Underprescription of Step III Opioids in French Cancer Survivors With Chronic Pain: A Call for Integrated Early Palliative Care in Oncology

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Under-prescription of Step III opioids in French cancer survivors with chronic pain: a call for integrated early palliative care in oncology

Running title: opioids prescription in survivors with chronic pain

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Abstract

Context: Chronic pain (CP) is a major concern in cancer survivors. Often underreported by patients, it is both under-assessed and undertreated by care providers.

Objectives: To assess CP prevalence and related treatment in cancer survivors five years after diagnosis; to identify factors associated with prescribing opioids among survivors with CP, focusing on access to palliative care (PC).

Methods: In 2015-2016, we interviewed 4,174 French patients diagnosed with cancer five years previously. Combining patient and clinical reported outcomes together with medico-administrative data, we studied factors associated with Step II and Step III opioid prescription in cancer survivors with CP. We performed multinomial logistic regression adjusting for various covariates, including self-reported health status variables and inpatient PC.

Results: Five years after cancer diagnosis, 63.5% of the respondents reported current chronic pain (CP) (i.e., pain ≥ 3 months). Of these, 64.6% and 14.4% were prescribed at least one Step II or Step III opioid, respectively. Only 1.9% had had inpatient PC since diagnosis. After adjustment for age, gender, clinical and self-reported variables, we found that the latter were more likely to receive Step III opioids (adjusted Relative Risk ratio: 5.33; 95% CI: 1.15, 24.58).

Conclusions: This study showed a high prevalence of CP five years after cancer diagnosis. Step III opioids were underprescribed but positively associated with inpatient PC. PC access in France remains limited, especially among cancer survivors. Integrating PC in oncology is essential to provide the best cancer-related symptoms management.

Keys messages: This article provides chronic pain prevalence and its related treatment among survivors, five years after a diagnosis. The findings show high prevalence rate of this symptom

and its association with other symptoms such as depression and poorer QOL, thus requiring multidisciplinary care such as that offered by palliative care.

Keywords: chronic pain, cancer, opioids, health insurance data, inpatient palliative care

Introduction

Pain is one of the most common cancer symptoms (1–8). Rarely occurring alone, it is mostly associated with fatigue, depression, anxiety and sleep disorders (9–12). Chronic pain, defined as persistent pain lasting longer than three months (13), is common among cancer survivors and may greatly impair their well-being and quality of life (QOL) (14–16). This type of pain may precede cancer diagnosis, may be caused by ongoing active disease, may be induced by anticancer treatments and procedures, or may be caused by cancer sequelae or its treatment (17,18).

The treatment of pain is a principal component of supportive care that should continue beyond the initial treatment of a disease (19,20). It includes psychological and social support, symptom management and palliative care (PC). The latter offers a patient-centered holistic approach and aims to ensure comfort and the best possible QOL, physically, psychologically, spiritually and socially (21). It takes into account patients' and relatives' specific needs, irrespective of age, of disease type and stage (22–26). Contrary to popular belief, PC could be integrated earlier in conjunction with curative treatment. Early PC access PC can reduce the occurrence of symptoms, including pain. One study reported that early access was associated with a 31% reduction in the risk of severe cancer pain (27).

Current guidelines and gold standards for cancer pain management, established by the World Health Organization (WHO) (28), comprise an analgesic three-step "ladder": non-opioid analgesics (Step I) for mild pain, weak opioids (Step II) for moderate pain, and strong opioids (Step III) for intense pain. Other drugs called adjuvant analgesics can be added when clinically required at any stage of the WHO ladder (29,30). Studies show that properly using this ladder should lead to effective pain relief for the majority of cancer patients at all disease stages

(31,32). Other updated versions of this ladder have been found in the literature. On the one hand, some authors have proposed the abolition of the WHO ladder' step II (weak opioids) in favor of the introduction of low doses of step III opioids (33). On the other hand, other authors have proposed a fourth step comprising interventional strategies intended to manage intense to very intense pain (i.e. nerve blocks, spinal administration of local anesthetics and opioids.) (34).

Despite several guidelines for cancer pain management, including those of the WHO (28,35,36), undertreatment is well documented and may concern up to 40% of patients (3,32,37–41). Undertreatment of pain may be explained by under-reporting by patients and under-assessment by doctors. Barriers to reporting include beliefs and meanings that each patient assigns to the experienced pain, together with his/her reluctance to initiate opioids (step III opioids especially) and PC more generally (25,42). The latter reason can also be attributed to care providers.

Given the complexity of pain in people diagnosed with cancer, in particular chronic pain (CP), its frequent association with other symptoms and its impact on QOL, pain management and the relief of psychological, social and spiritual suffering - as described in the concept of "total pain" (43) - could be enhanced by introducing PC early in the disease trajectory.

In France, little is known about the prevalence of chronic pain and its treatment five years after a cancer diagnosis. Accordingly, the aim of this study, using data from the French national survey VICAN (VIe après le CANcer) (44), was to: i) provide the prevalence of CP and related treatment in cancer survivors, five years after diagnosis, ii) study factors associated with opioid prescription in survivors with CP, with a specific focus on the impact of inpatient PC.

Methods

Study design: The VICAN survey

The VICAN survey assessed factors that may adversely affect or enhance the QOL of cancer survivors 2 and 5 years after diagnosis. The survey included adult survivors with primo-cancer diagnosed between January 2010 and December 2011, aged between 18 and 82 years old at diagnosis, still alive 5 years later, and insured under one of France's three main health insurance schemes. The survey was restricted to 12 primo-cancer sites, accounting for 88% of global cancer incidence in France in 2012: breast, lung, colorectal, prostate, upper aerodigestive tract, bladder, kidney, cervical, endometrial, thyroid, Non-Hodgkin lymphoma, and melanoma. A detailed description of the methodology and data collection were published elsewhere (44).

Data were collected from telephone interviews with patients, 2 and 5 years after diagnosis. The first questionnaire (VICAN 2) was administered in 2012 to 4,347 cancer survivors. The second questionnaire (VICAN 5) was administered in 2015 and 2016 to 4,174 individuals. The latter sample included 2,009 individuals who answered VICAN 2 in 2012 (attrition rate of approximately 54%).

The study methodology was approved by the following national ethics commissions: the CCTIRS (Consultative Committee on the Treatment of Health-related data, study registered under no. 11-143), the ISP (Institute of Public Health, study registered under no C11-63) and authorized by the CNIL (French Commission on Individual Data Protection and Public Liberties, study registered under no. 911290). With regard to personal responses and information provided, confidentiality was ensured through data anonymization.

Data sources

Patient questionnaires were complemented by medico-administrative data collected from the French national health insurance databases (Système National l'Information Interrégimes de l'Assurance Maladie, SNIIRAM). Patient questionnaires covered several areas such as socio-demographic and socio-economic status, treatments received and perceived adverse sequalae. Finally, data on routine medical prescriptions and hospital records were collected from the SNIIRAM.

Study population

Overall, 4,174 individuals participated in VICAN 5. For the present work, the study population was limited to respondents who answered questions concerning pain and for whom medico-administrative data were available (i.e. N=4,093).

Indicator measures

Pain measures

In the VICAN 5 survey, recent pain experience was assessed using a panel of questions including validated tool for neuropathic pain screening. Pain assessment combined both subjective (self-reported pain) and objective (SNIIRAM) data. The questionnaire included items on: 1) pain experience (during the previous two weeks, (i.e. yes or no)), 2) its intensity (extremely intense, very intense, quite intense, neither moderate nor intense, quite moderate, very moderate and extremely moderate), and its impact on daily activity (the question being phrased so as to measure respondents' level of agreement that it had in fact an impact: "completely agree", "mostly agree", "do not agree or disagree" , "mostly disagree" "completely disagree"). To screen for CP, respondents who self-reported pain during the previous two weeks were asked how long they had been in pain (<3 months, ≥ 3 months but < 6 months, and ≥ 6 months). The

usual 3-month threshold was used to define chronic pain (45). Neuropathic pain was assessed using the validated seven-item format of the French DN4 questionnaire (46). Other questions dealt with the use of non-conventional medicine such as acupuncture and hypnosis.

Opioids and adjuvant analgesics

For each respondent, we retrieved SNIIRAM data on dispensed drugs in community pharmacies from January 2009 to December 2016 using the Anatomical Therapeutic Chemical (ATC) Classification (47) as follows:

- Step II opioids: codeine (ATC: N02AA59, N02AA79), dextropropoxyphene (ATC: N02AC04, N02AC54, N02AC74), and tramadol (ATC: N02AX02, N02AX52).
- Step III opioids: morphine (ATC: N02AA01), fentanyl (ATC: N02AB03), oxycodone (ATC: N02AA55, N02AA05), buprenorphine (ATC: N02AE01), and nalbuphine (ATC: N02AF02).
- Psychotropic drugs: Anxiolytics (ATC: N05B), hypnotics (ATC: N05CD, N05CF, and NO5CX), and antipsychotics (ATC: N05A).

These data allowed us to construct binary variables for annual prescriptions of each drug category (Step II opioids, Step III opioids, psychotropic drugs). Another variable combining prescription of Step II and Step III opioids for each year and for the period between diagnosis and the survey (i.e., “no opioid prescription”, “Step II opioid prescription”, and “Step III opioid prescription”) was also created. It constituted our dependent variable.

Other measurements

In addition to pain, the patient questionnaire evaluated QOL using the SF-12 (48), and anxiety and depression using the HAD scale (49). Cancer-related fatigue was assessed from a score between 0 and 100 evaluated using three items from the EORTC QLQ scale (50). A threshold score of 40 defined a clinically significant (51). An individual comorbidity score was calculated

149 from the weighted average of chronic diseases identified over a period of one year (52). Cancer
150 treatment information between 2009 and 2016 (chemotherapy, radiotherapy), in addition to
151 information on metastases, was extracted from the SNIIRAM. We also used the medical
152 information system program (Programme de Médicalisation des Systèmes d'Information, PMSI)
153 database to extract information on hospital stays for PC. More specifically, inpatient PC stays
154 were identified using the ICD-10 PC code (Z.515) as primary diagnosis or related diagnosis.
155 Finally, occupational status was assessed with a ternary variable (Tradesperson/Employee,
156 supervisor and unemployed), which was created *ex post* from job characteristics reported in the
157 questionnaire.

158 ## Analyses

159 ### *Weighting method*

160 Weighting coefficients were calculated and applied to ensure the sample was representative of
161 the whole target population (i.e., French adults diagnosed with cancer (for the 12 cancer sites
162 studied) in 2010/2011, insured in one of the three main French health insurance schemes and
163 alive 5 years after diagnosis). Weights were constructed such that the sample structure for
164 these characteristics was comparable to that observed in the sampling frame (44,53).

165 ### *Statistical analyses*

166 Data were summarized using percentages for categorical variables and means (SD) for
167 continuous variables. First, we compared the distribution of respondents' sociodemographic
168 and medical characteristics between those with and without CP. Second, we limited the
169 analysis to survivors with CP in order to study variables associated with opioid prescription for
170 CP since diagnosis. Chi-squared tests, and *t* tests were used in univariate analyses. To identify
171 factors independently associated with opioid prescription since diagnosis (differentiating Step II

from Step III opioids), we performed multinomial logistic regression, adjusting for self-reported health status variables at the time of the survey, and for inpatient PC. All analyses were performed using STATA version 12 (STATA Corp, College Station, TX).

Results

Baseline characteristics

Of the 4,174 cancer survivors surveyed in VICAN 5, 4,093 (98.3%) answered questions concerning pain. Among the latter, 39.5% were aged 18-49 at diagnosis and 62.6% were women. Breast cancer accounted for almost half of our sample, while cervical and endometrial cancers were the least frequent.

Prevalence and variables associated with CP - Univariate analyses

The majority of survivors (73.4%) reported having experienced pain of some type during the previous two weeks. In 86.5% of cases, pain was chronic (i.e., ≥ 3 months). Overall, CP prevalence was 63.5% in our entire study population, ranging from 50.1 to 72.1% for bladder and breast cancer, respectively (Table 1).

CP was significantly more frequent in women diagnosed with breast cancer, in younger respondents, in those with a low education level and in those with neuropathic pain. Respondents who reported a clinically significant level of anxiety, depression and/or fatigue, those with a poorer physical and mental quality of life, and those with increased comorbidities were all more likely to experience CP (Table 1).

Variables associated with opioid prescription in cancer survivors with CP - Univariate analyses

Given the high prevalence of CP in respondents with other symptoms such as anxiety, depression and fatigue, and the significant need for PC in patients with CP compared with the

rest of the study population, we decided to limit the analyses to cancer survivors with CP, in order to investigate the relationship between opioid prescription in survivors with CP and PC access since diagnosis.

Among the 2,578 respondents with CP, 68.1% were women and nearly 41.7% were aged 18-49 years old. Moreover, one cancer survivor with CP in four reported having experienced intense pain in the last 15 days preceding the survey and only 1.9% had had inpatient PC at least once since diagnosis (Table 2, 2nd column) .A description of this sub-sample is provided in Table 2 where three specific groups are described. In the first group, 21.0% had no opioid prescription since diagnosis. The second group (64.6%) has been prescribed at least one Step II opioid since diagnosis (i.e. exclusively Step II opioid), while the third group (14.4%) has been prescribed at least one Step III opioid since diagnosis (4.2% in survey year).

When comparing the second and third groups consecutively with the first group 1 (Table 2), we found in both cases that opioid prescription was more frequent in respondents with neuropathic pain, in those reporting depression, fatigue, and in those with lower scores of physical and mental QOL. In addition, survivors who have experienced moderate pain in the last 15 days preceding the survey were more likely to be prescribed step II opioids, while those who have experienced intense pain were more likely to be prescribed step III opioids. Moreover, in both cases, survivors who underwent chemotherapy more frequently and those who had been prescribed psychotropic drugs were more likely to be prescribed opioids. With respect to participants' socio-demographic background, opioid prescription was more frequent in respondents with a lower education level. No significant gender or age difference was found for opioid prescription.

Compared with no opioid prescription, Step III opioid prescription was significantly more frequent in unemployed respondents (18.0% versus 9.3% among those with executive jobs and 9.3 % for supervisors, p<0.001), respondents with anxiety (15.4% versus 13.1% among those without anxiety, p=0.02) and in those with metastases (45.0% versus 11.4% among those without metastasis, p<0.001). Furthermore, Step III opioid prescription was more frequent among respondents who underwent radiotherapy (17.1% versus 10.1% in those who did not, p<0.001)), and among those who had had inpatient PC (67.3% versus 13.4% in those who did not, p<0.001). For those who had had PC and were prescribed a Step III opioid, prescription occurred either in the same year as PC or the following year.

Moreover, Figure 1 shows significant differences between cancer sites and opioid prescription in survivors with CP. More specifically, Step III opioid prescription was most frequent for upper aerodigestive tract cancer (48.5%), followed by lung cancer (35.3%), and least frequent for melanoma (6.5%).

Factors associated with opioid prescription in cancer survivors with CP- Multivariable analyses

After adjustment for age, gender, and occupational status at the time of the survey, a multivariable multinomial logistic regression (Table 3) showed that being aged 65-74 years old at diagnosis, having a poorer physical QOL, having fewer comorbidities at the time of the survey, and having been prescribed fewer psychotropic drugs since diagnosis, were all negatively associated with Step II and Step III opioid prescription.

Factors positively associated with Step III opioid prescription included being unemployed five years after diagnosis, reporting depressive symptoms, having metastases, having undergone radiotherapy or chemotherapy, and having had inpatient PC since diagnosis. Moreover, several

240 factors were negatively associated with Step III opioid prescription including being aged 50-64,
241 65-74 or 75-82 years old and being a woman.

242 ## Discussion

243 Five years after cancer diagnosis, CP was reported by two thirds of respondents (63.5%). CP was
244 more frequent in younger patients and in women, and was associated with a multitude of other
245 symptoms such as anxiety, depression, fatigue and poorer physical and mental QOL. Among
246 those with CP, access to opioids - especially Step III opioids - was very limited and differed
247 according to patients' sociodemographic and medical characteristics. More specifically, men,
248 younger respondents, people with metastases, respondents with a poorer physical QOL, people
249 with depression, individuals who had other comorbidities, and those who underwent
250 chemotherapy or radiotherapy since diagnosis were the populations most likely to have been
251 prescribed a Step III opioid since diagnosis. Furthermore, we found that benefiting from
252 inpatient PC was associated with Step III opioid prescription.

253 To the best of our knowledge, this is the first study to explore CP prevalence, associated
254 symptoms and related treatment, and more specifically, to study the association between
255 opioid prescription in survivors with CP and inpatient PC, in a nationally representative sample
256 of survivors for a range of cancer sites. Prevalence and characteristics of pain five years after
257 diagnosis were measured using patient reported outcomes (PRO), since pain is subjective.
258 Moreover, the SNIIRAM data allowed us to collect objective and exhaustive data on drug
259 prescription since diagnosis, and therefore to overcome possible biases linked to self-reporting
260 in the study questionnaire.

261 Despite our several data sources, several limitations should be considered when interpreting
262 the results. First, pain for which opioids were prescribed was self-reported but not clinically

diagnosed. In addition, the SNIIRAM opioid-prescribing data are only an indirect indicator of pain management history. It is therefore possible that the pain for which opioids were prescribed was not cancer related, especially since SNIIRAM data do not provide information on medical indications. In order to overcome this bias, we chose to limit our analyses to patients with CP, assuming that when CP occurs in cancer patients, it may have a higher probability of being related to cancer or cancer-related treatments than to other conditions. Another limitation is that our survey did not include questions about patients' preferences regarding opioids. The absence of these data did not allow us to assess the source of a possible under-treatment rather related to the reluctance of patients to seek or use these drugs than a problem of under-prescribing by doctors. Moreover, we did not account for opioids prescription prior to the cancer diagnosis. However, a previous study showed that this prescription , and in particular those of step III opioids, was very limited (54). Finally, we did not consider hospital stays occurring in PC beds in acute care units, or admissions in PC inpatient units. This may have led to an underestimation of PC access in this study.

Pain has been recognized as one of the most frequent cancer-related symptoms, with high prevalence rates from diagnosis to death (1,2,6,55). A recent systematic review indicated prevalence ranged from 40% to 66% depending on cancer stage and treatment (2). In our study, at five years after cancer diagnosis, more than three-quarters of our study sample reported pain of some type during the 15 days preceding the survey. Two-thirds of our study population (63.5%) reported CP, ranging from 50.1% to 72.1% depending on the primo-cancer site. Higher than those from existing studies (41,56), these prevalence rates - especially for CP – indicate that pain remains an important issue in cancer survivors long after diagnosis. Furthermore, these high CP prevalence rates raise questions about the true utility of various cancer, pain and

PC governmental programs and recommendations implemented in France over the last 15 years.

Previous studies have shown that chronic cancer pain could affect the global QOL of cancer survivors, influencing fatigue, anxiety, depression and daily activities (14,15), and, our results seem to reflect this. CP in our study was more frequent in respondents who reported more comorbidities, poorer physical and mental QOL scores, more depression, more anxiety, more fatigue, and among those who reported that their pain forced them to limit their daily activities, confirming the weight and the major impact of CP on cancer survivors' overall QOL, even years after diagnosis. These physical, psychological and social effects, together with the spiritual impact, are bi-directional and cumulative, combining to give an overall pain profile described as Total Pain (43), which requires global, multidisciplinary, holistic and patient-centered management.

Our findings showed a significant relationship between CP and 1) prescription of pharmacological options such as opioids and psychotropic drugs and, 2) the use of non-pharmacological options such as acupuncture, hypnosis and osteopathy. These findings were expected given the heavier burden of CP - with and without neuropathic pain - and the higher prevalence of associated symptoms in these individuals. However, we observed that only 14.4% of survivors with CP had been prescribed a Step III opioid since diagnosis (4.2% in the year of the survey), which is lower than the percentage of other drugs prescribed (sometimes as a substitute for Step III opioids), for example psychotropic drugs (73.2%). This under-prescription of Step III opioids, despite the high rate of intense (25.2%) and moderate to intense pain (9.2%) observed in our study, may have several explanations. Reluctance of health care providers to prescribe, and of patients and their families to adhere to these opioids, as well as the fear of

dependence and other side effects are the barriers reported most often in the literature (57–62). Moreover, we found that the presence of metastasis was associated with Step III opioid prescription. This finding may partially explain the under-prescription of Step III opioids in our study. It is possible that other drugs, such as adjuvant analgesics or weak opioids, may be preferred to treat those with early-stage cancer, while Step III opioids may be prescribed more frequently for advanced or terminal cancer patients (63,64). In addition, cancer-related treatments, such as chemotherapy, would be one of the leading causes of iatrogenic pain and painful neuropathy for example, which may partly explain why survivors who undergo chemotherapy have been prescribed more opioids (step III in particular) (35).

Previous studies have shown that access to opioids may depend on patients' socio-demographic and medical characteristics. For example, older patients and women are less likely to be prescribed opioids and therefore more likely to be undertreated for their cancer-related pain compared with younger patients and men (65–69). In line with these studies, age and gender were significantly associated with opioid prescription, especially Step III opioids. The probability of being prescribed Step III opioids decreased with age. This may seem logical since older people tend to report cancer pain less often than younger people (70), something also observed in our study. However, this may not reflect the possibility that older people may be the most exposed to experience pain but prefer not to report it, leading to under-evaluation and therefore under-treatment of that pain. Women in our study were more likely than men to report CP, something reported in at least one other study (15) , but less likely to be prescribed Step III opioids. The latter finding has already been reported in several studies and underlines the problem of under-treatment of cancer-related pain in this population (65,69). Moreover, our study showed a significant association between step III opioids prescription and access to PC among survivors with chronic pain. Indeed, one previous study have shown that people who

have more invasive and metastatic cancers and who undergo more frequently adjuvant cancer related-treatments such as chemotherapy and radiotherapy are the most likely to have an inpatient PC access (71).

Although very limited in our study (1.6% in the overall study population and 1.9% in cancer survivors with CP), inpatient PC care since diagnosis was positively associated with opioid prescription (Step III in particular). Given the increasing number of cancer survivors in France (i.e. 3 million in 2015), and the greater burden of the disease and its associated symptoms, including pain right through the disease trajectory, ensuring the best QOL through multimodal and multidisciplinary approaches remains a challenge for these survivors. Several studies have shown that integrating PC early in the disease trajectory in conjunction with curative treatment can enhance symptoms management, QOL and even survival (72,73). Our findings regarding the prevalence of inpatient PC among survivors at five years following diagnosis, suggest that common misconceptions about who should access this type of care and when, are still widespread, and may deprive survivors of adequate relief of physical and psychological symptoms (25).

Conclusion

Our study showed a high prevalence of CP in cancer survivors possibly due to an undertreatment by Step III opioids. We found also that there is limited access to PC. It is possible that we slightly underestimated this. Having said that, PC access was associated with an increased likelihood of Step III opioid prescription in cancer survivors with CP. These findings suggest the need to encourage greater Step III opioid prescription in this population, not just in end-of-life situations. Finally, early access to PC for cancer survivors should be urgently

promoted to ensure access to Step III opioids for better CP management, irrespective of disease stage.

Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

The study methodology was approved by the following national ethics commissions: the CCTIRS (Consultative Committee on the Treatment of Health-related data, study registered under no. 11-143), the ISP (Institute of Public Health, study registered under no C11-63) and authorized by the CNIL (French Commission on Individual Data Protection and Public Liberties, study registered under no. 911290). With regard to personal responses and information provided, confidentiality was ensured through data anonymization.

Informed consent

Informed consent was obtained from all individual participants included in the VICAN study.

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Author Contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be responsible for all aspects of the work.

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559 Table 1. Prevalence of chronic pain according to cancer survivor (5-year) study population

560 characteristics (National VICAN survey, N = 4,093)

	Total	No chronic pain [d]	Chronic pain, five years after diagnosis [d,f]
All	100%	36.5%	63.5%
	Column (%)	Row (%)	
Socio-demographic characteristics			
Age (years) [a]			
18-49	39.5	33.0	67.0 ***
50-64	33.0	35.9	64.1
65-74	21.2	42.1	57.9
75-82	6.3	42.9	57.1
Gender			
Men	37.4	45.8	54.2 ***
Women	62.6	30.9	69.1
Education level [b]			
< High school diploma	50.5	34.4	65.6 *
≥ High school diploma	49.5	38.6	61.4
Occupational status [b]			
Tradesperson/Employee	23.2	32.6	67.4 *
Supervisor	18.6	40.0	60.0
Unemployed	58.2	36.8	63.2

Medical characteristics			
Cancer site			
Breast	41.4	27.9	72.1 ***
Lung	3.6	31.2	68.8
Rectum/colon	10.0	43.7	56.3
Prostate	16.3	48.9	51.1
Aero-digestive tract	4.6	34.1	65.9
Bladder	3.2	49.9	50.1
Kidney	3.6	38.9	61.1
Thyroid	5.2	36.5	63.5
Non-Hodgkin lymphoma	3.8	43.8	56.2
Melanoma	4.9	44.6	55.4
Cervical	2.2	34.0	66.0
Endometrial	1.2	35.6	64.4
Neuropathic pain [b]			
No	26.5	100	0 ***
Negative screening (DN4)	47.3	17.0	83.0
Positive screening (DN4)	26.2	7.2	92.8
Limited daily activity due to pain [b, e]			
Disagree	60.1	49.9	50.1 ***
Agree	39.9	16.7	83.3
Depression [b]			
No	82.8	39.4	60.6 ***

Yes (doubtful or certain)	17.2	21.9	78.1
Anxiety [b]			
No	53.1	45.8	54.2 ***
Yes (doubtful or certain)	46.9	25.8	74.2
Fatigue (clinically significant score) [b]			
No	51.5	49.2	51.8 ***
Yes	48.5	22.9	77.1
Physical quality of life [b]			
Mean [Standard Deviation]	45.3 (9.9)	49.9 (8.6)	42.6 (9.6) ***
Mental quality of life [b]			
Mean [Standard Deviation]	45.2 (10.5)	48.3 (9.6)	43.4 (10.5) ***
Comorbidities [b]			
Mean [Standard Deviation]	0.7 (0.5)	0.6 (0.5)	0.7 (0.5) ***
Radiotherapy [c]			
No	42.5	41.8	58.2 ***
Yes	57.5	32.6	67.4
Chemotherapy [c]			
No	54.9	40.9	59.1 ***
Yes	45.1	31.1	48.9
Inpatient PC [c]			
No	98.4	36.7	63.3 ns
Yes	1.6	25.5	74.5
Step II opioid prescription [c]			

No	24.8	45.0	55.0 ***
Yes	75.2	33.7	66.3
Step III opioid prescription [c]			
No	87.9	38.1	61.9 ***
Yes	12.1	24.5	75.5
Opioid prescription [c]			
No opioid prescription	24.4	45.3	54.7 ***
Step II opioid prescription	63.5	35.4	64.6
Step III opioid prescription	12.1	24.5	75.5
Opioid prescription [b]			
No opioid prescription	73.9	38.7	61.3 ***
Step II opioid prescription	22.9	32.0	68.0
Step III opioid prescription	3.2	17.1	82.9
Psychotropic drug prescription [c]			
No	31.4	45.9	54.1 ***
Yes	68.6	32.2	67.8
Hypnosis [c]			
No	97.0	37.1	62.9 **
Yes	3.0	20.8	79.2
Acupuncture [c]			
No	89.7	38.3	61.7 ***
Yes	10.3	21.3	78.7
Osteopathy [c]			

No	73.4	41.1	58.9 ***
Yes	26.6	23.8	76.2

[a] At diagnosis

[b] Five years after diagnosis

[c] Since diagnosis (i.e., between diagnosis and the year of the survey) .

[d] The modalities of the two questions regarding pain prevalence and duration were merged to construct a single variable coded "**No Chronic pain**" which combined "No pain of any type in the previous 15 days" with "pain of some type in the previous 15 days but experienced for <3 months", and "**Chronic pain**" which combined pain experienced for "≥ 3 months but < 6 months", and "≥ 6 months"

[e] For the question on the impact of pain on daily activities, the items "mostly agree" and completely agree" were merged into the category "agree", and the categories, "neither agree nor disagree", "mostly disagree" and "completely disagree" were merged into the category "disagree".

[f] ***, **, *, significant at p < 0,001, p < 0,01, p < 0,05 (X^2 test or Student's t test)

572 Table 2. Variables associated with opioid prescription among cancer survivors with chronic pain

573 (National VICAN survey, N = 2,578)

	Total	No prescription [c] (ref.)	Step II opioid prescription [c,e]	Step III opioid prescription [c,e]
	Column (%)	Row (%)		
All (%, row)	100	21.0	64.6	14.4
Socio-demographic characteristics				
Age (years) [a]				
18-49	41.7	19.3	66.3 ns	14.4 ns
50-64	33.4	20.8	62.6	16.6
65-74	19.3	25.5	63.4	11.1
75-82	5.6	18.4	68.0	13.6
Gender				
Men	31.9	21.3	62.1 ns	16.6 ns
Women	68.1	20.8	65.8	13.4
Education level [b]				
< High-school diploma	52.2	18.0	65.5 **	16.5 ***
≥ High-school diploma	47.8	24.2	63.7	12.1
Occupational status [b]				
Tradesperson/Employee	24.6	20.7	70.0 ns	9.3 ***

Supervisor	17.6	21.8	68.9	9.3
Unemployed	57.8	20.8	61.2	18.0
Medical characteristics				
Neuropathic pain [b]				
Negative screening (DN4)	61.8	24.0	63.3 ***	12.7 ***
Positive screening (DN4)	38.2	16.2	66.7	17.1
Experienced pain intensity [b, d]				
Intense	25.2	13.0	63.9 **	23.1 ***
Neither intense nor moderate	9.2	24.4	57.6	18.0
Moderate	65.6	23.3	66.1	10.6
Limited daily activity due to pain [b]				
Disagree	47.5	26.0	65.6 ***	8.4 ***
Agree	52.5	16.6	63.8	19.6
Depression [b]				
No	78.9	23.1	65.3 **	11.6 ***
Yes (doubtful or certain)	21.1	12.8	62.7	24.5
Anxiety [b]				
No	45.3	23.2	63.7 ns	13.1*
Yes (doubtful or certain)	54.7	19.1	65.5	15.4
Fatigue (clinically significant score) [b]				

No	41.2	26.5	63.9 ***	9.6 ***
Yes	58.8	17.2	65.1	17.7
Physical quality of life [b]				
Mean [Standard Deviation]	42.6 (9.6)	45.5 [8.6]	42.9 [9.3] ***	37.3 [10.9] ***
Mental quality of life [b]				
Mean [Standard Deviation]	43.4 (10.5)	45.1 [9.6]	43.4 [10.6] **	40.8 [11.3] ***
Comorbidities [b]				
Mean [Standard Deviation]	0.7 (0.5)	0.5 [0.4]	0.7 [0.5] ***	1.0 [0.6] ***
Metastases [c]				
No	91.1	22.2	66.4 ns	11.4 ***
Yes	8.9	9.1	45.9	45.0
Radiotherapy [c]				
No	38.9	22.3	67.6 ns	10.1 ***
Yes	61.1	20.2	62.7	17.1
Chemotherapy [c]				
No	51.1	24.6	67.1 *	8.3 ***
Yes	48.9	17.2	62.1	20.7
Inpatient palliative care [c]				
No	98.1	21.3	65.3 ns	13.4 ***
Yes	1.9	3.5	29.2	67.3
Step II opioids prescription [c]				
No	21.5	97.6	0 ***	2.4 ***
Yes	78.5	0	82.3	17.7

Psychotropic drug prescription [c]				
No	26.8	35.8	59.6 ***	4.6 ***
Yes	73.2	15.6	66.4	18.0

[a] At diagnosis

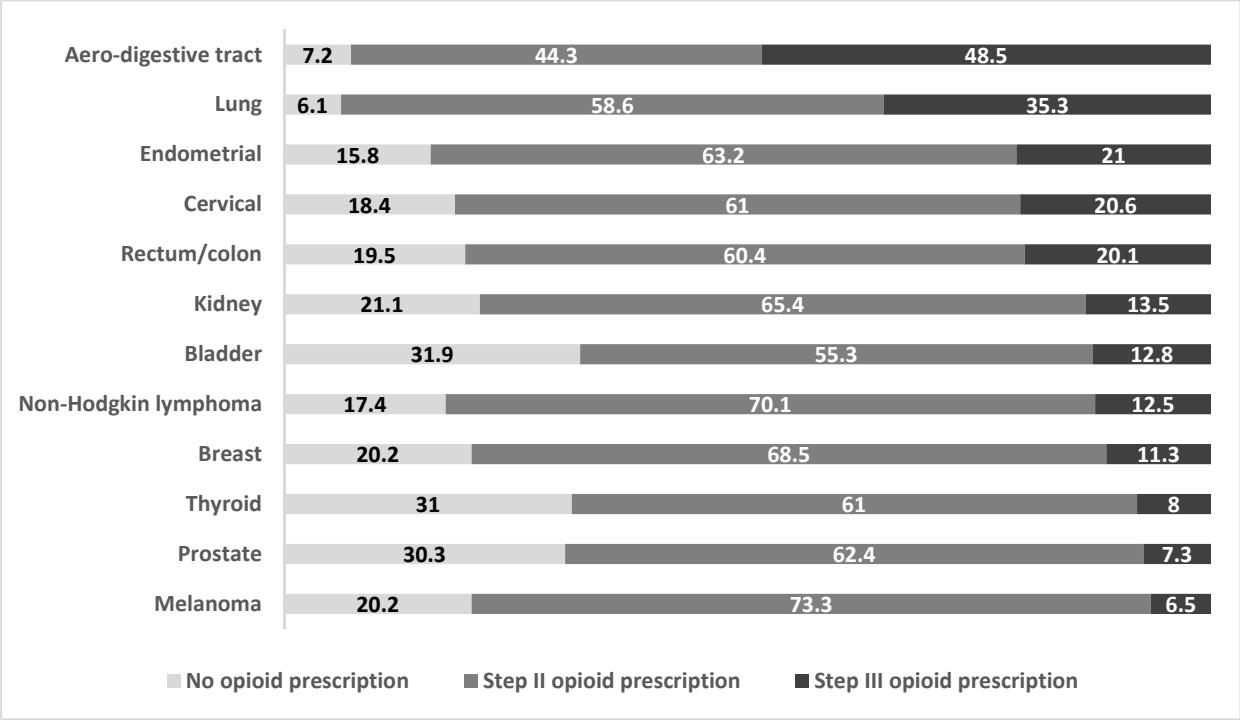
[b] Five years after diagnosis

[c] Since diagnosis (between diagnosis and the year of the survey)

[d] For pain intensity variable, the categories “extremely intense”, “very intense”, “quite intense”, were merged into the category “intense”, and the categories “quite moderate”, “very moderate” and “extremely moderate” were merged into the category “moderate”.

[e] ***, **, *, significant at p < 0,001, p < 0,01, p < 0,05 (chi-square test or Student's t test)

Figure 1. Opioid prescription among cancer survivors with chronic pain according to cancer site. (National VICAN survey, N = 2,578) (Row, %) (Chi-square test, P<0.001)



583 Table 3. Factors associated with opioid prescription among cancer survivors with chronic pain

584 using multinomial logistic regression (National VICAN survey, N=2,548)

	Step II opioid prescription [c, d]	**Step III opioid prescription** [c, d]
	(Adjusted Relative Risk Ratio [95% CI]) [d,e,f]	
Socio-demographic characteristics		
Age (years) [a] **(ref. 18-49 years)**		
50-64	0.81 [0.61,1.07]	0.64 [0.43,0.94] *
65-74	0.46 [0.32,0.67] ***	0.25 [0.15,0.42] ***
75-82	0.71 [0.40,1.24]	0.34 [0.16, 0.75] **
Gender (ref. Men)		
Women	0.80 [0.63,1.03]	0.48 [0.35,0.68] ***
Occupational status [b] **(ref. Tradesperson/Employee)**		
Supervisor	0.97 [0.70,1.33]	1.04 [0.63,1.71]
Unemployed	0.87 [0.64,1.19]	1.70 [1.10,2.64] *
Medical characteristics		
Physical health [b]	0.98 [0.97, 0.99] **	0.95 [0.93,0.96] ***
Depression [b] **(ref. No)**		
Yes (doubtful or certain)	1.31 [0.97,1.77]	1.57 [1.08,2.28] *
Comorbidities [b]	2.78 [2.10,3.67] ***	5.20 [3.67,7.38] ***
Metastases [c] **(ref. No)**		

Yes	1.60 [0.96,2.65]	2.52 [1.44,4.40]**
Radiotherapy [c] (ref. No)		
Yes	0.97 [0.78,1.21]	1.92 [1.40,2.65] ***
Chemotherapy [c] (ref. No)		
Yes	1.08 [0.86,1.36]	1.99 [1.43,2.76] ***
Inpatient palliative care [c] (ref. No)		
Yes	1.23 [0.27,5.69]	5.33 [1.15,24.58]*
Psychotropic drug prescription [c] (ref. No)		
Yes	2.03 [1.63,2.54]***	5.60 [3.70,8.48] ***

[a] At diagnosis

[b] Five years after diagnosis

[c] Since diagnosis (i.e., between diagnosis and the year of the survey)

[d] The two multivariate logistic models separately compare (1) individuals prescribed at least one Step II opioid over the period from diagnosis to the survey year with individuals who received no opioid in the same period, and (2) individuals prescribed at least one Step III opioid over the period from diagnosis to the survey year with individuals who received no opioid in the same period.

[e] All the variables presented in Table 2 were tested. Only those significant at a threshold of 20% were used to perform the multivariate logistic regressions. The latter was selected using a forward stepwise selection procedure (probability threshold = 20%, probability of staying in the model =5%).

[f] ***, **, *: significant at $p < 0.001$, $p < 0.01$, and $p < 0.05$