Study of the relationship between psychoactive substance use and pain in cancer patients and cancer survivors: A French nationwide cross-sectional study

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Article original : https://onlinelibrary.wiley.com/doi/full/10.1002/ijc.35006

Study of the relationship between psychoactive substance use and pain in cancer patients and cancer survivors: a French nationwide cross-sectional study

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Keywords: Pain, Tobacco, Cannabidiol, Cannabis, Cancer

Abbreviations
BMI: Body mass index
BPI-SF: Brief Pain Inventory – short form
ES: Effect size
HADS: Hospital Anxiety and Depression Scale
HRQoL Health-related quality of life
INSEE: National Institute of Statistics and Economic Studies
PSU: Psychoactive substance use
VAS: Visual analogue scale
95% CI: 95% confidence interval

Category
Cancer Therapy and Prevention

Novelty & Impact Statements
In a population of cancer patients and survivors, psychoactive substance use (tobacco and cannabidiol) was linked to pain. Moreover, cannabidiol users reported higher proportions of chronic and neuropathic pains. These findings emphasize the importance for physicians to prioritize smoking cessation and closely monitor the use of cannabidiol during and after cancer.

Abstract

Pain is a prevalent symptom among cancer patients and survivors. Psychoactive substance use (PSU) is associated with both the presence and severity of pain. However, little is known about this association in the context of cancer. The primary objective was to compare the prevalence of PSU and its relationship with pain during and after cancer. PSU was defined as the use of non-medication substances (alcohol, tobacco, e-cigarettes, cannabidiol, and cannabis), with frequency categorized as at least yearly, monthly, weekly, or daily. Secondary objectives aimed to explore the relationships between PSU and pain characteristics, health-related quality of life (HRQoL), anxiety, depression, deprivation, and individual characteristics. Among the 1,041 individuals included, pain prevalence was 44.7% (95% CI 41.6% to 47.8%). The overall prevalence of PSU at least monthly was 67.0% (95% CI 64.0% to 69.8%). The proportions of chronic and neuropathic pains were higher for at least monthly use of cannabidiol compared to non-use (70.0% vs. 39.3% and 55.7% vs. 28.1%, $P < 0.001$). In multivariate analysis, the monthly uses of tobacco and cannabidiol were higher in painful individuals than in non-painful ones (odds-ratios: 2.85 (95% CI 1.22 to 6.64) and 3.76 (95% CI 1.13 to 12.44), $P < 0.05$). From the point of view of the patient care, the study underscores the need for physicians to prioritize smoking cessation and pay attention to the use of cannabidiol during and after cancer.

1. Introduction

Pain represents a prominent symptom in cancer patients and survivors. About 40% of cancer patients undergo pain during treatment [1], rising to 64% for advanced disease [2]. In cancer survivors, cancer-related pain prevalence varies from 33% to 40% [2].

Pain and psychoactive substance use (PSU) co-occur with high frequency, and rates of co-occurrence increase with the severity of the condition [3]. More precisely, the prevalence of PSU is higher in individuals with chronic pain compared to those without such condition, including tobacco cigarettes [4], cannabis [5], and alcohol [6].

However, there is limited information in the literature on the relationship between PSU and pain in the context of cancer. For instance, in patients with advanced-stage prostate cancer, the prevalence of PSU disorder was approximately 10.6% and was associated with increased all-cause mortality [7]. Another study on advanced-stage prostate cancer reported a PSU prevalence of approximately 12.4% in younger patients and 7.4% in older ones [8]. In a review focused on opioid and alcohol use in cancer, PSU rates varied from 2% to 35%, with a median rate of opioid use of 18% and 25.5% for alcohol [9]. Additionally, adolescent and young adult cancer survivors were more likely to use alcohol (relative increase: 6%; P = 0.048) and illicit drugs (relative increase: 34%; P = 0.012) compared to non-cancer individuals [10]. However, these studies did not report any results on the participants' pain status.

Health-related quality of life (HRQoL) is an increasingly recognized aspect of cancer management for both patients and survivors [11]. It is acknowledged that maintaining a healthy lifestyle may have beneficial effects on the HRQoL of individuals affected by cancer [12,13].

Given the limited research in this area, further investigation is necessary to explore the intricate interplay between pain and PSU in the context of cancer. Therefore, the aim of this new study is to compare the prevalence of PSU and its relationship with pain during and after cancer.

2. Methods

2.1. Study design

This nationwide, cross-sectional, and web-based study aimed to compare PSU prevalence in adult individuals with and without pain, during and after cancer. Secondary objectives included exploring the relationships between PSU and pain characteristics, health-related quality of life (HRQoL), anxiety, depression, deprivation, and cancer and patient-related factors.

The online questionnaire has been designed thanks to the REDCap™ electronic data capture tools [14]. This online questionnaire was diffused thanks to French associations of cancer patients and Facebook groups to their members and followers. Each associations of cancer patients and Facebook groups were invited to diffuse the online questionnaire every 2 weeks for a maximum of 3 or 4 relaunches.

The study adhered to the STROBE guideline [15].

2.2. Setting

This study was conducted in France in collaboration with 12 French associations of cancer patients and 12 French Facebook groups, involving approximately 61,700 individuals (see

supplement). The inclusion of patients and data collection took place from January 27, 2023, to March 20, 2023.

2.3. Participants

The inclusion criteria encompassed patients aged ≥18 years, self-declared as currently or previously managed for a cancer, and recruited through appropriate communication systems (patients' associations, etc.). Exclusion criteria included individuals who did not speak French, resided outside of France, were caregivers for cancer patients, or were legally protected adults. Eligible patients were contacted via email, facilitated by French cancer patients' associations. Data collection involved online completion of the questionnaire using REDCap™ electronic data capture tools [14].

2.3. Variables

All variables were assessed at the time of questionnaire completion (for details of the questionnaire, see supplement). The primary endpoint was the prevalence of PSU (yes/no), in the past year, for each listed psychoactive substance, including alcohol (wine, beer, whisky...), tobacco (cigarette, tobacco pipe...), e-cigarette, cannabidiol, and cannabis. The frequency of substance use was also recorded, such as at least once last year, at least once last month, at least once last week, and at least once a day. For the analysis, the frequencies of use have been recoded as follows, at least yearly ("at least once last year" + "at least once last month" + "at least once last week" + "at least once a day"), at least monthly ("at least once last month" + "at least once last week" + "at least once a day"), at least weekly ("at least once last week" + "at least once a day"), and at least daily (at least once a day). Painful individuals were defined as those with a score ≥4/10 for the item "pain at its worst in the last 24 hours" assessed using the visual analogue scale (VAS) from the Brief Pain Inventory - Short Form (BPI-SF) [16]. Non-painful individuals were defined by a score <4/10 [16]. The secondary endpoints included:

- Pain severity for various pain assessments (BPI-SF; VAS from 0 to 10; higher scores indicating worse pain), impact of pain on daily activities (BPI-SF; VAS from 0 to 10; higher scores indicating worse impact) [17], pain duration, and neuropathic pain for those experiencing pain (score ≥3/7 of the DN4 interview questionnaire [18]);
- HRQoL assessed using the QLQ-C30 questionnaire, including global health status (scores from 0 to 100; higher scores indicating better health), functioning scales (scores from 0 to 100; higher scores indicating better functioning), and symptom scales (scores from 0 to 100; higher scores indicating worse symptoms) [19];
- Presence (normal scores: ≤7/21, suggestive scores: 8–10/21, and indicative scores: ≥11/21) and severity (raw scores of 0–21/21) of anxiety and/or depression using the Hospital Anxiety and Depression Scale (HADS) questionnaire (scores from 0 to 21; higher scores indicating worse anxiety and depression) [20];
- Presence (≥4/11) and scores of deprivation assessed using the EPICES questionnaire (score 0 to 11; higher scores indicating worse deprivation) [21];
- Sociodemographic characteristics, including age, gender, height, weight, body mass index (BMI), housing area, socio-professional status (National Institute of Statistics and Economic Studies - INSEE), and French department of living;
- Oncological characteristics, including cancer type, date of cancer diagnosis, and ongoing cancer management or past cancer management. Individuals with ongoing

cancer management were categorized as cancer patients, while those with past management were classified as cancer survivors.

2.4. Study size

The estimated number of individuals required is based on identifying the proportion of PSU between groups. Literature data suggest that approximately 40-50% of painful individuals experiences PSU [1,2] and 5-30% of the population engages in daily PSU [9]. To detect a relative difference of 33% from a proportion of 25% PSU (i.e., 25% vs. 16.75%), 400 individuals per group are needed, assuming a bilateral type I error risk of 5% and a power of 80%. To ensure sufficient statistical power for secondary objectives, the sample size will be increased to 1000 individuals (500 painful and 500 non-painful).

2.5. Statistical method

Quantitative data were expressed using the mean and standard deviation when following a normal distribution, and the median and interquartile range when not adhering to a normal distribution. The normality assumption was assessed through the Shapiro-Wilk test. Quantitative data between independent groups (pain: yes/no) were compared using either the unpaired Student t-test with Welch's correction or the Mann-Whitney test in situations where assumptions for the t-test were not met. Emphasis was given to assessing the magnitude of differences using Hedge's effect sizes (ES) and 95% confidence intervals (95% CI), and these were interpreted according to Cohen's recommendations defining ES as small (≥ |0.2|), medium (≥ |0.5|), and large (≥ |0.8|) [22,23]. To compare groups (pain: yes/no) based on categorical data (such as for each PSU), the Chi-squared or Fisher's exact tests were employed.

To determine factors associated with each PSU, a multivariate logistic regression was performed, considering clinically relevant fixed covariates: pain [3], gender [24], age [25], BMI [26], cancer status [27], anxiety [28], depression [28], global health status [29], and deprivation [30]. Special attention was given to assessing multicollinearity, studying the relationships between factors (by using correlation coefficients) and estimating variance inflation factor. Information criteria such as log-likelihood, Akaike Information Criterion and Bayesian Information Criterion were also estimated and used as model diagnostics. An initial model (Model A) was executed, incorporating pain, gender, age, BMI, and cancer status. Subsequently, a second model (Model B) was conducted, adding anxiety, depression, global health status, and deprivation. Anxiety, depression, deprivation, age, and BMI were categorized based on statistical distribution and clinically relevant thresholds as reported in the literature. Results were presented as odds-ratios (OR) and 95% CI. Interactions between pain and other covariates were also tested for each PSU. More precisely, for each PSU, covariate-pain interactions between pain and each of the following covariates (gender, age, cancer, BMI, global health status, depression, anxiety and deprivation) were analyzed to determine if the combination of two variables (i.e., each covariate with pain) had a significantly larger effect on PSU compared to the sum of the individual variables alone. In other words, it was examined whether the effect of pain depended on another variable. None of the interactions were statistically significant (data not shown).

Statistical analysis was performed using Stata 14 (StataCorp, College Station, TX). The tests were two-sided, with a type I error rate set at 5%. Each PSU was independently treated as a main endpoint. No correction for multiple testing was applied. The interpretations were mainly based on p-values. The findings need to be interpreted in consideration of the

magnitude of differences and the widths of the 95% CI. Missing data were deemed negligible (less than 5%). No data imputation method was employed.

3. Results

3.1. Study population

A total of 1,041 individuals were included in the study (Figure 1), mostly females (82.5%) with an average age of 55.2 ± 11.2 years (Table 1). Half had a normal BMI (51.3%), two-thirds were employed (67.5%), and living in areas with over 5,000 residents (68.3%). Half were cancer patients, and the other half were survivors, mostly with breast cancer (61.5%). Median time since cancer diagnosis was 39 months (Table 1). Participants covered 99% of French departments (data not shown).

Figure 1: Flowchart of individual inclusion

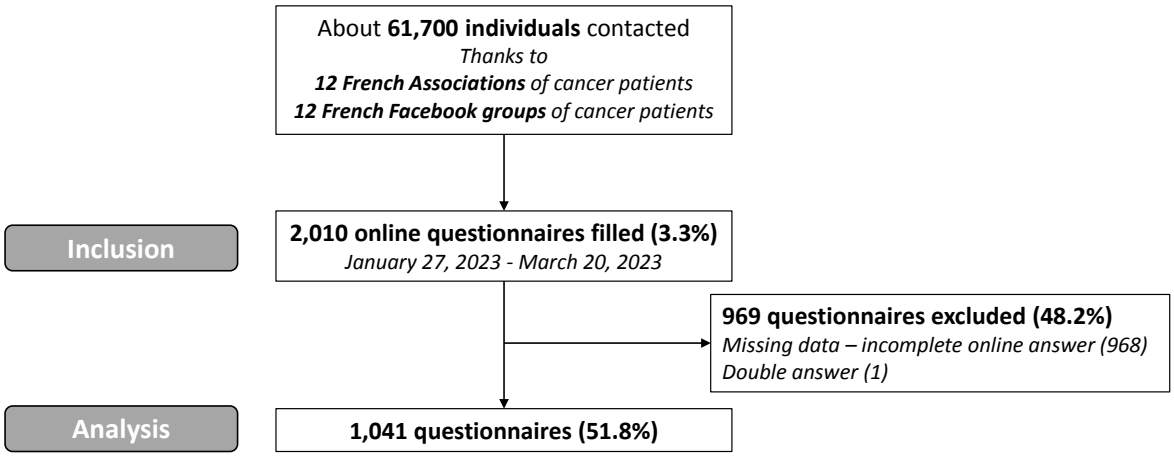

Table 1: Characteristics of individuals

Results are presented as mean ± standard deviation or median [interquartile range] for continuous variables, and as number (percentage) for categorical variables. Bold p-values (P < 0.05) indicate statistical significance in comparisons between painful and non-painful groups. Abbreviations: BMI - body mass index, INSEE - National Institute of Statistics and Economic Studies. 95% CI : 95% confidence interval; £: per log unit increase

Items	All N = 1041	Painful N = 465	Non-painful N = 576	Odds-ratios 95%CI	P-values
Gender					**<0.001**
Male	180 (17.3)	43 (9.2)	137 (23.8)	Ref.	
Female	860 (82.6)	422 (90.8)	438 (76.0)	**3.07 [2.13; 4.43]**	
Non-binary	1 (0.1)	0	1 (0.2)		
Age (years)	55.2 ± 11.2	54.1 ± 10.2	56.0 ± 11.9	**0.98 [0.97; 0.99]**	**0.005**
Age groups					**0.01**
≤ 44 years	681 (65.4)	322 (69.3)	359 (62.3)	Ref.	
44-65 years	171 (16.4)	77 (16.6)	94 (16.3)	0.92 [0.66; 1.29]	
≥ 66 years	189 (18.2)	66 (14.2)	123 (21.4)	**0.60 [0.43; 0.84]**	
BMI (kg/m²)	24.3 [21.5; 27.7]	25.94 [22.1; 29.0]	23.7 [21.2; 26.6]	**1.07 [1.04; 1.10]**	**<0.001**
BMI groups					**<0.001**
Normal weight	531 (51.3)	198 (42.86)	333 (58.1)	Ref.	
Underweight	54 (5.2)	23 (4.98)	31 (5.4)	1.25 [0.71; 2.20]	
Pre-obesity	295 (28.5)	149 (32.25)	146 (25.5)	**1.73 [1.30; 2.31]**	
Obesity	155 (15.0)	92 (19.91)	63 (11.0)	**2.46 [1.70; 3.54]**	

INSEE groups					**0.003**
Farmer	6 (0.6)	3 (0.7)	3 (0.5)	Ref.	
Artisan	4 (0.4)	2 (0.4)	2 (0.4)	1.37 [0.27; 6.92]	
Merchants / entrepreneurs	32 (3.1)	13 (2.8)	19 (3.3)	1.37 [0.19; 9.88]	
White-collar professionals	312 (30)	131 (28.4)	181 (31.8)	0.94 [0.45; 1.97]	
Intermediate professions	120 (11.5)	57 (12.3)	63 (11.1)	1.24 [0.81; 1.90]	
Employees	207 (20.0)	115 (24.9)	92 (16.1)	**1.72 [1.20; 2.45]**	
Workers	16 (1.5)	6 (1.3)	10 (1.8)	0.82 [0.29; 2.33]	
Retirees	246 (23.6)	87 (18.8)	159 (27.9)	0.75 [0.52; 1.06]	
Unemployed individuals	89 (8.6)	48 (10.4)	41 (7.2)	1.61 [1.00; 2.58]	
Housing area (residents)					0.62
≥ 50 000	332 (32.1)	140 (30.4)	192 (33.5)	Ref.	
[5 000-49 999]	374 (36.2)	174 (37.7)	200 (34.9)	1.19 [0.88; 1.60]	
[500-4 999]	258 (25.0)	118 (25.6)	140 (24.4)	1.15 [0.83; 1.60]	
< 500	70 (6.8)	29 (6.3)	41 (7.2)	0.96 [0.57; 1.63]	
Cancer status					**0.003**
Patients	525 (50.4)	259 (55.7)	266 (46.2)	Ref.	
Survivors	516 (49.6)	206 (44.3)	310 (53.8)	**1.21 [1.07; 1.37]**	
Cancer type					
Breast	640 (61.5)	330 (71.0)	310 (53.8)	**2.09 [1.61; 2.71]**	**<0.001**
Prostate	92 (8.8)	14 (3.0)	78 (13.5)	**0.20 [0.11; 0.35]**	**<0.001**
Pulmonary	78 (7.5)	35 (7.5)	43 (7.5)	1.01 [0.63; 1.60]	0.97
Blood	67 (6.4)	24 (5.2)	43 (7.5)	0.67 [0.40; 1.13]	0.13
Gynecological	66 (6.3)	28 (6.0)	38 (6.6)	0.91 [0.55; 1.50]	0.71
Kidney	57 (5.5)	15 (3.2)	42 (7.3)	**0.43 [0.24; 0.79]**	**0.004**
Colorectal	29 (2.8)	10 (2.2)	19 (3.3)	0.64 [0.30; 1.40]	0.26
Others	57 (6.2)	9 (1.9)	2 (0.3)	**5.65 [1.22; 26.3]**	**0.02**
Time since diagnosis (months)	39 [17; 82]	37 [17; 69]	41.5 [17; 90.5]	**0.89 [0.79; 0.99]**[£]	**0.027**
Care center					0.97
University hospital center	266 (25.6)	121 (26.0)	145 (25.2)	Ref.	
Cancer center	264 (25.4)	119 (25.6)	145 (25.2)	0.98 [0.69; 1.38]	
General hospital	170 (16.3)	78 (16.8)	92 (16.0)	1.01 [0.69; 1.49]	
Private clinic	265 (25.5)	114 (24.5)	151 (26.2)	0.90 [0.64; 1.27]	
Others	76 (7.3)	33 (7.1)	43 (7.5)	0.91 [0.55; 1.53]	
Anxiety					**<0.001**
Normal scores	531 (51.1)	184 (39.6)	347 (60.4)	Ref.	
Suggestive scores	249 (23.9)	114 (24.5)	135 (23.5)	**1.59 [1.17; 2.16]**	
Indicative scores	260 (25.0)	167 (35.9)	93 (16.2)	**3.39 [2.48; 4.62]**	
Depression					**<0.001**
Normal scores	693 (66.6)	245 (52.7)	448 (77.9)	Ref.	
Suggestive scores	183 (17.6)	110 (23.7)	73 (12.7)	**2.76 [1.97; 3.85]**	
Indicative scores	164 (15.8)	110 (23.7)	54 (9.4)	**3.72 [2.60; 5.34]**	
Deprivation	242 (23.3)	157 (33.8)	85 (14.8)	**2.94 [2.18; 3.97]**	**<0.001**

The global prevalence of pain was 44.7% (95% CI: 41.6% to 47.8%). Painful individuals had median pain duration of 24 months (range: 9 to 48). About 92.7% (95% CI: 89.9% to 94.9%) had chronic pain (≥3 months), and 67.1% (95% CI: 62.6% to 71.4%) had neuropathic pain. Higher proportions of individuals reported pain among females compared to males (OR: 3.07, 95% CI: 2.13 to 4.43), younger individuals compared to older ones, individuals with higher BMI compared to those with lower BMI, and among employees compared to other INSEE groups (socio-professional status) (Table 1).

The proportion of individual experiencing pain was higher among cancer patients than among cancer survivors (OR: 1.21, 95% CI: 1.07 to 1.37), and shorter time since cancer diagnosis was associated with higher likelihood of experiencing pain compared to non-painful individuals (OR: 0.89, 95% CI: 0.79 to 0.99, per log unit increase). A higher proportion of painful individuals was reported for breast cancer (OR: 2.09, 95% CI: 1.61 to 2.71), but was lower for prostate cancer (OR: 0.20, 95% CI 0.11 to 0.35), and kidney cancer (OR: 0.43, 95% CI: 0.24 to 0.79) (Table 1).
Greater proportions of indicative anxiety and depression scores were reported among individuals with pain compared to non-painful ones, along with a higher proportion of deprivation (for details of analysis see Table 1).

3.2. Psychoactive substance use according to pain

The details of the PSU are described in Table 2. Among all individuals, the global prevalence of any PSU at least yearly was 75.7% (95% CI 73.0% to 78.3%), monthly 67.0% (95% CI 64.0% to 69.8%), weekly 44.1% (95% CI 41.1% to 47.2%), and daily 16.9% (95% CI 14.7% to 19.3%). Only the prevalence of any substance use at least daily was higher in individuals experiencing pain compared to those without pain (OR: 1.42, 95% IC: 1.09 to 1.97; p <0.05) (Table 2). While no difference was reported between groups for alcohol use at least yearly, its monthly and weekly use were lower in painful individuals than in non-painful ones (OR: 0.74, 95% CI: 0.57 to 0.95, and OR: 0.74, 95% CI: 0.58 to 0.96; p < 0.05, respectively). Both tobacco and cannabidiol use were higher among painful individuals than non-painful ones, regardless of the frequency of use. For tobacco, the highest odds ratio (OR: 1.79, 95% CI: 1.25 to 2.56, p = 0.002) was reported for yearly use, while the lowest (OR: 1.56, 95% CI: 1.02 to 2.38, p = 0.04) was for weekly use. Conversely, for cannabidiol, the highest odds ratio (OR: 4.72, 95% CI: 1.90 to 11.7, p < 0.001) was for daily use, and the lowest (OR: 3.14, 95% CI: 2.14 to 4.61, p < 0.001) was for yearly use. Cannabis use at least yearly was higher among painful individuals compared to non-painful ones (OR: 1.91, 95% CI: 1.04 to 3.51, p < 0.05), but there was no significant difference in use for other frequencies. No difference was reported for e-cigarette use between groups.

Table 2: Psychoactive substance use and frequency in all individuals, painful, and non-painful individuals

Results are presented as number (percentage) for the entire sample, painful subgroup, and non-painful subgroup. Psychoactive substance use includes alcohol, tobacco, e-cigarette, cannabidiol, and cannabis, and according to the frequency of use. Bold p-values (P < 0.05) indicate statistical significance in comparisons between painful and non-painful groups. 95% CI : 95% confidence interval.

Substances	Frequency of use (at least)	All N = 1041	Painful N = 465	Non-painful N = 576	Odds-ratios 95% CI	P-values
Any substance	Yearly	788 (75.7)	349 (75.1)	439 (76.2)	0.94 [0.71; 1.25]	0.7
	Monthly	697 (67.0)	307 (66.0)	390 (67.7)	0.93 [0.72; 1.20]	0.6
	Weekly	459 (44.1)	204 (43.9)	255 (44.3)	0.99 [0.77; 1.26]	0.9
	Daily	176 (16.9)	**91 (19.6)**	**85 (14.8)**	**1.42 [1.09; 1.97]**	**0.046**
Alcohol	Yearly	723 (69.5)	310 (66.7)	413 (71.7)	0.79 [0.61; 1.03]	0.09
	Monthly	635 (61.0)	**265 (57.0)**	**370 (64.3)**	**0.74 [0.57; 0.95]**	**0.02**
	Weekly	377 (36.2)	**151 (32.5)**	**226 (39.2)**	**0.74 [0.58; 0.96]**	**0.03**
	Daily	61 (5.9)	27 (5.8)	34 (3.9)	0.98 [0.58; 1.65]	1
Tobacco	Yearly	140 (13.4)	**80 (17.2)**	**60 (10.4)**	**1.79 [1.25; 2.56]**	**0.002**
	Monthly	115 (11.0)	**63 (13.5)**	**52 (9.0)**	**1.58 [1.07; 2.33]**	**0.02**
	Weekly	95 (9.1)	**52 (11.2)**	**43 (7.5)**	**1.56 [1.02; 2.38]**	**0.04**
	Daily	78 (7.5)	**44 (9.5)**	**34 (5.9)**	**1.67 [1.05; 2.65]**	**0.03**

E-cigarette	Yearly	77 (7.4)	42 (9.0)	35 (6.1)	1.53 [0.96; 2.44]	0.08
	Monthly	64 (6.1)	34 (7.3)	30 (5.2)	1.43 [0.86; 2.38]	0.2
	Weekly	56 (5.4)	29 (6.2)	27 (4.7)	1.35 [0.79; 2.31]	0.3
	Daily	45 (4.3)	23 (5.0)	22 (3.8)	1.31 [0.72; 2.38]	0.4
Cannabidiol	Yearly	137 (13.2)	**94 (20.2)**	**43 (7.5)**	**3.14 [2.14; 4.61]**	**<0.001**
	Monthly	70 (6.7)	**53 (11.4)**	**17 (3.0)**	**4.23 [2.41; 7.41]**	**<0.001**
	Weekly	48 (4.6)	**37 (8.0)**	**11 (1.9)**	**4.44 [2.24; 8.81]**	**<0.001**
	Daily	28 (2.7)	**22 (4.3)**	**6 (1.0)**	**4.72 [1.90; 11.7]**	**<0.001**
Cannabis	Yearly	45 (4.3)	**27 (5.8)**	**18 (3.1)**	**1.91 [1.04; 3.51]**	**0.045**
	Monthly	29 (2.8)	18 (3.9)	11 (1.9)	2.06 [0.97; 4.42]	0.06
	Weekly	21 (2.0)	13 (2.8)	8 (1.4)	2.04 [0.84; 4.96]	0.1
	Daily	14 (1.3)	9 (1.9)	5 (0.9)	2.25 [0.75; 6.76]	0.2

Analyses of the relation between PSU and pain characteristics and impacts on daily living were done for at least monthly use, to avoid a high decrease of individuals the sample analyzed (Table 3).

The analysis of the relationship between PSU and pain characteristics, as well as its impacts on daily activities, focused on at least monthly use. This approach aimed to prevent a significant reduction in the analyzed sample size (refer to Table 3). Proportions of individuals with chronic pain or neuropathic pain were lower for alcohol users ($P < 0.05$). Conversely, these proportions were higher for cannabidiol users than for non-users. No other difference was reported for other PSU (tobacco, e-cigarette, and cannabis). Alcohol users tended to report lower scores of pain right now than non-users (small effect size (ES)), and as well as lower scores of pain interference with relation with other and enjoyment of life (small ES) (Table 3). Cannabis users reported higher scores of pain on average than non-users (small ES), but lower scores of pain interference with mood and relation with other (medium ES). Cannabidiol users had higher scores of worst pain than non-users (medium ES). E-cigarette users had higher scores of pain on average than non-users (medium ES). No variation of pain severity and interference with daily activities was reported by tobacco users (Table 3).

Items	Alcohol Users vs non-users	Tobacco Users vs non-users	E-cigarette Users vs non-users	Cannabidiol Users vs non-users	Cannabis Users vs non-users
Chronic pain (≥ 3 months)	246 (38.7) vs. 185 (45.6)* 0.75 [0.59; 0.96]	55 (47.8) vs. 376 (40.6) 1.30 [0.88; 1.92]	31 (48.4) vs. 400 (40.9) 1.28 [0.77; 2.12]	49 (70.0) vs. 382 (39.3)*** 3.63 [2.14; 6.15]	17 (58.6) vs. 414 (40.9) 2.06 [0.97; 4.37]
Neuropathic pain (DN4 interview)	173 (27.2) vs. 139 (34.2)* 0.72 [0.55; 0.94]	36 (31.3) vs. 276 (29.8) 1.07 [0.71; 1.63]	19 (29.7) vs. 293 (30.0) 0.99 [0.57; 1.71]	39 (55.7) vs. 273 (28.1)*** 3.22 [1.97; 5.26]	11 (37.9) vs. 301 (29.7) 1.45 [0.67; 3.09]
Worst pain (BPI-SF)	-0.10 (-0.28 to 0.09)	0.22 (-0.05 to 0.48)	0.19 (-0.15 to 0.55)	0.53 (0.24 to 0.82)***	0.32 (-0.15 to 0.79)
Least pain (BPI-SF)	-0.13 (-0.31 to 0.05)	0.19 (-0.07 to 0.46)	0.24 (-0.11 to 0.59)	-0.09 (-0.38 to 0.19)	0.32 (-0.15 to 0.79)
Pain on average (BPI-SF)	-0.05 (-0.23 to 0.13)	0.12 (-0.14 to 0.39)	0.52 (0.17 to 0.87)**	0.06 (-0.22 to 0.35)	0.48 (0.004 to 0.95)*
Pain right now (BPI-SF)	-0.20 (-0.38 to -0.02)*	0.11 (-0.16 to 0.38)	-0.07 (-0.42 to 0.28)	0.24 (-0.05 to 0.52)	0.01 (-0.46 to 0.48)
General activity (BPI-SF)	-0.11 (-0.29 to 0.08)	-0.01 (-0.28 to 0.25)	0.30 (-0.05 to 0.64)	0.11 (-0.18 to 0.39)	0.05 (-0.42 to 0.52)
Mood (BPI-SF)	-0.08 (-0.27 to 0.10)	-0.09 (-0.35 to 0.18)	0.09 (-0.26 to 0.43)	0.06 (-0.22 to 0.35)	-0.61 (-1.09 to -0.14)*
Walking ability (BPI-SF)	-0.17 (-0.35 to 0.02)	-0.09 (-0.35 to 0.18)	0.06 (-0.28 to 0.41)	-0.07 (-0.36 to 0.21)	0.15 (-0.32 to 0.62)
Normal work (BPI-SF)	-0.11 (-0.29 to 0.08)	-0.10 (-0.37 to 0.16)	0.10 (-0.25 to 0.45)	-0.07 (-0.36 to 0.21)	-0.26 (-0.73 to 0.21)
Relation with other (BPI-SF)	-0.25 (-0.43 to -0.07)**	-0.13 (-0.40 to 0.14)	0.03 (-0.32 to 0.38)	-0.07 (-0.35 to 0.22)	-0.58 (-1.10 to -0.11)*
Sleep (BPI-SF)	-0.08 (-0.26 to 0.11)	0.09 (-0.18 to 0.35)	0.14 (-0.21 to 0.48)	0.25 (-0.04 to 0.54)	-0.29 (-0.76 to 0.18)
Enjoyment of life (BPI-SF)	-0.29 (-0.48 to -0.11)**	-0.06 (-0.32 to 0.21)	0.33 (-0.02 to 0.68)	-0.01 (-0.30 to 0.27)	-0.31 (-0.78 to 0.16)

Table 3: Comparison of pain characteristics and daily activity interference based on monthly psychoactive substance use

Chronic pain (lasting ≥ 3 months) and neuropathic pain (assessed with the DN4 interview) are presented as the number (%) of individuals affected by each psychoactive substance used at least monthly. Odds-ratios and 95% confidence intervals are also calculated. Pain severity and interference with daily activities (assessed with the BPI-SF) are presented as effect sizes with 95% confidence intervals for painful individuals (N = 465). Emphasis is given to assessing the magnitude of differences using effect sizes and 95% confidence intervals and are interpreted according to Cohen's recommendations defining ES as small (≥ |0.2|), medium (≥ |0.5|), and large (≥ |0.8|). * P < 0.05, ** P < 0.01, and *** P < 0.001 are also calculated and indicate significance in the comparison between users and non-users.

3.3. Health-related quality of life, anxiety, depression, and deprivation according to psychoactive substance use (at least monthly)

Alcohol users reported better scores for HRQoL, symptoms (except insomnia), anxiety, depression, and deprivation than non-users (small ES) (Table 4). Tobacco users reported lower scores of social functioning, and higher scores of fatigue, nausea/vomiting, pain, insomnia, appetite loss, diarrhea, financial difficulties, and deprivation (small ES). E-cigarette users reported lower scores of social functioning, and higher scores of nausea/vomiting, anxiety, and deprivation (small ES). Cannabidiol users had lower scores for HRQoL (small ES), and higher scores for fatigue, nausea / vomiting, and pain (medium ES), and as well as for dyspnea, insomnia, appetite loss, financial difficulties, anxiety, and depression (small ES). Cannabis users reported lower scores for HRQoL (role functioning and social functioning (medium ES); emotional functioning and cognitive functioning (small ES)), and higher scores for financial difficulties (large ES); dyspnea, appetite loss, anxiety, and deprivation (medium ES); pain, diarrhea, and depression (small ES) (table 4).

Items (QLQ-C30)	Alcohol Users vs. non-users	Tobacco Users vs. non-users	E-cigarette Users vs. non-users	Cannabidiol Users vs. non-users	Cannabis Users vs. non-users
Global health status	0.22 (0.09 to 0.34)***	-0.11 (-0.31 to 0.08)	-0.03 (-0.29 to 0.22)	-0.29 (-0.54 to -0.05)*	-0.26 (-0.63 to 0.11)
Physical functioning	0.41 (0.29 to 0.54)***	-0.15 (-0.35 to 0.04)	-0.14 (-0.39 to 0.11)	-0.33 (-0.58 to -0.09)**	-0.34 (-0.71 to 0.03)
Role functioning	0.28 (0.15 to 0.40)***	-0.22 (-0.41 to -0.03)	-0.20 (-0.45 to 0.05)	-0.41 (-0.65 to -0.16)***	-0.50 (-0.87 to 0.14)*
Emotional functioning	0.15 (0.03 to 0.28)*	-0.16 (-0.35 to 0.03)*	-0.22 (-0.48 to 0.03)	-0.32 (-0.56 to -0.08)**	-0.35 (-0.72 to 0.02)*
Cognitive functioning	0.19 (0.07 to 0.32)*	-0.14 (-0.34 to 0.05)	-0.21 (-0.46 to 0.04)	-0.37 (-0.61 to -0.13)**	-0.39 (-0.76 to -0.02)*
Social functioning	0.38 (0.25 to 0.50)***	-0.33 (-0.52 to -0.14)**	-0.30 (-0.55 to -0.05)*	-0.23 (-0.47 to 0.01)*	-0.57 (-0.93 to -0.20)**
Fatigue	-0.29 (-0.42 to -0.16)***	0.32 (0.13 to 0.52)**	0.21 (-0.04 to 0.47)	0.50 (0.26 to 0.75)***	0.39 (0.02 to 0.76)*
Nausea / vomiting	-0.29 (-0.41 to -0.16)***	0.36 (0.16 to 0.55)***	0.39 (0.14 to 0.64)**	0.54 (0.29 to 0.78)***	0.35 (-0.02 to 0.72)
Pain	-0.29 (-0.42 to -0.16)***	0.32 (0.13 to 0.52)**	0.21 (-0.04 to 0.47)	0.50 (0.26 to 0.75)***	0.39 (0.02 to 0.76)*
Dyspnea	-0.17 (-0.29 to -0.05)**	0.14 (-0.05 to 0.33)	0.08 (-0.17 to 0.33)	0.41 (0.17 to 0.65)**	0.54 (0.17 to 0.91)**
Insomnia	-0.10 (-0.22 to 0.03)	0.23 (0.04 to 0.42)*	0.00 (0.25 to 0.25)	0.46 (0.22 to 0.70)***	0.21 (-0.16 to 0.58)
Appetite loss	-0.29 (-0.41 to -0.16)***	0.33 (0.13 to 0.52)*	0.18 (-0.07 to 0.43)	0.33 (0.09 to 0.57)*	0.67 (0.30 to 1.04)**
Constipation	-0.20 (-0.32 to -0.08)**	0.11 (-0.08 to 0.31)	0.01 (-0.24 to 0.26)	0.08 (-0.16 to 0.32)	0.18 (-0.19 to 0.55)
Diarrhea	-0.13 (-0.25 to -0.00)*	0.33 (0.14 to 0.24)**	0.03 (-0.22 to 0.28)	0.20 (-0.04 to 0.45)	0.46 (0.09 to 0.83)*
Financial difficulties	-0.27 (-0.40 to -0.15)***	0.32 (0.13 to 0.52)**	0.24 (-0.01 to 0.49)	0.42 (0.18 to 0.66)***	0.93 (0.56 to 1.30)***
Anxiety	-0.15 (-0.27 to -0.02)*	0.19 (-0.00 to 0.38)	0.41 (0.16 to 0.66)**	0.36 (0.11 to 0.60)**	0.56 (0.19 to 0.93)**
Depression	-0.28 (-0.40 to -0.15)***	0.09 (-0.11 to 0.28)	0.31 (0.05 to 0.56)	0.20 (-0.04 to 0.45)*	0.37 (0.00 to 0.74)*
Deprivation	-0.48 (-0.61 to -0.36)***	0.26 (0.06 to 0.45)*	0.49 (0.23 to 0.74)***	0.14 (-0.10 to 0.38)	0.61 (0.24 to 0.98)**

Table 4: Scores of global health status, functioning scales, symptom scales, anxiety, depression, and deprivation for all individuals based on at least monthly use of alcohol, tobacco, e-cigarette, cannabidiol, and cannabis

Results are presented as effect sizes with 95% confidence intervals, comparing scores from the QLQ-C30 questionnaire (global health status, functioning, and symptoms), the HADS questionnaire (anxiety and depression), and the EPICES questionnaire (deprivation) between users and non-users of psychoactive substances among all individuals (N = 1,041). Emphasis is given to assessing the magnitude of differences using effect sizes and 95% confidence intervals and are interpreted according to Cohen's recommendations defining ES as small (≥ |0.2|), medium (≥ |0.5|), and large (≥ |0.8|). *P < 0.05, ** P < 0.01, and *** P < 0.001 are also calculated and indicate significance in the comparison between users and non-users.

3.4. Multivariate analyses of psychoactive substances (at least monthly) and pain

Two multivariate analyses were done to explore the relationship between PSU and pain, the first model included patients' characteristics (Table 5A), and the second models additionally included global health status, anxiety, depression and deprivation (Table 5B).

Tobacco and cannabidiol were associated with painful status (Table 5A). Females were less likely to use alcohol, tobacco, and cannabis. Younger individuals were more likely to use cannabis, while older ones were less likely to use tobacco and e-cigarette. The relationship between BMI and PSU showed varying patterns across BMI groups (underweight individuals used less alcohol but more cannabidiol, overweight individuals used less e-cigarette, and obese individuals used less alcohol). In comparison to cancer survivors, cancer patients were less likely to use alcohol.

In the second model, similar results were found. The association between cannabis use and anxiety (suggestive scores) was highlighted (Table 5B). Additionally, deprivation showed associations with e-cigarette use, while exhibiting an inverse relationship with alcohol consumption.

Model A.	Alcohol	Tobacco	E-cigarette	Cannabidiol	Cannabis
Painful	1.01 (0.50 to 2.04)	**2.85 (1.22 to 6.64)***	1.99 (0.63 to 6.29)	**3.76 (1.13 to 12.44)***	1.04 (0.12 to 8.98)
Chronic pain	0.82 (0.40 to 1.67)	0.57 (0.25 to 1.31)	0.75 (0.24 to 2.37)	1.06 (0.34 to 3.27)	2.73 (0.32 to 23.17)
Gender (female)	**0.56 (0.38 to 0.84)****	**0.47 (0.27 to 0.83)****	0.89 (0.38 to 2.11)	1.33 (0.53 to 3.32)	**0.18 (0.07 to 0.47)*****
Age (years)					
[18-44]	1.01 (0.71 to 1.44)	1.10 (0.66 to 1.83)	1.05 (0.55 to 1.99)	1.50 (0.81 to 2.80)	**2.75 (1.19 to 6.34)***
[66-100]	0.97 (0.71 to 1.40)	**0.24 (0.10 to 0.54)****	**0.25 (0.07 to 0.84)***	0.73 (0.32 to 1.64)	**0.12 (0.02 to 0.99)***
BMI groups					
Underweight	**0.50 (0.28 to 0.88)***	1.92 (0.90 to 4.10)	1.72 (0.72 to 4.11)	**3.02 (1.26 to 7.22)***	2.00 (0.55 to 7.31)
Overweight	1.16 (0.85 to 1.58)	0.69 (0.42 to 1.15)	**0.33 (0.15 to 0.71)****	1.18 (0.63 to 2.21)	0.55 (0.21 to 1.46)
Obesity	**0.69 (0.47 to 0.99)***	0.86 (0.48 to 1.56)	0.43 (0.18 to 1.04)	1.84 (0.94 to 3.60)	0.53 (0.15 to 1.92)
Cancer patients	**0.68 (0.53 to 0.88)****	1.37 (0.90 to 2.07)	1.19 (0.70 to 2.02)	0.82 (0.49 to 1.38)	1.33 (0.61 to 2.88)
Model B.	**Alcohol**	**Tobacco**	**E-cigarette**	**Cannabidiol**	**Cannabis**
Painful	1.11 (0.54 to 2.32)	**3.16 (1.32 to 7.57)***	2.38 (0.71 to 7.94)	**3.42 (1.00 to 11.68)***	1.23 (0.14 to 11.10)
Chronic pain	0.90 (0.43 to 1.86)	0.49 (0.21 to 1.15)	0.56 (0.17 to 1.85)	1.08 (0.34 to 3.41)	1.91 (0.22 to 16.59)
Gender (female)	**0.60 (0.40 to 0.90)***	**0.45 (0.25 to 0.79)****	0.75 (0.31 to 1.80)	1.30 (0.52 to 3.27)	**0.17 (0.06 : 0.44)*****
Age (years)					
[18-44]	1.07 (0.75 to 1.54)	1.04 (0.62 to 1.75)	0.95 (0.49 to 1.82)	1.46 (0.78 to 2.74)	**2.35 (1.01 to 5.50)***
[66-100]	0.92 (0.63 to 1.33)	**0.24 (0.11 to 0.56)****	**0.26 (0.08 to 0.88)***	0.74 (0.32 to 1.66)	0.13 (0.02 to 1.10)
BMI groups					
Underweight	**0.55 (0.31 to 0.98)***	1.87 (0.87 to 4.0)	1.75 (0.72 to 4.28)	**2.96 (1.22 to 7.18)***	1.71 (0.46 to 6.45)
Overweight	1.23 (0.90 to 1.69)	0.69 (0.42 to 1.16)	**0.31 (0.14 to 0.69)****	1.20 (0.64 to 2.25)	0.56 (0.21 to 1.51)
Obesity	0.77 (0.53 to 1.13)	0.80 (0.44 to 1.45)	**0.36 (0.14 to 0.89)***	1.97 (0.99 to 3.90)	0.41 (0.11 to 1.52)
Cancer patients	**0.71 (0.54 to 0.93)***	1.41 (0.92 to 2.17)	1.21 (0.70 to 2.10)	0.84 (0.49 to 1.41)	1.30 (0.58 to 2.90)
Anxiety groups					
Suggestive scores	0.95 (0.68 to 1.33)	1.33 (0.79 to 2.23)	1.58 (0.79 to 3.17)	0.94 (0.48 to 1.84)	**4.69 (1.67 to 13.20)****
Indicative scores	0.95 (0.65 to 1.38)	1.20 (0.68 to 2.12)	1.70 (0.82 to 3.55)	1.42 (0.73 to 2.79)	2.38 (0.72 to 7.86)
Depression groups					
Suggestive scores	0.98 (0.67 to 1.45)	1.27 (0.72 to 2.24)	0.77 (0.33 to 1.80)	1.23 (0.64 to 2.35)	1.02 (0.37 to 2.80)
Indicative scores	0.84 (0.54 to 1.31)	1.16 (0.60 to 2.24)	1.99 (0.90 to 4.40)	0.50 (0.21 to 1.20)	0.84 (0.25 to 2.82)
Global health status	1.00 (0.99 to 1.01)	0.99 (0.98 to 1.00)	**0.98 (0.96 to 0.999)***	1.00 (0.99 to 1.02)	1.00 (0.97 to 1.02)
Deprivation	**0.45 (0.33 to 0.63)*****	1.51 (0.94 to 2.43)	**2.37 (1.31 to 4.30)****	1.07 (0.60 to 1.91)	1.94 (0.82 to 4.56)

Table 5: Multivariate analyses of monthly psychoactive substance use and pain status in all individuals

Multivariate analyses were conducted for painful status (reference: non-painful) and separately for each psychoactive substance used at least monthly. Models were adjusted for A. chronic pain (reference: no chronic pain), sex (reference: male; one non-binary individual excluded), age (reference: [45-65]), BMI groups (reference: normal

weight), and cancer status (reference: survivors), and B. model A plus anxiety groups (reference: normal scores), depression groups (reference: normal scores), global health status (scores), and deprivation (reference: no deprivation). Results are presented as odds ratios with 95% confidence intervals. Bold results indicate significance. * P < 0.05, ** P < 0.01, and *** P < 0.001.

4. Discussion

In this population of individuals during and after cancer, PSU at least monthly (tobacco and cannabidiol) was associated with pain (multivariate analysis).

PSU in painful individuals is based on complex constructs and processes, including negative reinforcement and self-medication, self-efficacy and outcome expectancies (social cognitive theory), and allostatic load [3]. PSU and pain share a bidirectional relationship, considering that most of the psychoactive substances have acute analgesic effects (nicotine [31], alcohol [32], cannabis [33]), and unpleasant and painful symptoms can be induced by nicotine, alcohol, and cannabis withdrawal [34]. Moreover, chronic PSU remains a risk factor for chronic pain (tobacco cigarettes [35], alcohol [36], cannabis [37]).

Importantly, in France, alcohol beverages, cigarettes, e-cigarettes, and cannabidiol are regulated and available substances. Medical cannabis (medication associating tetrahydrocannabinol and cannabidiol, and not the plant) must be prescribed by a physician. But the use of cannabis (plant) remains illegal. In the present study, the origin and the intent of the PSU were not recorded. This information would have been interesting, because we recently shown that pain was strongly associated with self-medication practices during and after cancer, and could be a driver for these practices [38].

Trends of daily PSU in the present study were lower than data in the French adult population, for daily alcohol use (10.0% [39]), daily tobacco use (24.5% [40]), daily cannabidiol use (10.1% [41]), but quite similar for daily e-cigarette use (5.5% [40]) and daily cannabis use (1.7% [42]). Interestingly, females were less likely to use alcohol, tobacco, and cannabis, which is in agreement with data from the literature [24]. In the same way, uses of tobacco, e-cigarette, and cannabis were lower in old individuals than young ones, since PSU declines with age of individuals [25].

Tobacco smoking and pain share a reciprocal relationship. Tobacco smoking provides acute analgesic effects, but pain threshold and tolerance levels decrease in smokers in comparison to nonsmokers. Moreover, nicotine withdrawal increases pain in smokers [43]. In cancer patients, smoking cessation is beneficial for overall survival and cancer-specific mortality [44], and importantly, can improve chronic pain [43]. Smoking cessation helps alleviate pain by preventing exacerbation of underlying causes (e.g., osteoporosis, lumbar disc disease, and delayed bone and wound healing). Smoking cessation can reduce pain and improve responsiveness to pain treatment, but it is not clear whether smoking cessation provides positive short-term pain relief benefits in a wide spectrum of patients with chronic pain [43]. However, smokers with co-occurring pain are less likely to initiate a quit attempt and maintain smoking abstinence than smokers without co-occurring pain [45]. Consequently, these patients require intensive interventional programs for a successful management of pain and tobacco dependence [43].

In the case of cannabidiol, it is not known if cannabidiol was used for pain or other disorders. The therapeutic efficacy of cannabidiol remains unclear, and particularly for the management of pain [46], whereas cannabidiol use during cancer management raises potential risks of drug interactions [47]. As suggested by some authors, cannabidiol discontinuation appears to be the most consistent option [47].

Although cannabis use did not show a direct relationship with individuals experiencing pain, it was associated with suggestive anxiety disorders. A recent US study reported that the most common reasons for cannabis use by cancer patients and survivors, were difficulty sleeping (50%), pain (46%), and mood changes and stress, anxiety, or depression (45%) [48]. Interestingly in the cited study, patients reported also a symptom improvement for pain

(57%), stress / anxiety / depression (64%), difficulty sleeping (64%), and loss of appetite (40%) [48]. Nevertheless, the recent guideline issued by the Multinational Association Of Supportive Care In Cancer advises against using cannabinoids as an adjuvant analgesic for cancer pain, emphasizing the importance of carefully considering the potential risks of harm and adverse events [49].

Among all individuals, prevalence of chronic pain (41.3%) and chronic neuropathic pain (28.8%) were higher than previously reported in French cancer patients (28.2% (95% CI 26.3% to 30.5%), and 5.9% (95% CI 4.8% to 7.0), respectively) [50]. Cancer pain can be related to tumor and/or disease progression, as well as therapeutics during and after cancer (iatrogenic sequalae). Surgery can induce chronic neuropathic pain (e.g. 37.1% of breast cancer patients) [51]. Neurotoxic anticancer drugs (e.g. platinum derivatives, taxanes), are responsible for chemotherapy-induced peripheral neuropathy, which affects about 68.1% of patients in the first month following chemotherapy end, and can last several months after treatment end [52]. Aromatase inhibitors, employed in postmenopausal breast cancer patients with hormone receptor-positive tumors, can lead to arthralgia, impacting as many as 50% of patients [53].

In the present study, alcohol use was not found to be associated with pain status in the multivariate analysis. However, it was observed to be more prevalent among cancer survivors compared to cancer patients, as well as among males compared to females. Importantly, the proportion of pain was higher in cancer patients than in cancer survivors, which may affect the relationship between pain and PSU in these two groups of patients. (N.B., an extensive analysis of pain characteristics between cancer patients and cancer survivors is not presented in this manuscript, but will be included in another specific manuscript on this topic). The relationship between cancer pain and alcohol use remains complex and context-dependent. Previous research has presented conflicting findings, with problem alcohol use predicting pain in head and neck cancer survivors at 12 months post-diagnosis [54], while other studies suggest an inverse association between cancer pain and alcohol consumption in cancer survivors [55]. The higher frequency of alcohol use in cancer survivors than in cancer patients could potentially be linked to hedonistic behaviors.

The primary limitation of this study lies in its lack of representativeness, primarily skewed towards breast cancer cases (58.3%), with only 8.4% representing prostate cancers. In contrast, in France, these two cancers exhibit equal prevalence (61,214 breast cancers and 59,885 prostate cancers) [56]. Furthermore, relying on self-reported endpoints may introduce a potential overestimation of the results. The study's inability to record risky substance uses, particularly alcohol, limits the assessment of the overall risk associated with psychoactive substance use in these individuals. Additionally, the analysis of secondary objectives and multivariate analyses focused on psychoactive substance use at least monthly (rather than weekly or daily) to prevent a substantial loss of individuals, despite univariate analysis indicating a link between any substance use and the pain status of individuals. Finally, uncorrected p-values were used for the interpretation of results.

In conclusion, this French nationwide cross-sectional study provides important insights into the prevalence of PSU and pain, during and after cancer. Our findings suggest that pain was related to uses of tobacco and cannabidiol. Physicians must seek and consider the PSU of their patients. It is still important to encourage cancer patients and cancer survivors to quit smoking. A cautious approach to the use of cannabidiol should be recommended. This study underscores the need for continued research in this area to develop and implement effective pain management strategies for cancer patients and survivors with PSU.

Author contributions
Conceptualization, D.B.; methodology, D.B. and B.P.; software, D.B. and C.R.; validation, D.B. and C.R.; formal analysis, D.B., C.R., and B.P.; investigation, C.R.; resources, D.B.; data curation, D.B. and C.R.; writing—original draft preparation, D.B., C.R., and B.P.; writing—review and editing, D.B., C.R., and B.P.; visualization, D.B., C.R., and B.P.; supervision, D.B.; project administration, D.B.; funding acquisition, D.B. All authors have read and agreed to the published version of the manuscript. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

Acknowledgments
The author warmly thanks the associations of cancer patients and their participants.

Declaration of interests
The authors declare that they have no conflict of interest.

Declaration of Generative AI and AI-assisted technologies in the writing process
During the preparation of this work the authors used ChatGPT-3.5 in order to improve language and readability. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

Ethics Statement
The study received ethical approval (Comité de protection des personnes Ile de France VII, 2022-A02460-43, December 12, 2022). Informed consent was obtained from all participants along with their questionnaire responses. The study protocol has been registered on ClinicalTrials.gov (NCT05684939).

Funding
The study was funded with the support of the National Institute of cancer (INCa) and Institut pour la recherche en santé publique (IReSP), grant number lNCa/lReSP-16651.

Data availability statement
Supporting data for the study will be made available upon request to the corresponding author.

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Supplement 1

French associations of cancer patients and French Facebook groups

Associations of patients	Number of individuals
ANAMACaP	1300
Vivre comme avant	100
ARTuR	1500
De l'air	100
Patients en réseau	5000
Laurette FUGAIN	600
Jeune et rose	800
Toujours femme	250
Rose Up	2315
Corasso	423
Odyssea	?
Vaincre le mélanome	?

Facebook groups	Number of followers
Ensemble contre le cancer	1893
Cancer du sein	726
Cancer de l'ovaire, parlons-en en toute liberté	473
Cancer alimentation et cie	1525
Le cancer et les proches	1259
La vie après le cancer	1645
Les roses : soutiens, infos et humour autour du cancer du sein	256
Cancer du rectum	385
Association Laurette FUGAIN	39391
Cancer / immunothérapie	412
Cancer du pancréas. Groupe de soutien	934
Vivre avec un cancer du poumon	414

Supplement 2

Questionnaires and scoring

Characteristics of cancer and treatments

Have you been or are you currently being treated for cancer?
- Yes, I am currently being treated for cancer.
- Yes, I have been treated for cancer (currently in remission and treatments completed).
- No

For what type of cancer are you or have you been treated?
- Bladder
- Blood (leukemia, myeloma)
- Breast
- Colorectal
- ENT (head, neck, tongue, mouth, lip, nose...)
- Gynecological (cervix, endometrium, ovary)
- Kidney
- Liver
- Nervous system (brain, spinal cord)
- Pancreas
- Prostate
- Pulmonary (lung, bronchus, pleura)
- Skin (melanoma...)
- Stomach
- Thyroid
- Other

When was the diagnosis of your cancer made? (approximate day)

What type of treatment have you already received (completed treatment)?
- Oral chemotherapy
- Injectable chemotherapy
- Hormone therapy
- Targeted therapy (oral)
- Immunotherapy
- Surgery
- Radiotherapy
- Hematopoietic stem cell transplant
- Other
- None

What type of treatment are you currently receiving?
- Oral chemotherapy
- Injectable chemotherapy
- Hormone therapy
- Targeted therapy (oral)
- Immunotherapy
- Surgery
- Radiotherapy
- Hematopoietic stem cell transplant
- Other
- None

In what type of facility have you been or are you being treated for your cancer?
- University hospital center
- Cancer center
- General hospital
- Private clinic
- Other

Use of psychoactive substance

Have you consumed alcohol (wine, beer, whiskey...) in the past year?
- Yes
- No

How often have you consumed alcohol (wine, beer, whiskey...)?
- At least once in the past year
- At least once in the past month
- At least once in the past week
- At least once a day

Have you smoked tobacco (cigarettes, pipe...) in the past year?
- Yes
- No

How often have you smoked tobacco (cigarettes, pipe...)?
- At least once in the past year
- At least once in the past month
- At least once in the past week
- At least once a day

Have you used an electronic cigarette in the past year?
- Yes
- No

How often have you used an electronic cigarette?
- At least once in the past year
- At least once in the past month
- At least once in the past week
- At least once a day

Have you consumed cannabidiol (CBD) in the past year?
- Yes
- No

How often have you consumed cannabidiol (CBD)?
- At least once in the past year
- At least once in the past month
- At least once in the past week
- At least once a day

Have you consumed cannabis in the past year?
- Yes
- No

How often have you consumed cannabis?
- At least once in the past year
- At least once in the past month
- At least once in the past week
- At least once a day

Brief Pain Inventory – short from

Every visual analogue scale (VAS) are rated from 0 (no pain / does not interfere) to 10 (pain as bad as you can imagine / completely interferes)

Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every- day kinds of pain today?
- Yes
- No

For how long have you had these pains? (number of months)

Which part(s) of your body is (are) painful? (open-ended question)

Move the cursor to the number that best describes the pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										pain as bad as you can imagine

Move the cursor to the number that best describes the pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										pain as bad as you can imagine

Move the cursor to the number that best describes the pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										pain as bad as you can imagine

Move the cursor to the number that best describes the pain right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										pain as bad as you can imagine

What treatments or medications are you receiving for your pain? (open-ended question)

Move the cursor to the number that describes how, during the last 24 hours, pain has interfered with your:

General activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

Walking ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

DN4 interview questionnaire (neuropathic pain)

Scoring of the DN4 interview is the sum of each answer (yes = 1 and no = 0). The maximum is 7 and the minimum 0.

Does the pain have one or more of the following characteristics?

Burning

- Yes
- No

Painful cold

- Yes
- No

Electric shocks

- Yes
- No

Is the pain associated with one or more of the following symptoms in the same area?

Tingling

- Yes
- No

Pins and needles

- Yes
- No

Numbness

- Yes
- No

Itching

- Yes
- No

Anxiety and depression
Hospital Anxiety and Depression Scale (HADS) questionnaire
For scoring see [1]

I feel tense or 'wound up':
- Most of the time
- A lot of the time
- From time to time, occasionally
- Not at all

I feel as if I am slowed down:
- Nearly all the time
- Very often
- Sometimes
- Not at all

I still enjoy the things I used to enjoy:
- Definitely as much
- Not quite so much
- Only a little
- Hardly at all

I get a sort of frightened feeling like 'butterflies' in the stomach:
- Not at all
- Occasionally
- Quite Often
- Very Often

I get a sort of frightened feeling as if something awful is about to happen:
- Very definitely and quite badly
- Yes, but not too badly
- A little, but it doesn't worry me
- Not at all

I have lost interest in my appearance:
- Definitely
- I don't take as much care as I should
- I may not take quite as much care
- I take just as much care as ever

I can laugh and see the funny side of things:
- As much as I always could
- Not quite so much now
- Definitely not so much now
- Not at all

I feel restless as I have to be on the move:
Very much indeed
Quite a lot
Not very much
Not at all

Worrying thoughts go through my mind:
- A great deal of the time
- A lot of the time
- From time to time, but not too often
- Only occasionally

I look forward with enjoyment to things:
- As much as I ever did
- Rather less than I used to
- Definitely less than I used to
- Hardly at all

I feel cheerful:
- Not at all
- Not often
- Sometimes
- Most of the time

I get sudden feelings of panic:
- Very often indeed
- Quite often
- Not very often
- Not at all

I can sit at ease and feel relaxed:
- Definitely
- Usually
- Not Often
- Not at all

I can enjoy a good book or radio or TV program:
- Often
- Sometimes
- Not often
- Very seldom

HRQoL and symptoms
QLQ-C30 questionnaire
For scoring see [2]

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?
- Not at all
- A little
- Quite a bit
- Very Much

Do you have any trouble taking a long walk?
- Not at all
- A little
- Quite a bit
- Very Much

Do you have any trouble taking a short walk outside of the house?
- Not at all
- A little
- Quite a bit
- Very Much

Do you need to stay in bed or a chair during the day?
- Not at all
- A little
- Quite a bit
- Very Much

During the past week
Do you need help with eating, dressing, washing yourself or using the toilet?
- Not at all
- A little
- Quite a bit
- Very Much

Were you limited in doing either your work or other daily activities?
- Not at all
- A little
- Quite a bit
- Very Much

Were you limited in pursuing your hobbies or other leisure time activities?
- Not at all
- A little
- Quite a bit
- Very Much

Were you short of breath?
- Not at all
- A little
- Quite a bit
- Very Much

Have you had pain?
- Not at all
- A little
- Quite a bit
- Very Much

Did you need to rest?
- Not at all
- A little
- Quite a bit
- Very Much

Have you had trouble sleeping?
- Not at all
- A little
- Quite a bit
- Very Much

Have you felt weak?
- Not at all
- A little
- Quite a bit
- Very Much

Have you lacked appetite?
- Not at all
- A little
- Quite a bit
- Very Much

Have you felt nauseated?
- Not at all
- A little
- Quite a bit
- Very Much

Have you vomited?
- Not at all
- A little
- Quite a bit
- Very Much

Have you been constipated?
- Not at all
- A little
- Quite a bit
- Very Much

Were you tired?
- Not at all
- A little
- Quite a bit
- Very Much

Did pain interfere with your daily activities?
- Not at all
- A little
- Quite a bit
- Very Much

Have you had difficulty in concentrating on things, like reading a newspaper or watching television?
- Not at all
- A little
- Quite a bit
- Very Much

Did you feel tense?
- Not at all
- A little
- Quite a bit
- Very Much

Did you worry?
- Not at all
- A little
- Quite a bit
- Very Much

Did you feel irritable?
- Not at all
- A little
- Quite a bit
- Very Much

Did you feel depressed?
- Not at all
- A little
- Quite a bit
- Very Much

Have you had difficulty remembering things?
- Not at all
- A little
- Quite a bit
- Very Much

Has your physical condition or medical treatment interfered with your family life?
- Not at all
- A little
- Quite a bit
- Very Much

Has your physical condition or medical treatment interfered with your social activities?
- Not at all
- A little
- Quite a bit
- Very Much

Has your physical condition or medical treatment caused you financial difficulties?
- Not at all
- A little
- Quite a bit
- Very Much

For the following questions please circle the number between 1 and 7 that best applies to you

How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Deprivation
EPICES questionnaire
For scoring see [3]

Do you sometimes meet with a social worker (welfare worker, educator)?
- Yes
- No

Do you have complementary health insurance (mutual insurance)?
- Yes
- No

Do you live as a couple?
- Yes
- No

Are you a homeowner or will you be one in the near future?
- Yes
- No

Are there periods in the month when you have real financial difficulties in facing you needs (food, rent, electricity)?
- Yes
- No

Have you participated in any sports activities in the last 12 months?
- Yes
- No

Have you gone to any shows (cinema, theatre) in the last 12 months?
- Yes
- No

Have you gone on holiday during the past 12 months?
- Yes
- No

Have you seen any family members in the past six months (other than your parents or children)?
- Yes
- No

Did you have difficulties (financial, family or health), is there anyone around you who could take you in for a few days?
- Yes
- No

Did you have difficulties (financial, family or health), is there anyone around you who could help you financially (material aid such as lending you money)?
- Yes
- No

Individual characteristics

What is your age?

Gender
- Male
- Female
- Non-binary

What is your height (in cm)?

What is your weight (in kg)?

In which department do you live?

In what type of residential area do you live? (Number of inhabitants in your municipality)
- Equal to or more than 50,000 inhabitants
- Between 5,000 and 49,999 inhabitants
- Between 500 and 4,999 inhabitants
- Less than 500 inhabitants

Socio-professional status (INSEE)
- Farmers and farm managers
- Craftsmen
- Shopkeepers and business owners
- Executives and higher intellectual professions
- Intermediate professions
- Employees
- Workers
- Retirees
- Other individuals without professional activity

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