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► To cite this version:

Emerline Assogba, Agnès Dumas, Anne-Sophie Woronoff, Caroline Mollevi, Charles Coutant, et al.. Cross-sectional nationwide mixed-methods population-based study of living conditions, and identification of sexual and fertility profiles among young women after breast cancer in France: the Candy study protocol. *BMJ Open*, 2022, 12 (9), pp.e056834. 10.1136/bmjopen-2021-056834 . hal-03812516

HAL Id: hal-03812516

<https://hal.science/hal-03812516v1>

Submitted on 1 Jun 2023


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BMJ Open Cross-sectional nationwide mixed-methods population-based study of living conditions, and identification of sexual and fertility profiles among young women after breast cancer in France: the Candy study protocol

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To cite: Assogba ELF, Dumas A, Woronoff A-S, *et al.* Cross-sectional nationwide mixed-methods population-based study of living conditions, and identification of sexual and fertility profiles among young women after breast cancer in France: the Candy study protocol. *BMJ Open* 2022;**12**:e056834. doi:10.1136/bmjopen-2021-056834

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-056834>).

Received 26 August 2021
Accepted 20 July 2022



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ABSTRACT

Introduction At the end of the treatment, many young breast cancer (BC) survivors face difficulties related to fertility and sexuality, mainly due to the side effects of treatment. Integrating patient needs into medical decisions is becoming increasingly essential for high quality care. To this end, there is a compelling need to elicit patients' perspectives through qualitative studies, to understand their experiences and needs in the aftermath of cancer. We aim to: (1) identify clinical, social and economic determinants of sexuality and fertility, and describe other living conditions of young BC survivors in France; and (2) explore young women's experience after BC in relation to clinical and information needs about fertility preservation and sexual health.

Methods and analysis This is a mixed-methods, cross-sectional, population-based study. In the quantitative component, women diagnosed with non-metastatic BC between 2009 and 2016 and aged 40 years or younger at diagnosis will be identified through the French network of cancer registries (FRANCIM). Participants will complete self-report questionnaires including standardised measures of sexuality, health-related quality of life (HRQoL), anxiety, depression, social deprivation and social support. Fertility and professional reintegration issues will also be assessed. Sexuality profiles will be identified by ascending hierarchical classification and fertility profiles will be identified by latent class models. Determinants of sexuality, fertility and HRQoL will be identified using a mixed regression model. Subsequently, semistructured interviews will be performed with a sample of 30 women who participated in the quantitative study. Interviews will be recorded, transcribed synthetically and content analysis will be performed, with the aid of NVivo software.

Ethics and dissemination This study will be performed in accordance with the declaration of Helsinki. The protocol was approved in October 2020 by the Committee for the Protection of Persons North-West III (20.07.16.44445) and by the French national data protection authority (CNIL-MR003 No1989764-v0).

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is a nationwide mixed-methods study using the databases of all French cancer registries, which are representative of regionally treated patients, enabling assessment of long-term outcomes. A mixed-methods combines quantitative and qualitative approaches, to take advantage of the complementarity of these two approaches.
- ⇒ In this study, sexuality, health-related quality of life (HRQoL), social support, social deprivation and psychological outcomes will be assessed using validated instruments.
- ⇒ This study will encompass most aspects of postcancer life in young women after breast cancer (sexuality, fertility, HRQoL, return to work, psychological distress, social support, right to be forgotten, access to mortgage insurance and difficulties obtaining a loan).
- ⇒ A major limitation of the study could be the amount and type of missing data. Moreover, sexuality, which is one of the main endpoints of the study, may raise concerns about missing data due to the fact that it is a sensitive issue.
- ⇒ The cross-sectional study design cannot determine causality and may raise concerns about recall bias, given that the questions are about events at diagnosis or during treatment.

The results of this project will be communicated to the scientific community through publications in international scientific peer-reviewed journals and communications to national and international congresses. Popularised results will also be provided to patient associations. The results of Candy project will also be published on the website of the sponsor, www.cgfl.fr.

INTRODUCTION

Breast cancer (BC) is the most frequent cancer and the leading cause of death by cancer in women, in France and around the world.¹ Survival after BC varies from one country to another.² In France, in women under 40 years old, an increase in the incidence of the disease has been observed, associated with a decrease in mortality, with respective annual variations of +0.9% and -1.6%.³ The 5-year net survival of women aged 40 or younger who are diagnosed with BC in France improved from 83% in 1990 to 93% in 2015.⁴ In recent decades, this improvement in survival has raised the question of improving the living conditions of survivors, with particular attention paid to sexuality, problems related to fertility, the right for their disease 'to be forgotten', access to mortgage insurance, difficulties obtaining loans and the socioprofessional reintegration of young women.⁵⁻¹¹ In fact, cancer affects more and more people with plans for pregnancy at diagnosis and who, at the end of treatment, face difficulties with fertility, sexuality and professional reintegration. The difficulties related to sexuality and fertility are mainly the consequences of the side effects of treatment.^{12 13} However, they may also result from a lack of communication and information about the side effects of treatment and fertility preservation techniques between the patient and the healthcare provider at the time of the consultation announcement. Moreover, this communication between the patient and the healthcare provider is a decisive factor in early referral of BC patients to a reproductive specialist at diagnosis.¹⁴ Young survivors also have a long professional life ahead of them. Returning to work is an important step in their recovery (in terms of health-related quality of life (HRQoL), mental and physical health).¹⁵ Therefore, attempts to improve the living conditions of young women after BC must address sexuality, fertility and professional reintegration. In this perspective, one of the measures listed under Objective 7 of the 2014–2019 cancer plan in France recommends allowing everyone to take an active role in their own care, with the aim of providing comprehensive and personalised care,¹⁶ and to involve patients in the medical decisions that concern them.¹⁷

To achieve this objective, it is first necessary to identify the needs considered to be priorities by women in their care, from diagnosis through to recovery after cancer. There is a compelling need to question women about their perceptions and feelings, and this will be the aim of the qualitative component of the present project. Several qualitative studies carried out in Australia,¹⁸ Norway¹⁹ and the USA,²⁰ as well as mixed-methods studies carried out in Australia²¹ and the USA²² in women with BC have explored this question. From these studies, it emerged that the most important aspects include the lack of information about the side effects of treatment in general, and in particular, on fertility and fertility preservation, giving the impression of a feeling of surprise in these women. In addition, women with BC often do not communicate their sexual concerns during routine consultations as part of

their care. Therefore, clinicians specialising in BC should address the issue of sexual health for all patients. Another important aspect mentioned by patients is their family,²³ and health professionals need to be aware of the possible needs of families accompanying young women with BC, to assess their adaptation to changing circumstances, and intervene by providing information and counselling to enhance coping.²⁴

To the best of our knowledge, few population-based studies addressing these questions have been conducted on young BC survivors in the world²⁵ or in France. In France, the study 'Life 5 years after a cancer diagnosis' (VICAN5), which sampled patients on the basis of health insurance data, investigated living conditions after cancer in cancer survivors of all ages including young survivors at 5 years after diagnosis.²⁶ The results showed that most young survivors reported sexual dysfunction and had unmet needs for information on fertility aspects. A preliminary study that we carried out on the same topic using data from the specialised Breast and Gynaecologic Cancer Registry of the Côte d'Or Department in France reported similar results.²⁷ Although studies mostly report sexual dysfunction and fertility-related problems in young women, the effect of cancer on sexuality depends on the treatment, the disease severity and how each woman experienced her sexuality before the onset of the disease.^{28 29} Regarding fertility-related difficulties after BC, they cannot be attributed solely to the treatment effects on ovarian function, but may also possibly be due to fertility-related difficulties before the BC diagnosis, and to life circumstances, like their conjugal relationship. It is therefore necessary to identify the fertility and sexuality profiles of young women with BC, as well as their clinical and socioeconomic determinants. These studies of quantitative parameters enable us to observe frequencies, practices, satisfaction and expectations, but in no way explain the reasons that underpin the existence of these situations. Only qualitative studies can enable us to understand the mechanisms of opinion, and understand the motives that guide the thoughts and practices of young survivors. To the best of our knowledge, few qualitative studies have explored aspects relating to sexuality and fertility in young women after BC in France.

Using data from the French network of cancer registries (FRANCIM), we will perform an explanatory mixed-methods, cross-sectional study, which will exploit the full complementarity of the quantitative and qualitative approaches.

Aims of the study

The Candy project comprises a quantitative and a qualitative component.

Quantitative component

The primary aim of the quantitative component of the study is to identify the clinical, social and economic determinants of fertility and sexuality among young BC survivors. Second, we aim to identify the sexuality and fertility

profiles, identify determinants of HRQoL, and describe other life conditions of young BC survivors (psychological distress, social and professional reintegration, right to be forgotten, access to mortgage insurance and difficulties obtaining a loan).

Qualitative component

In the qualitative component of the present project, we aim to describe and understand the experiences of young women after BC, with regard to clinical and information needs on fertility preservation and sexual health. In addition, we will attempt to understand the difficulties related to sexual health that women face after BC, examine the scope and content of information transmitted on fertility and sexuality during routine appointments during the management of BC and identify unmet support needs.

METHODS AND ANALYSIS

Study design

This is a mixed-methods, convergent, cross-sectional study using questionnaires and semistructured interviews. All registries of the FRANCIM network, which performs epidemiological surveillance of BC in France, will participate in this project, namely the specialised Breast and Gynaecologic Cancer Registry of the Côte d'Or; metropolitan general Registries (Bas-Rhin, Calvados, Doubs, Gironde, Haut-Rhin, Hérault, Isère, Loire-Atlantique et Vendée, Lille et sa Region, Limousin, Manche, Poitou-Charentes, Somme and Tarn) and the overseas general Registries (Guadeloupe, Guyane and Martinique). Cancer registries offer a unique opportunity to obtain exhaustive records of all cancer cases that have occurred in the departments covered, thus limiting selection bias. The 18 registries involved cover 23 French metropolitan and overseas departments, representing 27% of the French population. A simplified protocol diagram of Candy project is shown in [figure 1](#).

Selection of participants

Quantitative component

Eligible patients must meet all the following inclusion criteria: (1) women; (2) aged between 18 and 40; (3) histologically proven non-metastatic invasive BC (may include adenomyoepithelioma with carcinoma); (4) diagnosed between 1 January 2009 and 31 December 2016; (5) without progression (local relapse or distant metastasis) between the time of diagnosis and 31 December 2020; (6) living in France at the time of diagnosis and (7) alive on 31 December 2020. Women who present any one or more of the following characteristics will not be included in the study: (1) age at diagnosis <18 years or >40 years; (2) metastatic BC at diagnosis or secondary metastasis; (3) in situ BC at diagnosis; (4) second cancer occurring after the diagnosis of primary BC regardless of the location and type of the second cancer; (5) history of cancer (s) in situ or invasive (whatever the location and type) before the diagnosis of primary BC; (6) relapse

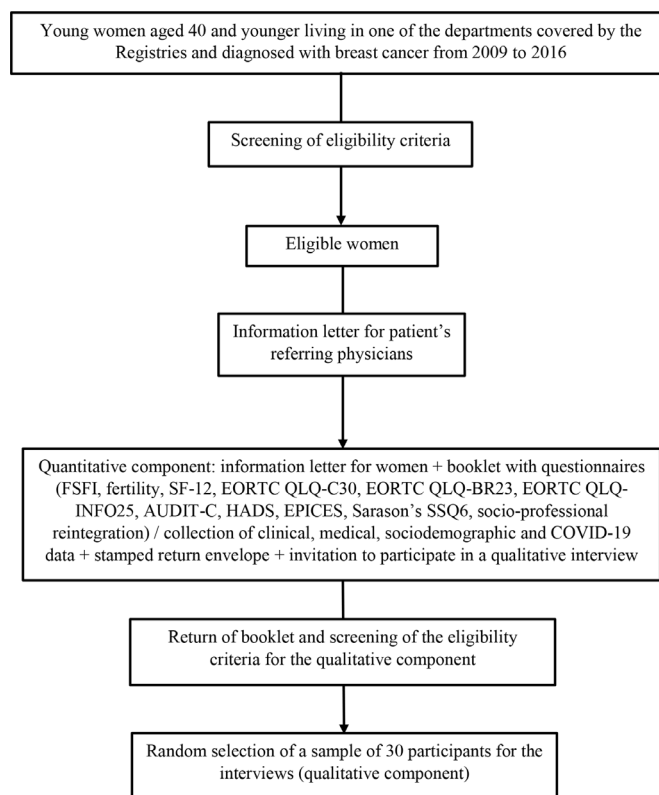


Figure 1 Simplified protocol diagram of Candy project. AUDIT-C, Alcohol Use Disorders Identification Test-Consumption; EORTC, European Organization for Research and Treatment of Cancer; EPICES, Evaluation de la Précarité et des Inégalités de santé pour les Centres d'Examen de Santé; FSFI, Female Sexual Function Index; HADS, Hospital Anxiety and Depression Scale; SF-12, Short Form 12; Sarason's SSQ6, Sarason's Social Support Questionnaire.

(local recurrence, in the form of an in situ or infiltrating contingent or at a distance); (7) bilateral tumours; (8) lymphoma, sarcoma, phyllodes tumours, Paget's disease with or without underlying invasive cancer and death between the time of diagnosis and 31 December 2020.

A sample of 2500 women will be drawn at random from among all eligible women. Once selected, the surname, first name, postal address of women as well as those of their referring physicians will be collected by each Registry. In June 2021, each Registry will provide the patient's referring physicians with information about the study and will inform them that their patients will be approached for participation. Two weeks later, each Registry will send a study information pack by post to eligible participants, including an information leaflet about the quantitative component, the booklet containing the various study questionnaires, an invitation to participate in the qualitative interview and a stamped return envelope for the return of booklet and invitation form. A reminder will be sent to patients who have not responded within 1 month. The information leaflet about the quantitative component will disclose exactly how the data will be used. The booklet will contain the Female Sexual Function Index (FSFI) questionnaire; Medical Outcomes Study Short

Form 12 (SF-12); European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30; EORTC QLQ-BR23; EORTC QLQ-INFO25; Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) questionnaire; Hospital Anxiety and Depression Scale (HADS) questionnaire; the French 'Evaluation de la Précarité et des Inégalités de santé pour les Centres d'Examen de Santé' (EPICES) questionnaire; Sarason's Social Support Questionnaire (SSQ6); additional questionnaires evaluating professional reintegration and collecting fertility data, sociodemographic data (age, weight, height, level of education and place of residence), COVID-19 data (care organisation, medical monitoring and impact of the health crisis), medical data, diagnostic data and data on tobacco consumption. For patients who respond, the data collected from the booklets will be supplemented by confidential medical data from the Registries. At this stage of the study, each patient will be represented by a unique confidentiality code both for the data in the booklet and for the data from the Registries. The booklet has been tested among a small sample of patients from the 'Jeune&Rose' association; a French national network of young patients who provide mutual support, and share and relay prevention messages.

The data from the booklet for the quantitative component will be entered into a database created using ClinSight software, a software package designed for the management of clinical studies. A data validation plan will be developed and will describe in detail the checks to be performed for each variable. Entries will be checked using error messages from validation programmes. The database will be frozen after a final quality control according to an automated and validated procedure. Using the confidentiality code, this database will be merged with the confidential database containing the participants' data collected from the Registries. It will only contain the data necessary for this study. No nominative data will be used during the analysis of the data from the booklet and Registries in the quantitative part of the study.

Qualitative component

Subsequently, presence-based semistructured interviews lasting approximately 45–60 min will be carried out by a sociologist trained in qualitative methods in a sample of approximately 30 women who participated in the quantitative component, until data saturation is reached. This sample will be drawn at random from among eligible women who answered the questionnaires in the booklet and who expressed difficulties relating to sexual function (women with sexual dysfunction according to the global FSFI score) or fertility (women having difficulty getting pregnant since BC diagnosis among those who wanted to become pregnant). The selection will be stratified by department, age and deprivation score. On the day of the interview, an information leaflet specific to the qualitative component will be given to each participant and their consent will be obtained. The interviews will be conducted at the participants' homes or any other place

at their convenience, using an interview guide in which the topics to be addressed will be defined beforehand.

Interviews will be recorded and fully transcribed. No nominative data will be used during the analysis of data from the qualitative interviews. Once the interview is transcribed, the voice recording will be destroyed. During the interview transcription, any personal or identifying data (direct or indirect) will be deleted.

Endpoints

Primary endpoints

The main outcomes of this study will be six subscales of sexual function and fertility, which will be assessed respectively by the FSFI questionnaire and a fertility study-specific questionnaire. The fertility of young women will be assessed by the number of pregnancies that have occurred since BC diagnosis in women who wanted to become pregnant, using a study-specific questionnaire developed with the help of oncologists, clinicians and surgeons.

Secondary endpoints

The secondary endpoints will be as follows: HRQoL scores assessed by the SF-12, EORTC QLQ-C30, EORTC QLQ-BR23 and EORTC QLQ-INFO25 questionnaires; anxiety and psychological distress scores assessed by the HADS questionnaire; social support availability and satisfaction scores evaluated by the SSQ6 questionnaire; socio-economic deprivation scores assessed using the EPICES questionnaire and professional reintegration assessed in these young women using another study-specific questionnaire developed in conjunction with sociologists and psychologists.

Data collection

Quantitative component

The data that will be collected in the booklet are shown in tables 1–3. The data collected from the booklet will be supplemented by data extracted from the cancer registries participating in the study, namely age at diagnosis, tumour stage, tumour grade, hormone status, Human Epidermal Growth Factor Receptor 2 (HER2) status, KI67 index and type of treatment (surgery, radiotherapy, chemotherapy, endocrine therapy, ovarian function suppression and targeted therapies). Tumour stage will be categorised and the analyses will be performed on the American Joint Commission of Cancer (AJCC) condensed stage according to the 8th edition of Tumour Nodes Metastasis (TNM)-AJCC classification.³⁰

Qualitative component

Data for the qualitative component will be generated during semistructured interviews performed using an interview guide that will be finalised on the basis of the results of the quantitative component. The interview guide will be created by the Human and Social Sciences teams and tested in a few patients who respond to the quantitative component and who would be eligible for the qualitative component of the study.

Table 1 Sexual function, fertility and HRQoL data collected in the questionnaire booklet sent to patients during the quantitative component

Questionnaire modules	Brief description
Sexual function module (FSFI questionnaire)	The FSFI questionnaire is a self-report questionnaire specific to sexual function in women. It was developed by Raymond Rosen ³⁷ and a French version has been validated. ³⁸ Through its 19 items, it optimally explores six scales (desire, excitement, lubrication, orgasm, satisfaction and pain) of sexual function. Global score ranges from 2 to 36; an overall score <26.5 corresponds to sexual dysfunction. For each scale, a score <3.9 is considered as a deterioration on that scale.
Fertility data module	Fertility concerns will be assessed using a study-specific questionnaire developed in conjunction with oncologists, clinicians and surgeons. The items of this module were created for the needs of the study on the basis of clinical routine and diverse French population-based surveys. ^{26 27 39 40} This study does not plan to validate the use of this fertility data module. The purpose of this questionnaire is to assess postcancer fertility in young women who have had BC. Fertility will be quantified by the number of pregnancies that have occurred since the diagnosis of BC. Other data will also be collected, that is: menstrual cycles before and after treatments, parity before and after diagnosis of BC, pregnancy plans at diagnosis and at the end of treatment, information on treatment effects and fertility preservation before treatment, fertility preservation techniques, adoption and current menopausal status.
HRQoL module	
SF-12	The SF-12 is a generic questionnaire designed to measure the HRQoL of a general population without specificity regardless of the pathology or even in the absence of pathology. This questionnaire was validated and adapted in French as part of the IQOLA project (International Quality of Life Assessment). ⁴¹ The questionnaire describes HRQoL in 8 dimensions using 12 items: general health, physical functioning, role physical, role emotional, bodily pain, mental health, vitality and social functioning. A score is calculated for each dimension, it is then possible to calculate an aggregate score of physical HRQoL (Physical Composite Score) as well as an aggregate score for social and mental HRQoL (Mental Composite Score). ⁴² Each of the scores ranges from 0 to 100; 100 representing the best HRQoL for the dimension concerned.
EORTC questionnaires	The EORTC questionnaires used in this study are validated in their French-language version and are available on the EORTC website (https://qol.eortc.org/questionnaires/).
EORTC QLQ-C30	The EORTC QLQ-C30 is a self-report questionnaire developed and validated in French by the Quality of Life group (QLG) of the EORTC. ⁴³ It assesses 5 functions, 9 symptoms and the overall health of patients through 30 items. ⁴⁴ Standardised scores are calculated such that 0 corresponds to the worst HRQoL and 100 to the best HRQoL for the multi-item dimensions. With regard to symptoms, 0 corresponds to their absence and 100 to their permanent presence.
EORTC QLQ-BR23	The BC-specific EORTC QLQ-BR23 questionnaire is an additional module of the EORTC QLQ-C30 questionnaire. It contains 23 items to assess 4 functional dimensions (body image, sexual functioning, sexual pleasure and future prospects) and 4 symptomatic dimensions (symptoms related to treatment, symptoms in the arm, symptoms in the breast, anxiety related to hair loss) specific to BC and its treatment options. The scoring method of this additional module is the same as for the EORTC QLQ-C30. Published in 1996, it has been translated into >60 languages including French. ⁴⁵
EORTC QLQ-INFO25	The EORTC QLQ-INFO25 questionnaire was also developed by the EORTC QLG. Through 25 items, this instrument evaluates the level of information that patients received about different areas of their disease, treatment and care and evaluates the qualitative aspects. It generates 4 subscales of disease information (4 items), medical examinations (3 items), treatments (6 items), and other services (4 items) and 8 single items. The 8 single items assess information on other areas and satisfaction with the information provided. The scoring method of the information module is the same as that of the EORTC QLQ-C30. ⁴⁶
BC, breast cancer; EORTC, European Organization for Research and Treatment of Cancer; FSFI, Female Sexual Function Index; HRQoL, health-related quality of life; SF-12, Short Form 12.	

The interviews will cover the following topics in particular: healthcare pathway; experience of the impact of treatment on fertility and sexual health, in light of the woman's life trajectory and her current marital and family situation; information received about the treatment effects on sexuality and fertility, and about fertility preservation; the motivations and subjective logic linked to abandoning plans for pregnancy at the end of treatment; opinion on research priorities in the field of sexual health after BC and advice on ways to improve sexual healthcare for women.

Sample size

The approximate number of women aged 40 and younger at the time of diagnosis of BC from 1 January 2009 to 31 December 2016, according to data from the centralised database at the 'Hospices Civils de Lyon' of cancer registries participating in the project is 5119 cases (figure 2). After this first selection, each Registry will perform a second round of selection by excluding patients presenting the following criteria: relapse, metastasis, death or other cancers occurring after the diagnosis of primary BC as of 31 December 2020. Each Registry will

Table 2 Lifestyle habits, anxiety, depression, deprivation, social and professional data collected in the questionnaire booklet sent to patients during the quantitative component

Questionnaire modules	Brief description
Module on lifestyle habits	Consumption of alcohol and tobacco will be recorded. Data on alcohol consumption will be collected using the validated French version of AUDIT-C questionnaire. AUDIT-C is a 3-question screening test to reveal problematic alcohol use. ⁴⁷ A score ≥ 3 in women should suggest misuse, while a score ≥ 10 suggests dependence.
Anxiety and depression module (HADS questionnaire)	The HADS questionnaire validated and adapted in French by Lepine <i>et al</i> ⁴⁸ will be used to detect anxiety and depressive disorders. This scale has 14 items rated from 0 to 3 and describes two dimensions, anxiety and depression, with subscale scores ranging from 0 to 21. A subscale score of 11 or more indicates the presence of anxiety or depression.
Module on socioeconomic deprivation (EPICES questionnaire)	Socioeconomic deprivation will be assessed using the French EPICES questionnaire. ⁴⁹ This questionnaire developed specifically for the French context, contains 11 items that take into account the overall living conditions and generates a deprivation score. Scores vary from 0 to 100 and allow classification of patients as deprived or not deprived (>30 and ≤ 30 , respectively).
Module on social life	Social support will be assessed by Sarason's social support questionnaire (SSQ6) validated and adapted in French by Rasclé <i>et al</i> . ⁵⁰ This 6-item questionnaire measures the availability of social support and the satisfaction with the perceived support. Availability scores range from 0 to 54 and satisfaction scores range from 6 to 36. ⁵¹ A higher social support satisfaction score represents better perceived social support. Additional questions on social life including the following data will be collected: being in contact with a patient association or a social worker, having received psychological assistance following the diagnosis of BC and the role played by spiritual life or religion.
Professional life module	Professional reintegration will be evaluated using another study-specific questionnaire developed in conjunction with sociologists and psychologists. The questionnaire gathers items from diverse French population-based surveys. It includes items from a large survey on cancer survivorship named VICAN. ^{26 40 52} These items were tested in an exploratory sample of 74 people with cancer in April 2004. It provided information on the impact of cancer on work, access to loans and professional reintegration. These items, not captured by any validated questionnaire, deal with factual elements about work. This study does not provide for any validation plan for the use of the professional life module. Data collected include problems relating to obtaining loans, income since diagnosis, ability to work (after treatment and at the time of the survey), impact of cancer and perceived discrimination in the patient's professional life.

AUDIT-C, Alcohol Use Disorders Identification Test-Consumption; BC, breast cancer; EPICES, Evaluation de la Précarité et des Inégalités de santé pour les Centres d'Examen de Santé; HADS, Hospital Anxiety and Depression Scale; Sarason's SSQ6, Sarason's Social Support Questionnaire.

perform a final update just before sending the questionnaire booklets to the patients. Then, 2500 women will be drawn at random from among all eligible women after these two rounds of selection. Assuming a participation rate in the study of 50% (rate obtained from previous questionnaire surveys carried out within the Côte d'Or Breast and Gynaecologic Cancer Registry), approximately

1250 participants are expected.^{27 31–33} Bonferroni correction will be used to take into account of the multiplicity of tests, due to the use of a composite endpoint (sexual function and fertility) and the adjusted α -risk will be set at 2.5%. The sample size was calculated to make it possible to demonstrate an OR of 2.5 for women treated with chemotherapy not to have a pregnancy after BC (7%)^{34 35}

Other data collected in the questionnaire booklet sent to patients during the quantitative component

Questionnaire modules	Brief description
Module on collecting sociodemographic data	The data to be collected are the date of birth, the number of people living in the woman's household.
Module on medical data collection and diagnosis	Weight, height, dominant arm, disease announcement, hospitalisation and/or treatment for disease progression, treatments received and comorbidities will be collected.
COVID-19 data module	This module aims to understand the organisation of care and medical monitoring during the COVID-19 pandemic, and the possible impact that the health crisis may have had on patients. The data to be collected are: organisation of medical appointments (oncologist, surgeon, radiotherapist ...); organisation of appointments with other caregivers (nurse, psychologist, dietician ...); organisation of examinations (CT scans, MRI ...); COVID-19 screening test; impact of physical distancing measures against COVID-19 on patients' daily life.

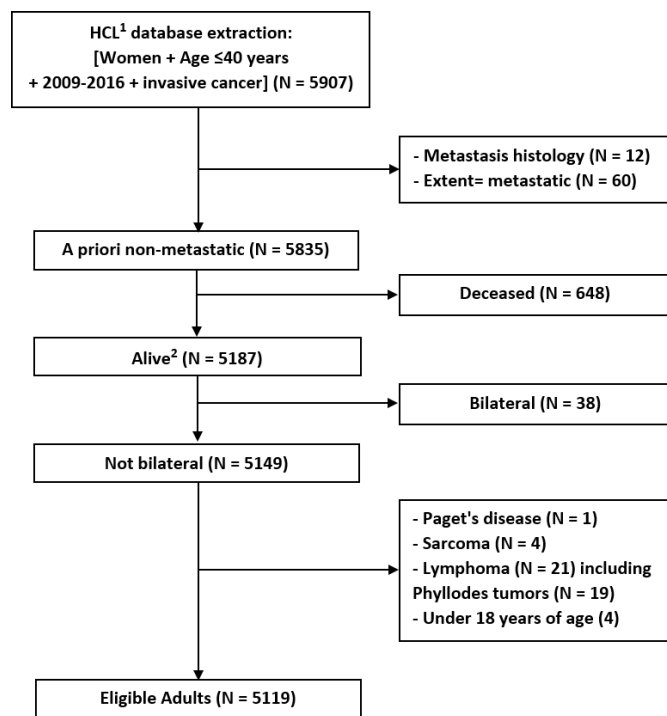


Figure 2 Flow chart of the selection of eligible patients for the Candy study. 1 HCL, Hospices Civils de Lyon; 2 These women were alive on June 1, 2018 based on data from the HCL database.

compared with women not treated with chemotherapy, with statistical power of 99% and an α -risk of 2.5%. Sexual function, which is our second main endpoint, will be evaluated by the FSFI questionnaire, which generates six dimensions (desire, arousal, lubrication, orgasm, satisfaction and pain). As the sexual function scores cannot be considered as independent of each other, Bonferroni correction will also be applied to adjust the α -risk according to the six dimensions analysed ($\alpha=0.4\%$). The number of women included would then make it possible to demonstrate an OR of 1.63 for women treated with endocrine therapy to have sexual dysfunction in the lubrication dimension (22%)⁶ compared with women not treated with endocrine therapy, with statistical power of 99% and an adjusted α -risk of 0.4%. Sample sizes were calculated using nQuery Advisor V.7 (Statsols, San Diego, USA).

Data analysis plan

Quantitative component

Booklet response rates will be provided as well as the proportion of missing items for each questionnaire. Sexual function, HRQoL, alcohol consumption, anxiety and depression, social support and deprivation scores will be generated according to validated algorithms. They will be categorised and described in addition to the other quantitative variables as mean (SD) or median (range). Fertility data, professional situation of participants as well as other qualitative variables (clinical data, treatments, etc.) will be described as number and percentage. Using

scores of the six subscales of sexual function, sexual function profiles will be identified by ascending hierarchical classification, and fertility profiles will be identified by latent class models. A generalised linear mixed model will be constructed to characterise fertility and sexual function profiles as well as to identify the clinical and socio-economic determinants of HRQoL in young women. This modelling will take into account the date of differential diagnosis between participants, the department effect as well as a possible process of missing-not-at-random (MNAR) data by adjusting for the year of diagnosis and the non-random missing data. In univariate analysis, variables to test as predictors for sexuality will be, among others, age at the time of the study, time since diagnosis, tumour stage, Charlson comorbidity index, hormone receptor status, surgery (lumpectomy, mastectomy, breast reconstruction), ovarian suppression, oophorectomy, endocrine therapy, radiotherapy, anxiety, depression, body image and current partner relationship. For fertility profiles, variables will include age at the time of the study, education, employment status, having children before diagnosis, current partner relationship, time since diagnosis, mastectomy, radiotherapy, chemotherapy, targeted therapy, current endocrine therapy, menstrual cycles before and after treatments, fertility preservation and desire for children at diagnosis. Dependent variables to be tested in the univariate model for each dimension of HRQoL will include age at the time of the study, time since diagnosis, Body Mass Index, anxiety, depression, deprivation, sexual function, social support availability, social support satisfaction, tumour stage, tumour grade, hormone receptor status, HER2 status, KI67 index, Charlson comorbidity index, surgery, chemotherapy, radiotherapy, endocrine therapy, targeted therapy, current partner relationship, having children, employment status and education. Correlations and interactions will be tested for eligible variables. The variables eligible for multivariate analyses will be those with a p value < 0.10 by univariate analysis. Correlations and interactions will be tested for eligible variables. Results will be reported as multivariate analysis coefficients, SDs and p values. Because dimensions of the FSFI, SF-12, EORTC QLQ-C30, EORTC QLQ-BR23 and EORTC QLQ-INFO25 questionnaires cannot be considered independent of each other, Bonferroni correction will be applied to adjust the α risk according to the number of dimensions analysed ($\alpha' = \alpha/n$ with n corresponding to the number of dimensions analysed) for each self-report questionnaire. Multiple imputation by chained equation (MICE) will be used in the event of missing-at-random (MAR) data. Before performing the MICE, an analysis of the observed data will make it possible to define MAR mechanisms depending on certain variables, and thus to anticipate variations between observed and imputed data. A graphical comparison making it possible to detect faults in the superposition of the observed and imputed distributions will be performed. This step is crucial to ensure both the validity of the MICE model used and the plausibility of

the MAR hypothesis. After MICE, the Wald test will be approximated by a Student test to test the regression coefficients. A Fisher test will also make it possible to jointly test a series of regression coefficients on all the imputed bases. In addition, sensitivity analysis will be performed to take into account any missing-not-at-random (MNAR) data and to assess the impact of a MNAR mechanism on the results of multiple imputation. Statistical analysis will be performed with R and SAS software V.9.4 (SAS Institute, Cary, NC, USA).

Qualitative component

Interviews will be recorded and fully transcribed. Analysis will begin as soon as a few interviews will have been performed, and will be carried out in conjunction with further data collection to determine when theoretical data saturation is reached, that is, the point beyond which further interviews yield no new information. It is believed that theoretical data saturation will be reached after around 30 interviews, but it is possible that some additional interviews will be necessary. The analysis will follow the conventional principles of qualitative analysis.³⁶ The content analysis will be assisted by NVivo software, which enables the themes emerging from the interviews to be coded and related to the individual characteristics of women and to the speech context.

Patient and public involvement

Patient and public participation was not sought in the design of this study protocol or in the development of the research questions. In accordance with the recommendations of the Cancer Plan III (Action 5.4.), all information leaflets (for quantitative and qualitative components) have been submitted for review, opinion and advice to the Patients' Committee for Clinical Research in Cancer of the National League Against Cancer. This committee also received for review the invitation to participate in the qualitative interviews and the study synopsis. In the study information leaflets, we will inform patients that they have the right to be informed of the overall results of the Candy project after it has been completed. These results will be published on the website of the Georges François Leclerc Comprehensive Cancer Centre (CGFL) (www.cgfl.fr). We will propose support for patients in the information leaflets: in fact, we will advise them to contact their doctor in the event that they experience mood disturbances or psychological difficulties after receiving and reading the information letter and booklet. In addition, we will add two links to contact patient associations and ERI ('Meeting and Information Spaces' offering support to patients and their caregivers).

DISCUSSION

To the best of our knowledge, the Candy project is the first to investigate sexuality and fertility profiles of young women with BC in France, in addition to examining their living conditions in general. The relevance and originality

of the project also lies in the use of a convergent mixed-methods approach. The quantitative aspect will make it possible to identify the profiles and the determinants of fertility and sexuality. As for the qualitative aspect, it will make it possible to collect the patients' point of view and experiences. The qualitative component will shed light on the unexplained results of the quantitative component and generate new research hypotheses. Through these multidisciplinary aspects, this project combines sexuality and fertility with socioeconomic and psychological components as well as HRQoL. Another advantage of this project is the participation of all the French cancer Registries (FRANCIM network); and the collaboration with other multidisciplinary research teams (sociologists and clinical oncologists). This project will be coordinated by the Epidemiology and Quality of Life Research Unit of the CGFL in Dijon, which hosts the Côte d'Or Breast and Gynaecological Cancer Registry. This team has methodological skills in the analysis of data relating to living conditions. A major limitation of the study could be the amount and type of missing data. Moreover, sexuality, which is one of the main endpoints of the study, may raise concerns about missing data due to the fact that it is a sensitive issue. The cross-sectional design precludes any conclusion regarding causality, which may be a limitation of this study. There may also be concerns about recall bias, especially given that the questions relate to events at diagnosis or during treatment. In the absence of a fertility questionnaire validated in French, fertility (one of the two main judgement criteria) will be assessed by a questionnaire constructed specifically for this study with oncologists, clinicians and surgeons.

At this stage of the study, 15 Registries have provided the patient's referring physicians with information about the study and informed them that their patients will be approached for participation. All 15 Registries have sent the study information pack by post to patients for the first time. Ten Registries have also sent reminders to patients who have not responded following the first mailing. In March 2022, the 10 registries that have finished with reminders will begin collecting clinical and treatment data from patients who responded to the questionnaires sent out for the quantitative component.

ETHICS AND DISSEMINATION

Ethics

This study will be performed in accordance with the declaration of Helsinki. The sponsor has registered the study with the competent authority, namely the French medicines agency (ANSM) by obtaining an IDRCB number (2020-A02130-39). The protocol was approved in October 2020 by the Committee for the Protection of Persons North-West III (20.07.16.44445) and by the French national data protection authority (CNIL-MR003 No1989764-v0).

Patients will be informed before their participation in the two components of the Candy project. Waiver of

informed consent for the quantitative component of the study was authorised by the Committee for the Protection of Persons North-West III. Written informed consent will be obtained for all participants prior to their participation in the qualitative component. All data will be analysed confidentially and anonymously.

Dissemination

At the end of the study, the results of the Candy project will (1) describe the postcancer living conditions of young women with BC: anxiety, depression and socio-professional reintegration; (2) identify and characterise sexuality and fertility profiles of young women with BC; (3) identify the clinical and socioeconomic determinants of sexuality, fertility and HRQoL and (4) identify the needs deemed by the patients themselves to have priority, in the management of their disease since diagnosis. The results obtained will provide clinicians with indicators for personalised care and will improve the care and living conditions of young women after BC. Clinicians will also be better informed, which in turn will enable them to advise future BC patients more appropriately, in order to better prepare them for the postcancer period in terms of sexuality and fertility. This should facilitate their strategies for coping with the disease. The integration into management of the aspects deemed to be priorities in terms of sexuality and fertility by young women in the improvement of their care and their conditions after BC will help to improve the experience of disease and post-cancer treatment by future patients. The results of this project will be communicated to the scientific community through publications in international scientific peer-reviewed journals and communications to national and international congresses. Popularised results will also be provided to patient associations. The results of Candy project will also be published on the website of the sponsor, www.cgfl.fr.

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Acknowledgements We thank Zoe UHRY for 'Hospices Civils de Lyon' for database extraction and Fiona Ecarnot, PhD (EA3920, University of Franche-Comté, Besançon, France) for English language editing. We also thank the patients of the 'Jeune & Rose' association for the proofreading and the testing of the study booklet.

Collaborators French Network of Cancer Registries (FRANCIM): Simona BARA (Registre des cancers de la Manche), Bénédicte LAPOTRE-LEDOUX (Registre général des cancers de la Somme), Sandrine PLOUVIER (Registre des cancers de Lille et de sa région), Karima HAMMAS (Registre des cancers du Haut-Rhin), Tienhan Sandrine DABAKUYO-YONLI (Registre des cancers du sein et autres cancers gynécologiques de Côte d'Or), Pascale GROSCLAUDE and Laëtitia DAUBISSE-MARLIAC (Registre des cancers généraux du Tarn), Brigitte TRETARRE (Registre général des tumeurs de l'Hérault), Florence MOLINIÉ and Anne COWPLI-BONY (Registre des tumeurs de Loire-Atlantique/Vendée), Anne-Sophie WORONOFF (Registre des tumeurs du Doubs), Gaëlle COUREAU (Registre général des cancers de la Gironde), Marc COLONNA and Patricia DELAFOSSE (Registre général des cancers de l'Isère), Michel VELTEN (Registre général des cancers du Bas-Rhin), Tania d'ALMEIDA (Registre général des cancers en région Limousin), Anne-Valérie GUIZARD (Registre général des tumeurs du Calvados), Gautier DEFOSSEZ (Registre des cancers de Poitou-Charentes), Jacqueline DELOUMEAUX (Registre de Guadeloupe), Clarisse JOACHIM-CONTARET (Registre général des cancers de la Martinique), Juliette PLENET and L. Manuella IMOUNGA-DESROZIERES (Registre des cancers de la Guyane).

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Funding This work was supported by the Fonds de Dotation PFIZER INNOVATION FRANCE (grant number 1150-1DASA19) and the European Regional Development Fund (FEDER) (grant number BG0027160).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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