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Benefits of Homeopathic Complementary Treatment in Patients With Breast Cancer: A Retrospective Cohort Study Based on the French Nationwide Healthcare Database

Jacques Medioni,^{1,2} Daniel Scimeca,³ Yecenia Lopez Marquez,⁴ Emmanuelle Leray,⁵ Marie Dalichampt,⁶ Nicolas Hoertel,^{2,7} Mohammed Bannani,⁸ Pascal Tremplat,⁹ Naoual Boujedaini⁹

Abstract

This study evaluated the benefits of homeopathy on the quality of life (QOL) of patients with nonmetastatic breast cancer (BC). There is an increasing use of homeopathy in patients with BC after diagnosis, leading to an overall decrease in medications that palliate the side effects of cancer treatment. This may indicate that QOL is improved in patients with BC who use homeopathy.

Background: Complementary therapy in oncology aims to help patients better cope with the illness and side effects (SEs) of cancer treatments that affect their quality of life (QOL). This study aimed to assess the benefits of homeopathic treatment on the health-related QOL (HRQOL) of patients with non-metastatic breast cancer (BC) prescribed in postsurgical complementary therapy. **Patients and Methods:** An extraction from the French nationwide healthcare database targeted all patients who underwent mastectomy for newly diagnosed BC between 2012 and 2013. HRQOL was proxied by the quantity of medication used to palliate the SEs of cancer treatments. **Results:** A total of 98,009 patients were included (mean age: 61 ± 13 years). Homeopathy was used in 11%, 26%, and 22% of patients respectively during the 7 to 12 months before surgery, the 6 months before, and 6 months after. Thereafter, the use remained stable at 15% for 4 years. Six months after surgery, there was a significant overall decrease ($RR = 0.88$, confidence interval $(CI)_{95} = 0.87-0.89$) in the dispensing of medication associated with SEs in patients treated with ≥ 3 dispensing of homeopathy compared to none. The decrease appeared to be greater for immunostimulants ($RR = 0.79$, $(CI)_{95} = 0.74-0.84$), corticosteroids ($RR = 0.82$, $(CI)_{95} = 0.79-0.85$), and antidiarrheals ($RR = 0.83$, $(CI)_{95} = 0.77-0.88$). **Conclusion:** The study showed an increasing use of homeopathy in patients with BC following diagnosis. This use was maintained after surgery and seemed to play a role in helping patients to better tolerate the SEs of cancer treatments.

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Keywords: Breast cancer, Complementary therapy, Homeopathy, HRQOL, Quality of life

Introduction

Breast cancer (BC) is the most common cancer in women worldwide. It is estimated that 2.3 million new BC cases were diagnosed in 2020.¹ Since 2008, there has been a 20% increase in the incidence of BC worldwide, and the overall mortality rate has increased by 14%.² The prognosis of patients with BC has clearly improved over the past few years. With BC survival rates being improved, attention is now being paid to the side effects (SEs) and possible sequelae of cancer therapies and patients' quality of life (QOL). Treatment of BC

¹APHP Hôpital Européen Georges Pompidou, Paris, France

²Université Paris Cité, Paris, France

³Maisons-Alfort, France

⁴Service d'Hépatogastroentérologie, Hôpital de la Croix Rousse, Lyon, France

⁵Univ Rennes, EHESP, CNRS, Inserm, ARENES UMR 6051, RSMS U 1309, F-35000 Rennes, France

⁶Nantes, France

⁷APHP Coeur de la Croix, Paris, France

⁸Qualees, Paris, France

⁹Boiron, Messimy, France

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Address for correspondence: Mohammed Bannani, Qualees, 10 rue bleue, 75009, Paris, France.

E-mail contact: mohammed.bannani@qualees.com

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may include surgery, radiotherapy, chemotherapy, and/or hormone treatment. These treatments may have acute adverse effects, creating an additional burden on patients.³⁻⁵ These may be some of the reasons why increasing numbers of patients with BC nowadays wish to use complementary methods as supportive care in cancer therapy.

In Europe, use of complementary medicine (CM) in oncology is growing, with the frequency of use varying from 14.8% in Greece to 73.1% in Italy.⁶ Its purpose is to help patients better cope with the illness and SEs of cancer treatments that particularly affect their health-related QOL (HRQOL). Most European countries show similarities in the use of complementary medicine. Homeopathy is one of the most commonly used complementary therapies along with herbs, vitamins, and medicinal teas in 7 out of 14 European countries⁶; it is reported to be used in an average of 31.4% of cancer patients.^{7,8} In some studies, the use of homeopathy in patients with cancer has been associated with an improvement in QOL and a decrease in fatigue symptoms, although the benefits of homeopathy on QOL have rarely been investigated.⁹

Studies have documented relief from adverse drug reactions and better HRQOL in patients with cancer receiving additive homeopathic treatment.⁹ These observations suggest that homeopathy may provide benefits to patients when combined with conventional cancer care. However, these conclusions are largely based on case reports, and data regarding patient survival are limited.¹⁰⁻¹³ Thus, there are a few comparative studies, particularly with large-scale patient numbers, that use a nationwide healthcare database, most of which deal with descriptive epidemiology. Homeopathy is one of the most common complementary and alternative medicine therapies used for cancer treatment, while it has been reported to be used in 12% to 19% of patients with BC.¹⁴ Studies have documented relief from adverse drug reactions and better HRQOL in patients with cancer receiving additive homeopathic treatment.⁹ Comparative studies with a larger number of patients are therefore needed to investigate these findings.

Objectives

The objective of this study was to assess the benefits of homeopathy treatment in association with conventional medicine in supportive oncology care on the HRQOL of patients with non-metastatic BC compared to conventional medicine without homeopathy in a French cohort. Secondary objectives included the description of patients' profiles and care with or without homeopathy, the impact of homeopathy on costs, and the investigation of predictive factors for homeopathy use.

Materials and Methods

Study Design and Inclusion Criteria

This was a national retrospective cohort study based on extraction from the French nationwide healthcare database (Système National des Données de Santé; SNDS).¹⁵ This database registered all beneficiaries covered by the health insurance regimes and collected several data: (1) the dates of care and costs reimbursed by the health insurance and those paid by the patients; (2) data on hospital stays, including medical information; (3) patients' characteristics (age, sex, place of residence, long-term illness (ALD30), affiliation to the Universal Health Coverage (Couverture Maladie

Universelle, CMU), date of death if applicable); and (4) data on medical causes of death.¹⁵ All women who underwent mastectomy for newly diagnosed nonmetastatic BC between 2012 and 2013 were included. As supportive care may have been involved before and after surgery, 2 observational phases were identified for each patient: time between diagnosis of BC and surgery (presurgical time) and time after surgery with a follow-up end date to December 31, 2018 (postsurgical time). This post-surgical time lasts 5 complete years, regardless of the year of the surgery, and takes into account the death of patients, which may have occurred during the follow-up. Diagnostic data were identified by the first occurrence of international classification of disease (ICD)-10 code C50 (whole C50.x, C77.3, D48.6, D05.0, D05.1, D05.7, D05.9, Z85.3) in hospital data or by the date of disease onset in ALD30 declaration. The ALD30 declaration gathers severe and/or chronic diseases which can lead to a total refund. All patients who underwent surgery for newly diagnosed breast cancer during 2012 to 2013 were identified using the combination of codes: common classification of medical acts (CCAM, classification commune des actes médicaux) for the surgical procedure and ICD-10 for the associated principal diagnosis. Descriptions of the variables used in this study and their associated ICD codes are provided in Supplemental Material 1. Patients with recurrent or metastatic BC were excluded from the study. Recurrence was identified by scanning a historical 2-year time span before surgery and considering the period between diagnosis and surgery.

The study was approved by the French CERES (Comité d'Expertise pour les Recherches, les Etudes et les Evaluations dans le domaine de la Santé) ethics committee (authorisation number 1129159bis) in February 2020, and the French data protection authority CNIL (Commission Nationale de l'Informatique et des Libertés) in April 2020. All data were centralized in a secure database.

Exposition Evaluation

Homeopathy exposure was determined by identifying the number of dispensing treatments. This information is available in the inter-regime consumption data mart (datamart de consommation inter-régime, DCIR), which compiles all individual data of health insurance beneficiaries used for epidemiological studies. Successive periods of 180 days were considered. The exposition and outcomes were assessed over a 180-day period and over the first period following the exposition. The first year of follow-up was distinguished based on the presence of radiotherapy and/or chemotherapy. The distinction of the first year was justified by the duration of the common sequence of successive treatments for BC after mastectomy (chemotherapy and radiotherapy) before the initiation of long-term hormone therapy. This distinction is pointed out in a national cancer institute (Institut National du Cancer, INCa) report about the takeover deadline of BC, from diagnosis to the end of radiotherapy.¹⁶ The number of patients dispensing for 6 months following inclusion determined several exposure levels. This count was first analyzed as a discrete quantitative variable, from 0 (no exposure) to the maximum dispensing for one patient in the cohort. It was then divided into 3 classes: no exposition = no use (class 1), intermediate exposition = 1-2 homeopathic medications dispensing (class 2), and elevated exposition = regular use

above a threshold of ≥ 3 homeopathic dispensing (class 3). As the French SNDS collected data on refund treatments, we only identified dispensed homeopathic treatments. No information was available for the patients on self-medication.

Outcome Criteria

The main outcome was HRQOL. Considering the impact of the illness and the SEs of cancer treatments that particularly affect HRQOL, we primarily retained 2 categories of medications that can be used as proxies of HRQOL in patients with BC. The first category included medications or acts that palliate SEs associated with cancer treatments affecting HRQOL (antiemetics, antidiarrhea, mouthwashes, antalgics, corticoids, antibiotics, antifungals, immunostimulants [drugs or processes which induce or enhance an immune response], topical medications [such as ointments, creams, or gels applied to the affected skin]). The second category included medications prescribed for the treatment of anxiety, depression, and sleeping disorders (antidepressants, anxiolytics, antiepileptics that showed efficiency in anxiety disorder treatment, antipsychotics, hypnotics other than benzodiazepines, and sedative antihistaminic anticholinergics). We also explored sick leave and disabilities linked to exhaustion, reduced motivation, and activity. For the analysis of sick leave, we only included women of working age (i.e., between 18 and 60 years old). Descriptive variables included sex, age at surgery, type of surgery, CMU, presence of a referring physician, number of historical mammograms, the French DEPrivation index (FDEP), sick leave history, times of homeopathic treatment dispensing, comorbidities (coronary heart disease, arterial hypertension, diabetes, chronic obstructive pulmonary disease (COPD), other chronic diseases, history of depression, anxiety and sleep disorders, and history of cancer other than BC). CMU care is a free extended health care for people who earn less than 7611€ per year. The FDEP is an index that characterizes the socioeconomic status of patients according to their municipality of residence.¹⁷

Statistical Analysis

Statistical analyses were performed using SAS software (9.x version, SAS Institute, NC). Qualitative variables are presented as percentages per class, and continuous variables are presented as means and standard deviations. All models were adjusted for patients' characteristics at inclusion (sex, age, type of surgery, type of adjuvant therapy [radiotherapy/chemotherapy], comorbidities) and those of the physician implied in cancer care (socio-demographic characteristics, localization, type of activity, volume of prescription). The continuity of care (COC) was assessed to represent the durability of the relationship between a patient and its physician.¹⁸ The COC index is a time-dependent variable developed by Bice and Boxerman, which was used to measure this variable.¹⁹ Models used for the analysis of the consumption of medications related to the treatment of anxiety and depression and sick leave were also adjusted for the level of exposure during the 180 days before the evaluation period (based on the number of dispensing medications), the number of months after surgery, the COC index during the last 180 days, and the cumulative duration of homeopathy treatment after surgery. Models used for the analysis of the consumption of medications used to palliate SEs related to cancer treatments were

also adjusted for the level of exposure during the 180 days before the evaluation period (based on the number of dispensing medications), the number of months after surgery, the COC index during the last 180 days, and the cumulative duration of homeopathic treatment since the start of radiotherapy or chemotherapy. The analysis of the consumption of medications related to the treatment of anxiety and depression or palliate SEs related to cancer treatments was performed using a Poisson mixed model with random effects on patients. The analysis of sick leave was performed using a linear mixed model. Multivariate analysis was conducted using a logistic model to identify predictive factors for the use of homeopathy as supportive care. All analyses were performed with an alpha risk of 5%.

Results

All patients responding to the inclusion/exclusion criteria from the SNDS healthcare database between 2012 and 2013 were included (Figure 1). A total of 98,009 patients were included, with a mean age at surgery of 61 ± 13 years (Table 1; Figure 1). A large majority of patients underwent partial mastectomy (or breast tumorectomy) ($N = 77,896$, 80%), and total mastectomy was performed in 21% ($n = 20,113$) of the patients (Figure 1). Moreover, 43% of the patients ($N = 41,670$) were treated to minimize vascular risk in the year before surgery.

A 5-year follow-up was completed in 89% of the patients. The remaining 11% of the patients died (9%) or lost sight (2%) before the end of the follow-up period (Table 1).

Homeopathy was observed in 11% of patients 7 to 12 months before surgery, 26% during the 6 months before surgery, 22% during the 6 months after surgery, 18% 7 to 12 months after surgery, and 15% for 4 years (Figure 2). Six months after surgery, 9% of women took at least 3 homeopathic drugs; this percentage was maintained for the rest of the follow-up period (Figure 2). Before surgery, patients receiving homeopathy (class 2) appeared to get more benefit (14% vs. 18%) and to have less reported diabetes (6% vs. 8%), cardiovascular (8% vs. 10%), and hypertensive (38% vs. 44%) comorbidities compared to patients without homeopathy (all $P < .01$) (Supplemental Material 2). These results were similar at 6 and 12 months postoperatively. There was also a lower proportion of deaths in women that received homeopathy than in women that did not (6% vs. 10%) (Supplemental Material 2).

Radiotherapy, Chemotherapy, and Hormonotherapy

During the follow-up of 5 years, 37%, 82%, and 71% of women were treated with chemotherapy, radiotherapy, and hormonotherapy, respectively (Table 1). Most women who were treated with chemotherapy (92%) and radiotherapy (49%) started treatment within 3 months following surgery. Women treated with hormonotherapy (40%) started treatment between 3 and 6 months after surgery. The combination of radiotherapy-hormone therapy or chemotherapy-radiotherapy-hormone therapy was administered to 63% of the patients (Table 1). Approximately a quarter of patients that underwent chemotherapy, radiotherapy, and hormone therapy also received homeopathy (Supplemental Material 3).

Table 1 Description of the Population

| | Total N = 98,009 | Total Mastectomy N = 20,113 | Partial Mastectomy and Tumorectomy N = 77,896 | P-Value |
|---|---------------------|-----------------------------------|---|---------|
| Mean age at surgery (years) | 61 (±13) | 63 (±16) | 60 (±12) | < .01 |
| French Deprivation index (FDEP, quintile) | | | | |
| Unknown | 7414 (8%) | 1607 (8%) | 5807 (7%) | < .01 |
| 1st quintile (less disadvantaged) | 19,409 (20%) | 3790 (19%) | 15,619 (20%) | < .01 |
| 2nd quintile | 17,782 (18%) | 3471 (17%) | 14,311 (18%) | < .01 |
| 3rd quintile | 18,166 (19%) | 3587 (18%) | 14,579 (19%) | < .01 |
| 4th quintile | 18,145 (19%) | 3792 (19%) | 14,353 (18%) | < .01 |
| 5th quintile (most disadvantaged) | 17,093 (17%) | 3866 (19%) | 13,227 (17%) | < .01 |
| Affiliation to the Universal Health Coverage (CMU) | 6994 (7%) | 1602 (8%) | 5392 (7%) | < .01 |
| Histories | | | | |
| Treated for diabetes in the year prior to surgery (at least 3 dispensing) | 7135 (7%) | 1709 (8%) | 5426 (7%) | < .01 |
| Treated for chronic obstructive pulmonary disease in the year prior to surgery (at least 3 dispensing) | 5438 (6%) | 1178 (6%) | 4260 (5%) | .03 |
| History of cancer other than breast cancer | 5155 (5%) | 1129 (6%) | 4026 (5%) | .01 |
| History of cardiovascular disease | 9258 (9%) | 2756 (14%) | 6502 (8%) | < .01 |
| Treated for vascular risk (antihypertensive or hypolipidemic treatments) in the year preceding surgery (at least 3 dispensing) | 41,670 (43%) | 9065 (45%) | 32,605 (42%) | < .01 |
| Death | 8756 (9%) | 3630 (18%) | 5126 (7%) | < .01 |
| Follow-up time | | | | |
| Less than 1 y | 1234 (1%) | 619 (3%) | 615 (1%) | < .01 |
| Between 1 and 2 y | 1743 (2%) | 817 (4%) | 926 (1%) | < .01 |
| Between 2 and 3 y | 1960 (2%) | 837 (4%) | 1123 (1%) | < .01 |
| Between 3 and 4 y | 2078 (2%) | 822 (4%) | 1266 (2%) | < .01 |
| Between 4 and 5 y | 3432 (4%) | 992 (5%) | 2440 (3%) | < .01 |
| 5 y (complete follow-up) | 87,562 (89%) | 16,026 (80%) | 71,536 (92%) | < .01 |
| Treatments | | | | |
| Treated with chemotherapy during the 5 y after surgery | 36,122 (37%) | 9695 (48%) | 26,427 (34%) | < .01 |
| Time between surgery and first session of chemotherapy | | | | |
| [0-3] mo | 33,117 (92%) | 8847 (91%) | 24,270 (92%) | < .01 |
| [3-6] mo | 1260 (3%) | 250 (3%) | 1010 (4%) | < .01 |
| [6-9] mo | 144 (0%) | 54 (1%) | 90 (0%) | < .01 |
| [9-12] mo | 119 (0%) | 51 (1%) | 68 (0%) | < .01 |
| [1-5] y | 1482 (4%) | 493 (5%) | 989 (4%) | < .01 |
| Treated with radiotherapy during the 5 y after surgery | 80,544 (82%) | 12604 (63%) | 67,940 (87%) | < .01 |
| Time between surgery and first session of radiotherapy | | | | |
| [0-3] mo | 39,178 (49%) | 4102 (33%) | 35,076 (52%) | < .01 |
| [3-6] mo | 20,101 (25%) | 3466 (27%) | 16,635 (24%) | < .01 |
| [6-9] mo | 19,350 (24%) | 4520 (36%) | 14,830 (22%) | < .01 |
| [9-12] mo | 1105 (1%) | 205 (2%) | 900 (1%) | < .01 |
| Treated with hormone therapy during the 5 y after surgery | 69,894 (71%) | 14,618 (73%) | 55,276 (71%) | < .01 |
| Mean duration of hormone therapy (years) | 3.53 (±1.54) | - | - | |
| Time between surgery and first session of hormone therapy | | | | |
| [0-3] mo | 16,564 (24%) | 5162 (35%) | 11,402 (21%) | < .01 |
| [3-6] mo | 28,077 (40%) | 3202 (22%) | 24,875 (45%) | < .01 |
| [6-9] mo | 18,993 (27%) | 5000 (34%) | 13,993 (25%) | < .01 |
| [9-12] mo | 4443 (6%) | 833 (6%) | 3610 (7%) | < .01 |
| [1-5] y | 1817 (3%) | 421 (3%) | 1396 (3%) | < .01 |

(continued on next page)

Table 1 (continued)

| | Total N = 98,009 | Total Mastectomy N = 20,113 | Partial Mastectomy and Tumorectomy N = 77,896 | P-Value |
|--|---------------------|-----------------------------------|---|---------|
| Treatment received in the 5 y following surgery | | | | |
| No treatment | 8469 (9%) | 2562 (13%) | 5907 (8%) | < .01 |
| Chemotherapy only | 979 (1%) | 486 (2%) | 493 (1%) | < .01 |
| Radiotherapy only | 10,952 (11%) | 752 (4%) | 10,200 (13%) | < .01 |
| Hormone therapy only | 5955 (6%) | 3341 (17%) | 2614 (3%) | < .01 |
| Chemotherapy - Radiotherapy | 7715 (8%) | 1695 (8%) | 6020 (8%) | < .01 |
| Chemotherapy – Hormone therapy | 2062 (2%) | 1120 (6%) | 942 (1%) | < .01 |
| Radiotherapy – Hormone therapy | 36,511 (37%) | 3763 (19%) | 32,748 (42%) | < .01 |
| Chemotherapy - Radiotherapy – Hormone therapy | 25,366 (26%) | 6394 (32%) | 18,972 (24%) | < .01 |

Medications prescribed to palliate SEs of cancer

During the 6 months after surgery (first semester), 95% of patients took medications to palliate SEs of cancer treatments, among which 74% had ≥ 3 dispensing (Supplemental Material 4). The global percentage of consumption of these medications was decreased to 79% during the 7 to 12 months after surgery and then maintained at approximately 75% during the remaining follow-up. The most frequently prescribed medications were antalgics (91%), corticosteroids (40%), and antiemetics (36%). During the first semester after surgery, there was a significant overall decrease

(Relative Risk $RR = 0.88$, confidence interval $(CI)_{95} = 0.87-0.89$) in SEs associated with the dispensing of medications in patients who had ≥ 3 homeopathy dispensing during the previous semester compared to those who had none (Figure 3). The decrease appeared to be greater for immunostimulants ($RR = 0.79$, $(CI)_{95} = 0.74-0.84$), corticosteroids ($RR = 0.82$, $(CI)_{95} = 0.79-0.85$), antiarrhythmals ($RR = 0.83$, $(CI)_{95} = 0.77-0.88$), systemic antifungals ($RR = 0.86$, $(CI)_{95} = 0.80-0.92$), and antiemetics ($RR = 0.90$, $(CI)_{95} = 0.87-0.93$) (Table 2). There was also a significant decrease in the use of antalgics, systemic antibiotics, and

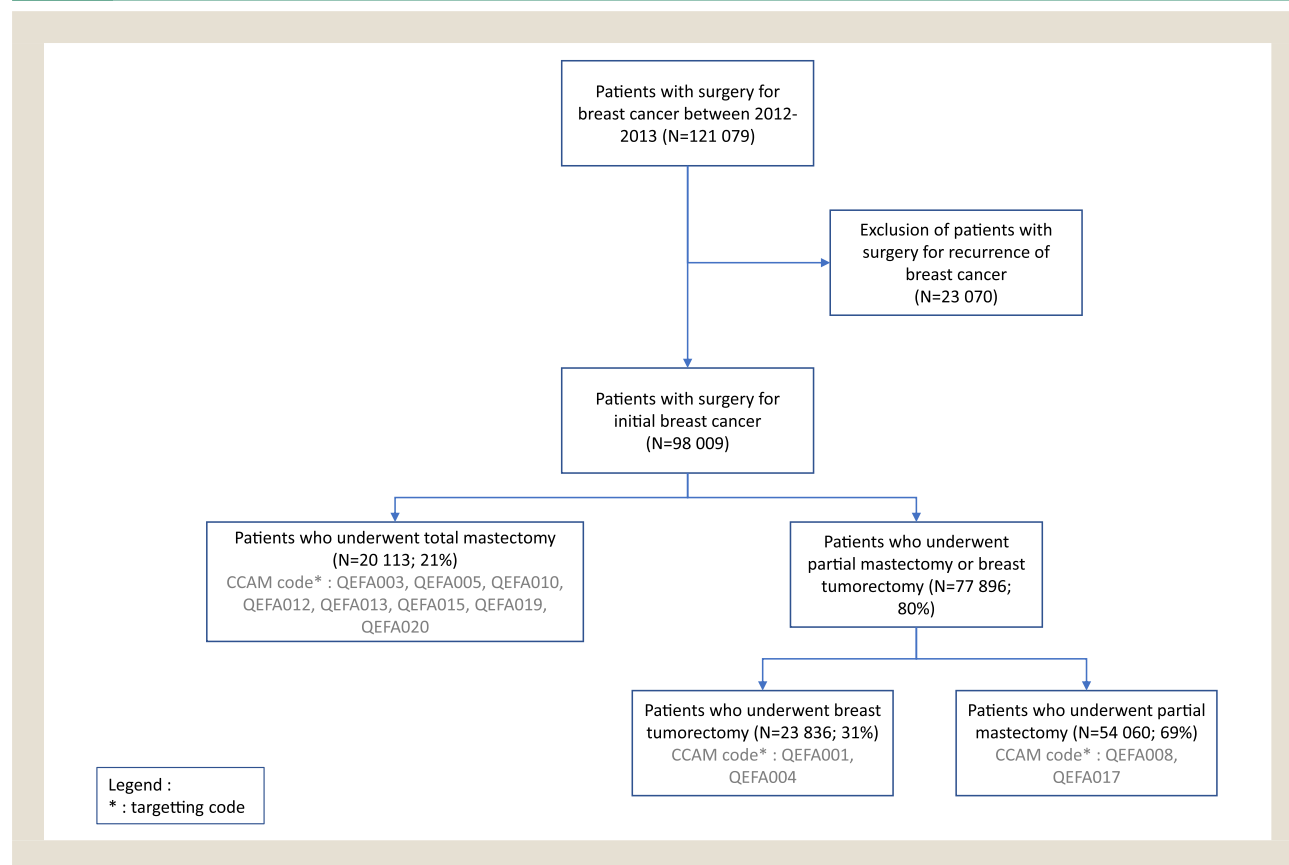
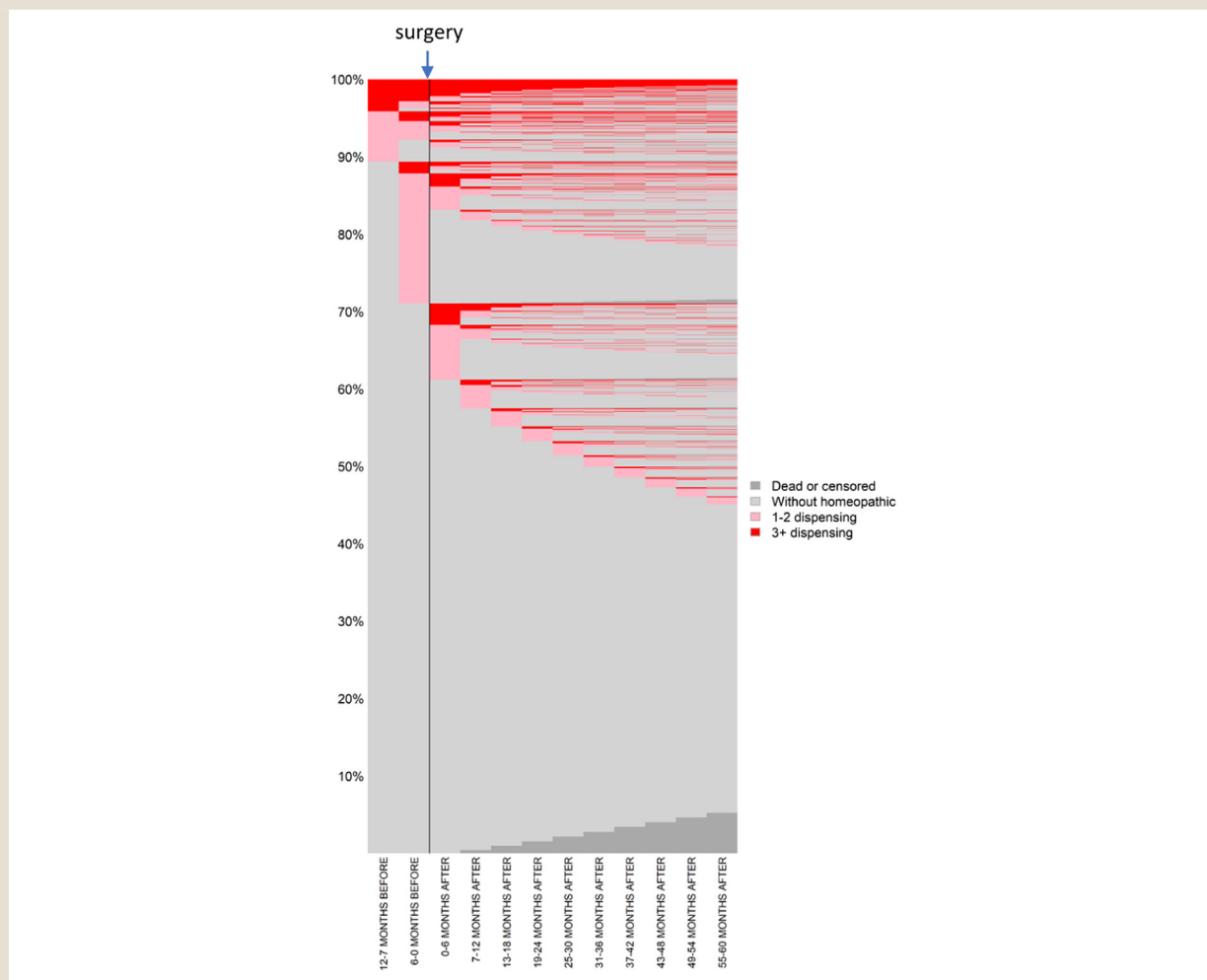
Figure 1 Flowchart of study population.

Table 2 Assessment of the Evolution in the use of Medications Administered to Palliate SEs of Cancer Treatments Received During the First and Second Semester After Surgery

| | Without Adjustment | | | With Adjustment | | | | |
|--|--------------------|--------------|---------|-----------------|--------------|---------|----------------------------|---------------------------|
| | RR (3+ vs 0) | IC95%(RR) | P-value | RR (3+ vs 0) | IC95%(RR) | P-value | Decrease Before Adjustment | Decrease After Adjustment |
| Treatments received during the first semester after surgery | | | | | | | | |
| Medications palliating SEs of treatments for cancer | 0.87 | [0.86; 0.88] | <.01 | 0.88 | [0.87; 0.89] | <.01 | 13% | 12% |
| Immunostimulants | 0.64 | [0.6; 0.69] | <.01 | 0.79 | [0.74; 0.84] | <.01 | 36% | 21% |
| Corticoids | 0.79 | [0.76; 0.81] | <.01 | 0.82 | [0.79; 0.85] | <.01 | 21% | 18% |
| Antidiarrheals | 0.80 | [0.74; 0.85] | <.01 | 0.83 | [0.77; 0.88] | <.01 | 20% | 17% |
| Systemic antifungals | 0.77 | [0.72; 0.83] | <.01 | 0.86 | [0.80; 0.92] | <.01 | 23% | 14% |
| Antiemetics | 0.69 | [0.66; 0.72] | <.01 | 0.90 | [0.87; 0.93] | <.01 | 31% | 10% |
| Mouthwashes | 0.92 | [0.87; 0.98] | <.01 | 0.94 | [0.89; 1.00] | 0.04 | 8% | 6% |
| Antalgics | 0.93 | [0.92; 0.95] | <.01 | 0.94 | [0.92; 0.95] | <.01 | 7% | 6% |
| Systemic antibiotics | 0.93 | [0.90; 0.96] | <.01 | 0.94 | [0.91; 0.97] | <.01 | 7% | 6% |
| Emollients et protectives | 0.97 | [0.93; 1.02] | 0.28 | 0.99 | [0.95; 1.04] | 0.77 | 3% | 1% |
| Treatments received during the second semester after surgery | | | | | | | | |
| Medications palliating SEs of treatments for cancer | 0.94 | [0.92; 0.95] | <.01 | 0.94 | [0.93; 0.95] | <.01 | 6% | 6% |
| Immunostimulants | 0.83 | [0.75; 0.92] | <.01 | 0.86 | [0.78; 0.95] | <.01 | 17% | 14% |
| Corticoids | 0.84 | [0.80; 0.88] | <.01 | 0.81 | [0.77; 0.85] | <.01 | 16% | 19% |
| Antidiarrheals | 1.00 | [0.93; 1.08] | 0.89 | 0.99 | [0.92; 1.07] | 0.85 | 0% | 1% |
| Systemic antifungals | 0.97 | [0.88; 1.06] | 0.47 | 0.93 | [0.85; 1.02] | 0.15 | 3% | 7% |
| Antiemetics | 0.69 | [0.63; 0.75] | <.01 | 0.72 | [0.66; 0.78] | <.01 | 31% | 28% |
| Mouthwashes | 1.07 | [1.00; 1.13] | 0.05 | 1.03 | [0.97; 1.10] | 0.35 | -7% | -3% |
| Antalgics | 0.98 | [0.96; 1.00] | 0.02 | 0.99 | [0.97; 1.00] | 0.16 | 2% | 1% |
| Systemic antibiotics | 1.01 | [0.98; 1.04] | 0.39 | 1.01 | [0.98; 1.04] | 0.48 | -1% | -1% |
| Emollients et protectives | 1.13 | [1.07; 1.18] | <.01 | 1.12 | [1.07; 1.18] | <.01 | -13% | -12% |

In this table, risk ratios (RR) are calculated taking into account homeopathy dispensing during the previous semester.

Figure 2 Number of homeopathic drugs dispensing for 6-months periods before and after surgery. This figure shows the evolution of the consumption of homeopathic drugs on a 6-month period according to the previous one. For example, 7 to 12 months before surgery, 11% of women used homeopathy, with 7% having 1 to 2 dispensing (in pink) and 4% having > 3 dispensing sessions (in red). Among women who had more than 3 dispensing sessions, 60% of them had still more than 3 dispensing sessions 6 months before till surgery, 30% had 1 to 2 dispensing, and 10% did not use homeopathy thereafter. This figure shows also that 17% of women received homeopathy for the first time in the 6 months before surgery.



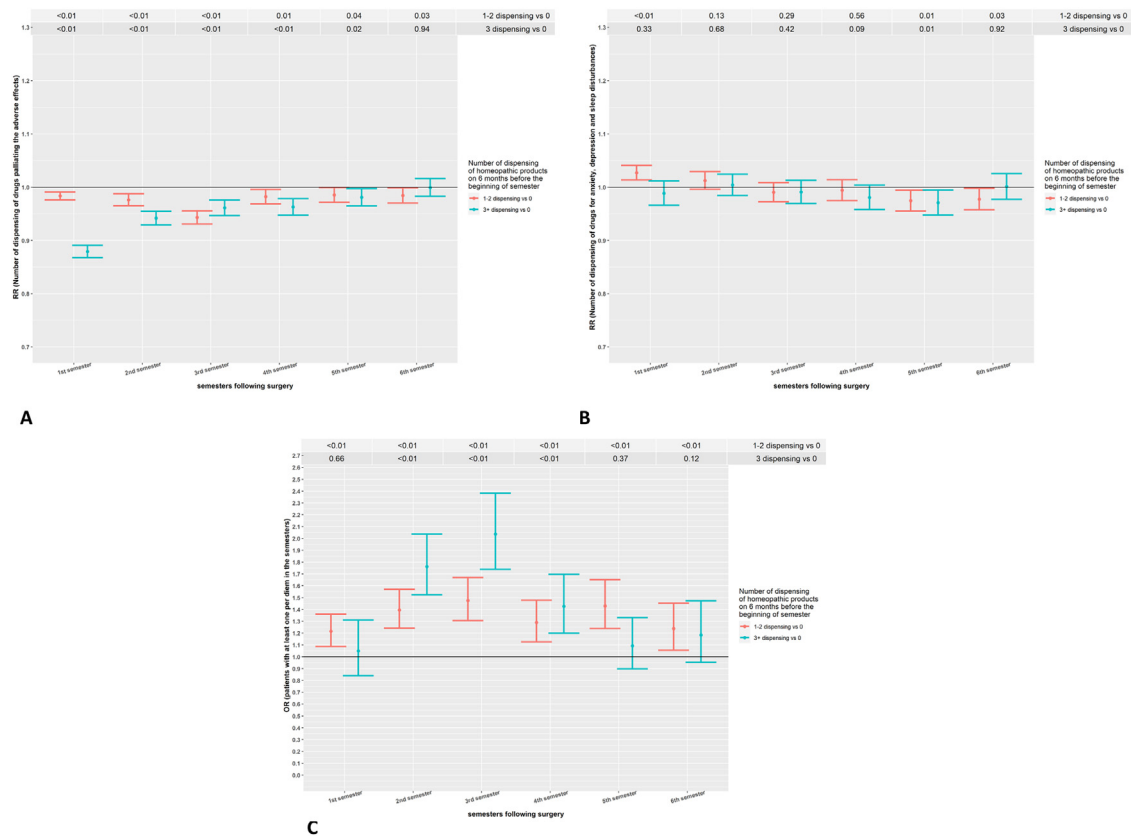
mouthwash. During the second semester after surgery, there was also a significant overall decrease ($RR = 0.94$, $(CI)_{95} = 0.93-0.95$) in SEs associated with the dispensing of medications in patients who had ≥ 3 homeopathy dispensing during the previous semester compared to those who had none. The decrease appeared to be greater for antiemetics ($RR = 0.72$, $(CI)_{95} = 0.66-0.78$), corticoids ($RR = 0.81$, $(CI)_{95} = 0.77-0.85$), and immunostimulants ($RR = 0.86$, $(CI)_{95} = 0.78-0.95$) (Table 2).

Medications prescribed for the treatment of anxiety, depression and sleeping disorders

Six months after surgery, half (49%) of the population took medications for anxiety, depression, or sleeping disorders. There was an overall decrease in dispensing medication against anxiety

after this period (from 41% during the 7-12 months after surgery to 36% following 43 months after surgery or later) (Supplemental Material 4). The decrease was greater for anxiolytics (from 36% to 22% at 5 years postsurgery) and hypnotics (from 16% to 9% at 5 years postsurgery). Antidepressants were taken by 18% of the population 6 months postsurgery and remained stable during the 5-years follow-up. Antidepressant, antiepileptic, antipsychotic, and sedative antihistaminic anticholinergic dispensing remained stable after surgery. There was no difference in the dispensing of these medications after surgery between patients receiving homeopathy and those who did not (Figure 3).

Figure 3 Results of the mixed Poisson model on: A. Number of dispensing of drugs administered to palliate the adverse effects of cancer treatments over the semesters following surgery as a function of the number of dispensing of homeopathy over the 6 months preceding each semester (adjusted model); B. Number of dispensing of drugs against anxiety, depression and sleeping disorders over the semesters following surgery as a function of the number of dispensing of homeopathy over the 6 months preceding each semester (adjusted model); C. Number of dispensing for at least one day of sick leave over the semesters following surgery as a function of the number of dispensing of homeopathy over the 6 months preceding each semester (adjusted model).



Impact on sick leave

The proportion of women who took at least one day of sick leave was 64% in the year after surgery, 41% in the second year, 28% in the third year, and 19% in the following years (Supplemental Material 4). Half of the women took > 310 days of sick leave in the first year, 200 days in the second year and 67 days in the third year. During the first semester, there was no difference in the duration of sick leave between women that had received homeopathy and those who had not (Figure 3). During the second and third semesters, women that had received ≥ 3 homeopathy dispensing took significantly more days of sick leave than women that had not received homeopathy (RR = 1.76, CI₉₅ = 1.52-2.04 for the second semester, RR = 2.03, CI₉₅ = 1.74-2.38 for the third semester). Among patients who took at least one sick leave during the semester, women that had received ≥ 3 homeopathy dispensing took on average more days of sick leave (from 4 to 10 days according to the semester) than women that had not received homeopathy.

Predictive Factors for Homeopathy use After Surgery

Women in more advantaged areas, younger, who underwent a partial mastectomy, without a medical history, consulting several physicians, and with stage 1 cancer experienced an increase in the number of prescriptions of homeopathy (Table 3).

Impact on reimbursed costs by health insurance the year after surgery

The mean cost of medications administered to palliate SEs of cancer treatments during the first semester after surgery was 963€ \pm 1842€. During the first semester after surgery, this cost was lower for women who received ≥ 3 homeopathy dispensing (843€ \pm 1703€) than for women who did not receive homeopathy (1056€ \pm 1907€). This difference was not observed during the second semester (93€ \pm 365€ vs. 90€ \pm 332€).

The mean hospital cost in the first semester after surgery was 7153€ \pm 5309€. This cost was lower for women who received ≥ 3 homeopathy dispensing (7123€ \pm 5407€ vs. 7246€ \pm 5355€),

Table 3 Description of Predictive Factors for the use of Homeopathy After Surgery

| Variable | 1-2 Homeopathic Medication Dispensing vs. 0 | | | 3+ Homeopathic Medication Dispensing vs. 0 | | |
|---|---|--------------|---------|--|--------------|---------|
| | OR | CI95% | P-Value | OR | CI95% | P-Value |
| Affiliation to the Universal Health Coverage (CMU) | 0.79 | [0.73; 0.86] | <.001 | 0.42 | [0.38; 0.48] | <.001 |
| French Deprivation index (FDEP, quintile) | | | | | | |
| 2nd quintile vs. 1st quintile (less disadvantaged) | 1.12 | [1.06; 1.19] | <.001 | 1.08 | [1.01; 1.15] | .03 |
| 3rd quintile vs. 1st quintile (less disadvantaged) | 1.01 | [0.95; 1.07] | .73 | 1.02 | [0.96; 1.10] | .42 |
| 4th quintile vs. 1st quintile (less disadvantaged) | 0.90 | [0.85; 0.96] | <.01 | 0.89 | [0.83; 0.96] | .001 |
| 5th quintile (the most disadvantaged) vs. 1st quintile (less disadvantaged) | 0.79 | [0.75; 0.85] | <.001 | 0.72 | [0.67; 0.78] | <.001 |
| Age at surgery*10 (years) | 0.86 | [0.85; 0.88] | <.001 | 0.87 | [0.86; 0.89] | <.001 |
| Type of surgery (Partial mastectomy/tumorectomy vs. total mastectomy) | 1.27 | [1.21; 1.33] | <.001 | 1.17 | [1.11; 1.24] | <.001 |
| Treated for diabetes in the year prior to surgery (at least 3 dispensing) | 0.69 | [0.63; 0.74] | <.001 | 0.44 | [0.39; 0.49] | <.001 |
| Treated for chronic obstructive pulmonary disease in the year prior to surgery (at least 3 dispensing) | 0.87 | [0.80; 0.95] | <.01 | 0.85 | [0.77; 0.94] | <.01 |
| History of cancer other than breast cancer | 0.91 | [0.83; 0.99] | .03 | 0.86 | [0.78; 0.96] | <.01 |
| History of cardiovascular disease | 0.74 | [0.70; 0.80] | <.001 | 0.66 | [0.61; 0.72] | <.001 |
| Treated for vascular risk (antihypertensive or hypolipidemic treatments) in the year preceding surgery (at least 3 dispensing) | 0.72 | [0.69; 0.75] | <.001 | 0.6 | [0.57; 0.63] | <.001 |

whereas it was higher during the second semester after surgery for this population (5769€ \pm 6766€ vs. 5544€ \pm 7424€) compared to women who did not receive homeopathy.

Discussion

Our results indicated that the use of homeopathy could have a positive impact on the reduction of dispensing of medications used to palliate SEs of BC treatments in the year following surgery, regardless of the type of surgery and treatment. This may indicate that QOL can be improved in patients with BC receiving homeopathy.

This study highlights the benefits of homeopathy treatment in combination with conventional medicine in supportive oncology care on the HRQOL of patients with non-metastatic BC compared to conventional medicine without homeopathy. Supportive care is defined as care and support that are necessary for patients affected by serious disease and is used in conjunction with medical and specific treatments.²⁰ Their goal is to improve the QOL of patients through physical, psychological, and social plans. They include a wide range of therapies (drugs, hypnosis, physical activity, massages, etc.) that consider the implications of the disease, psychological and emotional impact, and SEs linked to cancer treatments.

The use and type of CM (acupuncture, homeopathy, phytotherapy, hypnosis) vary across countries.^{6,10,11,21} In France, the prevalence of complementary therapy varies greatly in studies, from 16.4% to 60%, regardless of the type of cancer.^{12,13,22,23} A systematic review showed increasing use of these medicines, with an average rate of 31.4% in 1998 to 40% in 2012.²⁴ In a recent multicenter European survey, homeopathy was found to be the fourth most frequently prescribed CM to cancer patients (40.4 %), after acupuncture (55.3%), and before herbal medicine (38.3%) and traditional Chinese medicine (21.3%).²⁵

With the development of supportive care and complementary therapies, patients are increasingly willing to use alternative drugs, especially to palliate the adverse effects of conventional treatments, such as chemotherapy, radiotherapy, or hormonotherapy.²⁶ Patients are aware that homeopathy is a complementary therapy that will help them to better support specific treatments and the psychological consequences of cancer.^{23,27} It is important for physicians to identify the needs of their patients and include supportive care in the care pathway when requested.

However, only a few comparative studies have evaluated the benefits of homeopathy in patients with cancer, and none of them have been conducted in France. In 2019, a literature review identified 8 randomized controlled trials evaluating the effects of homeopathy on the adverse effects of cancer treatments.⁷ Five of these studies showed a positive impact of homeopathy on patients' QOL. In 1988, a randomized, placebo-controlled, double-blind trial including 82 patients showed a reduction in the symptoms severity score.²⁸ In 2001, a randomized, placebo-controlled, double-blind trial showed a significant reduction in the severity and duration of chemotherapy-induced stomatitis in 30 children that underwent bone marrow transplantation.²⁹ In 2004, a randomized, single-blind trial of 254 patients showed better prevention with *Calendula officinalis* of acute skin toxicity and greater patient satisfaction with regard to pain and dermatitis.³⁰ In 2015, a monocentric randomized controlled trial of 410 patients showed amelioration of health state and subjective well-being.⁸ The 3 last studies showed no benefits.³¹⁻³³ The first study aimed to evaluate the efficacy observed in the study reported by Traumeel et al. on the control of chemotherapy-induced oral mucositis in 190 Israeli patients with hematopoietic stem cell transplantation (SCT) and oral mucositis.³¹ The second study aimed to evaluate the efficacy of the additive cocculine on the control of chemotherapy-induced nausea and vomiting in 431 French patients with BC.³² The third

study assessed the efficacy of homeopathic antiemetic therapy in 44 patients with BC.³³

Several psychometric tools are commonly used to evaluate QOL in patients with BC^{34,35}: anxiety, depression, tiredness, social impact, motivation and activity reduction, and SE of treatments. In our study, since none of these data were available in the French nationwide healthcare database, we mainly retained substitute indicators: the consumption of medications used to palliate SEs of cancer treatments and the consumption of medications prescribed for anxiety, depression, and sleeping disorders.

In several studies, reducing adverse reactions to cancer treatments was the main indication for using complementary medicine, including homeopathy.²⁵ In our study, the use of homeopathy was associated with a decrease in medications administered to palliate SEs of cancer treatments during the first and second semesters after surgery, especially antiemetics, corticosteroids, immunostimulants, and antidiarrheals. SEs play a major role in the reduction of QOL in patients with BC. The decrease in the consumption of these medications in the 2 semesters following surgery using homeopathy may encourage the use of homeopathy in patients with BC. Nevertheless, there was no difference in the use of medications prescribed for anxiety, depression, and/or sleep disorders between the groups.

Furthermore, homeopathy is associated with an increase in the duration of sick leave, but only during the second and third semesters after surgery. These results are consistent with those of a previous study.³⁶ This may be influenced by patient profiles. Patients with homeopathy are mostly younger and less socially disadvantaged. These patients may come from a more privileged class, take better care of themselves, and probably have a healthier lifestyle.¹⁰

Our study has several strengths. Exploitation of the French nationwide healthcare database presents a major benefit in longitudinal follow-up over a long period, with a small number of patients lost to follow-up. This database allows the constitution of an exhaustive cohort that covers 98% of the general French population. The population of patients analyzed can be considered almost exhaustive, thus avoiding the risks and uncertainties associated with sampling.

This study had several limitations. The source database includes only refunded treatments or consultations. Self-medication and other supportive care (acupuncture, phytotherapy, hypnosis) were not included. Furthermore, the name and quantity of homeopathic therapies are not available in this database, which is why exposition was measured according to the number of dispensing procedures. The function of supportive care for homeopathic drugs has not been fully established. Another limitation is that treatment compliance could not be measured. Therefore, the dispensed treatments are not necessarily consumed. Finally, no causality could be definitively drawn from the observational results. However, it encourages the performance of additional randomized control trials, especially given the very low risks associated with homeopathy.

Conclusion

Homeopathy is increasingly used in patients with BC, starting immediately after diagnosis. This use was sustained after surgery and seemed to play an important role in helping patients to better tolerate the SEs of cancer treatments. To our best knowledge, this is the first study to evaluate the QOL of patients based on exploitation

of the French nationwide healthcare database. Further studies are needed to support our results, but the use of homeopathy seems to be an efficient way to reduce SEs in cancer treatment. Better communication is needed between the oncologists, homeopaths, and patients to provide the latter with a good QOL.

Clinical Practice Points

Despite the progress in cancer treatment, patients continue to experience distress and disability during and after cancer treatment. Complementary medicines (CMs), such as homeopathy, are used to address these symptoms. In recent years, there has been an increasing use of homeopathy as supportive care for conventional cancer treatment. Evidence shows that homeopathy can alleviate the side effects (SEs) of conventional treatments, resulting in improved quality of life (QOL) and better compliance with cancer treatments, especially in patients with breast cancer (BC). However, only a few comparative studies have used nationwide healthcare databases in oncology. The objective of this study was to assess the benefits of homeopathy treatment on the QOL of patients with nonmetastatic BC dispensed as post-surgical complementary therapy.

Our study showed a consistent evolution of homeopathy consumption over a long follow-up period (7 years). There was an increase in the use of homeopathy in patients with BC, starting immediately after diagnosis (from 11% to 26%). This consumption was higher during the first year following surgery (22% and 18%, respectively), and then maintained at 14% to 15% for the next 4 years. The use of homeopathy can have an important impact on the QOL of women with BC by helping them better cope with the illness and SEs of cancer treatments. This time-consistent evolution was confirmed regardless of the type of surgery and treatment.

These results can help improve the care and management of cancer patients and promote communication between the oncologist, homeopath physician, and patient.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.clbc.2022.10.001](https://doi.org/10.1016/j.clbc.2022.10.001).

References

1. The Global Cancer Observatory. Cancer facts sheet - Breast. <https://gco.iarc.fr/today/data/factsheets/cancers/20-Breast-fact-sheet.pdf> (1 December 2021).
2. Leggett S, Koczwara B, Miller M. The impact of complementary and alternative medicines on cancer symptoms, treatment side effects, quality of life, and survival in women with breast cancer—a systematic review. *Nutrition and Cancer*. 2015;67:373–391.
3. Buijs C, Vries EGE de, Mourits MJE, Willemse PHB. The influence of endocrine treatments for breast cancer on health-related quality of life. *Cancer Treat Rev*. 2008;34:640–655.

4. Odle TG. Adverse effects of breast cancer treatment. *Radiol Technol.* 2014;85:297M-319M; quiz 320M-323M.
5. Jiwa M, Long A, Shaw T, et al. The management of acute adverse effects of breast cancer treatment in general practice: a video-vignette study. *J Med Internet Res.* 2014;16.
6. Molassiotis A, Fernandez-Ortega P, Pud D, et al. Use of complementary and alternative medicine in cancer patients: a European survey. *Ann Oncol.* 2005;16:655-663.
7. Shukla P, Nayak C, Baig MQ, Misra P. A systematic review of controlled trials of homeopathy in adverse effects of radiotherapy and chemotherapy in cancer. *Homeopathic Links.* 2019;32:131-140.
8. Frass M, Friehs H, Thallinger C, et al. Influence of adjunctive classical homeopathy on global health status and subjective wellbeing in cancer patients – a pragmatic randomized controlled trial. *Complementary Therapies in Med.* 2015;23:309-317.
9. Rostock M, Naumann J, Guethlin C, Guenther L, Bartsch HH, Walach H. Classical homeopathy in the treatment of cancer patients - a prospective observational study of two independent cohorts. *BMC Cancer.* 2011;11:19.
10. Crocetti E, Crotti N, Feltrin A, Ponton P, Geddes M, Buiatti E. The use of complementary therapies by breast cancer patients attending conventional treatment. *Eur J Cancer.* 1998;34:324-328.
11. Downer SM, Cody MM, McCluskey P, et al. Pursuit and practice of complementary therapies by cancer patients receiving conventional treatment. *BMJ.* 1994;309:86-89.
12. Simon L, Prebay D, Beretz A, et al. Médecines complémentaires et alternatives suivies par les patients cancéreux en France. 2007.
13. Saghathian M, Bihan C, Chenailler C, Mazouni C, Dauchy S, Delalogue S. Exploring frontiers: use of complementary and alternative medicine among patients with early-stage breast cancer. *Breast.* 2014;23:279-285.
14. Molassiotis A, Scott JA, Kearney N, et al. Complementary and alternative medicine use in breast cancer patients in Europe. *Support Care Cancer.* 2006;14:260-267.
15. Tuppin P, Roquefeuil L de, Weill A, Ricordeau P, Merlière Y. French national health insurance information system and the permanent beneficiaries sample. *Revue d'Epidémiologie et de Santé Publique.* 2010;58:286-290.
16. Institut National du Cancer (INCa). *Etude sur les délais de prise en charge des cancers du sein et du poumon dans plusieurs régions de France en; 2011..*
17. Rey G, Rican S, Jouglà E. Mesure des inégalités de mortalité par cause de décès. Approche écologique à l'aide d'un indice de désavantage social. *BEH.* 2011:87-90.
18. Hoertel N, Limosin F, Leleu H. Poor longitudinal continuity of care is associated with an increased mortality rate among patients with mental disorders: Results from the French National Health Insurance Reimbursement Database. *Eur Psychiatry.* 2014;29:358-364.
19. Bice TW, Boxerman SB. A quantitative measure of continuity of care. *Med Care.* 1977;15:347-349.
20. Que sont les soins de support ? - AFSOS. *Association Francophone des Soins Oncologiques de Support.*
21. Cassileth BR, Deng G. Complementary and alternative therapies for cancer. *The Oncologist.* 2004;9:80-89.
22. Sarraon-Eck A, Bouhnik A-D, Rey D, Bendiane M-K, Huiart L, Peretti-Watel P. Use of non-conventional medicine two years after cancer diagnosis in France: evidence from the VICAN survey. *J Cancer Surviv.* 2017;11:421-430.
23. Bagot J-L, Legrand A, Theunissen I. Use of homeopathy in integrative oncology in strasbourg, france: multi-center cross-sectional descriptive study of patients undergoing cancer treatment. *Homeopathy.* 2021;3:168-173.
24. Horneber M, Bueschel G, Dennert G, Less D, Ritter E, Zwahlen M. How many cancer patients use complementary and alternative medicine: a systematic review and metaanalysis. *Integr Cancer Ther.* 2012;11:187-203.
25. Rossi E, Vita A, Baccetti S, Stefano M, Voller F, Zanolini A. Complementary and alternative medicine for cancer patients: results of the EPAAC survey on integrative oncology centres in Europe. *Supportive care in cancer : off j Multinational Assoc Supportive Care in Cancer.* 2014;23:1795-1806.
26. Bagot J-L, Karp J-C, Messerschmitt C, et al. Recommandations thérapeutiques de la Société Homéopathique Internationale de Soins de Support en Oncologie (SHISSO) - Therapeutic recommendations of the International Homeopathic Society of Supportive Care in Oncology (IHSSCO). *La Revue d'Homéopathie.* 2017;8:183-191.
27. Schmitz O. Les points d'articulation entre homéopathie et oncologie conventionnelle. *Anthropologie & Santé Revue internationale francophone d'anthropologie de la santé.* 2011.
28. Kulkarni A, Nagarkar B, Burde G. Radiation protection by use of homeopathic medicines. *Hahnemann Hom Sand.* 1988:20-23.
29. Oberbaum M, Yaniv I, Ben-Gal Y, et al. A randomized, controlled clinical trial of the homeopathic medication TRAUMEEL s® in the treatment of chemotherapy-induced stomatitis in children undergoing stem cell transplantation. *Cancer.* 2001;92:684-690.
30. Pommier P, Gomez F, Sunyach MP, D'Hombres A, Carrie C, Montbarbon X. Phase III randomized trial of calendula officinalis compared with trolamine for the prevention of acute dermatitis during irradiation for breast cancer. *JCO.* 2004;22:1447-1453.
31. Sencer S, Zhou T, Freedman L, et al. Traumeel S in preventing and treating mucositis in young patients undergoing SCT: a report of the Children's Oncology Group. *Bone Marrow Transpl.* 2012;47:1409-1414.
32. Pérol D, Provençal J, Hardy-Bessard A, et al. Can treatment with Cocculine improve the control of chemotherapy-induced emesis in early breast cancer patients? A randomized, multi-centered, double-blind, placebo-controlled Phase III trial. *BMC Cancer.* 2012;12:603.
33. Daub E, Gerhard I, Bastert G. Homeopathic antiemetics in Chemotherapy : a prospective, randomized trial. *Obstetrics and gynecol.* 2000;60.
34. Mercier M, Schraub S. Qualité de vie : quels outils de mesure ? - Quality of life : what are the assessment instruments ? *Deauville.* 2005.
35. Klein D, Mercier M, Abeillard E, et al. Long-term quality of life after breast cancer: a French registry-based controlled study. *Breast Cancer Res Treat.* 2011;129:125-134.
36. Ostermann JK, Reinhold T, Witt CM. Can additional homeopathic treatment save costs? A retrospective cost-analysis based on 44500 insured persons. *PLoS One.* 2015;10.