in the study, without mentioning the multifaceted discussion on

screening (23, 24). Owing to the necessity to highlight the latest news, media leans toward a "last reading" of a complex health theme as a rule, releasing contradictory and often inconsistent information. The social media can offer a different approach with an abundance of voices reflecting different points of view.

1.4 Information and scientific societies

In Italy, the Italian Group for Mammography Screening (GISMA) and the National Centre for Screening Monitoring (ONS) addressed many efforts in promoting a high quality level communication for women invited by a population-based breast cancer screening programme. A Working Group on Communication has been created with the involvement of all screening professionals who have developed experience and knowledge on this issue over the years, with a multidisciplinary approach. The main objective of this group is to increase the awareness and knowledge on mammography screening among women, health operators, advocacy groups, and stakeholders. How to build a comprehensive and effective communication strategy, in order to obtain an informed participation, has been extensively debated within this group as long as what kind of experimental communication strategies with a multilevel and multi-professional approach should be set up in a screening context (25). However, the several GISMA screening centers adopted different leaflets to invite the women to participate in the breast cancer screening programme.

The debate concerning mammography screening is still lively although most of the stakeholders - physicians, policy makers, as well as lay people or patients' associations - agree on the need to inform women properly and consider this an ethical obligation. There is in fact an agreement in public health community about the relevance of communication of the outcomes in mammography screening. The uncertainties about the estimates, especially of potential harms deriving from mammography screening, should be explicitate in screening communication tools. Cancer screenings share with other health sectors the communication issue. Communicating by considering patients' needs and willingness is a widespread problem in biomedicine today, and in several countries there are efforts to move for a better communication, taking into account the level of information requested by each woman. Furthermore, the current debate on mammography screening adds a new challenge: how disagreement among scientists should be managed, and how public health institutions and scientists should cope with communication in presence of divergences and conflicts on data.

2. STUDY RATIONAL

In consideration of the above mentioned issues, who can decide the amount and kind of information that should be delivered to women invited to mammography screening? In this project the distinction between the decision-making process at population/community level and at individual level has been considered. In the population framework, the decision making process should be based only on a rational and honest balance between benefits and harms, and the final responsibility for the choice between controversial estimates and interpretations belongs to the screening proponents, after considering the stakeholders' point of view. On the other hand, at individual level, the decision belongs to screened participants, that decide also what and how much information is essential for them to reach a completely informed decision. The individual final choice can diverge from a pure rational process and should be based on values and preferences, not only on a simple balance sheet which, for its intrinsic characteristics, cannot be applied at individual level. This distinction is based on the evidence that individual decision making process is not wholly consequence of a rational understanding of facts and figures, but can also be related to other individual-related factors as values, emotions, preferences, confidence, trust and so on. All these elements greatly vary from person to person, and also over time. The "rational agent" model of decision making is today widely under revision by the cognitive science approach, and also by the results achieved in the game theory and economics fields. The screening promoters have the duty to provide all the relevant information for an informed choice, including those related to the uncertainty of the estimates and the scientific controversy. Furthermore, it is up to the screening promoters to decide what are the best estimates of a balance sheet from the community point of view. All this information must be organized and modulated through a multilevel model that leave women free to reach the depth and the breadth of information necessary to make a weighted decision, in a personalized way that should respect also the "right of not know".

A personalized informative model could influence not only the participation in breast cancer screening, but also the awareness, the realistic expectations and the satisfaction of women about the decision process and their empowerment. The focus of the study is the informative process related to the decision about the participation in breast cancer screening within the national Health service screening programme. In this platform, benefits, harms and controversy of mammography screening will be fully presented.

3. STUDY OBJECTIVES

3.1 Primary

To assess the effect of an interactive web decision aid on informed choice – measured via knowledge, attitudes and intentions concerning breast cancer screening – comparing the decision aid with a standard information provided via web (web brochure).

3.2 Secondary

- To compare the participation rate in breast cancer screening between intervention (web decision aid) and control group (web brochure).
- To compare the satisfaction between the intervention (web decision aid) and the control group (web brochure) on information in terms of length, quantity, clarity, balance, helpfulness in making decision and women willingness to recommend it to other women.
- To measure the time spent on web pages between the intervention (web decision aid) and the control group (web brochure). Only for the intervention group, to measure number of pages visited, frequency of access, level of information and level of detail reached on the main topics.
- To compare the decisional conflict process between the intervention and the control group.

4. STUDY DESIGN

This is a multi-centre, randomised, controlled study to assess the efficacy of the high quality information approach driven by a multilevel web platform. The screening centres involved are based in different cities of Italy. In accordance with the target age of the women invited to the regional screening programmes, the present study will include 45-69 years or 50-69 years old new invited women. The eligible women will be invited to participate to the study through an ad-hoc letter by the belonging screening centre. The letter, delivered 30-45 days before of the standard screening program invitation letter, will provide information regarding the study and how to access to the web platform.

The women will be randomized to receive:

- Web platform with a multilevel information and an aid for the decision to be taken (whether participating or not to the mammography screening organised for free by the Italian Health Service). (Intervention group).
- Web platform with a standard brochure (Control group). This standard brochure represents a combination of the best information available from participant centre' brochures, see the

Appendix 1.

4.1 Intervention group: multilevel information and decision-aid

The content, in the web platform, is splitted in 16-20 screens (see Appendix 2); each screen contains the answer to a common question (i.e. What is mammography screening? What are its benefits and harms? What results can be expected from the participation to mammography screening? What is breast cancer?). The language is plain and the contents are defined on the basis of the literature. The information covers also controversial topics as overdiagnosis, overtreatment and the disagreement among scientists about harms and benefits' quantification.

Articles and review available in the literature, reports of Institutional organizations, such as ONS, GISMA, IARC, UK and USA guidelines, other screening materials (leaflets, website, brochure) are carefully considered in order to collect all the information needed to have a balanced and honest tool.

The content can be accessed through links that allow a more detailed comprehension of the topic (multilevel information).

The navigation is personalised; with a "nudging" approach the platform induces women to become aware of the relevant matters, nevertheless they can stop reading whenever they feel ready to decide. When women think of knowing enough and they are ready to decide (rational part) the platform provides a Decision Aid module where issues and concerns that can affect their decision are listed. Women are asked to say, for each items, the relevance and the impact on their decision (irrational part).

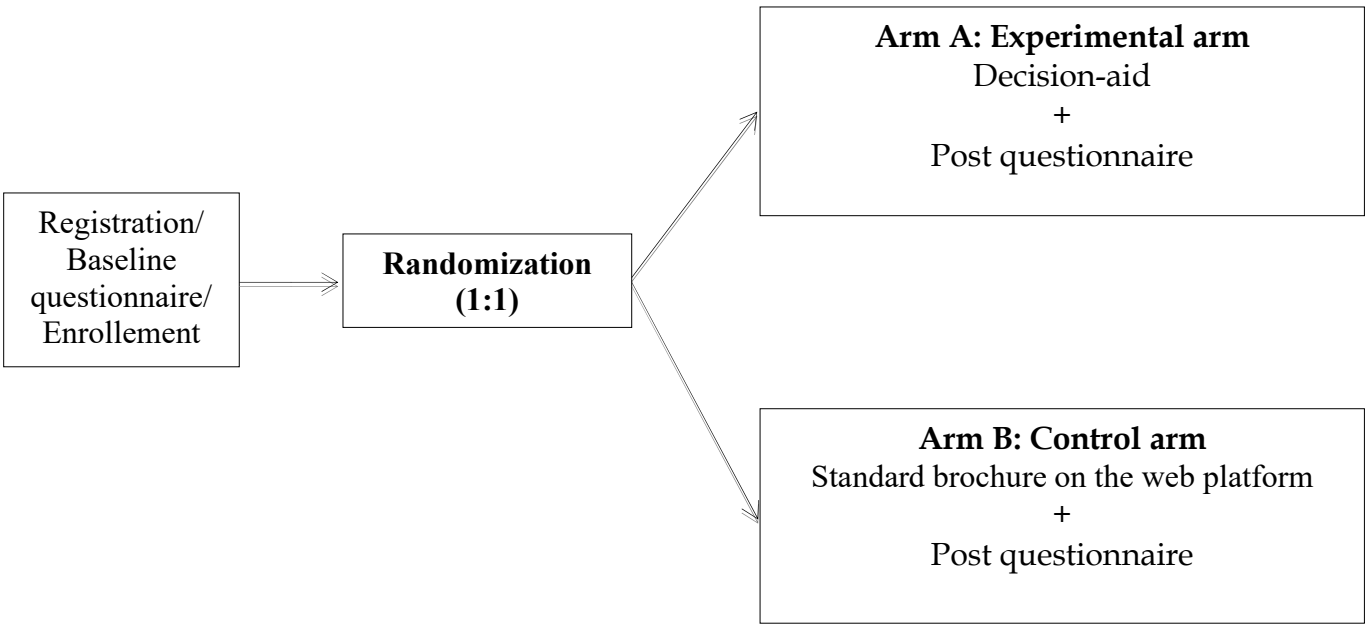
4.2 Randomization

A central system for randomization will be used inside the web platform. The women will be randomized after they register to the platform, sign the informed consent and fill-in the baseline questionnaire. The random allocation will be on a 1:1 ratio basis.

The overall duration of the study is 15 months: 14 months for invitation of the women and maximum 1 months of follow-up.

The study outline is illustrated in Figure 1.

Figure 1 Study flow-chart



4.3 End of study

The study will end when the proper number of the follow-up questionnaires will be reached according with the sample size (see paragraph 9.2).

5. STUDY ENDPOINTS

In order to setup the questionnaires for primary and secondary endpoints, a systematic review of the literature has been performed using the following key words “Breast cancer and decision aid”. At the end of the process accomplished by two independent reviewers, a total of 9 trials has been included. The comparative analysis of the tools used in the trials has been presented and discussed with partners and scientific committee, allowing to identify areas and items to consider within the questionnaires of the study (described below).

5.1 Primary endpoints

Informed choice will be measured according to the three-dimensional framework of Marteau et al. (26), which covers knowledge, attitude and intention. The statistical hypothesis for the primary

endpoint is of superiority, the study is designed to detect a 10% difference between the control and the intervention group, according to the literature available (22, 27).

Knowledge will be measured using a questionnaire developed on the basis of literature (22, 27). It will be structured in thirteen questions with multiple choice answers, with two to three options. Ten questions will be qualitative and 3 will be numerical. The score and threshold to reach an "adequate knowledge" were decided *a priori*, following the approach described in the literature (22, 27). Each correct answer will receive one point. The maximum total score is 13 out of 13. A score of 8 out of 13 (about 60%) or higher would be considered "adequate knowledge".

Attitude will be measured through a scale used in the literature available (22, 27), consisting of six items with five response options from 1 to 5, with a total score from 6 to 30. For informed choice, we set the threshold for a positive attitude at 24 and consequently the score <24 point a negative attitude.

Intention to be screened will be measured using one item with five responses: Definitely will, Likely to, Unsure, Not likely to, Definitely will not. For informed choice, we classified "definitely will" and "likely to" as positive intentions. This item will be collected at the end of the information session on the web and in the follow-up questionnaire. In case of no consistency between the two answers, the answer in the follow-up questionnaire will be considered as conclusive.

The informed choice will be assessed as a dichotomous outcome. A woman will be considered as able to expressed an informed choice if she has adequate knowledge and her attitudes and intentions are consistent (both positive or both negative) in the follow-up questionnaire.

5.2 Secondary endpoints

Participation rate to the breast cancer screening programme will be assessed as a percentage of women who participate, both in intervention and in the control group. The statistical hypothesis for the secondary endpoint is of non-inferiority. This hypothesis will be considered only if the null hypothesis related to the primary endpoint will be rejected.

Satisfaction with the information given (intervention and control group) will be measured using 8 items regarding length, quantity, clarity, balance, helpfulness in making decision and women willingness to recommend it to other women with three points scale.

The time spent on the pages in the web decision aid and in the web brochure will be assessed trough Pickwick software. Only for the web decision aid, through the same software, the number of pages visited, the frequency of access and level of detail reached will be calculated.

Use of/experience with other screenings will be measured using one item on the participating in other screenings programme.

Decisional conflict will be assessed using the validated and widely used Decisional Conflict Scale-SURE version (28). This four-item scale will assess the women's knowledge of the options available, the clarity about the benefits and risks most important for them, sufficient level of support and being sure about the best choice. Since no Italian translation of this scale is available, the scale will be translated for this study.

The perceived risk of breast cancer will be assessed using one item with a five verbal response categories ranging from "much lower" to "much higher" than the average.

Internet use will be measured using one item regarding the frequency of the Internet use for health information.

5.3 Translation of items

The items have been translated in Italian through a multistep process employing a standardized methodology. Briefly, one professional translator and two members of coordinating center (IRCCS Istituto Mario Negri) produced three independent Italian translations. After discussion, a common Italian version was produced. This version has been evaluated by partners (epidemiologists with experience in breast cancer screening, experts in communication, researchers of the project) in terms of use of simple, and correct language.

The preliminary Italian version of the questionnaires has been tested in a small group of women in order to evaluate clarity, understandability and length.

At the end of this process a final version has been established (Appendix 3).

6. PATIENT SELECTION CRITERIA

6.1 Study participants

All the women eligible to receive an invitation letter to be screened will be contacted to enter the trial.

6.2 Inclusion criteria

- Women aged 45-69, according to the target age of the screening centres involved;
- New invited women in mammography screening programme.

6.3 Exclusion criteria

- None.

7. STUDY ASSESSMENTS

After registering in the web platform and signing the informed consent, participants must fill in a baseline questionnaire for participation in the study.

At baseline questionnaire, the following parameters will be evaluated:

- ✓ Demographics
- ✓ Use of internet
- ✓ Previous mammography test
- ✓ Previous participation at screening programmes
- ✓ Family history of breast cancer
- ✓ Perceived risk of breast cancer
- ✓ Knowledge on the breast cancer screening
- ✓ Attitude on the breast cancer screening
- ✓ Intention on the breast cancer screening

Baseline questionnaire will be performed prior to the randomization.

Follow-up questionnaire will be performed 7-10 days after randomization, before the appointment at the breast cancer screening.

At follow-up questionnaire, the following parameters will be evaluated:

- ✓ Knowledge on the breast cancer screening
- ✓ Attitude on the breast cancer screening
- ✓ Intention on the breast cancer screening
- ✓ Satisfaction and acceptability of the information received (web decision aid and web brochure)
- ✓ Decisional conflict

See Appendix 3 for both the baseline and the follow-up questionnaires.

8. WOMEN AND STUDY WITHDRAWAL

8.1 Women withdrawal

The women have the right to voluntarily withdraw from the study at any time for any reason. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Women withdrawal of consent at any time
- Loss to follow-up.

9. STATISTICAL CONSIDERATION AND ANALYTICAL PLAN

9.1 Definition of study populations

9.1.1 All Participants Analysis Set

The All Participants Analysis Set is defined as all women who provided informed consent, were enrolled in the study and filled the baseline questionnaire. The listings of all variables will be based on the All Participants Analysis Set.

9.1.2 Intent-to-Treat (ITT) Analysis Set

The ITT analysis set is defined as all randomized women that respond to the follow-up questionnaire. Women will be analyzed according to the randomization arm.

9.1.3 Sample size

The primary analysis will compare the proportion of women who make an informed choice, using the chi-squared test in the two study groups. Based on the previous studies (21, 22) we judge an absolute difference of 10% as the minimum important difference for the sample size calculation. Assuming that one of the group proportions is 50%, in order to achieve 80% power to detect a group difference with a two-sided significance level of 5%, we require 816 women at follow-up. Allowing for an estimated response rate of 15% and early drop-out of one-third of initial participants, we will invite 8160 women to take part in the study.

If the null hypothesis related to the primary endpoint will be rejected, the first of the secondary endpoints will be analysed. The power of the analysis for this non-inferiority test - with one-sided tail - will be considered according with the participation rate at breast cancer screening, as reported in the table below.

Participation rate at breast cancer screening (control group)	Participation rate at breast cancer screening (intervention group)	Δ	Number of patients for each arm	Power (1-β)
40%	35%	5%	408	0.29122
40%	30%	10%	408	0.82777
40%	25%	15%	408	0.99289
40%	20%	20%	408	0.99996

9.2 Statistical analysis

We will conduct a descriptive analyses to describe the study participants. Possible baseline differences between trial arms will be statistically tested.

For primary endpoint statistical analysis will be performed on an intention to treat approach: all the randomised women compliant to follow-up will be included in the analysis in the groups assigned at the randomization. The impact of the web decision aid on the primary endpoint will be analysed using Chi-square test.

For secondary endpoints we will use Chi-square test to analyse binary endpoints and 2-sided t-test for continuous endpoints, with a significance level of 5%.

We will use SAS statistical software, version 9.2.

9.2.1 Interim analyses

No interim analyses are planned.

10. DATA MANAGEMENT

10.1 Source data

Source documents are where data is first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, web platform records with the questionnaires.

On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code.

10.2 Access to on trial participant data and study e-CRFs

Direct access to data will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

Access to the study clinical data entry web platform will be granted to trial staff through a computer-based credential generation system in the following manner:

- Centre PIs: will be granted Centre data entry credentials to allow for electronic signature of SAE forms, completed CRFs and meta-data entries which require PI approval (i.e. protocol deviations).

10.3 Data recording

Data collection will be performed using electronic CRFs exclusively.

The data will be registered in a MySQL database, to which only the site administrators (Zadig) will have access. The site administrators will insert users, who enter through centre lists. The system will give users an unambiguous ID, with which the data of each individual platform user will be associated. These data includes navigation, decisions, and questions. In this form, the data will be sent in CSV format. The data, subjected to statistical analysis, will be made anonymous, and provided in CSV format to the Mario Negri Institute. In general, the system permits tracing users in an unambiguous mode.

11. ETHICAL AND REGULATORY REQUIREMENTS

11.1 Ethical conduct of the study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements Participant data protection.

11.2 Compliance with Laws and Regulations

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013), the International Conference on Harmonization consolidated Guideline E6 for Good Clinical Practice and applicable regulatory requirement(s) including the following:

- Legislative Decree 08-11- 2012, n. 189 (Conversione in legge, con modificazioni, del decreto-

legge 13 settembre 2012, n. 158, recante disposizioni urgenti per promuovere lo sviluppo del Paese mediante un più alto livello di tutela della salute);

- Decision AIFA 07-03-2011 (Modifica delle appendici 5 e 6 al decreto del Ministro della salute 21 Dicembre 2007 concernente i modelli e le documentazioni necessarie per inoltrare la richiesta di autorizzazione, all'Autorità Competente, per la comunicazione di emendamenti sostanziali e la dichiarazione di conclusione della sperimentazione clinica e per la richiesta di parere al Comitato Etico);
- Ministerial Decree 08-02-2013 (Criteri per la composizione e il funzionamento dei comitati etici);
- Ministerial Decree 12-05-2006 (Requisiti minimi per l'istituzione, l'organizzazione e il funzionamento dei Comitati Etici per le sperimentazioni cliniche dei medicinali);
- Ministerial Decree 21-12-2007 (Modalità di inoltro della richiesta di autorizzazione all'Autorità competente, per la comunicazione di emendamenti sostanziali e la dichiarazione di conclusione della sperimentazione clinica e per la richiesta di parere al comitato etico);
- Authorization n. 9/2014 (Autorizzazione generale al trattamento dei dati personali effettuato per scopi di ricerca scientifica);
- Legislative Decree 30-06-2003, n. 196 (Codice in materia di protezione dei dati personali).

11.3 Ethics and regulatory review

The coordinating Independent Ethics Committee (IEC) should approve the final study protocol and related study documents including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the participants. The investigator will ensure the distribution of these documents to the centres' Ethics Committee.

11.4 Informed consent

Due to the nature of the study intervention, the informed consent should be signed online and the informed consent process should be documented in the electronic record. The date that informed consent is given must be recorded on the eCRF.

11.5 Confidentiality

The Sponsor maintains confidentiality standards by coding each participant enrolled in the study through assignment of a unique participant identification number.

11.6 Changes to the protocol and informed consent form

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee before implementation.

11.7 Audits and inspections

Authorised representatives of a regulatory authority or Ethics Committee may perform audits or inspections at the study centres, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements.

12. STUDY MANAGEMENT

12.1 Administrative Structure

This study is sponsored by the IRCCS, Istituto di Ricerche Farmacologiche Mario Negri. The Sponsor will provide data management support.

The study Sponsor will allocate qualified personnel to the present trial. All the figures involved in the study design, management and conduct are qualified according to Italian laws and regulations concerning clinical trials, and specifically trained on the objectives, procedures and instruments of this trial.

12.2 Publication of Data

Results derived from the trial are property of the Sponsor, which shares them with all participating investigators.

Every publication of the trial results will be written on the basis of the analyses performed by the Sponsor. Publications will be decided by the Sponsor. The name list at the end of each article will include all the other participants who contributed to study coordination and data analysis. Furthermore, all manuscripts will include an appropriate acknowledgment section.

Rules for abstract presentation will be the same as for extended papers.

12.3 Clinical Study Report

At the end of the study, clinical study report will be written and distributed to all centres.

12.4 Finances

The study is Sponsored by the IRCCS, Istituto di Ricerche Farmacologiche "Mario Negri" which plays the role of not-for-profit sponsor.

The AIRC-Italian Association for Cancer Research (Number IG2015-17274) supports the entire project study, providing also the economical support for the study.

12.5 Insurance

Not applicable.

12.6 Study timetable and end of study

The end of the study is defined as 'the last follow-up questionnaire of the last participant undergoing the study'.

The study is expected to start in September 2017 and to end in December 2018.

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14. APPENDIX

14.1 Appendix 2: Control group – Web brochure

Screening is a public health program where healthy population, at an age judged to be at risk, is invited by local health system to undergo free preventive examinations, such as mammography, Pap test or fecal occult blood test.

Screening may help anticipate cancer diagnosis and treatment, allowing less invasive surgical interventions. For breast cancer screening every woman, between 50 and 69 years of age, receives a letter of invitation with a fixed appointment to carry out a free mammography every 2 years. Scientific research has proven that screening for breast, uterus, and colorectal cancers can save many lives.

MAMMOGRAPHY

Currently, for women aged between 50 and 69, mammography is the most effective test to detect tumors that are not yet symptomatic and are not palpable.

It is a radiograph of the breast that uses very low X-ray doses.

To obtain a clear result it is necessary to compress the breasts. This compression can be bothersome or may cause slightly pain, but lasts a few seconds. The radiographer is highly qualified and the equipment used is technologically advanced and controlled. All this makes it possible to obtain images of excellent quality.

For greater security on the diagnosis, the images are examined separately by two radiologists to ensure greater accuracy. However, like all tests, it is not foolproof: in some cases, it may not recognize a tumor that is there or suspect a non-existent tumor.

WHY A MAMMOGRAPHY?

In Italy, breast cancer is the first cancer among women due to incidence, i.e. number of new cases of breast cancer in a year. It is the most common cancer among women, with tens of thousands new cases and 11,000 deaths. The mammography performed regularly allows an early diagnosis, before the onset of symptoms, and the possibility of intervening with a high probability of definitive recovery. Data support that, for every 1000 women aged between 50 and 69 years who regularly perform mammography, 7-9 lives are saved within 20 years.

WHAT ARE THE LIMITS OF THE MAMMOGRAPHY?

■ In general, every 100 women who had a mammography, about 5 must repeat the exam or undergo in-depth examinations. For 4 of them it is actually a "false alarms", as the in-depth analyses exclude the presence of a tumor (the so-called false positives). The disadvantage is mainly represented by the anxiety that a woman can experience in such situation.

■ Mammography is not always able to detect the tumor when it is present. In some cases the breast is very dense (i.e. it contains many glands) and this makes it difficult to detect the tumor (the so-

called false negatives).

■ In some cases the disease develops very quickly in the interval between two screening tests (so-called interval cancers). Even if the mammography did not show anomalies, it is important to pay attention to breast changes such as hardening, skin deformation, leakage of fluid from the nipple and the presence of axillary nodules. If you note such anomalies, you should contact your doctor immediately.

■ Some anomalies, among those detected by mammography, are not destined to become invasive tumors and to compromise the woman's health (the so-called overdiagnosis).

In these cases (1 case of cancer every 10 diagnosed) it is possible to have not necessary interventions. Unfortunately, this is inevitable as it is still not possible to distinguish from the beginning life-threatening tumors from the others.

WHAT CAN THE OUTCOME OF THE MAMMOGRAPHY BE?

■ If nothing suspicious appears, you will receive a negative result letter.

It is important to know that the purpose of mammographic screening is to identify malignant tumors recognizable by x-rays; other breast diseases are not considered.

■ If mammography shows doubtful images, you will be contacted and invited to go to the screening center to carry out in-depth examinations, which can include other mammography, echography or a collection of a small sample of breast tissue (biopsy). Most of these doubt cases are not due to the presence of a tumor, nevertheless it is necessary to perform these additional exams to be sure.

14.2 Appendix 1: Intervention group – Web decision aid. Content of decision aid.

Home-page

Dear Miss, thank you for having agreed to help us.

In a few weeks, you will receive an invitation to take part in an organized mammography screening program. According to the Italian Ministry of Health recommendations, based on scientific studies, the use of this test in the screening program can reduce mortality due to breast cancer among women of your age.

Obviously, the decision to participate or not is entirely up to you.

Here you will find some up-to-date information about mammography screening, its pros and cons, including the controversies and different opinions of experts.

We know that your choice will not be based only on this information but other aspects too will affect the decision: your life experience, your perception of the risk of developing this disease and your own values. These are very important aspects that drive many of our choices: they shall therefore recall at the end of the navigation when you make your final decision.

Before taking a decision, explore these pages, in your own time: the icon at the top "Where I am" will help you navigate When you feel you know enough, just click on "Ready to choose" at the bottom of the page.

What is mammography screening?

Mammography is a radiological breast examination that uses very low X-ray doses.

Mammography can identify lesions or nodes you cannot yet feel. This is why it is used for screening in women who have no symptoms or signs, so as to detect any breast cancers at an early stage.

It is advisable to take part in an organized mammography screening program because it is reliable, with quality control and a standard care schedule already sets up in case further examinations are required. Outside organized mammography screening programs there is no regular quality control by third parties, so quality is not guaranteed.

The mammography screening and any subsequent diagnosis and treatment (if necessary) within the organized mammography screening program are free of charge.

The pros and cons of mammography screening

Mammography screening can provide both benefits and harms, like any other medical examination.

Mammography does not prevent breast cancer but it helps find tumors in an early stage when there is less invasive and more effective treatment.

The main advantage is the reduction of mortality due to breast cancer for women who participate in the organized screening program.

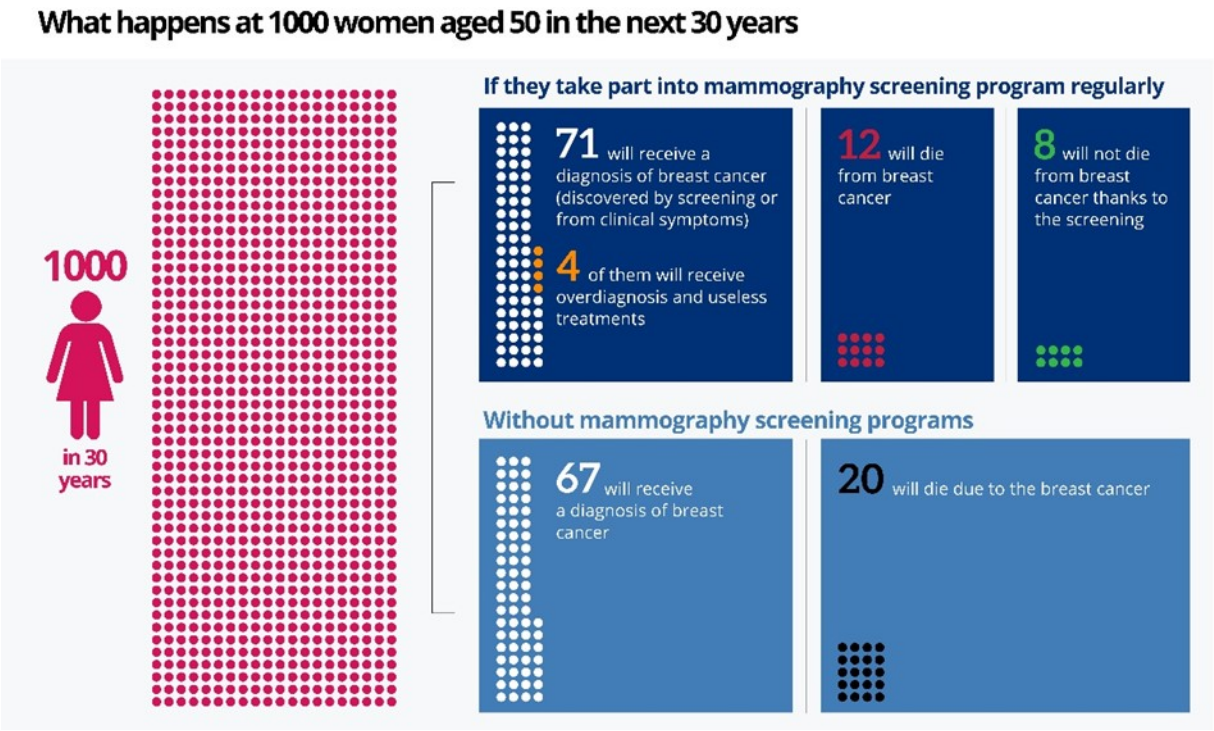
The principal disadvantage is harder to grasp. Sometimes there is unnecessary and useless treatment (overtreatment), and if it is useless it is harmful, of tumors discovered by the screening that would resolve themselves spontaneously during the woman's life (overdiagnosis). These malignancies look just like other tumors but either do not grow or grow very slowly. Unfortunately, so far there is no way to distinguish whether a tumor is actually not harmful, so all cases are treated and the woman will not know what her situation was.

It is only possible to estimate the reduction of mortality due to breast cancer by the mammography screening program, and of extra tumor diagnosis (overdiagnosis).

Participation in the screening provides the following benefits and harms to be assessed before taking a decision:

- Reduction of mortality due to breast cancer
- Overdiagnosis
- Less invasive treatments
- False positives or false negatives
- Radiation damage
- Inconvenience of the examination

What happens in the next 30 years?



Out of 1000 women aged 50 who regularly participate in a mammography screening program, in

the next 30 years:

- 71 will receive a diagnosis of breast cancer (discovered by screening or from clinical symptoms)
- 12 will die from breast cancer
- 8 will not die from breast cancer thanks to the screening
- 4 will receive overdiagnosis and useless treatments

If the same 1000 women are followed without a mammography screening program:

- 67 will receive a diagnosis of breast cancer
- 20 of them will die due to the breast cancer

In other words, in the next 30 years:

Some women will die from breast cancer anyway: 12 of the 1000 who participate in the mammography screening program compared to 20 if the screening program did not exist. Therefore 8 out of 1000 women are saved from death due to breast cancer; 4 of the 1000 women receive a diagnosis and are then treated uselessly for tumors detected by the screening that would probably never emerge. If there is no mammography screening program, there is no overdiagnosis and only evident tumors are treated.

At what age is mammography screening recommended?

In Italy the mammography screening program is carried out every two years for women aged 50-69 because there is impressive evidence of the reduction of mortality.

In some Italian regions (Emilia Romagna, Piedmont and Tuscany), the mammography screening program is extended to women aged from 45 to 49 every year and between 70 and 74 every two years. For these age bands the demonstration of the utility of screening is considered sufficient, though the balance of the related benefits and harms is still debated.

The European Code against Cancer (2015) confirmed the recommendation for women aged 50-69 to do the organized mammography screening and, in certain circumstances, also women aged 45-49 and 70-74.

The risks related to radiation

Mammography uses X-rays, namely high-energy radiation (also called ionizing) that may damage cells that absorb it, including the development of tumors. Mammography based on quality criteria employs low doses of X-rays so the risk of tumors developing is practically zero.

The amount of radiation from a mammography is comparable to that absorbed in a few weeks from "background radiation", meaning from radioactive substances in the ground and buildings and to which everyone is normally exposed.

Mammography is comparable to a chest X-ray and is much less dangerous than an abdominal tomography scan.

Comparison of doses of radiation from different examinations in adults

Method	***Effective dose in adults****	***Time needed to absorb the same dose from background radiation***
Computerized Bone Mineralometry	*0.001 mSv*	*3 hours*
Limb X-ray	*0.001 mSv*	*3 hours*
Intraoral X-ray	*0.005 mSv*	*1 day*
Chest X-ray	*0.1 mSv*	*10 days*
Mammography	*0.4 mSv*	*7 weeks*
Spinal X-ray	*1.5 mSv*	*6 months*
Upper abdomen X-ray	*6 mSv*	*2 years*
Chest computed axial tomography (CAT scan)	*7 mSv*	*More than 2 years*
Lower abdomen X-ray	*8 mSv*	*About 3 years*
Abdomen-pelvi CAT scan	*10 mSv*	*More than 3 years*

* The effective dose used for the comparison is quantified considering the type of radiation and the specific sensitivity of the body part involved; the measurement units are milliSievert (mSv).

Organized mammography screening program, a quality program

In the organized mammography screening program, all women of your age are regularly invited for a free mammography at a clinical center involved in the program that guarantees full assistance, for diagnosis and treatment of any breast cancer.

The quality of all Italian organized mammography screening programs, including the one you are invited to, is monitored and evaluated within national and international initiatives (see the sources above and on the right). Outside this program there is no way of judging, as there is no regular data collection.

At your appointment, a radiographer will take two X-rays for each breast from different angles. The breast is pressed between two plastic plates and this may cause slight discomfort. However, the stronger compression the less radiation you will receive and the more accurate will be the exam.

The X-rays are then assessed by two expert medical radiologists who read at least 5000 exams a year as a quality standard.

If all is well, you will receive a letter or an e-mail. If there is any doubt you will be contacted by phone.

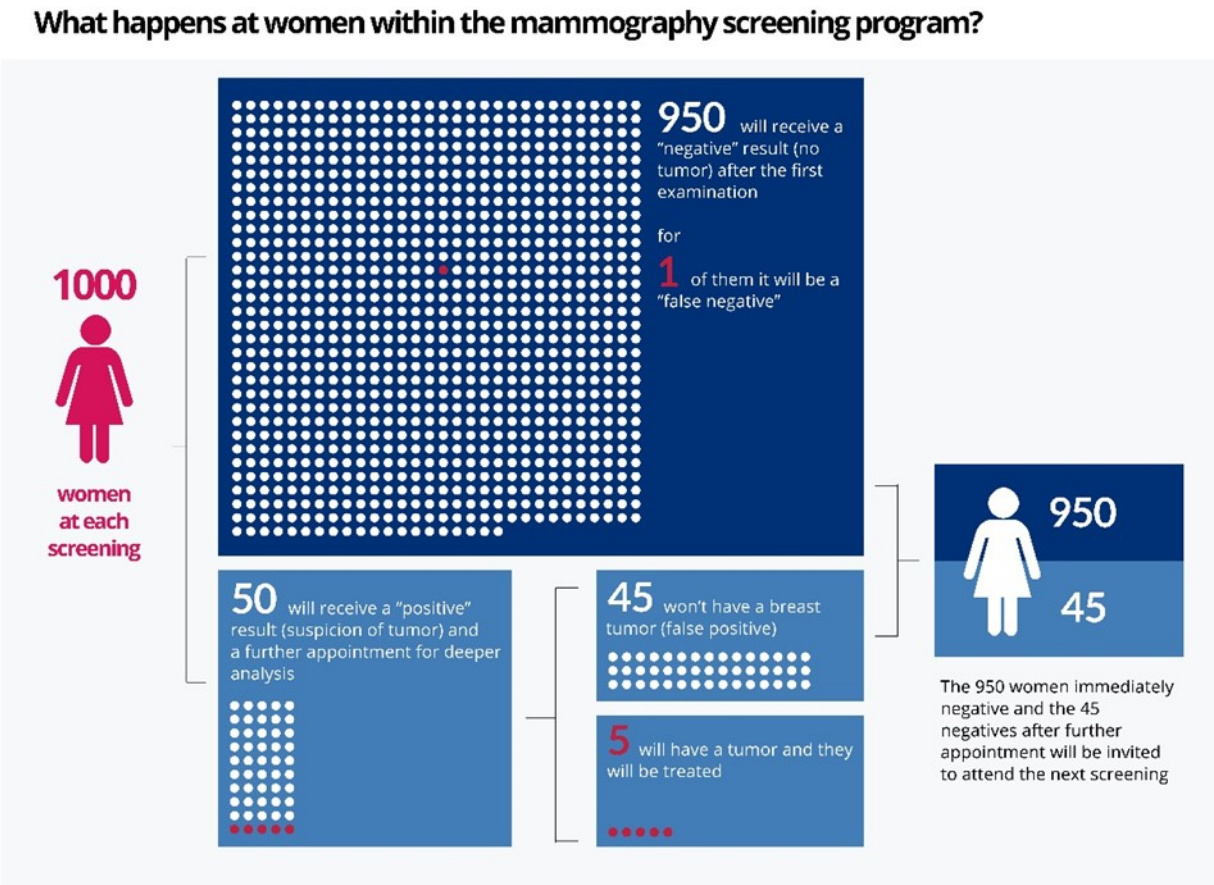
What result will the mammography give?

For most women, the result is normal, meaning nothing has been found (negative result). A negative result is reassuring but it does not mean no tumor will ever develop.

Rarely, the tumor can escape observation, (called "false negatives"), for example in hard-to-interpret cases, namely if the breast is dense, or it might develop between this screening mammography and the next invitation: these are referred to as "interval tumors". Therefore, talk to your doctor if you notice any changes in your breast between two exams, such as nodules you can feel, skin deformation or hardening, or a bleeding or retracting nipple.

A doubtful result or "positive mammography" means the radiologist has seen images like nodules, masses, calcifications or others that could signal a tumor and thus call for more investigation. This may cause you anxiety and concern but it does not imply a malignant disease. If the suspicion is not confirmed by further tests it is called a "false positive".

What happens at each screening?



Data from the Italian organized mammography screening program

In Italy, out of 1000 women participating in each screening, on average:

- 950 women will receive a "negative" result (no tumor) after the first examination and will be invited to attend the next examination; for 1-2 of them it will prove to be a "false negative";
- 50 women of the 1000 will receive a "positive" result (suspicion of tumor) and a further appointment will be set for deeper analysis.

Among these 50 women:

- for 45 of them, the suspicion of a tumor will prove unfounded (false positive) and they will be invited to attend the next screening;
- for the other 5 the suspicion will be confirmed and they will be treated in qualified centers.

In other words:

- In the majority of cases the mammography is normal (negative results for 950 out of 1000 women);
- Many doubtful cases prove normal after further analysis (false positive for 45 out of 50 women);
- There is the extremely rare possibility that a tumor is not identified (false negative). This may happen to 1-2 women out of 1000 and the tumor is generally discovered because of a nodule or breast lesion.

To discover what you can expect 30 years after taking part in a screening program, click here.

Diagnostic programs in uncertain cases

When the first mammography gives a doubtful result, the woman is invited for a breast examination and a second mammography and/or echography (both not invasive) to confirm or exclude the real presence of a tumor.

The breast examination is done by a skilled physician who will recognize visually and by palpation even small but significant breast changes.

When it is not possible to exclude a tumor even after further examinations, sampling the suspect nodule is generally suggested (biopsy or fine-needle aspiration): this occurs in about 30% of cases. The result of the biopsy is communicated by the physician who first visited the patient, at her next appointment.

Breast density

The breast comprises a glandular part and an adipose one (fat). When the adipose part is the main one the mammography profile is clear, while the appearance is denser when the glandular component is greater.

When the breast is dense the mammography is harder to interpret and a very small tumor may not be detected giving a “false negative” result.

Usually the density changes over time as the glandular part decreases with age. That explains why in general mammography is clearer in older women.

What is breast cancer and how can it be treated?

The risk of breast cancer depends on different factors (such as age, family history and life-style) and it is the female tumor that causes the most deaths (see chart 1 *I numeri del cancro in Italia. Rapporto AIOM AIRTUM, 2016).* Nowadays, there is every chance of a cure (see chart 2 *I numeri del cancro in Italia. Rapporto AIOM AIRTUM, 2016)* through the risk of recurrence remains for many years. The probability of a cure depends on the tumor’s biological features.

A tumor can appear in several forms and is caused by uncontrolled growth of breast cells that become malignant.

The tumor cells can grow (when inside the mammary gland this is defined as an *in situ tumor*) and migrate to other organs, in the form of metastasis. A metastatic tumor is harder to fight so prompt intervention is always important.

If the tumor is diagnosed at an early stage, usually treatment is less aggressive.

For most women with breast cancer only the tumor is removed, surgically, with its surrounding tissue, or the whole breast, depending on the extent of local disease. Other treatments, in addition and in different sequences, include radiotherapy, chemotherapy or hormone therapy, which are useful to reduce the chances of the disease recurring. Further therapies are possible or are being tested, especially with biologic drugs for specific groups of patients.

The main risk and protective factors

The risk of breast cancer depends on several factors that can be divided into two groups: those that are unchangeable and those that can be reduced by adopting a correct life-style.

Age: the risk rises with age and more than 75% of breast cancers are in women over 50.

Family history: some families report several cases of breast cancer among first-degree (mother-daughter) or second-degree relations (sisters).

Genes: BRCA1 and BRCA2 genetic mutations are responsible for almost half of hereditary breast cancers (5-7% of the total).

Age, family history and genetic patterns are factors to be considered in assessing one's own risk, though they cannot be change. In addition, other factors can influence the risk of breast cancer, raising or lowering it. For example, a high level of estrogen - the main female hormone - facilitates breast cancer. Any other factors that boost their expression, such as hormone replacement therapy (HRT) increase the risks. Pregnancies lower estrogens production, with a protective effect.

In general, a healthy life-style with a diet rich in fruit and vegetables (unrefined cereals, legumes, non-starchy vegetables, and fruit), less alcohol (no or only one glass of wine a day), weight control, especially after the menopause, can all be protective against breast cancer.

To reduce the probability of breast cancer

What to do	***What not to do***
Keep ideal weight (BMI <24,9 kg/m2) with a diet based on vegetables (unrefined cereals, legumes, starchy vegetables, and fruits), no alcohol or 1 glass of wine a day at the most	*Marked overweight (BMI>28) in menopause*
Follow the Mediterranean diet with a supplement of extra-virgin olive oil	*Suffer of metabolic syndrome after menopause*
Eat fruit and vegetable during adolescence (≥3 portions a day)	*Drink more than a single dose of alcohol a day (most risk during adolescence)*

What to do	***What not to do***
Physical activity (150 minutes of moderate intensity a week at least)	*Eat large amounts of red meat (≥3 a week)*
Eat fiber (around 30g a day benefits is greatest especially during adolescence)	*Smoke (most risk during adolescence)*
Follow a vegan diet though it is considered an incomplete diet	*Use HRT (hormone replacement therapy) in menopause*
Breastfeeding	

Differences between false positives and overdiagnosis

It is important to explain the differences between false positives and overdiagnosis.

A "positive result" is considered false when further examinations after mammography exclude breast cancer. "Overdiagnosis" instead means that there is a tumor, it is malignant but will not show itself in the rest of life. Unfortunately, it is still not possible to distinguish a tumor of this type so all are treated and the woman will never know what her situation really was.

The balance between benefits and harms

In medicine and healthcare a balance must be drawn up between positive effects (benefits) and negative ones (harm) to decide on the utility of an intervention. For mammography screening, the main benefit is the reduction of mortality due to breast cancer in the long-term, while the main harm is the risk of useless treatments.

Once the main results have been established, a balance must be set to gain an idea of their numbers: how many deaths due to breast cancer are avoided by screening programs? How much overdiagnosis is there, namely cases diagnosed in excess?

When the balance is positive, the health authorities can organize a screening program. Leading scientific authorities and societies, following different strategies, sometimes reach different conclusions on the benefits and especially on the harms.

How many fewer women die of breast cancer thanks to screening?	***How many excess tumors are diagnosed by the screening?***
The mortality reduction found by researchers is between 20% and 38%. The difference depends on the methods used to calculate these estimates, and no single one is universally considered better than another	*Overdiagnosis ranges from 5% to 30%. The difference depends on the methods used to calculate these estimates, and no single one is universally considered better than another*
How experts have calculated the mortality reduction due to breast cancer	*How experts have calculated overdiagnosis*

How are the rates of specific mortality reduction and overdiagnosis measured?

Current medical science bases its knowledge on the results of experimental or observational studies, on samples of the subset population. This rigorous method reduces the differences in opinion among physicians but does not eliminate them. The studies cannot give exact figures, but only a range of estimates that are probably close to the real figure (a bit like poll results for elections).

For mammography screening too, experimental and observational studies are analyzed. Experimental ones follow women for some time, dividing them into two groups: those who are take part in the periodical screening program; those who are not invited serve for "comparison". Each woman is assigned by chance, as if by tossing a coin, to one group or the other. Later, mortality rates and breast cancer frequency in both groups are measured and compared. Experimental studies about mammography screening (8 clinical trials between 1963 and 1991) have evaluated around 500,000 women aged 40-74 in Europe and North America. The observational studies we consider examined screening programs in the 2000s and refer to women included in the screening programs organized according to the European guidelines who received the first invitation for screening, most of them aged 50 and 74 years.

To reach the most reliable conclusion, decisions are based on the results of many studies, called systematic reviews, that analyze together the results of experimental or observational studies, even if they have some different features. A method to decide what type of studies to include (for example only experimental, only observational, or both) is needed in order to weigh their different quality.

Screening programs started on the basis of experimental study results, in the early 1990s. The age for starting screening was debated: 40 years in the USA and more than 50 in Europe (usually up to 69). After that, several research groups conducted systematic reviews of all the studies using methods and strategies for quality assessment that have given different results, leading to debate among the researchers themselves.
For further reviews of results about mortality rates click here; for those about overdiagnosis click here.

Different estimates of the reduction of mortality due to breast cancer

The main reviews considered are the recent ones by the Cochrane collaboration (systematic review of experimental studies updated to 2013) and the Independent UK Panel (2012) that also evaluated only experimental studies; the Euroscreen Group included only observational studies based on European programs (2012) (see the sources).

The Cochrane review of experimental studies considers all invited women aged 40-74 and followed for 13 years, and estimates around a reduction of 20% of specific mortality for the whole series of studies, and around 0% omitting the less reliable studies.

The Independent UK Panel review, based on the same experimental studies and on all invited women aged 40-74 and followed for 13 years, also found a 20% mortality reduction, considering all the sufficiently reliable studies.

The Euroscreen review of European observational studies estimated a reduction of mortality due to breast cancer around 25% for women aged 50-69 in an organized mammography screening program. In addition, the reduction of mortality due to breast cancer for women regularly participating in a mammography screening program was about 38%.

Both the Cochrane and the UK Panel estimates are based on the same studies but used different methods and definitions. Those used by the Euroscreen group were similar to those used by the UK Panel even though the former examined observational studies, so the three reviews are not directly comparable. The Euroscreen appraisal answers to the question of what a woman would expect on deciding to take part in a European screening program, concerning the reduction of specific mortality. Therefore, the planners of the screening program you are invited to attend consider the Euroscreen estimates as most reliable to inform individual choices.

Different overdiagnosis estimates

The main reviews considered are the recent ones by the Cochrane collaboration (systematic review of experimental studies updated to 2013) and the Independent UK Panel (2012) that also evaluated only experimental studies; the Euroscreen Group included only observational studies based on European programs (2012) (see the sources).

To quantify overdiagnosis:

- From a general population perspective, the question is: "Out of all the women aged between 50 and 80 years who receive a diagnosis of breast cancer, what is the proportion overdiagnosed by the screening?". To answer, the Euroscreen review in 2012, that included only observational studies, estimated that out of 1000 women aged 50 starting with a regular screening program, over the next 30 years 71 cancers will be found and 4 of them will be overdiagnosed and treated uselessly. That harm is around 5% in relative terms (measure A);
- From an individual perspective, the question is: "Participating in a screening program and receiving a diagnosis of tumor by the screening, what is the probability that it is an overdiagnosis?". The estimate is around 10% (measure B)

The difference is due in particular to the fact that measure B considers only women diagnosed due to the screening.

In the Independent UK Panel's review, based on three experimental studies, overdiagnosis reached about 11% when expressed as the proportion of all tumors found among the invited women (measure A), and 19% as the proportion of only tumors diagnosed during the active screening period (measure B).

The Cochrane review, based on several experimental studies (ages 40-74), analyzed the excess of treatments (mastectomies and conservative procedures), indirectly reaching an estimate of overdiagnosis around 30%, including - as the denominator - all tumors diagnosed in the control group at the end of the follow-up.

The Cochrane and UK Panel's estimates are both based on experimental studies but used different methods and definitions. Those used by the Euroscreen group were similar to those used by the UK Panel but analyzed observational studies, so the three reviews are not directly comparable.

Who we are

This project is coordinated by IRCCS Istituto di Ricerche Farmacologiche Mario Negri in collaboration with Lega Italiana Lotta contro i Tumori-Firenze, Zadig Agenzia di Editoria Scientifica, GISMa Gruppo Italiano Screening Mammografico and with Prevenzione Serena di Torino, dell'Unità Operativa Centro Gestionale Screening di Palermo e dell'Istituto per lo Studio e la Prevenzione Oncologica di Firenze.

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14.3 Appendix 3: baseline and follow-up questionnaires

BASELINE QUESTIONNAIRE

SOCIODEMOGRAFIC

Nationality:

a) Italian

b) Other, please specify_____

Education

☐ Elementary

☐ Lower middle

☐ Higher middle

☐ Degree

☐ Other

Marital status

☐ Single

☐ Married or living together

☐ Separated or divorced

☐ Widowed

Employment status

☐ Paid work (full or part time)

☐ No paid work (retired, housewife, other)

Do you use internet to search for health information?

☐ Never

☐ A few times a month

☐ At least once a week

☐ Several times a week

☐ Daily

Have you already had a mammography?

☐ Yes, in a public facility, when? _____(year)

☐ Yes, in a private facility, when? _____(year)

☐ No

Has anyone in your family or your friends had breast cancer?

☐ Yes

☐ No

Have you ever had a tumor?

☐ Yes If Yes, type of tumor _____

☐ No

Have you participated in other organized screening programs?

Fecal occult blood tests for colorectal cancer ☐ Yes ☐ No

Pap test for cervical cancer ☐ Yes ☐ No

PERCEIVED RISK

Perceived risk of breast cancer relative to the average woman

Much lower	A bit lower	About the same	A bit higher	Much higher

KNOWLEDGE

What is a SCREENING mammogram?

☐ A mammogram you have when you're healthy

☐ A mammogram you have if you notice a change or lump in your breast

An organized mammography screening program can detect a breast cancer in an early stage and lead to less invasive surgery and treatment

☐ True

☐ False

Which of the following statements about mammography reflects your opinion?

***Regular mammography every two years in women who are well*:**

☐ Prevents the risk of breast cancer

☐ Does not prevents the risk of breast cancer

Who do you think is more likely to die from breast cancer?

☐ Women who have screening mammograms

☐ Women who do not have screening mammograms

Do you think a screening mammogram will find every breast cancer?

☐ Yes

☐ No

Do all women with an abnormal screening mammogram result have breast cancer?

☐ Yes

☐ No

Which of these 2 statements best describes over-detection?

☐ Screening finds a cancer that would never have caused trouble

☐ Screening finds an abnormality but extra tests show it is not cancer

Screening leads some women with a harmless cancer to get treatment they do not need.

☐ True

☐ False

In the organized mammography screening program, the presence of two expert radiologists increases the ability to identify a breast tumor

☐ True

☐ False

The usefulness of an organized mammography screening program is:

☐ Totally recognized by doctors and researchers

☐ Questioned by some doctors and researchers

For the next few questions, I would like you to imagine 1000 ordinary women who are 50 years old who have participated regularly in organized mammography screening program for 30 years

How many women do you think will avoid dying from breast cancer because of screening?

☐ 8

☐ 50

☐ 150

How many women do you think will be diagnosed and treated for a breast cancer that is not harmful?

☐ 4

☐ 25

☐ 70

Now, I would like you to imagine 1000 ordinary women who are 50 years old who have not participated in organized mammography screening program, in their next 30 years…. How many die of breast cancer?

☐ 20

☐ 80

☐ 140

ATTITUDE

For you, having breast screening is…..

A bad thing						Not a bad thing
	1	2	3	4	5	
Beneficial						Not beneficial
	1	2	3	4	5	
Harmful						Not harmful
	1	2	3	4	5	
A good thing						Not a good thing
	1	2	3	4	5	
Worthwhile						Not worthwhile
	1	2	3	4	5	
Important						Unimportant
	1	2	3	4	5	

INTENTION

Intending to be screened

Definitely will	Likely to	Unsure	Not likely to	Definitely will not

FOLLOW-UP QUESTIONNAIRE

ATTITUDE

For you, having breast screening is…..

A bad thing 1 2 3 4 5 Not a bad thing

Beneficial 1 2 3 4 5 Not beneficial

Harmful 1 2 3 4 5 Not harmful

A good thing 1 2 3 4 5 Not a good thing

Worthwhile 1 2 3 4 5 Not worthwhile

Important 1 2 3 4 5 Unimportant

SATISFACTION/ACCEPTABILITY OF THE INFORMATION

Thinking back to the type of information material you have read ...			
Was there enough information?	Too much	Too little	Fair
Was the information on benefit new to you?	All or almost all	Some	None
Was the information on harm new to	All or almost all	Some	None

you?			
Was the information clear?	All or almost all	Some	None
The information seemed…	In favor of screening	Balanced	Against screening
Didi t help you to decide?	Yes	Not much	No
Would you recommend it to other women?	Yes	Not much	No
Only for Decision-Aid Was the controversy new to you?	All or almost all	Some	None

DECISIONAL CONFLICT (SURE QUESTIONNAIRE)

Sure of myself

Do you feel SURE about the best choice for you?

☐ Yes

☐ No

Understanding information

Do you know the benefits and risks of each option?

☐ Yes

☐ No

Risk-benefit ratio

Are you clear about which benefits and risks matter most to you?

☐ Yes

☐ No

Encouragement

Do you have enough support and advice to make a choice?

☐ Yes

☐ No

INTENTION

Intending to be screened

Definitely will	Likely to	Unsure	Not likely to	Definitely will not

KNOWLEDGE

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