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Determinants of maintenance at work of breast cancer patients: results from the OPTISOINS01 prospective study.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-020276
Article Type:	Research
Date Submitted by the Author:	29-Oct-2017
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Keywords:	Breast tumours < ONCOLOGY, OCCUPATIONAL & INDUSTRIAL MEDICINE, PUBLIC HEALTH

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Manuscripts

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3 **Determinants of maintenance at work of breast cancer patients: results from the**
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5 **OPTISOINS01 prospective study.**
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25 Word count: 2431

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Delphine Hequet, Roman Rouzier and Sandrine Baffert designed the study.

Bernard Asselain and Souhr Neffati contributed to the design and implementation of the research.

Sandrine Baffert and Anne-Laure Soilly performed the health economic analysis.

Alexandra Arfi and Delphine Hequet performed all the remaining statistical analysis and wrote the manuscript.

Cyrille Huchon and Fabien Reyal contributed to the clinical study, patients' inclusion and analysis of the results.

All the authors reviewed and approved the final version of the manuscript.

ABSTRACT

Introduction: Return to work (RTW) after breast cancer (BC) is still a new field of research. The factors determining maintenance at work of BC patients have not been clearly identified. The aim of this study was to describe work during BC management and to identify factors associated with maintenance at work.

Materials and methods: An observational, prospective, multicenter study was conducted among women with operable BC. A logbook was given to all working patients to record sociodemographic and work-related data over a one-year period.

Results: Work-related data after BC were available for 178 patients (60%). Sick leave was prescribed for 165 patients (92.7%) for a median of 155 days. On univariate analysis, invasive BC ($p=0.025$), lymph node involvement ($p=0.005$), radical surgery ($p=0.025$), axillary dissection ($p=0.004$), chemotherapy ($p<0.001$), personal income $< \text{€}1,900/\text{month}$ ($p=0.03$) and not having received the patient information booklet on RTW ($p=0.047$) were associated with a longer duration of sick leave. On multivariate analysis, chemotherapy was associated with longer sick leave (OR: 3.5; [95%CI: 1.6-7.9]; $p=0.002$). The cost of sick leave to French National Health Insurance was fourfold higher in the case of chemotherapy ($p<0.001$).

Conclusion: Advanced disease and chemotherapy are major factors that influence maintenance at work during the management of BC. Systematic screening can help to diagnose earlier disease and reduce the need for aggressive therapy.

Keywords: breast cancer, return to work, maintenance at work, absence duration, chemotherapy.

Article summary

- This study explored prospectively maintenance and return to work during 1 year follow-up after diagnosis of breast cancer.
- The analysis is multimodal, exploring the impact of cancer on professional activity, determinants of longer sick leaves and cost of sick leaves.
- The results highlight the need to develop patients' support to improve return to work and decrease sick leaves.
- The main factor of longer sick leaves is adjuvant chemotherapy.
- section consisting of the heading: 'Strengths and limitations of this study', and containing up to five bullet points that relate specifically to the study reported

Data sharing statement: No additional data available

Ethics: This study was registered with ClinicalTrials.gov (Identifier: NCT02813317) and was approved by the French National ethics committee (CCTIRS Authorization No. 14.602 and CNIL DR-2014-167) covering research at all participating hospitals.

Funding: This study was supported by a grant from the French National Cancer Institute, dedicated to economic studies of innovative techniques. Delphine Hequet benefitted from a "Fondation pour la Recherche Medicale" (FDM20140630453) grant to conduct this study.

What is already known on this subject?

Return to work after breast cancer is a delicate step in the real-life reintegration. Breast cancer patients have difficulties at work even 5 years after the end of the treatments. The factors that maintain patients at work during breast cancer are rarely described.

What this study adds?

This prospective study describes work maintenance and sick leaves during the first year following the diagnosis of early breast cancer. After one year, 20% of the patients did not return to work. Chemotherapy dramatically increased the duration of sick leaves, whereas an early information on support can reduce sick leaves. Costs of sick leaves are major

INTRODUCTION

Improvements in early detection and treatment have resulted in an increasing number of breast cancer (BC) survivors.[1] Treatments mostly focus on curing the disease and preventing metastatic relapse. About one-third of women diagnosed with BC are under the age of 55 with a 10-year survival close to 80%.[2] Many patients therefore recover and resume their activities of daily living during or after treatment, including return to work (RTW). RTW after BC is still a new, but important aspect of survivorship research, not only from a societal point of view, as it provides financial resources for rehabilitation of cancer survivors,[3,4] and contributes to psychosocial well-being, including physical and mental health.[5] Some BC cancer survivors experience reduced work ability.[6-11] Difficulties at work or unemployment differ according to the type of BC treatment. Cancer treatment varies according to the stage of the disease and can include surgery, chemotherapy, radiotherapy and hormone therapy. For many cancer patients, return to work helps them to recover from treatment and also constitutes a positive step towards the future. However, factors that maintain patients at work during treatment of their BC have not been clearly identified. The identification of these factors could help healthcare professionals to more accurately identify patients at risk of RTW difficulties in order to provide them with adapted support during BC management designed to maintain them at work. The aim of this prospective study was to describe work during BC management and identify factors associated with either cessation or maintenance at work.

MATERIALS AND METHODS

OPTISOINS01 was an observational, prospective, multicenter study conducted from December 2014 to March 2016 among BC patients from a regional health territory. The primary objective of the Optisoins01 study was to identify the main care pathway after 1 year of early BC and to evaluate costs from various perspectives. Maintenance and return to work evaluation was one of the secondary objectives of the study. The Optisoins01 study design has been previously described.[12] Eight nonprofit hospitals participated in the study: 3 teaching hospitals, 4 general hospitals and 1 comprehensive cancer center. Inclusion criteria were: women aged ≥ 18 years with previously untreated, first, histologically confirmed, operable BC. Exclusion criteria were: metastatic, locally advanced, or inflammatory BC, previous history of BC.

After BC diagnosis, a work and cancer information booklet had to be given to all working patients. Our Institute has designed an information booklet in collaboration with occupational physicians and the Paris Regional Health Insurance (Caisse Régionale d'Assurance Maladie d'Île-de-France). This document includes the testimonies from employees, advice and practical information to help patients anticipate difficulties and find support: possibility of part-time work, career development plan, roles of occupational physicians and general practitioners. The booklet is freely available online with the support of the "ARC" Foundation.[13]

After inclusion, all patients were given a logbook in which to record, throughout the year, sociodemographic data, out-of-pocket health expenses and an occupational questionnaire for employed women including dates of work and absence from work during treatments, job adjustments, on-shift status and the perceived quality of reintegration. During the second half of the year, clinical research assistants made 2 phone calls to remind patients to fill in

1
2
3 the logbook. Types of occupations were classified according to the French *Institut National*
4 *de la Statistique et des Etudes Economiques (INSEE)* classification.

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7 Two groups of patients were compared in order to determine the factors associated with
8
9 maintenance at work: longer sick leave (longer than the median duration) and shorter sick
10
11 leave (shorter than the median duration). Fisher's exact test or Student's t-test were used to
12
13 analyze these factors. Multivariate analysis was performed using a logistic regression model.
14
15 Sick leave over a 1-year period was described according to whether or not the patients were
16
17 treated by chemotherapy. Differences in the areas under the curves of the 2 populations
18
19 were compared to 1,000 permutations of random allocation of chemotherapy. The same
20
21 analysis was performed according to whether or not the patients had received the work
22
23 information booklet. Differences were considered significant for $p < 0.05$. All statistical
24
25 analyses were performed with R software.[14]

26
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29
30 The cost of sick leave for National Health Insurance was calculated on the basis of the
31
32 monthly income declared by the patients, the duration of sick leave and the national sick
33
34 leave allowance scale.

35
36
37 This study was registered with ClinicalTrials.gov (Identifier: NCT02813317) and was approved
38
39 by the French National ethics committee (CCTIRS Authorization No. 14.602 and CNIL DR-
40
41 2014-167) covering research at all participating hospitals.

42 43 44 45 46 **RESULTS**

47
48 Six hundred and four patients with a median age of 58 years (range: 24-98) were included in
49
50 the Optisoins01 study, including 297 patients (48.2%) who were working at the time of BC
51
52 diagnosis. The present study focused on these 297 patients.

Detailed patient characteristics and cancer characteristics are presented in Table 1. The median age of the women was 50 (range: 37-77) years, 54 women (18.2%) were single, 153 (51.5%) were married, 39 (13.1%) were divorced and 3 (1.0%) were widows. Two hundred and sixty-one patients (87.9%) had invasive BC and 35 (11.8%) had *in situ* BC. Seventy-five women (25.3%) presented axillary lymph node involvement.

Table 1: Patient and cancer characteristics and breast cancer treatments (n=297)

	n or median	% or range
Patient characteristics		
Age (years)	50	(27-77)
Marital status		
<i>Single</i>	54	18.2%
<i>Married</i>	153	51.5%
<i>Divorced</i>	39	13.1%
<i>Widow</i>	3	1%
<i>NA</i>	48	16.2%
Breast cancer characteristics		
Modes of diagnosis		
<i>Organized screening</i>	60	20.2%
<i>Individual screening</i>	114	38.4%
<i>Clinical signs</i>	123	41.4%
Type of cancer		
<i>Invasive</i>	261	87.9%
<i>In situ</i>	35	11.8%
<i>NA</i>	1	0.3%
Lymph node involvement		
<i>Yes</i>	75	25.3%
<i>No</i>	222	74.7%
Surgery		
Breast surgery		
<i>Conservative</i>	220	74.1%
<i>Radical</i>	77	25.9%
Lymph node surgery		
<i>Sentinel lymph node procedure</i>	203	68.4%
<i>Axillary dissection</i>	72	24.2%

	<i>NA</i>	22	7.4%
Surgical revision	<i>no</i>	227	76.4%
	<i>1</i>	60	20.2%
	<i>>1</i>	10	3.4%
Type of hospitalization			
	<i>Outpatient surgery</i>	107	36%
	<i>Conventional surgery</i>	190	64%
Adjuvant therapies			
Radiotherapy			
	<i>No</i>	27	9.1%
	<i>Yes</i>	270	90.9%
Chemotherapy			
	<i>Yes</i>	143	48.1%
	<i>No</i>	154	51.9%
Trastuzumab			
	<i>Yes</i>	36	12.1%
	<i>No</i>	100	33.7%
	<i>NA</i>	161	54.2%
Hormone therapy			
	<i>Yes</i>	220	74.1%
	<i>No</i>	77	25.9%

Two hundred and twenty women (74.1%) underwent breast-conserving surgery and 77 (25.9%) underwent radical mastectomy (Table 1). A sentinel lymph node procedure was performed for 203 patients (68.4%). Seventy patients required at least 1 reoperation for the following reasons: positive surgical margins and secondary mastectomy, sentinel lymph node procedure following discovery of an invasive tumor, axillary dissection following positive sentinel lymph node biopsy and surgical complications (abscess, hematoma, etc.). After surgery, 90.9% of patients received radiotherapy 48.1% of patients received adjuvant chemotherapy and 74.1% of patients received hormone therapy.

Most patients were executives (31.4%) or employees (33.3%). Most patients (47.1%) had a monthly income > €1,900. Work data after BC were available for 178 patients (60%,

supplemental Figure 1). Patients who did not complete the 1-year work questionnaire were globally less compliant with the study and less medicalized (supplemental table 1). Sick leave was prescribed for 165 patients (92.7%). Patients had only one sick leave in 52.2% of cases, 2 sick leaves in 21.9% of cases and 3 or more sick leaves in 18.5% of cases. Median duration of sick leave was 155 days (range: 5-365). After treatment, 7 patients (3.9%) lost their jobs and 46.1% had reduced income. Patients encountered difficulties with their co-workers in 3.4% of cases, with their superiors in 3.9% of cases and for undocumented reasons in 12.9% of cases. Work-related factors are summarized in Table 2.

Table 2: Work characteristics before and after BC

	n or median	% or range
Work characteristics before breast cancer, n=297		
Type of occupation		
<i>Farmer</i>	1	0.3%
<i>Self-employed</i>	8	2.5%
<i>Executive</i>	99	31.4%
<i>Employee</i>	105	33.3%
<i>Intermediate profession</i>	29	9.2%
<i>Blue-collar worker</i>	2	0.6%
NA	53	22.9%
Personal income per month (€)		
<i>no income</i>	6	2%
<i>< 1900</i>	104	35%
<i>>1900</i>	140	47.1%
NA	47	15.8%
Work characteristics after breast cancer, n=178		
Dismissal	7	3.9%
Income change		
<i>decreased</i>	82	46.1%
<i>increased</i>	3	1.7%
<i>stable</i>	73	41%
NA	20	11.2%
Decreased income (%), n=82		
<i><10%</i>	37	45.1%
<i>10-30%</i>	13	15.8%

	30-60%	5	6.1%
	>60%	3	3.7%
	NA	24	29.3%
Sick leave			
	Yes	165	92.7%
	No	13	7.3%
Number of sick leaves			
	1	93	52.2%
	2	39	21.9%
	>2	33	18.5%
Duration of sick leave (days)		155	(5-365)
Difficulties at work			
	with coworkers	6	3.4%
	with superiors	7	3.9%
	other	23	12.9%

On univariate analysis, the presence of clinical signs leading to a diagnosis of BC ($p<0.001$), an invasive form of BC ($p=0.02$), lymph node involvement ($p=0.005$), radical surgery ($p=0.02$), axillary dissection ($p<0.001$), chemotherapy ($p<0.001$), personal income $< \text{€}1,900/\text{month}$ ($p=0.03$) and not having received the work and cancer information booklet ($p=0.047$) were associated with a longer total duration of sick leave (Table 3). Moreover, patients with longer sick leave were more likely to have reduced income after treatment of their disease ($p=0.0012$).

Table 3: Determinants and consequences of long sick leave

	Sick leave <155 days, n=79		Sick leave >155, days n=77		p
	n or median	% or range	n or median	% or range	
Patient characteristics					
Age (years)	50.6	(27-59)	50	(29-77)	0.52
Type of occupation					0.09
	<i>Farmer</i>	0	0%	0	0%

	<i>Self-employed</i>	3	3.8%	1	1.3%	
	<i>Executive</i>	36	45.6%	29	37.7%	
	<i>Employee</i>	25	31.6%	38	49.4%	
	<i>Intermediate profession</i>	13	16.5%	7	9.1%	
	<i>Blue-collar worker</i>	1	1.3%	0	0%	
	NA	1	1.3%	2		
	Personal income per month (€)					0.03
	< 1900	25	31.6%	37	48.1%	
	> 1900	54	68.4%	38	49.4%	
	NA	0	0%	2	2.6%	
Marital status						0.76
	<i>Single</i>	18	22.8%	12	15.6%	
	<i>Married</i>	47	59.5%	49	63.6%	
	<i>Divorced</i>	12	15.2%	14	18.2%	
	<i>Widow</i>	1	1.3%	1	1.3%	
	NA	1	1.3%	1	1.3%	
Breast cancer characteristics						
Type of cancer						<0.001
	<i>Invasive</i>	63	79.7%	74	96.1%	
	<i>In situ</i>	16	20.3%	3	3.9%	
Lymph node involvement						0.005
	<i>Yes</i>	11	13.9%	26	33.8%	
	<i>No</i>	68	86.1%	52	67.5%	
Surgery						
Breast surgery						0.02
	<i>Conservative</i>	66	83.5%	50	64.9%	
	<i>Radical</i>	13	16.5%	27	35.1%	
Lymph node surgery						<0.001
	<i>Sentinel lymph node procedure</i>	62	78.5%	48	62.3%	
	<i>Axillary dissection</i>	9	11.4%	26	33.8%	
	NA	8	10.1%	3	3.9%	
Surgical revision						0.06
	<i>Yes</i>	13	16.5%	23	29.9%	
	<i>No</i>	66	83.5%	54	70.1%	
Radiotherapy						0.53
	<i>Yes</i>	72	91.1%	74	96.1%	
	<i>No</i>	7	8.9%	3	3.9%	
Chemotherapy						<0.001
	<i>Yes</i>	25	31.6%	56	72.7%	
	<i>No</i>	54	68.4%	21	27.3%	

1							
2							
3	Trastuzumab						0.54
4		Yes	9	11.4%	12	15.6%	
5		No	16	20.3%	40	51.9%	
6		NA	54	68.4%	25	32.5%	
7							
8	Hormone therapy						0.05
9		Yes	50	63.3%	61	79.2%	
10		No	29	36.7%	16	20.8%	
11							
12	Patient management						
13	Modes of diagnosis						<0.001
14		<i>Organized screening</i>	15	19%	21	27.3%	
15		<i>Individual screening</i>	43	54.4%	20	26%	
16		<i>Clinical signs</i>	21	26.6%	36	46.8%	
17							
18	Type of hospitalization						<0.001
19		<i>Outpatient surgery</i>	58	73.4%	34	44.2%	
20		<i>Inpatient surgery</i>	21	26.6%	43	55.8%	
21							
22	Work and cancer information booklet						
23		Yes	64	81%	52	67.5%	0.047
24		No	15	19%	25	32.5%	
25							
26	Return to work						
27							
28	Dismissal		1	1.3%	3	3.9%	0.62
29	Income change						
30		<i>decreased</i>	23	29.1%	48	62.3%	<0.001
31		<i>increased</i>	0	0%	2	2.6%	
32		<i>stable</i>	37	46.8%	24	31.2%	
33		NA	19	24.1%	3	3.9%	
34							
35	Decreased income (%)						0.61
36		<10%	11	13.9%	21	27.3%	
37		10-30%	4	5.1%	7	9.1%	
38		30-60%	0	0%	4	5.2%	
39		>60%	0	0%	3	3.9%	
40		NA	64	81%	42	54.5%	
41							
42	Difficulties at work						
43		<i>with coworkers</i>	2	2.5%	3	3.9%	0.67
44		<i>with superiors</i>	0	0%	6	7.8%	0.17
45		<i>other</i>	7	8.9%	14	18.2%	0.93
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53							
54	On multivariate analysis, chemotherapy was the only independent factor associated with						
55	longer sick leave (OR: 3.5, [95%CI: 1.6-7.9], p=0.002). Patients treated by chemotherapy had						
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2
3 longer sick leave than those not treated by chemotherapy (Figure 1). The difference in terms
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5 of the 1-year distribution of sick leave was not statistically significant between patients
6
7 according to whether or not they had received the work information booklet (Figure 2). The
8
9 cost of sick leave for National Health Insurance was fourfold higher in patients treated by
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11 chemotherapy with a median allowance of €8,841.
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16 **DISCUSSION**

17
18 This study confirms that RTW after BC is a difficult process. Sick leave is frequently
19
20 prescribed and is often long, with a median sick leave of 155 days in this study.
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22
23

24 Factors associated with long sick leave (>155 days) were severe or advanced forms of BC.
25
26 The duration of sick leave was also associated with the mode of diagnosis, as patients
27
28 diagnosed by breast screening presented shorter sick leaves. Public health authorities should
29
30 therefore promote breast screening in order to decrease the proportion of advanced forms
31
32 of BC and aggressive therapies with severe consequences on work and personal activities.
33
34 Consequently, longer sick leave was also associated with more aggressive therapy, such as
35
36 radical surgery, axillary dissection, and chemotherapy. These results are similar to those
37
38 published in the literature.[6,10,11, 15-17] Chemotherapy is an aggressive treatment that is
39
40 necessary in order to ensure survival, but which has long-lasting consequences in terms of
41
42 self-esteem (alopecia...), chronic pain (neuropathy...), and chronic fatigue, that play an
43
44 important role in return to work and maintenance at work.[9] BC survivors may have to deal
45
46 with the side effects specific to this type of treatment. Although many side effects of
47
48 chemotherapy are only temporary,[18] some studies have shown that chemotherapy may
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50 impact on cognitive functioning [19] and fatigue [20] up to 10 years after diagnosis.
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3 Cognitive functioning and fatigue have both been associated with impaired work
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5 functioning.[21] Munir et al [22] reported that up to 62–84% of women resumed work either
6
7 during treatment with chemotherapy or following completion of treatment. As a result of
8
9 their cognitive limitations, women reported that they experienced difficulties with their
10
11 work ability, particularly difficulties doing multiple tasks, reduced clarity of decisions, deficits
12
13 in clear thinking and feelings of being inept due to short-term memory.[15] Rapid progress is
14
15 being made in the field of chemotherapy with the routine use of new genomic signature
16
17 tests that allow more accurate targeting of patient likely to benefit from chemotherapy.
18
19 According to Nesvold et al [23] and Eaker et al,[18] mastectomy and axillary lymph node
20
21 dissection may influence working life long after treatment due to an increased risk of chronic
22
23 pain. BC survivors are more likely to suffer from upper extremity impairments or
24
25 lymphedema than are other cancer survivors,[24-28] which are responsible for difficulties
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27 returning to work or maintenance at work.[27,29-31]

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33 The work and cancer information booklet appeared to help patients return to work with
34
35 significantly shorter sick leave. The first key to successful return to work is anticipation. The
36
37 information booklet advises women to attend the occupational medicine service. In France,
38
39 occupational medicine plays an essential role, but the patient is not obliged to consult the
40
41 occupational physician when sick leave is < 3 months. However, at 3 months, the
42
43 occupational physician and the employee must determine the modalities of return to work,
44
45 based on the employee's state of health and the characteristics of the workplace. These
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47 arrangements concern the employee himself and the work collective with, if necessary,
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49 actions so that the reception is assured to the return. Setting up of a schedule, reduction of
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51 working hours, modification of physical, mental or workplace loads can also be instituted at
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3 the time of return to work. The occupational physician can provide recommendations to the
4
5 employer, unless the employer refuses. The results obtained with this handbook are
6
7 particularly encouraging and suggest that more individual supports should be developed.
8
9 Patient support appears to be one of the keys to successful RTW. Health coaching by
10
11 telephone and/or face-to-face interview have already been tested,[30,32,33] showing
12
13 positive significant outcomes on physical activity, body mass index, pain management,
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15 acceptance of disease and self-confidence among cancer survivors. Coaching methods have
16
17 never been tested in the management of work maintenance. Our Institute is therefore
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19 setting up a prospective randomized study (OPTICOACH) with tailored support intervention
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21 to enhance RTW after BC in collaboration with a professional coach, consisting of individual
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23 interviews or small group workshops over a period of 3 years.
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28 Difficulties returning to work appear to extend over a period of many years. Sevellec et al
29
30 [34] showed that, six years after returning to work, one employee out of two was still
31
32 working in the same company. Rather than disappearing, the difficulties identified many
33
34 years after BC persist for a long time after stopping treatment. It is therefore essential to
35
36 identify the factors associated with longer sick leave and RTW difficulties in order to help
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38 working patients and prevent these long-term problems. The VICAN 2 study focused on
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40 the factors associated to difficulties at RTW.[33] This large study was carried out in 2014
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42 by the French National Cancer Institute, on the living conditions of people with cancer (not
43
44 only BC), two years after the diagnosis. The people most vulnerable to job loss two years
45
46 after the cancer diagnosis are mainly those working in the so-called socio-professional
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48 execution categories, the youngest and oldest, married people with a level of education
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50 below the baccalaureate level, and those with precarious contracts.
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3 One of the potential biases of this study concerns the characteristics of the study
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5 population, as almost the majority of women belonged to the wealthiest social classes, as
6
7 45.6% of patients were executives and only 1.3% were blue collar workers. More than
8
9 sixty-eight percent of patients had a personal monthly income > €1,900 and 36.7% had a
10
11 personal monthly income > €2,600. This distribution does not exactly reflect French
12
13 society; in France, according to the INSEE statistics of 2014, the median monthly income
14
15 was €1,772. Similarly to our results, a Canadian team [34] has shown that women with an
16
17 annual income less than C\$20,000 were less likely to return to work than those whose
18
19 income exceeded C\$50,000. The French social protection system also plays a role, as it
20
21 provides cancer survivors with the possibility of replacement income, allowing women to
22
23 decide whether or not they wish to return to work immediately. Moreover, BC almost
24
25 exclusively concerns women, affecting them in their roles as mother, wife and working
26
27 woman; after treatment, some women sometimes prefer to devote themselves more to
28
29 their personal life and therefore decide to stop working. This notion of changing priorities
30
31 has already been reported. [35,36] After reassessing their priorities, some women choose
32
33 to lower their career ambitions and devote more time to their family and themselves.
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35 However, this attitude would particularly concern patients with other sources of income.
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37 Providing assistance and support to all working patients should therefore be a priority.
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46 **CONCLUSION**

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48 Advanced disease and chemotherapy are major factors that influence maintenance at work.
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50 Systematic screening or use of innovative tools, such as genomic signatures, can facilitate
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52 earlier diagnosis and reduce aggressive therapies. One of the keys to success of RTW is
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54 anticipation; a cancer and work information booklet given to the patient during treatment,
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3 together with strong support by the occupational medicine service appear promote return
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5 to work and maintenance at work. Personalized coaching methods have been successfully
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7 used to promote acceptance of disease and self-confidence and should be tested in the
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9 management of maintenance at work.
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Supplemental Table 1: Differences between patients who returned the 1-year questionnaire and patients who did not return the questionnaire

	Data on sick leave, n=178		No data on sick leave, n=70		p
	n or median	% or range	n or median	% or range	
Patient characteristics					
Age (years)	50	(29-67)	49	(27-77)	0.36
Type of occupation					<0.05
	<i>Farmer</i>	1	1%	0	0%
	<i>Self-employed</i>	5	3%	0	0%
	<i>Executive</i>	72	40%	3	4%
	<i>Employee</i>	72	40%	27	39%
	<i>Intermediate profession</i>	22	12%	33	47%
	<i>Blue-collar worker</i>	2	1%	7	10%
	<i>NA</i>	4	2%	0	0%
Personal income per month (€)					<0.05
	<1900	71	40%	20	29%
	>1900	103	58%	37	53%
	<i>NA</i>	4	2%	13	19%
Marital status					<0.05
	<i>Single</i>	34	19%	18	26%
	<i>Married</i>	110	62%	39	56%
	<i>Divorced</i>	29	16%	10	14%
	<i>Widow</i>	2	1%	1	1%
	<i>NA</i>	3	2%	2	3%
Breast cancer characteristics					
Type of cancer					0.32
	<i>Invasive</i>	156	87,6%	61	87%
	<i>In situ</i>	21	11,8%	9	13%
Lymph node involvement					0.12
	<i>Yes</i>	43	24%	23	33%
	<i>No</i>	135	76%	47	67%
Surgical patient care					
Breast surgery					<0.05
	<i>Conservative</i>	133	75%	46	66%
	<i>Radical</i>	45	25%	24	34%
Lymph node surgery					0.48

	<i>Sentinel lymph node procedure</i>	122	69%	40	57%	
	<i>Axillary dissection</i>	42	24%	24	34%	
	<i>NA</i>	14	8%	6	9%	
	Surgical revision					0.24
	<i>Yes</i>	43	24%	16	23%	
	<i>No</i>	135	76%	54	77%	
	Radiotherapy					<0.05
	<i>Yes</i>	167	94%	61	87%	
	<i>No</i>	11	6%	9	13%	
	Chemotherapy					<0.05
	<i>Yes</i>	92	52%	33	47%	
	<i>No</i>	86	48%	37	53%	
	Trastuzumab					0.42
	<i>Yes</i>	24	13%	9	13%	
	<i>No</i>	63	35%	22	31%	
	<i>NA</i>	91	51%	39	56%	
	Hormone therapy					0.69
	<i>Yes</i>	129	72%	49	70%	
	<i>No</i>	49	28%	21	30%	
	Patient management					
	Modes of diagnosis					0.45
	<i>Organized screening</i>	37	21%	12	17%	
	<i>Individual screening</i>	74	42%	26	37%	
	<i>Clinical signs</i>	67	38%	32	46%	
	Type of hospitalization					0.78
	<i>Outpatient surgery</i>	108	61%	43	61%	
	<i>Inpatient surgery</i>	70	39%	27	39%	

Figures:

Figure 1: Percentage of patients on sick leave at 1-year follow-up depending on the presence or absence of chemotherapy

Figure 2: Percentage of patients on sick leave at 1-year follow-up depending on whether or not they had been given the work information booklet

Supplemental Figure 1: Flow Chart

Competing Interests: The authors declare that they have no competing interests.

Funding: This study was supported by a grant from the French National Cancer Institute dedicated to economic studies of innovative techniques. Delphine Héquet benefit from a grant of “Fondation pour la Recherche Médicale” to conduct this study.

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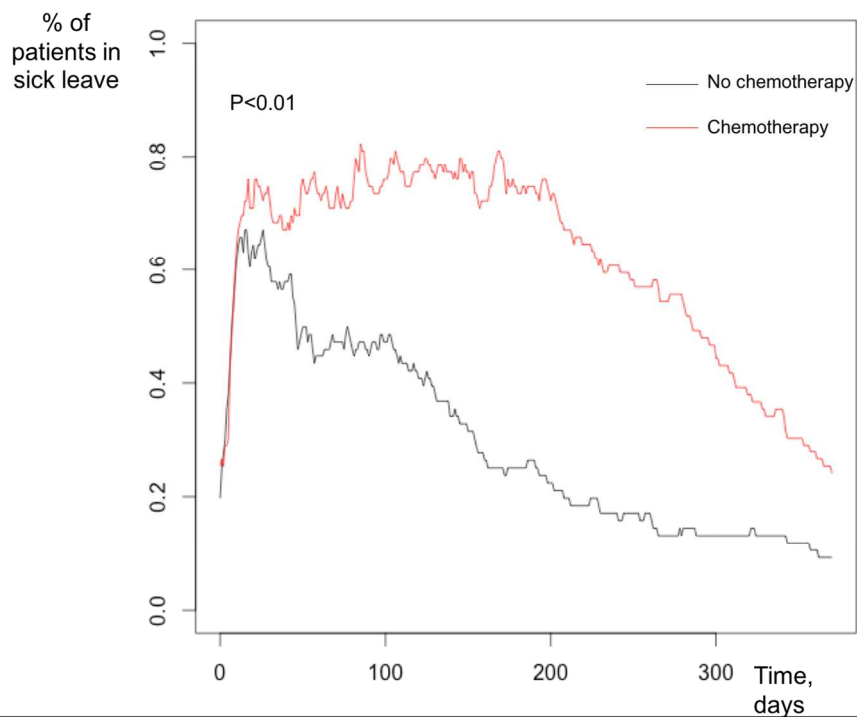


Figure 1: Percentage of patients on sick leave at 1-year follow-up depending on the presence or absence of chemotherapy

264x200mm (150 x 150 DPI)

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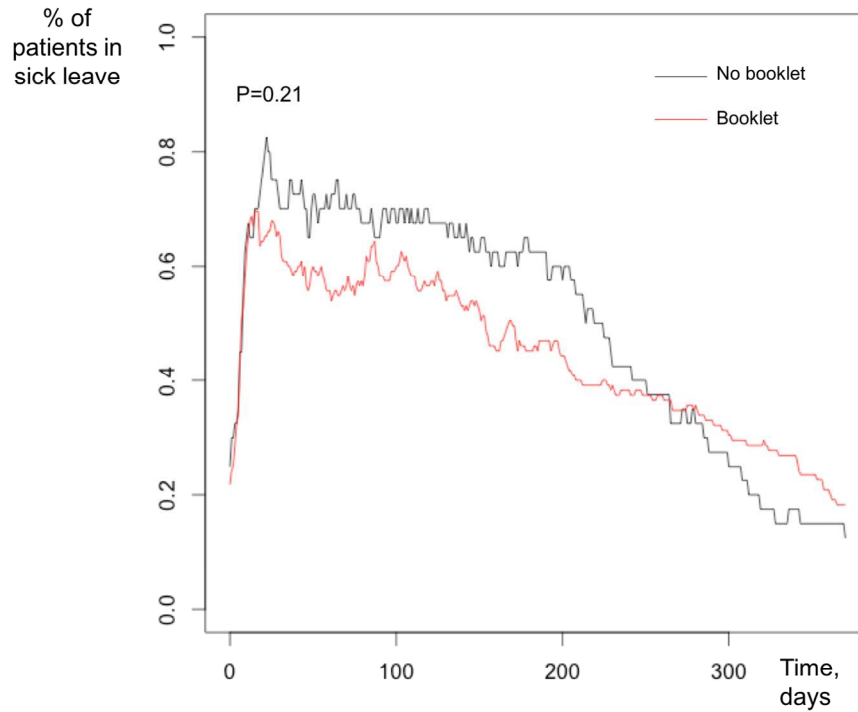
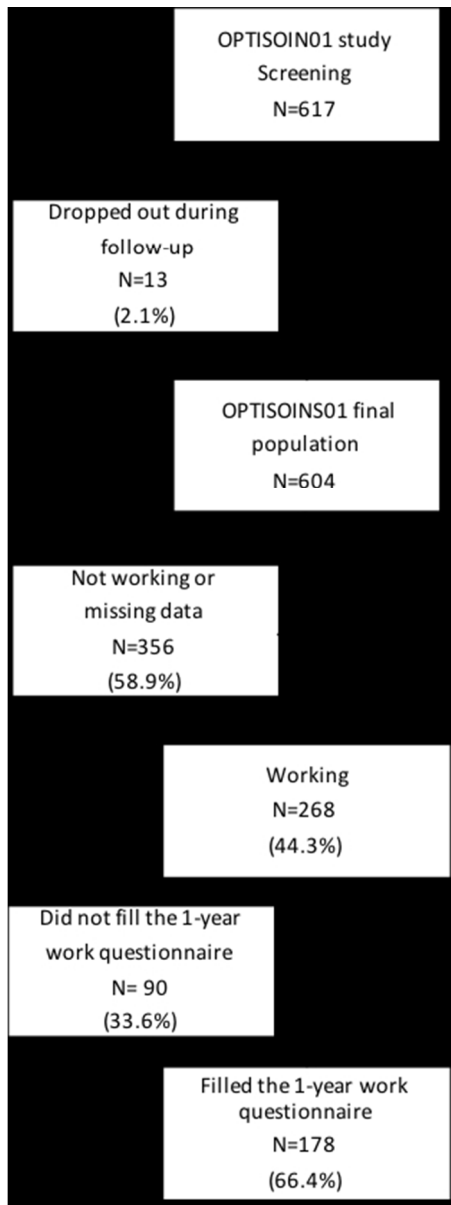


Figure 2: Percentage of patients on sick leave at 1-year follow-up depending on whether or not they had been given the work information booklet

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	4 and 5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8
		(b) For matched studies, give matching criteria and number of exposed and unexposed	8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9
		(b) Describe any methods used to examine subgroups and interactions	9
		(c) Explain how missing data were addressed	9
		(d) If applicable, explain how loss to follow-up was addressed	9
		(e) Describe any sensitivity analyses	9
Results			9

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	Supplemental figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10 and 11
		(b) Indicate number of participants with missing data for each variable of interest	11
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	11
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-14
		(b) Report category boundaries when continuous variables were categorized	12-14
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12-14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13, 14
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Determinants of maintenance at work of breast cancer patients: results from the OPTISOINS01 prospective study.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-020276.R1
Article Type:	Research
Date Submitted by the Author:	07-Feb-2018
Complete List of Authors:	Arfi, Alexandra; Institut Curie, Surgery Baffert, Sandrine; CEMKA-EVAL, Health Economist Soilly, A-L; Universite de Bourgogne IUT Dijon-Auxerre, Health Economist huchon, cyrille; Hôpital Poissy, Gynecology Reyal, Fabien; Institut Curie, Surgery Asselain, Bernard; Institut Curie, Biostatistics Neffati, Souhir; Institut Curie, Clinical Research and Innovation Department Rouzier, Roman; Institut Curie, Surgery Hequet, Delphine; Institut Curie-Centre René Huguenin, Surgical oncology
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Occupational and environmental medicine
Keywords:	Breast tumours < ONCOLOGY, OCCUPATIONAL & INDUSTRIAL MEDICINE, PUBLIC HEALTH

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3 **Determinants of maintenance at work of breast cancer patients: results from the**
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5 **OPTISOINS01 prospective study.**
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25 Word count: 2431

Contributorship statement:

Delphine Hequet, Roman Rouzier and Sandrine Baffert designed the study.

Bernard Asselain and Souhr Neffati contributed to the design and implementation of the research.

Sandrine Baffert and Anne-Laure Soilly performed the health economic analysis.

Alexandra Arfi and Delphine Hequet performed all the remaining statistical analysis and wrote the manuscript.

Cyrille Huchon and Fabien Reyal contributed to the clinical study, patients' inclusion and analysis of the results.

All the authors reviewed and approved the final version of the manuscript.

ABSTRACT

Introduction: Return to work (RTW) after breast cancer (BC) is still a new field of research. The factors determining maintenance at work of BC patients have not been clearly identified. The aim of this study was to describe work during BC treatment and to identify factors associated with maintenance at work.

Materials and methods: An observational, prospective, multicenter study was conducted among women with operable BC. A logbook was given to all working patients to record sociodemographic and work-related data over a one-year period.

Results: Work-related data after BC were available for 178 patients (60%). Median age at diagnosis was 50 years (27-77), 87.9% of patients had an invasive form of BC and 25.3% a lymph node involvement. 25.9% had a radical surgery and 24.2% had an axillary dissection. Radiotherapy was performed in 90.9% of patients and chemotherapy in 48.1%. Sick leave was prescribed for 165 patients (92.7%) for a median of 155 days. On univariate analysis, invasive BC ($p=0.025$), lymph node involvement ($p=0.005$), radical surgery ($p=0.025$), axillary dissection ($p=0.004$), chemotherapy ($p<0.001$), personal income $< \text{€}1,900/\text{month}$ ($p=0.03$) and not having received the patient information booklet on RTW ($p=0.047$) were associated with a longer duration of sick leave. On multivariate analysis, chemotherapy was associated with longer sick leave (OR: 3.5; [95%CI: 1.6-7.9]; $p=0.002$). The cost of sick leave to French National Health Insurance was fourfold higher in the case of chemotherapy ($p<0.001$).

Conclusion: Advanced disease and chemotherapy are major factors that influence maintenance at work during the management of BC. Systematic screening can help to diagnose earlier disease and reduce the need for aggressive therapy.

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3 **Strengths and limitations of this study:**
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6 - Prospective multicentric study
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8 - Description of factors associated to long sick leave
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10 - Multimodal analysis including evaluation of costs of sick leave
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12 - Few qualitative information
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18 **Keywords:** breast cancer, return to work, maintenance at work, absence duration,
19 chemotherapy.
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26 **Data sharing statement:** No additional data available
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28 **Ethics:** This study was registered with ClinicalTrials.gov (Identifier: NCT02813317) and was
29 approved by the French National ethics committee (CCTIRS Authorization No. 14.602 and
30 CNIL DR-2014-167) covering research at all participating hospitals.
31
32

33 **Funding:** Delphine Hequet benefitted from a “Fondation pour la Recherche Medicale”
34 (FDM20140630453) grant to conduct this study. This study was supported by a grant from
35 the French National Cancer Institute (Institut National du Cancer, PRME-K2013), dedicated
36 to economic studies of innovative techniques.
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What is already known on this subject?

Return to work after breast cancer is a delicate step in the real-life reintegration. Breast cancer patients have difficulties at work even 5 years after the end of the treatments. The factors that maintain patients at work during breast cancer are rarely described.

What this study adds?

This prospective study describes work maintenance and sick leaves during the first year following the diagnosis of early breast cancer. After one year, 20% of the patients did not return to work. Chemotherapy dramatically increased the duration of sick leaves, whereas an early information on support can reduce sick leaves. Costs of sick leaves are major.

INTRODUCTION

Improvements in early detection and treatment have resulted in an increasing number of breast cancer (BC) survivors [1]. Treatments mostly focus on curing the disease and preventing metastatic relapse. About one-third of women diagnosed with BC are under the age of 55 with a 10-year survival close to 80% [2]. Many patients therefore recover and resume their activities of daily living during or after treatment, including return to work (RTW). RTW after BC is still a new, but important aspect of survivorship research, not only from a societal point of view, as it provides financial resources for rehabilitation of cancer survivors and contributes to psychosocial well-being, including physical and mental health [3]. Some BC cancer survivors experience reduced work ability [4–8]. Difficulties at work or unemployment differ according to the type of BC treatment. Cancer treatment varies according to the stage of the disease and can include surgery, chemotherapy, radiotherapy and hormone therapy. For many cancer patients, return to work helps them to recover from treatment and also constitutes a positive step towards the future. The identification of factors that maintain patients at work during and after BC treatment could help healthcare professionals to more accurately identify patients at risk of RTW difficulties in order to provide them with adapted support during BC management. The aim of this prospective study was to describe work during and after BC management and identify factors associated with either cessation or maintenance at work.

MATERIALS AND METHODS

OPTISOINS01 was an observational, prospective, multicenter study conducted from December 2014 to March 2016 among BC patients from a regional health territory. The

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2
3 primary objective of the Optisoins01 study was to identify the main care pathway after 1
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5 year of early BC and to evaluate costs from various perspectives. Maintenance and return to
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7 work evaluation was one of the secondary objectives of the study. The Optisoins01 study
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9 design has been previously described [9]. Eight non-profit hospitals participated in the study:
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11 3 teaching hospitals, 4 general hospitals and 1 comprehensive cancer center. Inclusion
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13 criteria were: women aged ≥ 18 years with previously untreated, first, histologically
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15 confirmed, operable BC. Exclusion criteria were: metastatic, locally advanced, or
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17 inflammatory BC, previous history of BC.
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21 After BC diagnosis, a work and cancer information booklet had to be given to all working
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23 patients. Our Institute has designed an information booklet in collaboration with
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25 occupational physicians and the Paris Regional Health Insurance (Caisse Régionale
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27 d'Assurance Maladie d'Île-de-France). This document includes the testimonies from
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29 employees, advice and practical information to help patients anticipate difficulties and find
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31 support: possibility of part-time work, career development plan, roles of occupational
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33 physicians and general practitioners. The booklet is freely available online with the support
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35 of the "ARC" Foundation [10].
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40 After inclusion, all patients were given a logbook in which to record, throughout the year,
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42 sociodemographic data (age, marital status, type of occupation, personal income...), out-of-
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44 pocket health expenses and an 1-year-occupational questionnaire for employed women
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46 including dates of work and absence from work during treatments, job adjustments, on-shift
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48 status and the perceived quality of reintegration with standardized self-questionnaire
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50 (income change, difficulties at work with co-workers and/or with superiors...). Patients were
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52 asked to fill the questionnaire prospectively during the all study period. During the second
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54 half of the year, clinical research assistants made 2 phone calls to remind patients to fill in
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3 the logbook. Questionnaires were collected at the end of the study. Types of occupations
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5 were classified according to the French *Institut National de la Statistique et des Etudes*
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7 *Economiques (INSEE)* classification.
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10 Two groups of patients were compared in order to determine the factors associated with
11
12 maintenance at work: longer sick leave (longer or equal to the median duration) and shorter
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14 sick leave (shorter than the median duration). Fisher's exact test or Student's t-test were
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16 used to analyze these factors. These tests were two sided with a 0.05 level of significance.
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18 Multivariate analysis was performed using a logistic regression model. We considered
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20 adjusted p-value for multiple comparisons. Sick leave over a 1-year period was described
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22 according to whether or not the patients were treated by chemotherapy. Differences in the
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24 areas under the curves of the 2 populations were compared to 1,000 permutations of
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26 random allocation of chemotherapy. The same analysis was performed according to whether
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28 or not the patients had received the work information booklet. Differences were considered
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30 significant for $p < 0.05$. All statistical analyses were performed with R software [11].
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35 The cost of sick leave for National Health Insurance was calculated on the basis of the
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37 monthly income declared by the patients, the duration of sick leave and the national sick
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39 leave allowance scale.
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42 This study was registered with ClinicalTrials.gov (Identifier: NCT02813317) and was approved
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44 by the French National ethics committee (CCTIRS Authorization No. 14.602 and CNIL DR-
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46 2014-167) covering research at all participating hospitals.
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50 51 **RESULTS**

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Six hundred and four patients with a median age of 58 years (range: 24-98) were included in the Optisoins01 study, including 297 patients (48.2%) who were working at the time of BC diagnosis. The present study focused on these 297 patients.

Detailed patient characteristics and cancer characteristics are presented in Table 1. The median age of the women was 50 (range: 27-77) years, 54 women (18.2%) were single, 153 (51.5%) were married, 39 (13.1%) were divorced and 3 (1.0%) were widows. Two hundred and sixty-one patients (87.9%) had invasive BC and 35 (11.8%) had *in situ* BC. Seventy-five women (25.3%) presented axillary lymph node involvement.

Table 1: Patient and cancer characteristics and breast cancer treatments (n=297)

	n or median	% or range
Patient characteristics		
Age (years)	50	(27-77)
Marital status		
<i>Single</i>	54	18.2%
<i>Married</i>	153	51.5%
<i>Divorced</i>	39	13.1%
<i>Widow</i>	3	1%
<i>NA</i>	48	16.2%
Breast cancer characteristics		
Modes of diagnosis		
<i>Organized screening</i>	60	20.2%
<i>Individual screening</i>	114	38.4%
<i>Clinical signs</i>	123	41.4%
Type of cancer		
<i>Invasive</i>	261	87.9%
<i>In situ</i>	35	11.8%
<i>NA</i>	1	0.3%
Lymph node involvement		
<i>Yes</i>	75	25.3%
<i>No</i>	222	74.7%
Surgery		
Breast surgery		

	<i>Conservative</i>	220	74.1%
	<i>Radical</i>	77	25.9%
Lymph node surgery			
	<i>Sentinel lymph node procedure</i>	203	68.4%
	<i>Axillary dissection</i>	72	24.2%
	<i>NA</i>	22	7.4%
Surgical revision			
	<i>no</i>	227	76.4%
	<i>1</i>	60	20.2%
	<i>>1</i>	10	3.4%
Type of hospitalization			
	<i>Outpatient surgery</i>	107	36%
	<i>Conventional surgery</i>	190	64%
Adjuvant therapies			
Radiotherapy			
	<i>No</i>	27	9.1%
	<i>Yes</i>	270	90.9%
Chemotherapy			
	<i>Yes</i>	143	48.1%
	<i>No</i>	154	51.9%
Trastuzumab			
	<i>Yes</i>	36	12.1%
	<i>No</i>	100	33.7%
	<i>NA</i>	161	54.2%
Hormone therapy			
	<i>Yes</i>	220	74.1%
	<i>No</i>	77	25.9%

Two hundred and twenty women (74.1%) underwent breast-conserving surgery and 77 (25.9%) underwent radical mastectomy (Table 1). A sentinel lymph node procedure was performed for 203 patients (68.4%). Seventy patients required at least 1 reoperation for the following reasons: positive surgical margins and secondary mastectomy, sentinel lymph node procedure following discovery of an invasive tumor, axillary dissection following positive sentinel lymph node biopsy and surgical complications (abscess, hematoma, etc.).

After surgery, 90.9% of patients received radiotherapy 48.1% of patients received adjuvant chemotherapy and 74.1% of patients received hormone therapy.

Most patients were executives (31.4%) or employees (33.3%). Most patients (47.1%) had a monthly income > €1,900. Work data after BC were available for 178 patients (60%, supplemental Figure 1). Patients who did not complete the 1-year work questionnaire in the logbook during one year were globally less compliant with the study and less medicalized (supplemental table 1). Sick leave was prescribed for 165 patients (92.7%). Patients had only one sick leave in 52.2% of cases, 2 sick leaves in 21.9% of cases and 3 or more sick leaves in 18.5% of cases. Median duration of sick leave was 155 days (range: 5-365). After treatment, 7 patients (3.9%) lost their jobs and 46.1% had reduced income. Patients encountered difficulties with their co-workers in 3.4% of cases, with their superiors in 3.9% of cases and for undocumented reasons in 12.9% of cases. Work-related factors are summarized in Table 2.

Table 2: Work characteristics before and after BC

	n or median	% or range
Work characteristics before breast cancer, n=297		
Type of occupation		
<i>Farmer</i>	1	0.3%
<i>Self-employed</i>	8	2.5%
<i>Executive</i>	99	31.4%
<i>Employee</i>	105	33.3%
<i>Intermediate profession</i>	29	9.2%
<i>Blue-collar worker</i>	2	0.6%
<i>NA</i>	53	22.9%
Personal income per month (€)		
<i>no income</i>	6	2%
< 1900	104	35%
>1900	140	47.1%
<i>NA</i>	47	15.8%
Work characteristics after breast cancer, n=178		

Dismissal		7	3.9%
Income change			
	<i>decreased</i>	82	46.1%
	<i>increased</i>	3	1.7%
	<i>stable</i>	73	41%
	<i>NA</i>	20	11.2%
Decreased income (%), n=82			
	<10%	37	45.1%
	10-30%	13	15.8%
	30-60%	5	6.1%
	>60%	3	3.7%
	<i>NA</i>	24	29.3%
Sick leave			
	<i>Yes</i>	165	92.7%
	<i>No</i>	13	7.3%
Number of sick leaves			
	<i>1</i>	93	52.2%
	<i>2</i>	39	21.9%
	<i>>2</i>	33	18.5%
Duration of sick leave (days)		155	(5-365)
Difficulties at work			
	<i>with coworkers</i>	6	3.4%
	<i>with superiors</i>	7	3.9%
	<i>other</i>	23	12.9%

On univariate analysis, the presence of clinical signs leading to a diagnosis of BC ($p<0.001$), an invasive form of BC ($p=0.02$), lymph node involvement ($p=0.005$), radical surgery ($p=0.02$), axillary dissection ($p<0.001$), chemotherapy ($p<0.001$), personal income < €1,900/month ($p=0.03$) and not having received the work and cancer information booklet ($p=0.047$) were associated with a longer total duration of sick leave (Table 3). Moreover, patients with longer sick leave were more likely to have reduced income after treatment of their disease ($p=0.0012$).

Table 3: Determinants and consequences of long sick leave

	Sick leave <155 days, n=79		Sick leave ≥155, days n=77		p
	n or median	% or range	n or median	% or range	
Patient characteristics					
Age (years)	50.6	(27-59)	50	(29-77)	0.52
Type of occupation					0.09
<i>Farmer</i>	0	0%	0	0%	
<i>Self-employed</i>	3	3.8%	1	1.3%	
<i>Executive</i>	36	45.6%	29	37.7%	
<i>Employee</i>	25	31.6%	38	49.4%	
<i>Intermediate profession</i>	13	16.5%	7	9.1%	
<i>Blue-collar worker</i>	1	1.3%	0	0%	
NA	1	1.3%	2		
Personal income per month (€)					0.03
< 1900	25	31.6%	37	48.1%	
> 1900	54	68.4%	38	49.4%	
NA	0	0%	2	2.6%	
Marital status					0.76
<i>Single</i>	18	22.8%	12	15.6%	
<i>Married</i>	47	59.5%	49	63.6%	
<i>Divorced</i>	12	15.2%	14	18.2%	
<i>Widow</i>	1	1.3%	1	1.3%	
NA	1	1.3%	1	1.3%	
Breast cancer characteristics					
Type of cancer					<0.001
<i>Invasive</i>	63	79.7%	74	96.1%	
<i>In situ</i>	16	20.3%	3	3.9%	
Lymph node involvement					0.005
Yes	11	13.9%	26	33.8%	
No	68	86.1%	52	67.5%	
Surgery					
Breast surgery					0.02
<i>Conservative</i>	66	83.5%	50	64.9%	
<i>Radical</i>	13	16.5%	27	35.1%	
Lymph node surgery					<0.001
<i>Sentinel lymph node procedure</i>	62	78.5%	48	62.3%	
<i>Axillary dissection</i>	9	11.4%	26	33.8%	
NA	8	10.1%	3	3.9%	
Surgical revision					0.06

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2						
3		Yes	13	16.5%	23	29.9%
4		No	66	83.5%	54	70.1%
5	Radiotherapy					0.53
6		Yes	72	91.1%	74	96.1%
7		No	7	8.9%	3	3.9%
8	Chemotherapy					<0.001
9		Yes	25	31.6%	56	72.7%
10		No	54	68.4%	21	27.3%
11	Trastuzumab					0.54
12		Yes	9	11.4%	12	15.6%
13		No	16	20.3%	40	51.9%
14		NA	54	68.4%	25	32.5%
15	Hormone therapy					0.05
16		Yes	50	63.3%	61	79.2%
17		No	29	36.7%	16	20.8%
18	Patient management					
19	Modes of diagnosis					<0.001
20		<i>Organized screening</i>	15	19%	21	27.3%
21		<i>Individual screening</i>	43	54.4%	20	26%
22		<i>Clinical signs</i>	21	26.6%	36	46.8%
23	Type of hospitalization					<0.001
24		<i>Outpatient surgery</i>	58	73.4%	34	44.2%
25		<i>Inpatient surgery</i>	21	26.6%	43	55.8%
26	Work and cancer information booklet					
27		Yes	64	81%	52	67.5%
28		No	15	19%	25	32.5%
29	Return to work					
30	Dismissal		1	1.3%	3	3.9%
31	Income change					0.62
32		<i>decreased</i>	23	29.1%	48	62.3%
33		<i>increased</i>	0	0%	2	2.6%
34		<i>stable</i>	37	46.8%	24	31.2%
35		NA	19	24.1%	3	3.9%
36	Decreased income (%)					0.61
37		<10%	11	13.9%	21	27.3%
38		10-30%	4	5.1%	7	9.1%
39		30-60%	0	0%	4	5.2%
40		>60%	0	0%	3	3.9%
41		NA	64	81%	42	54.5%
42	Difficulties at work					
43		<i>with coworkers</i>	2	2.5%	3	3.9%
44		<i>with superiors</i>	0	0%	6	7.8%
45						0.17
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<i>other</i>	7	8.9%	14	18.2%	0.93
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On multivariate analysis, chemotherapy was the only independent factor associated with longer sick leave (OR: 3.5, [95%CI: 1.6-7.9], $p=0.002$). Patients treated by chemotherapy had longer sick leave than those not treated by chemotherapy (Figure 1). The difference in terms of the 1-year distribution of sick leave was not statistically significant between patients according to whether or not they had received the work information booklet (Figure 2).

Considering the working population of OPTISOINS01 study with complete data on sick leave and salary, the median cost of sick leave for National Health Insurance was €8,841 per patient per year from diagnosis. In univariate and multivariate analysis, the only determinant of sick leave costs found in this study was the administration of chemotherapy, with a fourfold higher median allowance for patients treated with adjuvant chemotherapy.

DISCUSSION

Although many BC cancer survivors are able to return to a normal work life after treatment, our study confirms that many women of working ages do not. Sick leave is frequently prescribed and is often long, with a median sick leave of 155 days in this study.

Factors associated with long sick leave (>155 days) were severe or advanced forms of BC. The duration of sick leave was also associated with the mode of diagnosis, as patients diagnosed by breast screening presented shorter sick leaves. Public health authorities should therefore promote breast screening in order to decrease the proportion of advanced forms of BC and aggressive therapies with severe consequences on work and personal activities.

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3 Consequently, longer sick leave was also associated with more aggressive therapy, such as
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5 radical surgery, axillary dissection, and chemotherapy. These results are similar to those
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7 published in the literature [4,7,8,12,13]. Chemotherapy is an aggressive treatment that is
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9 necessary in order to ensure survival, but which has long-lasting consequences in terms of
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11 self-esteem (alopecia...), chronic pain (neuropathy...), and chronic fatigue, that play an
12
13 important role in return to work and maintenance at work [6]. BC survivors may have to deal
14
15 with the side effects specific to this type of treatment. Although many side effects of
16
17 chemotherapy are only temporary [14], some studies have shown that chemotherapy may
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19 impact on cognitive functioning [15] and fatigue [16] up to 10 years after diagnosis.
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21 Cognitive functioning and fatigue have both been associated with impaired work functioning
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23 [17]. Munir et al [18] reported that up to 62–84% of women resumed work either during
24
25 treatment with chemotherapy or following completion of treatment. As a result of their
26
27 cognitive limitations, women reported that they experienced difficulties with their work
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29 ability, particularly difficulties doing multiple tasks, reduced clarity of decisions, deficits in
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31 clear thinking and feelings of being inept due to short-term memory [19]. Rapid progress is
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33 being made in the field of chemotherapy with the routine use of new genomic signature
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35 tests that allow more accurate targeting of patient likely to benefit from chemotherapy.
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37 According to Nesvold et al [20] and Eaker et al [14] mastectomy and axillary lymph node
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39 dissection may influence working life long after treatment due to an increased risk of chronic
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41 pain. BC survivors are more likely to suffer from upper extremity impairments or
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43 lymphedema than are other cancer survivors [21–24], which are responsible for difficulties
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45 returning to work or maintenance at work [25,26].
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3 The work and cancer information booklet appeared to help patients return to work with
4 significantly shorter sick leave in univariate analysis. The strong impact of chemotherapy on
5 sick leave duration eliminated the influence of booklet in the multivariate analysis. However,
6 this suggests that an action, such as an active support, could help to reduce sick leave
7 duration. The information booklet advises women to attend the occupational medicine
8 service. In France, occupational medicine plays an essential role, but the patient is not
9 obliged to consult the occupational physician when sick leave is < 3 months. However, at 3
10 months, the occupational physician and the employee must determine the modalities of
11 return to work, based on the employee's state of health and the characteristics of the
12 workplace. These arrangements concern the employee himself and the work collective with,
13 if necessary, actions so that the reception is assured to the return. Setting up of a schedule,
14 reduction of working hours, modification of physical, mental or workplace loads can also be
15 instituted at the time of return to work. The occupational physician can provide
16 recommendations to the employer, unless the employer refuses. The results obtained with
17 this handbook are particularly encouraging and suggest that more individual supports should
18 be developed. Health coaching by telephone and/or face-to-face interview have already
19 been tested [27–29], showing positive significant outcomes on physical activity, body mass
20 index, pain management, acceptance of disease and self-confidence among cancer survivors.
21 Coaching methods have never been tested in the management of work maintenance. Our
22 Institute is therefore setting up a prospective randomized study (OPTICOACH) with tailored
23 support intervention to enhance RTW after BC in collaboration with a professional coach,
24 consisting of individual interviews or small group workshops over a period of 3 years.

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53 Difficulties returning to work appear to extend over a period of many years. Sevellec et al
54 [28] showed that, six years after returning to work, one employee out of two was still
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3 working in the same company. Rather than disappearing, the difficulties identified many
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5 years after BC persist for a long time after stopping treatment. It is therefore essential to
6
7 identify the factors associated with longer sick leave and RTW difficulties in order to help
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9 working patients and prevent these long-term problems. The VICAN 2 study [29] focused
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11 on the factors associated to difficulties at RTW. This large study was carried out in 2014 by
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13 the French National Cancer Institute, on the living conditions of people with cancer (not
14
15 only BC), two years after the diagnosis. The people most vulnerable to job loss two years
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17 after the cancer diagnosis are mainly those working in the so-called socio-professional
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19 execution categories, the youngest and oldest, married people with a level of education
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21 below the baccalaureate level, and those with precarious contracts.
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25 One of the potential biases of this study concerns the characteristics of the study
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27 population, as almost the majority of women belonged to the wealthiest social classes, as
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29 45.6% of patients were executives and only 1.3% were blue collar workers. More than
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31 sixty-eight percent of patients had a personal monthly income > €1,900 and 36.7% had a
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33 personal monthly income > €2,600. This distribution does not exactly reflect French
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35 society; in France, according to the INSEE statistics of 2014, the median monthly income
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37 was €1,772. Similarly to our results, a Canadian team [30] has shown that women with an
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39 annual income less than C\$20,000 were less likely to return to work than those whose
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41 income exceeded C\$50,000. The French social protection system also plays a role, as it
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43 provides cancer survivors with the possibility of replacement income, allowing women to
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45 decide whether or not they wish to return to work immediately. Providing assistance and
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47 support to all working patients should therefore be a priority.
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55 **CONCLUSION**

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3 Advanced disease and chemotherapy are major factors that influence return to work with
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5 longer sick-leave. Systematic screening or use of innovative tools, such as genomic
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7 signatures, can facilitate earlier diagnosis and reduce aggressive therapies.
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10 Depending on the type of treatment, on the stage of the disease and on the type of
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12 occupation, information and coaching methods with the occupational medicine service
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14 should systematically be given to working women, helping them to anticipate job
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16 adjustments with flexibility of work schedule for example.
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19 Personalized coaching methods have been successfully used to promote acceptance of
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21 disease and self-confidence and should be tested in the management of return to work and
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23 maintenance at work.
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Figures:

Figure 1: Percentage of patients on sick leave at 1-year follow-up depending on the presence or absence of chemotherapy

Figure 2: Percentage of patients on sick leave at 1-year follow-up depending on whether or not they had been given the work information booklet

Supplemental Figure 1: Flow Chart

Competing Interests: The authors declare that they have no competing interests.

Funding: This study was supported by a grant from the French National Cancer Institute dedicated to economic studies of innovative techniques. Delphine Héquet benefit from a grant of “Fondation pour la Recherche Médicale” to conduct this study.

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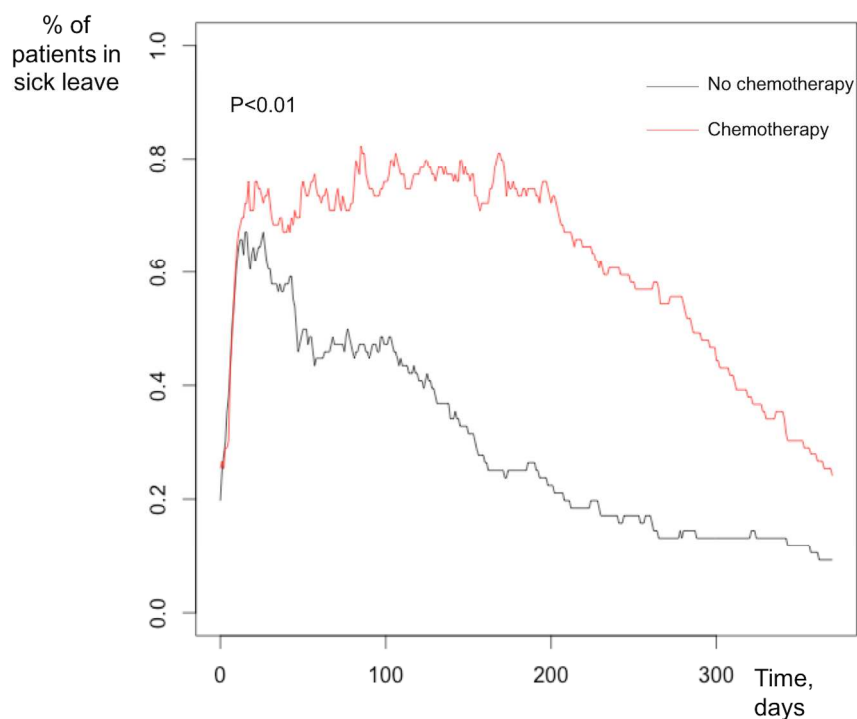


Figure 1: Percentage of patients on sick leave at 1-year follow-up depending on the presence or absence of chemotherapy

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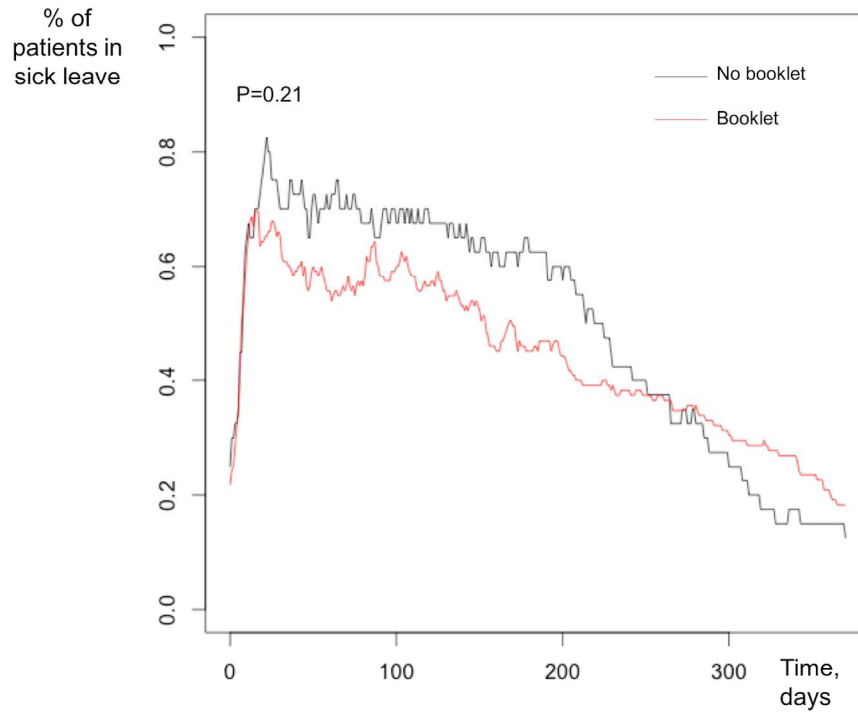
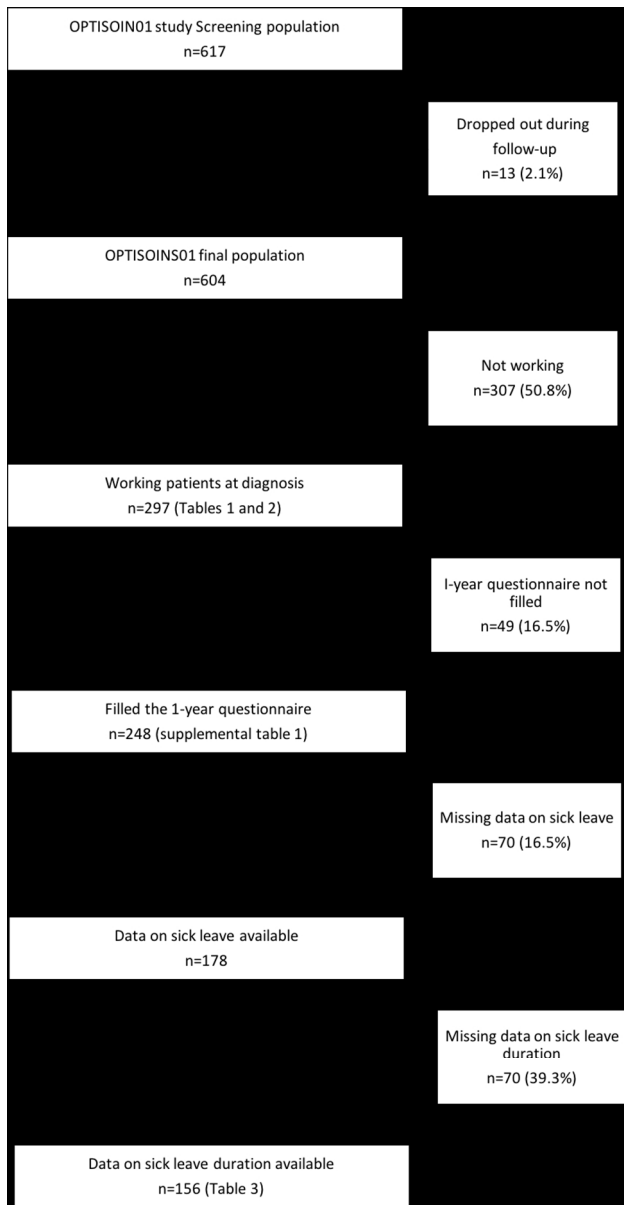


Figure 2: Percentage of patients on sick leave at 1-year follow-up depending on whether or not they had been given the work information booklet

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Supplemental Table 1: Differences between patients who returned the 1-year questionnaire with data on sick leave (n=178) and no data on sick leave (n=70)

	Data on sick leave, n=178		No data on sick leave, n=70		p
	n or median	% or range	n or median	% or range	
Patient characteristics					
Age (years)	50	(29-67)	49	(27-77)	0.36
Type of occupation					<0.05
	<i>Farmer</i>	1	1%	0	0%
	<i>Self-employed</i>	5	3%	0	0%
	<i>Executive</i>	72	40%	3	4%
	<i>Employee</i>	72	40%	27	39%
	<i>Intermediate profession</i>	22	12%	33	47%
	<i>Blue-collar worker</i>	2	1%	7	10%
	NA	4	2%	0	0%
Personal income per month (€)					<0.05
	<1900	71	40%	20	29%
	>1900	103	58%	37	53%
	NA	4	2%	13	19%
Marital status					<0.05
	<i>Single</i>	34	19%	18	26%
	<i>Married</i>	110	62%	39	56%
	<i>Divorced</i>	29	16%	10	14%
	<i>Widow</i>	2	1%	1	1%
	NA	3	2%	2	3%
Breast cancer characteristics					
Type of cancer					0.32
	<i>Invasive</i>	156	87,6%	61	87%
	<i>In situ</i>	21	11,8%	9	13%
Lymph node involvement					0.12
	<i>Yes</i>	43	24%	23	33%
	<i>No</i>	135	76%	47	67%
Surgical patient care					
Breast surgery					<0.05
	<i>Conservative</i>	133	75%	46	66%
	<i>Radical</i>	45	25%	24	34%
Lymph node surgery					0.48
	<i>Sentinel lymph node procedure</i>	122	69%	40	57%
	<i>Axillary dissection</i>	42	24%	24	34%

	NA	14	8%	6	9%	
Surgical revision						0.24
	Yes	43	24%	16	23%	
	No	135	76%	54	77%	
Radiotherapy						<0.05
	Yes	167	94%	61	87%	
	No	11	6%	9	13%	
Chemotherapy						<0.05
	Yes	92	52%	33	47%	
	No	86	48%	37	53%	
Trastuzumab						0.42
	Yes	24	13%	9	13%	
	No	63	35%	22	31%	
	NA	91	51%	39	56%	
Hormone therapy						0.69
	Yes	129	72%	49	70%	
	No	49	28%	21	30%	
Patient management						
Modes of diagnosis						0.45
	<i>Organized screening</i>	37	21%	12	17%	
	<i>Individual screening</i>	74	42%	26	37%	
	<i>Clinical signs</i>	67	38%	32	46%	
Type of hospitalization						0.78
	<i>Outpatient surgery</i>	108	61%	43	61%	
	<i>Inpatient surgery</i>	70	39%	27	39%	

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	4 and 5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8
		(b) For matched studies, give matching criteria and number of exposed and unexposed	8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9
		(b) Describe any methods used to examine subgroups and interactions	9
		(c) Explain how missing data were addressed	9
		(d) If applicable, explain how loss to follow-up was addressed	9
		(e) Describe any sensitivity analyses	9
Results			9

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	Supplemental figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10 and 11
		(b) Indicate number of participants with missing data for each variable of interest	11
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	11
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-14
		(b) Report category boundaries when continuous variables were categorized	12-14
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12-14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13, 14
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Determinants of return at work of breast cancer patients: results from the OPTISOINS01 French prospective study.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-020276.R2
Article Type:	Research
Date Submitted by the Author:	01-Mar-2018
Complete List of Authors:	Arfi, Alexandra; Institut Curie, Surgery Baffert, Sandrine; CEMKA-EVAL, Health Economist Soilly, A-L; Universite de Bourgogne IUT Dijon-Auxerre, Health Economist huchon, cyrille; Hôpital Poissy, Gynecology Reyal, Fabien; Institut Curie, Surgery Asselain, Bernard; Institut Curie, Biostatistics Neffati, Souhir; Institut Curie, Clinical Research and Innovation Department Rouzier, Roman; Institut Curie, Surgery Hequet, Delphine; Institut Curie-Centre René Huguenin, Surgical oncology
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Occupational and environmental medicine
Keywords:	Breast tumours < ONCOLOGY, OCCUPATIONAL & INDUSTRIAL MEDICINE, PUBLIC HEALTH

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Manuscripts

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3 **Determinants of return at work of breast cancer patients: results from the OPTISOINS01**
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5 **French prospective study.**
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25 Word count: 2431
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Contributorship statement:

Delphine Hequet, Roman Rouzier and Sandrine Baffert designed the study.

Bernard Asselain and Souhr Neffati contributed to the design and implementation of the research.

Sandrine Baffert and Anne-Laure Soilly performed the health economic analysis.

Alexandra Arfi and Delphine Hequet performed all the remaining statistical analysis and wrote the manuscript.

Cyrille Huchon and Fabien Reyal contributed to the clinical study, patients' inclusion and analysis of the results.

All the authors reviewed and approved the final version of the manuscript.

ABSTRACT

Introduction: Return to work (RTW) after breast cancer (BC) is still a new field of research. The factors determining shorter sick leave duration of BC patients have not been clearly identified. The aim of this study was to describe work during BC treatment and to identify factors associated with sick leave duration.

Materials and methods: An observational, prospective, multicenter study was conducted among women with operable BC. A logbook was given to all working patients to record sociodemographic and work-related data over a one-year period.

Results: Work-related data after BC were available for 178 patients (60%). Median age at diagnosis was 50 years (27-77), 87.9% of patients had an invasive form of BC and 25.3% a lymph node involvement. 25.9% had a radical surgery and 24.2% had an axillary dissection. Radiotherapy was performed in 90.9% of patients and chemotherapy in 48.1%. Sick leave was prescribed for 165 patients (92.7%) for a median of 155 days. On univariate analysis, invasive BC ($p=0.025$), lymph node involvement ($p=0.005$), radical surgery ($p=0.025$), axillary dissection ($p=0.004$), chemotherapy ($p<0.001$), personal income $< \text{€}1,900/\text{month}$ ($p=0.03$) and not having received the patient information booklet on RTW ($p=0.047$) were associated with a longer duration of sick leave. On multivariate analysis, chemotherapy was associated with longer sick leave (OR: 3.5; [95%CI: 1.6-7.9]; $p=0.002$). The cost of sick leave to French National Health Insurance was fourfold higher in the case of chemotherapy ($p<0.001$).

Conclusion: Advanced disease and chemotherapy are major factors that influence sick leave duration during the management of BC.

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3 **Strengths and limitations of this study:**
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- 5
6 - Prospective multicentric study
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8 - Description of factors associated to long sick leave
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10 - Multimodal analysis including evaluation of costs of sick leave
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12 - Few qualitative information
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18 **Keywords:** breast cancer, return to work, absence duration, chemotherapy.
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24 **Data sharing statement:** No additional data available
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26 **Ethics:** This study was registered with ClinicalTrials.gov (Identifier: NCT02813317) and was
27 approved by the French National ethics committee (CCTIRS Authorization No. 14.602 and
28 CNIL DR-2014-167) covering research at all participating hospitals.
29
30

31 **Funding:** Delphine Hequet benefitted from a “Fondation pour la Recherche Medicale”
32 (FDM20140630453) grant to conduct this study. This study was supported by a grant from
33 the French National Cancer Institute (Institut National du Cancer, PRME-K2013), dedicated
34 to economic studies of innovative techniques.
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What is already known on this subject?

Return to work after breast cancer is a delicate step in the real-life reintegration. Breast cancer patients have difficulties at work even 5 years after the end of the treatments. The factors that maintain patients at work during breast cancer are rarely described.

What this study adds?

This prospective study describes sick leaves during the first year following the diagnosis of early breast cancer. After one year, 20% of the patients did not return to work. Chemotherapy dramatically increased the duration of sick leaves, whereas an early information on support can reduce sick leaves. Costs of sick leaves are major.

INTRODUCTION

Improvements in early detection and treatment have resulted in an increasing number of breast cancer (BC) survivors [1]. Treatments mostly focus on curing the disease and preventing metastatic relapse. About one-third of women diagnosed with BC are under the age of 55 with a 10-year survival close to 80% [2]. Many patients therefore recover and resume their activities of daily living during or after treatment. Return to work (RTW) is an event at the end of sick leave, consisting in resuming professional activity. RTW after BC is still a new, but important aspect of survivorship research, not only from a societal point of view, as it provides financial resources for rehabilitation of cancer survivors and contributes to psychosocial well-being, including physical and mental health [3]. Some BC cancer survivors experience reduced work ability [4–8]. Difficulties at work or unemployment differ according to the type of BC treatment. Cancer treatment varies according to the stage of the disease and can include surgery, chemotherapy, radiotherapy and hormone therapy. For many cancer patients, return to work helps them to recover from treatment and also constitutes a positive step towards the future. The identification of factors that maintain patients at work during and after BC treatment could help healthcare professionals to more accurately identify patients at risk of RTW work-related difficulties in order to provide them with adapted support during BC management. The aim of this prospective study was to describe work during and after BC management and identify factors associated with either cessation or maintenance at work.

MATERIALS AND METHODS

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3 OPTISOINS01 was an observational, prospective, multicenter study conducted from
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5 December 2014 to March 2016 among BC patients from a regional health territory. The
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7 primary objective of the Optisoins01 study was to identify the main care pathway after 1
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9 year of early BC and to evaluate costs from various perspectives. Return to work evaluation
10
11 was one of the secondary objectives of the study. The Optisoins01 study design has been
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13 previously described [9]. Eight non-profit hospitals participated in the study: 3 teaching
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15 hospitals, 4 general hospitals and 1 comprehensive cancer center. Inclusion criteria were:
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17 women aged ≥ 18 years with previously untreated, first, histologically confirmed, operable
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19 BC. Exclusion criteria were: metastatic, locally advanced, or inflammatory BC, previous
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21 history of BC.
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26 After BC diagnosis, a work and cancer information booklet had to be given to all working
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28 patients. Our Institute has designed an information booklet in collaboration with
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30 occupational physicians and the Paris Regional Health Insurance (Caisse Régionale
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32 d'Assurance Maladie d'Île-de-France). This document includes the testimonies from
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34 employees, advice and practical information to help patients anticipate difficulties and find
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36 support: possibility of part-time work, career development plan, roles of occupational
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38 physicians and general practitioners. The booklet is freely available online with the support
39
40 of the "ARC" Foundation [10].
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45 After inclusion, all patients were given a logbook in which to record, throughout the year,
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47 sociodemographic data (age, marital status, type of occupation, personal income...), out-of-
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49 pocket health expenses and an 1-year-occupational questionnaire for employed women
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51 including dates of work and absence from work during treatments, job adjustments, on-shift
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53 status and the perceived quality of reintegration with standardized self-questionnaire
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55 (income change, difficulties at work with co-workers and/or with superiors...). Patients were
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3 asked to fill in the questionnaire prospectively during the all study period. During the second
4
5 half of the year, clinical research assistants made 2 phone calls to remind patients to fill in
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7 the logbook. Questionnaires were collected at the end of the study. Types of occupations
8
9 were classified according to the French *Institut National de la Statistique et des Etudes*
10
11 *Economiques (INSEE)* classification.
12

13
14 Two groups of patients were compared in order to determine the factors associated with
15
16 sick leave duration: longer sick leave (longer or equal to the median duration) and shorter
17
18 sick leave (shorter than the median duration). Fisher's exact test or Student's t-test were
19
20 used to analyze these factors. These tests were two sided with a 0.05 level of significance.
21
22 Multivariate analysis was performed using a logistic regression model. We considered
23
24 adjusted p-value for multiple comparisons. Sick leave over a 1-year period was described
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26 according to whether or not the patients were treated by chemotherapy. Differences in the
27
28 areas under the curves of the 2 populations were compared to 1,000 permutations of
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30 random allocation of chemotherapy. The same analysis was performed according to whether
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32 or not the patients had received the work information booklet. Differences were considered
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34 significant for $p < 0.05$. All statistical analyses were performed with R software [11].
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39 The cost of sick leave for National Health Insurance was calculated on the basis of the
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41 monthly income declared by the patients, the duration of sick leave and the national sick
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43 leave allowance scale.
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46 This study was registered with ClinicalTrials.gov (Identifier: NCT02813317) and was approved
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48 by the French National ethics committee (CCTIRS Authorization No. 14.602 and CNIL DR-
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50 2014-167) covering research at all participating hospitals.
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53 Patient and public Involvement: A sample of patients participated to the questionnaire
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55 development concerning work activity before implementation of the study. Patients were
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involved in the study by actively completing the questionnaires during 1 year. A results report will be sent to the study participants.

RESULTS

Six hundred and four patients with a median age of 58 years (range: 24-98) were included in the Optisoins01 study, including 297 patients (48.2%) who were working at the time of BC diagnosis. The present study focused on these 297 patients.

Detailed patient characteristics and cancer characteristics are presented in Table 1. The median age of the women was 50 (range: 27-77) years, 54 women (18.2%) were single, 153 (51.5%) were married, 39 (13.1%) were divorced and 3 (1.0%) were widows. Two hundred and sixty-one patients (87.9%) had invasive BC and 35 (11.8%) had *in situ* BC. Seventy-five women (25.3%) presented axillary lymph node involvement.

Table 1: Patient and cancer characteristics and breast cancer treatments (n=297)

	n or median	% or range
Patient characteristics		
Age (years)	50	(27-77)
Marital status		
<i>Single</i>	54	18.2%
<i>Married</i>	153	51.5%
<i>Divorced</i>	39	13.1%
<i>Widow</i>	3	1%
<i>NA</i>	48	16.2%
Breast cancer characteristics		
Modes of diagnosis		
<i>Organized screening</i>	60	20.2%
<i>Individual screening</i>	114	38.4%
<i>Clinical signs</i>	123	41.4%
Type of cancer		
<i>Invasive</i>	261	87.9%
<i>In situ</i>	35	11.8%
<i>NA</i>	1	0.3%

Lymph node involvement			
	Yes	75	25.3%
	No	222	74.7%
Surgery			
Breast surgery			
	<i>Conservative</i>	220	74.1%
	<i>Radical</i>	77	25.9%
Lymph node surgery			
	<i>Sentinel lymph node procedure</i>	203	68.4%
	<i>Axillary dissection</i>	72	24.2%
	NA	22	7.4%
Surgical revision			
	<i>no</i>	227	76.4%
	<i>1</i>	60	20.2%
	<i>>1</i>	10	3.4%
Type of hospitalization			
	<i>Outpatient surgery</i>	107	36%
	<i>Conventional surgery</i>	190	64%
Adjuvant therapies			
Radiotherapy			
	No	27	9.1%
	Yes	270	90.9%
Chemotherapy			
	Yes	143	48.1%
	No	154	51.9%
Trastuzumab			
	Yes	36	12.1%
	No	100	33.7%
	NA	161	54.2%
Hormone therapy			
	Yes	220	74.1%
	No	77	25.9%

Two hundred and twenty women (74.1%) underwent breast-conserving surgery and 77 (25.9%) underwent radical mastectomy (Table 1). A sentinel lymph node procedure was performed for 203 patients (68.4%). Seventy patients required at least 1 reoperation for the following reasons: positive surgical margins and secondary mastectomy, sentinel lymph

node procedure following discovery of an invasive tumor, axillary dissection following positive sentinel lymph node biopsy and surgical complications (abscess, hematoma, etc.). After surgery, 90.9% of patients received radiotherapy 48.1% of patients received adjuvant chemotherapy and 74.1% of patients received hormone therapy.

Most patients were executives (31.4%) or employees (33.3%). Most patients (47.1%) had a monthly income > €1,900. Work data after BC were available for 178 patients (60%, supplemental Figure 1). Patients who did not complete the 1-year work questionnaire in the logbook during one year were globally less compliant with the study and less medicalized (supplemental table 1). Sick leave was prescribed for 165 patients (92.7%). Patients had only one sick leave in 52.2% of cases, 2 sick leaves in 21.9% of cases and 3 or more sick leaves in 18.5% of cases. Median duration of sick leave was 155 days (range: 5-365). After treatment, 7 patients (3.9%) lost their jobs and 46.1% had reduced income. Patients encountered difficulties with their co-workers in 3.4% of cases, with their superiors in 3.9% of cases and for undocumented reasons in 12.9% of cases. Work-related factors are summarized in Table 2.

Table 2: Work characteristics before and after BC

	n or median	% or range
Work characteristics before breast cancer, n=297		
Type of occupation		
<i>Farmer</i>	1	0.3%
<i>Self-employed</i>	8	2.5%
<i>Executive</i>	99	31.4%
<i>Employee</i>	105	33.3%
<i>Intermediate profession</i>	29	9.2%
<i>Blue-collar worker</i>	2	0.6%
<i>NA</i>	53	22.9%
Personal income per month (€)		
<i>no income</i>	6	2%

	< 1900	104	35%
	>1900	140	47.1%
	<i>NA</i>	47	15.8%
Work characteristics after breast cancer, n=178			
Dismissal		7	3.9%
Income change			
	<i>decreased</i>	82	46.1%
	<i>increased</i>	3	1.7%
	<i>stable</i>	73	41%
	<i>NA</i>	20	11.2%
Decreased income (%), n=82			
	<i><10%</i>	37	45.1%
	<i>10-30%</i>	13	15.8%
	<i>30-60%</i>	5	6.1%
	<i>>60%</i>	3	3.7%
	<i>NA</i>	24	29.3%
Sick leave			
	<i>Yes</i>	165	92.7%
	<i>No</i>	13	7.3%
Number of sick leaves (n=165)			
	<i>1</i>	93	52.2%
	<i>2</i>	39	21.9%
	<i>>2</i>	33	18.5%
Duration of sick leave (days)		155	(5-365)
Difficulties at work (n=36)			
	<i>with coworkers</i>	6	3.4%
	<i>with superiors</i>	7	3.9%
	<i>other</i>	23	12.9%

On univariate analysis, the presence of clinical signs leading to a diagnosis of BC ($p<0.001$), an invasive form of BC ($p=0.02$), lymph node involvement ($p=0.005$), radical surgery ($p=0.02$), axillary dissection ($p<0.001$), chemotherapy ($p<0.001$), personal income $< \text{€}1,900/\text{month}$ ($p=0.03$) and not having received the work and cancer information booklet ($p=0.047$) were associated with a longer total duration of sick leave (Table 3). Moreover, patients with

longer sick leave were more likely to have reduced income after treatment of their disease
(p=0.0012).

Table 3: Determinants and consequences of long sick leave

	Sick leave <155 days, n=79		Sick leave ≥155, days n=77		p
	n or median	% or range	n or median	% or range	
Patient characteristics					
Age (years)	50.6	(27-59)	50	(29-77)	0.52
Type of occupation					0.09
<i>Farmer</i>	0	0%	0	0%	
<i>Self-employed</i>	3	3.8%	1	1.3%	
<i>Executive</i>	36	45.6%	29	37.7%	
<i>Employee</i>	25	31.6%	38	49.4%	
<i>Intermediate profession</i>	13	16.5%	7	9.1%	
<i>Blue-collar worker</i>	1	1.3%	0	0%	
NA	1	1.3%	2		
Personal income per month (€)					0.03
< 1900	25	31.6%	37	48.1%	
> 1900	54	68.4%	38	49.4%	
NA	0	0%	2	2.6%	
Marital status					0.76
<i>Single</i>	18	22.8%	12	15.6%	
<i>Married</i>	47	59.5%	49	63.6%	
<i>Divorced</i>	12	15.2%	14	18.2%	
<i>Widow</i>	1	1.3%	1	1.3%	
NA	1	1.3%	1	1.3%	
Breast cancer characteristics					
Type of cancer					<0.001
<i>Invasive</i>	63	79.7%	74	96.1%	
<i>In situ</i>	16	20.3%	3	3.9%	
Lymph node involvement					0.005
Yes	11	13.9%	26	33.8%	
No	68	86.1%	52	67.5%	
Surgery					
Breast surgery					0.02
<i>Conservative</i>	66	83.5%	50	64.9%	
<i>Radical</i>	13	16.5%	27	35.1%	
Lymph node surgery					<0.001

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2						
3	<i>Sentinel lymph node procedure</i>	62	78.5%	48	62.3%	
4	<i>Axillary dissection</i>	9	11.4%	26	33.8%	
5	NA	8	10.1%	3	3.9%	
6						
7						
8	Surgical revision					0.06
9	Yes	13	16.5%	23	29.9%	
10	No	66	83.5%	54	70.1%	
11						
12	Radiotherapy					0.53
13	Yes	72	91.1%	74	96.1%	
14	No	7	8.9%	3	3.9%	
15						
16	Chemotherapy					<0.001
17	Yes	25	31.6%	56	72.7%	
18	No	54	68.4%	21	27.3%	
19						
20	Trastuzumab					0.54
21	Yes	9	11.4%	12	15.6%	
22	No	16	20.3%	40	51.9%	
23	NA	54	68.4%	25	32.5%	
24						
25	Hormone therapy					0.05
26	Yes	50	63.3%	61	79.2%	
27	No	29	36.7%	16	20.8%	
28	Patient management					
29	Modes of diagnosis					<0.001
30	<i>Organized screening</i>	15	19%	21	27.3%	
31	<i>Individual screening</i>	43	54.4%	20	26%	
32	<i>Clinical signs</i>	21	26.6%	36	46.8%	
33						
34	Type of hospitalization					<0.001
35	<i>Outpatient surgery</i>	58	73.4%	34	44.2%	
36	<i>Inpatient surgery</i>	21	26.6%	43	55.8%	
37						
38	Work and cancer information booklet					
39						
40	Yes	64	81%	52	67.5%	0.047
41	No	15	19%	25	32.5%	
42						
43	Return to work					
44						
45	Dismissal	1	1.3%	3	3.9%	0.62
46	Income change					
47	<i>decreased</i>	23	29.1%	48	62.3%	<0.001
48	<i>increased</i>	0	0%	2	2.6%	
49	<i>stable</i>	37	46.8%	24	31.2%	
50	NA	19	24.1%	3	3.9%	
51						
52	Decreased income (%)					0.61
53	<10%	11	13.9%	21	27.3%	
54	10-30%	4	5.1%	7	9.1%	
55	30-60%	0	0%	4	5.2%	
56						
57						
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60						

	>60%	0	0%	3	3.9%	
	NA	64	81%	42	54.5%	
Difficulties at work						
	<i>with coworkers</i>	2	2.5%	3	3.9%	0.67
	<i>with superiors</i>	0	0%	6	7.8%	0.17
	<i>other</i>	7	8.9%	14	18.2%	0.93

On multivariate analysis, chemotherapy was the only independent factor associated with longer sick leave (OR: 3.5, [95%CI: 1.6-7.9], p=0.002). Patients treated by chemotherapy had longer sick leave than those not treated by chemotherapy (Figure 1). The difference in terms of the 1-year distribution of sick leave was not statistically significant between patients according to whether or not they had received the work information booklet (Figure 2).

Considering the working population of OPTISOINS01 study with complete data on sick leave and salary, the median cost of sick leave for National Health Insurance was €8,841 per patient per year from diagnosis. In univariate and multivariate analysis, the only determinant of sick leave costs found in this study was the administration of chemotherapy, with a fourfold higher median allowance for patients treated with adjuvant chemotherapy.

DISCUSSION

Although many BC cancer survivors are able to return to a normal work life after treatment, our study confirms that many women of working ages do not. Sick leave is frequently prescribed and is often long, with a median sick leave of 155 days in this study.

Factors associated with long sick leave (>155 days) were severe or advanced forms of BC. The duration of sick leave was also associated with the mode of diagnosis, as patients diagnosed by breast screening presented shorter sick leaves. Public health authorities should

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2
3 therefore promote breast screening in order to decrease the proportion of advanced forms
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5 of BC and aggressive therapies with severe consequences on work and personal activities.
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7 Consequently, longer sick leave was also associated with more aggressive therapy, such as
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9 radical surgery, axillary dissection, and chemotherapy. These results are similar to those
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11 published in the literature [4,7,8,12,13]. Chemotherapy is an aggressive treatment that can
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13 be necessary in order to improve survival, but which has long-lasting consequences in terms
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15 of self-esteem (alopecia...), chronic pain (neuropathy...), and chronic fatigue, that play an
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17 important role in return to work and maintenance at work [6]. BC survivors may have to deal
18
19 with the side effects specific to this type of treatment. Although many side effects of
20
21 chemotherapy are only temporary [14], some studies have shown that chemotherapy may
22
23 impact on cognitive functioning [15] and fatigue [16] up to 10 years after diagnosis.
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25 Cognitive functioning and fatigue have both been associated with impaired work functioning
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27 [17]. Munir et al [18] reported that up to 62–84% of women resumed work either during
28
29 treatment with chemotherapy or following completion of treatment. As a result of their
30
31 cognitive limitations, women reported that they experienced difficulties with their work
32
33 ability, particularly difficulties doing multiple tasks, reduced clarity of decisions, deficits in
34
35 clear thinking and feelings of being inept due to short-term memory [19]. Rapid progress is
36
37 being made in the field of chemotherapy with the routine use of new genomic signature
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39 tests that allow more accurate targeting of patient likely to benefit from chemotherapy.
40
41 According to Nesvold et al [20] and Eaker et al [14] mastectomy and axillary lymph node
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43 dissection may influence working life long after treatment due to an increased risk of chronic
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45 pain. BC survivors are more likely to suffer from upper extremity impairments or
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47 lymphedema than are other cancer survivors [21–24], which are responsible for difficulties
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49 returning to work [25,26].
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3 The work and cancer information booklet appeared to help patients return to work with
4 significantly shorter sick leave in univariate analysis, but not in the multivariate analysis.
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6 However, this suggests that an action, such as an active support, could help to reduce sick
7
8 leave duration. The information booklet advises women to attend the occupational medicine
9
10 service. In France, occupational medicine plays an essential role, but the patient is not
11
12 obliged to consult the occupational physician when sick leave is < 3 months. However, at 3
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14 months, the occupational physician and the employee must determine the modalities of
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16 return to work, based on the employee's state of health and the characteristics of the
17
18 workplace. These arrangements concern the employee himself and the work collective with,
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20 if necessary, actions so that the reception is assured to the return. Setting up of a schedule,
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22 reduction of working hours, modification of physical, mental or workplace loads can also be
23
24 instituted at the time of return to work. The occupational physician can provide
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26 recommendations to the employer, unless the employer refuses. The results obtained with
27
28 this handbook are particularly encouraging and suggest that more individual supports should
29
30 be developed. Health coaching by telephone and/or face-to-face interview have already
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32 been tested [27–29], showing positive significant outcomes on physical activity, body mass
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34 index, pain management, acceptance of disease and self-confidence among cancer survivors.
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36 Coaching methods have never been tested in the management of working patients during
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38 cancer treatment maintenance. Our Institute is therefore setting up a prospective
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40 randomized study (OPTICOACH) with tailored support intervention to enhance RTW after BC
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42 in collaboration with a professional coach, consisting of individual interviews or small group
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44 workshops over a period of 3 years.

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47 Difficulties returning to work appear to extend over a period of many years. Sevellec et al
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49 [28] showed that, six years after returning to work, one employee out of two was still
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3 working in the same company. Rather than disappearing, the difficulties identified many
4
5 years after BC persist for a long time after stopping treatment. It is therefore essential to
6
7 identify the factors associated with longer sick leave and RTW difficulties in order to help
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9 working patients and prevent these long-term problems. The VICAN 2 study [29] focused
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11 on the factors associated to difficulties at RTW. This large study was carried out in 2014 by
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13 the French National Cancer Institute, on the living conditions of people with cancer (not
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15 only BC), two years after the diagnosis. The people most vulnerable to job loss two years
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17 after the cancer diagnosis are mainly those working in the so-called socio-professional
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19 execution categories, the youngest and oldest, married people with a level of education
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21 below the baccalaureate level, and those with precarious contracts.
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24
25 One of the potential biases of this study concerns the characteristics of the study
26
27 population, as almost the majority of women belonged to the wealthiest social classes, as
28
29 45.6% of patients were executives and only 1.3% were blue collar workers. More than
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31 sixty-eight percent of patients had a personal monthly income > €1,900 and 36.7% had a
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33 personal monthly income > €2,600. This distribution does not exactly reflect French
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35 society; in France, according to the INSEE statistics of 2014, the median monthly income
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37 was €1,772. Similarly to our results, a Canadian team [30] has shown that women with an
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39 annual income less than C\$20,000 were less likely to return to work than those whose
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41 income exceeded C\$50,000. The French social protection system also plays a role, as it
42
43 provides cancer survivors with the possibility of replacement income, allowing women to
44
45 decide whether or not they wish to return to work immediately. Providing assistance and
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47 support to all working patients should therefore be a priority.
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55 **CONCLUSION**

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3 Advanced disease and chemotherapy are major factors that influence return to work with
4 longer sick-leave. Systematic screening or use of innovative tools, such as genomic
5 signatures, can facilitate earlier diagnosis and reduce aggressive therapies.
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10 Depending on the type of treatment, on the stage of the disease and on the type of
11 occupation, information and coaching methods with the occupational medicine service
12 should systematically be given to working women, helping them to anticipate job
13 adjustments with flexibility of work schedule for example.
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19 Personalized coaching methods have been successfully used to promote acceptance of
20 disease and self-confidence and should be tested in the management of return to work.
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Figures:

Figure 1: Percentage of patients on sick leave at 1-year follow-up depending on the presence or absence of chemotherapy

Figure 2: Percentage of patients on sick leave at 1-year follow-up depending on whether or not they had been given the work information booklet

Supplemental Figure 1: Flow Chart

Competing Interests: The authors declare that they have no competing interests.

Funding: This study was supported by a grant from the French National Cancer Institute dedicated to economic studies of innovative techniques. Delphine Héquet benefit from a grant of “Fondation pour la Recherche Médicale” to conduct this study.

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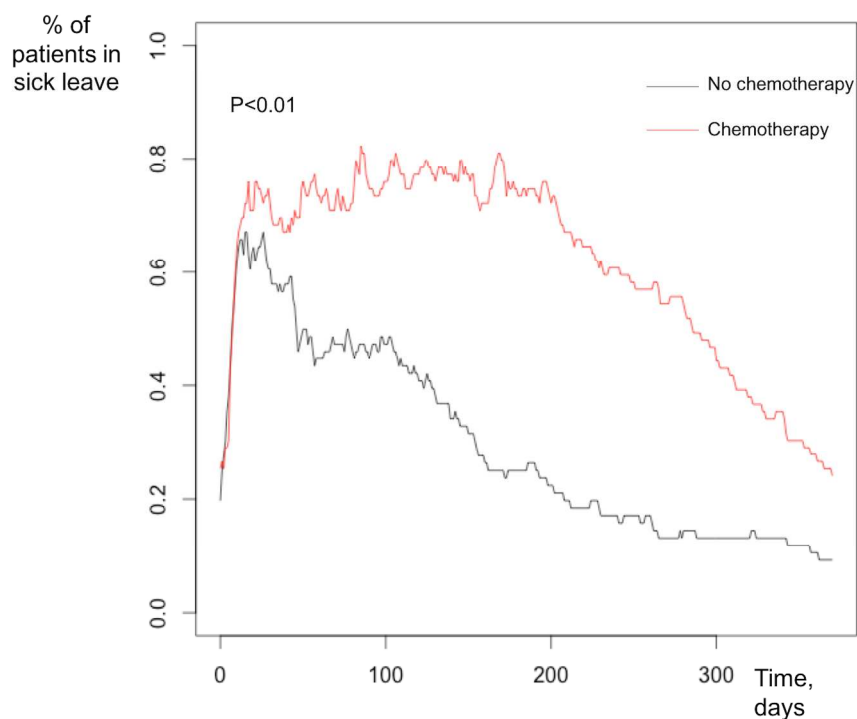


Figure 1: Percentage of patients on sick leave at 1-year follow-up depending on the presence or absence of chemotherapy

264x200mm (300 x 300 DPI)

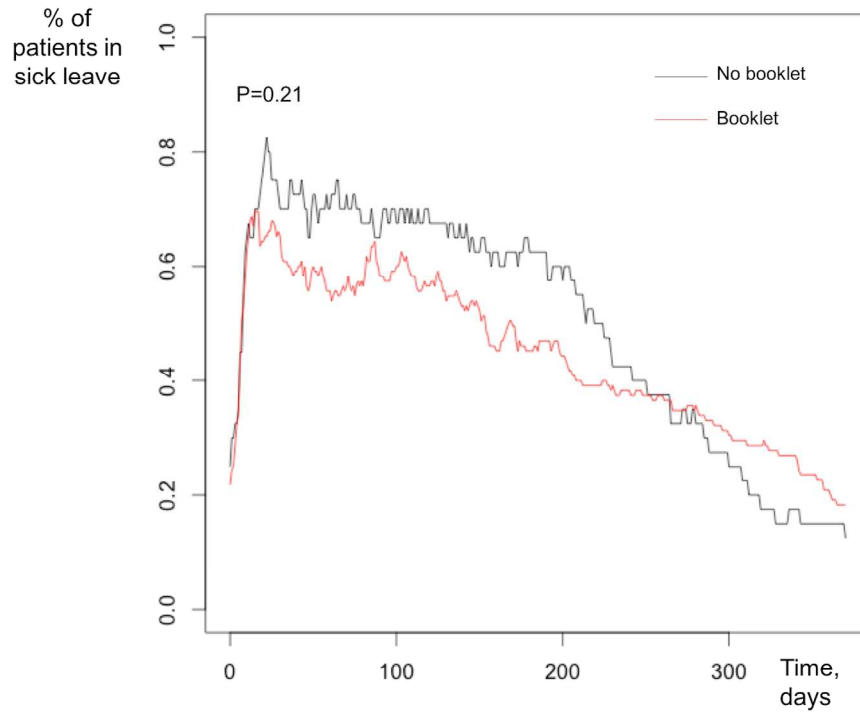
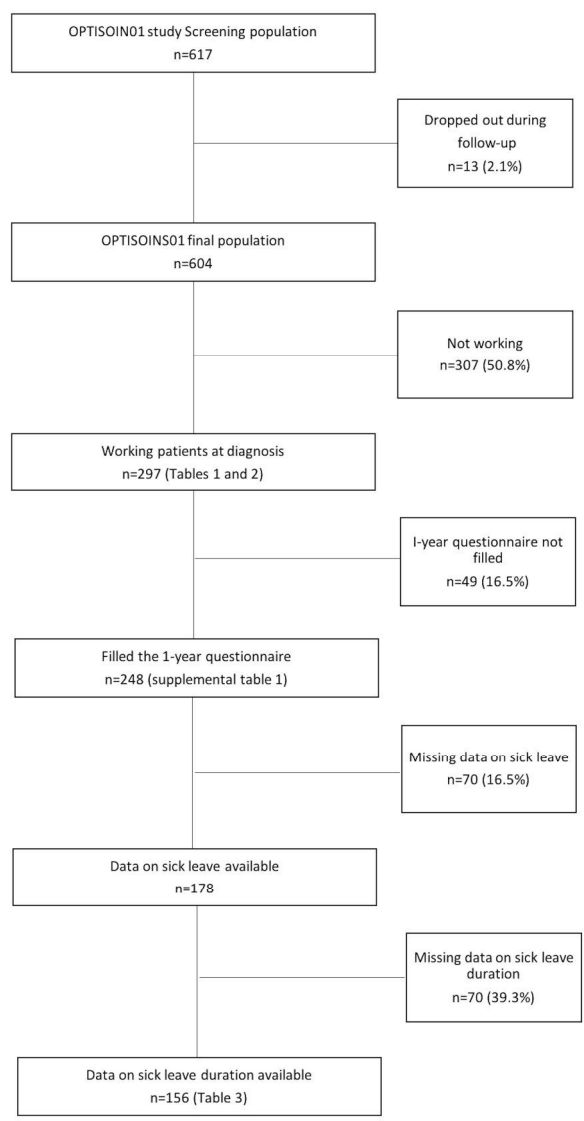


Figure 2: Percentage of patients on sick leave at 1-year follow-up depending on whether or not they had been given the work information booklet

262x205mm (300 x 300 DPI)

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Supplemental Table 1: Differences between patients who returned the 1-year questionnaire with data on sick leave (n=178) and no data on sick leave (n=70)

	Data on sick leave, n=178		No data on sick leave, n=70		p
	n or median	% or range	n or median	% or range	
Patient characteristics					
Age (years)	50	(29-67)	49	(27-77)	0.36
Type of occupation					<0.05
	<i>Farmer</i>	1	1%	0	0%
	<i>Self-employed</i>	5	3%	0	0%
	<i>Executive</i>	72	40%	3	4%
	<i>Employee</i>	72	40%	27	39%
	<i>Intermediate profession</i>	22	12%	33	47%
	<i>Blue-collar worker</i>	2	1%	7	10%
	<i>NA</i>	4	2%	0	0%
Personal income per month (€)					<0.05
	<i><1900</i>	71	40%	20	29%
	<i>>1900</i>	103	58%	37	53%
	<i>NA</i>	4	2%	13	19%
Marital status					<0.05
	<i>Single</i>	34	19%	18	26%
	<i>Married</i>	110	62%	39	56%
	<i>Divorced</i>	29	16%	10	14%
	<i>Widow</i>	2	1%	1	1%
	<i>NA</i>	3	2%	2	3%
Breast cancer characteristics					
Type of cancer					0.32
	<i>Invasive</i>	156	87,6%	61	87%
	<i>In situ</i>	21	11,8%	9	13%
Lymph node involvement					0.12
	<i>Yes</i>	43	24%	23	33%
	<i>No</i>	135	76%	47	67%
Surgical patient care					
Breast surgery					<0.05
	<i>Conservative</i>	133	75%	46	66%
	<i>Radical</i>	45	25%	24	34%
Lymph node surgery					0.48
	<i>Sentinel lymph node procedure</i>	122	69%	40	57%
	<i>Axillary dissection</i>	42	24%	24	34%

	NA	14	8%	6	9%	
Surgical revision						0.24
	Yes	43	24%	16	23%	
	No	135	76%	54	77%	
Radiotherapy						<0.05
	Yes	167	94%	61	87%	
	No	11	6%	9	13%	
Chemotherapy						<0.05
	Yes	92	52%	33	47%	
	No	86	48%	37	53%	
Trastuzumab						0.42
	Yes	24	13%	9	13%	
	No	63	35%	22	31%	
	NA	91	51%	39	56%	
Hormone therapy						0.69
	Yes	129	72%	49	70%	
	No	49	28%	21	30%	
Patient management						
Modes of diagnosis						0.45
	<i>Organized screening</i>	37	21%	12	17%	
	<i>Individual screening</i>	74	42%	26	37%	
	<i>Clinical signs</i>	67	38%	32	46%	
Type of hospitalization						0.78
	<i>Outpatient surgery</i>	108	61%	43	61%	
	<i>Inpatient surgery</i>	70	39%	27	39%	

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	4 and 5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8
		(b) For matched studies, give matching criteria and number of exposed and unexposed	8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9
		(b) Describe any methods used to examine subgroups and interactions	9
		(c) Explain how missing data were addressed	9
		(d) If applicable, explain how loss to follow-up was addressed	9
		(e) Describe any sensitivity analyses	9
Results			9

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	Supplemental figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10 and 11
		(b) Indicate number of participants with missing data for each variable of interest	11
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	11
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-14
		(b) Report category boundaries when continuous variables were categorized	12-14
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12-14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13, 14
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.