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

4 Running title: opioids prescription in survivors with chronic pain

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13 Abstract

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

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

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

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

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

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

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

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

38 Introduction

39 Pain is one of the most common cancer symptoms (1–8). Rarely occurring alone, it is mostly
40 associated with fatigue, depression, anxiety and sleep disorders (9–12). Chronic pain, defined as
41 persistent pain lasting longer than three months (13), is common among cancer survivors and
42 may greatly impair their well-being and quality of life (QOL) (14–16). This type of pain may
43 precede cancer diagnosis, may be caused by ongoing active disease, may be induced by
44 anticancer treatments and procedures, or may be caused by cancer sequelae or its treatment
45 (17,18).

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

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

61 (31,32). Other updated versions of this ladder have been found in the literature. On the one hand,
62 some authors have proposed the abolition of the WHO ladder' step II (weak opioids) in favor of
63 the introduction of low doses of step III opioids (33). On the other hand, other authors have
64 proposed a fourth step comprising interventional strategies intended to manage intense to very
65 intense pain (i.e. nerve blocks, spinal administration of local anesthetics and opioids.) (34).

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

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

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

82 Methods

83 Study design: The VICAN survey

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

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

97 The study methodology was approved by the following national ethics commissions: the CCTIRS
98 (Consultative Committee on the Treatment of Health-related data, study registered under no.
99 11-143), the ISP (Institute of Public Health, study registered under no C11-63) and authorized
100 by the CNIL (French Commission on Individual Data Protection and Public Liberties, study
101 registered under no. 911290). With regard to personal responses and information provided,
102 confidentiality was ensured through data anonymization.

103 Data sources

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

110 Study population

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

114 Indicator measures

115 ***Pain measures***

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

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

129 ***Opioids and adjuvant analgesics***

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

- 133 - Step II opioids: codeine (ATC: N02AA59, N02AA79), dextropropoxyphene (ATC:
134 N02AC04, N02AC54, N02AC74), and tramadol (ATC: N02AX02, N02AX52).
- 135 - Step III opioids: morphine (ATC: N02AA01), fentanyl (ATC: N02AB03), oxycodone (ATC:
136 N02AA55, N02AA05), buprenorphine (ATC: N02AE01), and nalbuphine (ATC: N02AF02).
- 137 - Psychotropic drugs: Anxiolytics (ATC: N05B), hypnotics (ATC: N05CD, N05CF, and
138 N05CX), and antipsychotics (ATC: N05A).

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

144 ***Other measurements***

145 In addition to pain, the patient questionnaire evaluated QOL using the SF-12 (48), and anxiety
146 and depression using the HAD scale (49). Cancer-related fatigue was assessed from a score
147 between 0 and 100 evaluated using three items from the EORTC QLQ scale (50). A threshold
148 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

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

175 Results

176 Baseline characteristics

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

181 Prevalence and variables associated with CP - Univariate analyses

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

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

191 Variables associated with opioid prescription in cancer survivors with CP - Univariate 192 analyses

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

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

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

206 When comparing the second and third groups consecutively with the first group 1 (Table 2), we
207 found in both cases that opioid prescription was more frequent in respondents with
208 neuropathic pain, in those reporting depression, fatigue, and in those with lower scores of
209 physical and mental QOL. In addition, survivors who have experienced moderate pain in the last
210 15 days preceding the survey were more likely to be prescribed step II opioids, while those who
211 have experienced intense pain were more likely to be prescribed step III opioids. Moreover, in
212 both cases, survivors who underwent chemotherapy more frequently and those who had been
213 prescribed psychotropic drugs were more likely to be prescribed opioids. With respect to
214 participants' socio-demographic background, opioid prescription was more frequent in
215 respondents with a lower education level. No significant gender or age difference was found
216 for opioid prescription.

217 Compared with no opioid prescription, Step III opioid prescription was significantly more
218 frequent in unemployed respondents (18.0% versus 9.3% among those with executive jobs and
219 9.3 % for supervisors, $p<0.001$), respondents with anxiety (15.4% versus 13.1% among those
220 without anxiety, $p=0.02$) and in those with metastases (45.0% versus 11.4% among those
221 without metastasis, $p<0.001$). Furthermore, Step III opioid prescription was more frequent
222 among respondents who underwent radiotherapy (17.1% versus 10.1% in those who did not,
223 $p<0.001$), and among those who had had inpatient PC (67.3% versus 13.4% in those who did
224 not, $p<0.001$). For those who had had PC and were prescribed a Step III opioid, prescription
225 occurred either in the same year as PC or the following year.

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

230 Factors associated with opioid prescription in cancer survivors with CP- Multivariable 231 analyses

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

237 Factors positively associated with Step III opioid prescription included being unemployed five
238 years after diagnosis, reporting depressive symptoms, having metastases, having undergone
239 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

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

277 Pain has been recognized as one of the most frequent cancer-related symptoms, with high
278 prevalence rates from diagnosis to death (1,2,6,55). A recent systematic review indicated
279 prevalence ranged from 40% to 66% depending on cancer stage and treatment (2). In our study,
280 at five years after cancer diagnosis, more than three-quarters of our study sample reported
281 pain of some type during the 15 days preceding the survey. Two-thirds of our study population
282 (63.5%) reported CP, ranging from 50.1% to 72.1% depending on the primo-cancer site. Higher
283 than those from existing studies (41,56), these prevalence rates - especially for CP – indicate
284 that pain remains an important issue in cancer survivors long after diagnosis. Furthermore,
285 these high CP prevalence rates raise questions about the true utility of various cancer, pain and

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

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

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

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

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

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

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

348 Conclusion

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

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

357 *Compliance with ethical standards*

358 *Conflict of interest*

359 The authors declare that they have no conflict of interest.

360 *Ethical approval*

361 The study methodology was approved by the following national ethics commissions: the CCTIRS
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366 confidentiality was ensured through data anonymization.

367 *Informed consent*

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

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372 *Author Contributions*

373 All authors contributed to data analysis, drafting and revising the article, gave final approval of
374 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 (%)	
<u>Socio-demographic characteristics</u>			
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

- 561 ^a At diagnosis
- 562 ^b Five years after diagnosis
- 563 ^c Since diagnosis (i.e., between diagnosis and the year of the survey) .
- 564 ^d The modalities of the two questions regarding pain prevalence and duration were merged to construct a single variable coded
- 565 **“No Chronic pain”** which combined “No pain of any type in the previous 15 days” with “pain of some type in the previous 15
- 566 days but experienced for <3 months”, and **“Chronic pain”** which combined pain experienced for “≥ 3 months but < 6 months”,
- 567 and “≥ 6 months”
- 568 ^e For the question on the impact of pain on daily activities, the items “mostly agree” and completely agree” were merged into
- 569 the category “agree”, and the categories, “neither agree nor disagree”, “mostly disagree” and “completely disagree” were
- 570 merged into the category “disagree”.
- 571 ^f ***, **, *, significant at p < 0,001, p < 0,01, p < 0,05 (X² 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 n^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
<u>Socio-demographic characteristics</u>				
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
<u>Medical characteristics</u>				
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

574 ^a At diagnosis

575 ^b Five years after diagnosis

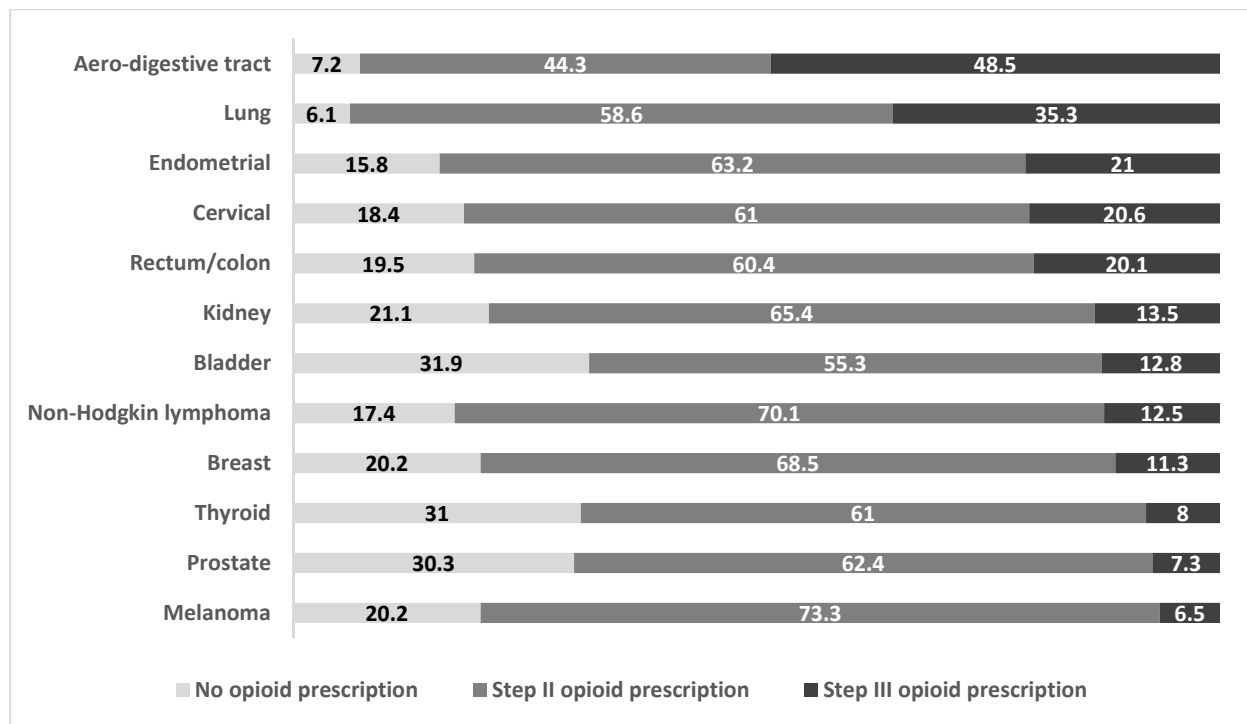
576 ^c Since diagnosis (between diagnosis and the year of the survey)

577 ^d For pain intensity variable, the categories “extremely intense”, “very intense”, “quite intense”, were merged into the category
578 “intense”, and the categories “quite moderate”, “very moderate” and “extremely moderate” were merged into the category
579 “moderate”.

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

581 Figure 1. Opioid prescription among cancer survivors with chronic pain according to cancer site.

582 (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}	
<u>Socio-demographic characteristics</u>		
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] *
<u>Medical characteristics</u>		
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] ***

585 ^a At diagnosis
586 ^b Five years after diagnosis
587 ^c Since diagnosis (i.e., between diagnosis and the year of the survey)
588 ^d The two multivariate logistic models separately compare (1) individuals prescribed at least one Step II opioid over the period
589 from diagnosis to the survey year with individuals who received no opioid in the same period, and (2) individuals prescribed
590 at least one Step III opioid over the period from diagnosis to the survey year with individuals who received no opioid in the
591 same period.
592 ^e All the variables presented in Table 2 were tested. Only those significant at a threshold of 20% were used to perform the
593 multivariate logistic regressions. The latter was selected using a forward stepwise selection procedure (probability threshold
594 = 20%, probability of staying in the model =5%).
595 ^f***, **, *: significant at p < 0.001, p < 0.01, and p < 0.05