Pain 132 (2007) 312–320

PAIN

www.elsevier.com/locate/pain

High prevalence of pain in patients with cancer in a large population-based study in The Netherlands

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Received 30 March 2007; received in revised form 26 June 2007; accepted 20 August 2007

Abstract

At present, no definite conclusions can be drawn about the real extent of the pain suffered by cancer patients. A population-based study was conducted to obtain reliable information about the prevalence and severity of pain in cancer patients (all phases) and about predictors of pain. A representative sample of cancer patients was recruited in the area from a cancer registry. Pain was assessed by the Brief Pain Inventory (BPI). Adequacy of pain treatment was assessed with the Pain Management Index (PMI). We found that 55% of the 1429 respondents had experienced pain past week; in 44% ($n = 351$), the pain was moderate to severe (BPI score $\geqslant 4$). Total prevalence of pain/moderate to severe pain was present in 49%/41% in patients with curative treatment $\geqslant 6$ months ago, 57%/43% in patients with current curative treatment or treatment <6 months ago, 56%/43% in patients with current palliative anti-cancer treatment and in 75%/70% in patients for whom treatment was no longer feasible. Positive predictors of the prevalence of pain were lower education level, more advanced disease and haematological (excluding (non)-Hodgkin lymphoma), gastro-intestinal, lung, or breast malignancies. According to the PMI, analgesic treatment was inadequate in 42% of the patients. Negative predictors of adequate treatment were current curative anti-cancer treatment and low education level. *Conclusion:* A substantial proportion of cancer patients does suffer from moderate to severe pain and does not receive adequate pain treatment.

Keywords: Cancer pain; Epidemiology; Pain treatment

1. Introduction

By using a combination of appropriate dosage guidelines and the use of the WHO pain ladder [101], it should be possible to achieve adequate pain relief in 70–90% of patients with cancer [30,53,55,95,97,105]. Studies described in the literature give the impression that this level of pain relief is not being fulfilled. Early publications drew attention to high prevalence rates that ranged from 52% to 77% [2,45,73,87,92]. More recent studies showed prevalence figures that ranged from 24% to 60% in patients on active anti-cancer treatment [63,68,71,72,74] and 62% to 86% in patients with advanced cancer [8,23,26,38,86,102]. These data illustrate that the problem of cancer pain has not yet been solved. A systematic review [6] performed by our research group revealed methodological flaws in many prevalence studies. Only 54 out of 160 (33%) cancer pain prevalence studies appeared to be of acceptable quality for further analysis. Based on pooled data, prevalence

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0304-3959/$32.00
doi:10.1016/j.pain.2007.08.022

rates of cancer pain were high: 54% in all disease phases combined, 60% in patients with metastatic or advanced disease and 58% in patients under anti-cancer treatment. Few data were available on the severity of the pain in different phases of cancer and they were mostly inconclusive [8,11,14,21,23,27,33,46,62,63,7578,80,82,83,89,106,107]. The same applied to the relation between the prevalence of cancer pain and the type of cancer [33,36,46,63,64,65,74,89], phase of disease [7,31,35,67], age [5,22], gender [56], marital status and education level. More studies with well-designed methodology are needed to gain greater insight into the real extent of the pain suffered by cancer patients.

To make reliable estimations of the prevalence and severity of pain in cancer patients and to map predictors of cancer pain, a population-based study was conducted on a large group of patients that included all disease phases.

2. Methods

2.1. Patients

Over a 5 month period between November 2004 and June 2005, cancer patients were recruited at 4 general hospitals, one university hospital, one clinic for radiotherapy, 11 nursing home organisations, 5 hospices and by a large number of general practitioners (GPs), in the area of a comprehensive cancer centre (Comprehensive Cancer Centre Limburg), in The Netherlands. Patients were eligible if they 1, had been diagnosed with cancer; 2, had been informed of their diagnosis; 3, were 18 years or older; 4, able to understand and complete the questionnaire; and 5, agreed to participate in the study.

A consistent finding in reviews on cancer pain was that the prevalence of pain was higher in the patients with more advanced disease [6,7,35,66]. Therefore, we subdivided the patients into 4 categories: group 1a, patients who had been treated with curative intent, last treatment more than 6 months ago; group 1b, patients receiving anti-cancer treatment with curative intent or last treatment less than 6 months ago; group 2, patients who were receiving palliative anti-cancer treatment; and group 3, patients for whom anti-cancer treatment was not or no longer feasible. These categories are indicated as disease group 1a, disease group 1b, etc.

2.2. Measurements

A self-report patient questionnaire and a medical data form filled in by the treating physician were developed for this study to obtain the following sets of measurements:

Demographic data: gender, age, marital status (cohabiting, widow(er), divorced, single) and education level: low (none or primary education), middle (lower and higher general secondary education and intermediate vocational education and high (pre-university education, higher vocational education, university).

Medical data: cancer type, disease group and date of last treatment (medical form) and information about medication received (patient questionnaire).

Pain was measured by the pain questions from the EORTC-C30 [1] (verbal rating scale) and by 4 questions (pain now and pain over the past week: least, worst and average) derived from the Brief Pain Inventory (BPI) [19]. Scores could be given on an 11-point Likert scale that ranged from 0 (no pain) to 10 (worst pain ever). The BPI has a high internal consistency with coefficient alphas that ranged from.78 to.97 in various cancer population samples in different countries [10,27,44,57,69,70,79,81,93,99].

Adequacy of pain treatment was measured by Ward's variation [100] of the Pain Management Index (PMI) [14], which is based on the patient's worst level of pain, categorized as 0 (no pain), 1 (VAS 1–3) mild pain, 2 (VAS 4–7) moderate pain, or 3 (VAS 8–10) severe pain. The pain level is then subtracted from the most potent level of analgesic treatment received by the patient, scored as 0 (no analgesic dug), 1 (non-opioids), 2 (weak opioids), or 3 (strong opioids). Scores can range from −3 (a patient had not received analgesic drugs, but had severe pain) to +3 (a patient had received strong opioids and did not have pain). These scores are then dichotomised: negative scores indicate the inadequate prescription of analgesic drugs, whereas scores of 0 or higher are considered to indicate acceptable pain treatment.

2.3. Procedure

At the outpatient clinics of the medical institutes, the treating physician filled out the medical data form on all the consecutive patients with cancer over a period of 10 days and gave them a flyer that explained the goals of this study.

The day after the visit to the outpatient clinic, each patient was sent the self-report questionnaire, an patient information brochure and an informed consent form at their home address. Patients were asked to return the questionnaire even if they did not wish to participate.

To identify patients for disease group 3 all the GPs in the region were informed about the study and invited to recruit suitable patients. Every 4 weeks, they were contacted by telephone. The GPs informed eligible patients about the study and gave them the necessary papers. At the nursing homes and hospices, a physician and/or nurse were asked to recruit patients for disease group 3, to inform them about the study and give them the necessary papers. GPs and nursing home doctors filled in separate medical forms.

2.4. Statistics

Descriptive statistics were obtained with SPSS version 12.0. All the regression analyses were performed using STATA SE 8.

Outcome variables were the presence of moderate to severe pain (yes/no) and inadequate use of analgesia according to the PMI (yes/no). The results of the BPI were used for the pain analyses. Pain was considered mild with the BPI score 1–3, moderate with score 4–6 and severe with score 7–10. Logistic regression analyses were used to identify factors associated with the dichotomous outcome variables. In a stepwise regression model, the contribution of the following variables was examined: age, gender, marital status (living alone vs not living alone), education (low, middle, high (reference group), cancer type (prostate cancer as reference category) and disease group

with $p < 0.10$ as the criterion to add a variable. To account for selection bias namely the underrepresentation of patients aged 80 years or older, all regression analyses were performed using the sampling weight option with weight equal to the inverse of the probability to be included in the study.

The study was approved by the Medical Ethics Committee of the University Hospital Maastricht, by the local Ethics Committees of the hospitals and by the group that coordinates studies involving general practitioners (CEL).

3. Results

In the out-patient settings, 1782 questionnaires were given to eligible patients and 1348 were returned correctly filled in (response 76%). Only 81 questionnaires were offered to patients by the 87 participating GPs (out of 417), 5 hospices and 12 nursing home organisations. All the patients returned the questionnaire; a total of 1429 could be analysed.

Patient characteristics are listed in Table 1. Most patients were between 60 and 80 years of age, married and living at home. The sample was representative for tumour types according to the cancer registration of the comprehensive cancer centres in The Netherlands [40].

No significant differences in the distribution of gender, cancer types or disease group were found between the participants ($n = 1429$) and non-participants ($n = 434$) (Table 1). However, there was significant overrepresentation of patients aged $\geqslant 80$ years among the non-participants. To account for this potential selection bias, weighting was used in all the analyses.

The informed consent form was not returned by 64% ($n = 276$) of the non-participants. No reason for refusal was given by 59 of the 158 non-participants who returned the informed consent form. Reasons for non-participation in the remaining 99 patients were: too ill or too tired (6%), no longer have cancer (4%), no pain [43], too blind/deaf/old or demented [43], deceased [43], comorbidity (1%), psychological problems (1%) and miscellaneous (4%).

In the total study population, 55% of the patients had pain. In 44% ($n = 351$) pain moderate to severe (VAS $\geqslant 4$). Pain percentages and confidence intervals per disease group are shown in Fig. 1. In group 1a ($n = 388$), 49% of the patients were suffering from pain ($n = 190$), of whom 41% ($n = 78$) had moderate to severe pain. In group 1b ($n = 385$), 57% were suffering from pain ($n = 218$), of whom 43% ($n = 94$) had moderate to severe pain. In group 2 ($n = 575$), 56% experienced pain ($n = 320$), of whom 43% ($n = 136$) had moderate to severe pain. In group 3 ($n = 81$), 75% were suffering from pain ($n = 61$), of whom 70% ($n = 43$) had moderate to severe pain.

No striking differences were found in the prevalence of average pain in the past week and the different cancer types (Fig. 2).

Table 1
Demographic characteristics

	Participants *n* (%)
Gender	
Men	686 (48)
Women	743 (52)
Missing data	
Age groups (years)	
20–40	55 (4)
40–60	475 (33)
60–80	800 (56)
$\geqslant 80$	99 (7)
Missing data	
Marital status	
Cohabiting	1059 (74)
Widow(er)	179 (13)
Divorced	76 (5)
Single	94 (7)
Missing data	21 (1)
Education	
Primary school	812 (57)
Secondary school	360 (25)
College/university	257 (18)
Residence	
Home (not alone)	1082 (76)
Home (alone)	278 (20)
Nursing home	19 (1)
Hospice	23 (1)
Hospital	1 (0)
Other	26 (2)
Type of cancer	
Head and neck	65 (4)
Gastrointestinal	222 (15)
Lung	141 (10)
Breast	367 (26)
Prostate	203 (14)
Urogenital other	103 (7)
Gynaecological	109 (8)
(Non)Hodgkin	64 (4)
Haematological other	89 (6)
Other	66 (6)
Missing	
Disease group[a]	
Group 1a	388 (27)
Group 1b	385 (27)
Group 2	575 (40)
Group 3	81 (6)
Missing	
Total	1429 (100)

[a] 1a = patients who received anti-cancer treatment with curative intent $\geqslant 6$ months ago, 1b = patients receiving anti-cancer treatment with curative intent or last treatment less than 6 months ago, 2 = patients receiving palliative anti-cancer treatment and group 3 = treatment not or no longer feasible.

Logistic regression analysis revealed that gender, age and marital status were not found to be significant predictors of the prevalence of pain, whereas the status of "treatment not feasible" held a significantly greater risk (odds ratio (OR) 3.3%, 95% confidence interval (CI)

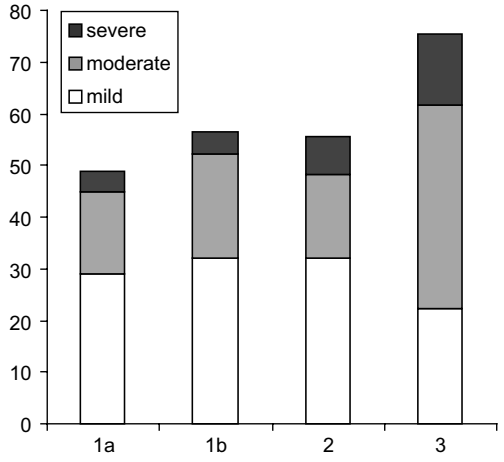

Fig. 1. Prevalence of pain in patients with cancer per disease group. 1a = patients who received anti-cancer treatment with curative intent ⩾6 months ago, 1b = patients receiving anti-cancer treatment with curative intent or last treatment less than 6 months ago, 2 = patients receiving palliative anti-cancer treatment and group 3 = treatment not or no longer feasible.

1.9–5.6) than the status of "current palliative anti-cancer treatment" (Table 2). In addition, a low (OR 2.0, CI 1.4–2.8) or middle education level (OR 1.7, CI 1.2–2.3) held a significantly higher risk than a high education level.

The risk of moderate to severe pain was significantly higher in patients with gastro-intestinal (OR 1.5, CI 0.9–2.5), lung (OR 1.7, CI 1.0–2.9), breast (OR 1.6, CI 1.0–2.5), other haematological malignancies, including 27% multiple myeloma (OR 3.0, CI 1.7–5.4), or "other" malignancies, including 8% two different tumours, 18% central nervous system and 23% melanomas (OR 2.5, CI 1.3–4.9) than in patients with prostate cancer (Table 2).

According to the pain management index (PMI), the treatment of pain was insufficient in 42% of the 1383 patients (Table 3). Less than 30% of the patients used medication belonging to the WHO 3-step pain ladder: 15% ($n = 202$) used step 1 medication (paracetamol and/or NSAIDs), 6% ($n = 78$) used step 2 medication (weak opioids) and 7% ($n = 95$) used step 3 medication (strong opioids). Adjuvant pain medication (tricyclic antidepressants, anti-epileptics, *N*-methyl-D-aspartate antagonists) was being used by 7% ($n = 95$) of the patients (Table 3). In many cases, pain medication was not being used according to the WHO guidelines: 42% of the patients using a weak opioid were not on step 1 medication, while this applied to 53% of the patients using strong opioids. Seven patients who were using strong opioids were also on weak opioids.

Current curative anti-cancer treatment (OR 1.3, CI 1.0–1.7) and a low education level (OR 1.5, CI 1.1–2.0) were negative predictors (Fig. 3) of adequate pain treatment. Advanced age (OR 0.8, CI 0.6–0.9) and more advanced disease (OR 0.5, CI 0.27–0.82) were positive predictors of adequate pain treatment.

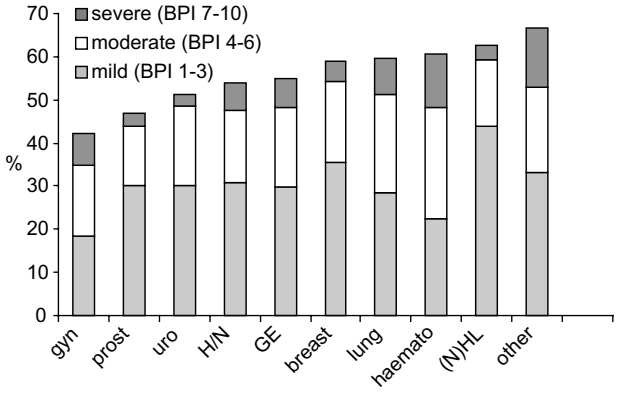

Fig. 2. Prevalence of pain in patients with cancer by type. gy*n* = Gynaecological, prost = prostate, uro = other urogenital, H/N = head and neck, GE = gastro-intestinal, haemato = other haematological, (N)HL = m. Hodgkin and non-Hodgkin.

4. Discussion

A high prevalence of pain (55%) was found in our total study population of 1429 cancer patients; 44% had moderate to severe pain.

In group 1a, 20% of the patients were suffering from moderate to severe pain, which was an even higher percentage than that reported in patients with chronic post-operative pain (5–10%) [41], osteoarthritis of the knee (10–14%) [3] or back pain (18–32%) [50].

Moderate to severe pain was reported by 22% and 23% of the patients currently under anti-cancer treatment, respectively, curative or palliative. Earlier studies reported prevalences of between 23 and 63% [21,63,71,98].

In the patients for whom treatment was not feasible, 75% had pain. In a recent systematic review [90] of symptom prevalence in 37 studies on patients with incurable cancer, the pooled prevalence rate of pain was 71% in 21,917 patients. In our population, 53% reported moderate to severe pain. Other studies found 20–65% with moderate to severe pain [8,14,23,62,80,82,83].

In the literature, little information is available about predictors of the prevalence of cancer pain. In our study, a low or middle education level held a significantly higher risk of pain than a high education level (OR 2.0 and 1.6, respectively). One study [75] found a higher (non-significant) prevalence of pain in cancer patients with basic schooling than in patients with high education levels. Studies on chronic pain in the general population reported that persons with low education had more pain complaints (occurrence and intensity); the difference was highly significant [39,76,77,91]. Explanations might be less involvement of these patients in

Table 2
Significant predictors of the prevalence of moderate to severe pain in patients with cancer[a]

	N[b]	Odds ratio	Confidence interval	p-Value[c]
Education level				
Low	812	1.97	1.38–2.82	**<0.001**
Middle	360	1.66	1.21–2.28	**0.002**
High	257	1.00 (reference)		
Disease group[d]				
1a	388	0.84	0.60–1.16	0.291
1b	385	1.13	0.82–1.55	0.459
2	575	1.00 (reference)		
3	81	3.28	1.93–5.56	**<0.001**
Cancer type				
Head and neck	65	1.61	0.80–3.24	0.183
Gastro-intestinal	222	1.53	0.94–2.47	**0.085**
Lung	141	1.71	0.98–2.97	0.057
Breast	367	1.57	1.01–2.46	**0.046**
Prostate	203	1.00 (reference)		
Other urogenital	103	1.38	0.75–2.54	0.304
Gynaecological	109	1.63	0.90–2.93	0.106
(Non)-Hodgkin	64	1.16	0.55–2.43	0.693
Other haematological	89	3.01	1.69–5.38	**0.001**
Other	66	2.53	1.31–4.89	**0.006**

Note: The bold values are the values reaching significance.
[a] Age and gender appeared not to be significant factors.
[b] N = number of patients.
[c] p-Value was considered significant at $p \leqslant 0.10$.
[d] 1a = patients who received anti-cancer treatment with curative intent ⩾6 months ago, 1b = patients receiving anti-cancer treatment with curative intent or last treatment less than 6 months ago, 2 = patients receiving palliative anti-cancer treatment and group 3 = treatment not or no longer feasible.

treatment issues [9] and increased financial strain 39]. Another prominent predictor of moderate to severe pain was the disease group (phase), which was in accordance with the consistent finding in reviews on the prevalence of cancer pain [7,35,66,94].

Although textbooks associate particular malignancies with a high risk of pain (bone, pancreas, oesophagus) or a low risk (lymphoma, leukaemia, soft tissue) [32,103], it is not clear what evidence these statements are based on. Previously [94], we did not find any significant relationships between pain prevalence and tumour type. A recent study on a cohort of end-stage cancer patients [61] concluded that cancer pain was not restricted to specific sites. Reyes-Gibby et al. studied patients under anti-cancer treatment and found high prevalences of moderate to severe pain in patients with head and neck, gastro-intestinal and breast malignancies [71]. Nevertheless, type of cancer did not prove to be a predictor, although our patients with gastro-intestinal, lung, breast, other haematological and "other" malignancies had a significantly higher risk of moderate to severe pain than the prostate cancer patients. This was remarkable, because 46% of our prostate cancer patients were in the palliative groups 2 and 3. Our linear regression analyses showed that head and neck cancer held a fairly high risk of mild pain. The focus of attention should lie on providing relief to patients with moderate to severe pain. Subdivision of pain severity into mild, moderate or severe is arbitrary. Especially, the NRS scores 4 (mild [15,27, 28,42,60,71,78,79,81] or moderate [4,8,24,25,63,84]) and 7 (moderate [4,8,25,60] or severe [11,15,24,27,60,63,71, 78, 79,81,84,88] give rise to discussion. In our study, the brief pain inventory pain and the EORTC quality of life questionnaire were used to measure pain. Therefore we were able to examine how our patients interpreted their pain: more of the patients considered a score of 4 to represent moderate pain than mild pain, while slightly more patients considered a score of 7 to represent severe pain rather than moderate pain.

On the pain management index (PMI), 42% of our patients had negative scores, which indicated inadequate analgesic treatment. Previous studies reported negative PMI-scores in 30–82% of the patients [4,17,23,44, 48,52,58,79,85,99,100,104]. Although the PMI is widely used to determine the adequacy of pain management, it does not take into account adequate dosage and the

Table 3
Pain management in patients with cancer by disease group[a]

	1a (n = 374) n (%)	1b (n = 375) n (%)	2 (n = 559) n (%)	3 (n = 75) n (%)	Total (n = 1383) n (%)
PMI[b]					
Insufficient	154 (41)	183 (48)	226 (40)	18 (24)	581 (42)
Medication[c]					
WHO 1	48 (13)	42 (11)	79 (14)	33 (44)	202 (15)
WHO 2	9 (2)	16 (4)	39 (7)	14 (19)	78 (6)
WHO 3	9 (2)	11 (3)	41 (7)	34 (45)	95 (7)
Co-analgesics	19 (5)	23 (6)	35 (6)	18 (24)	95 (7)

[a] 1a = patients who received anti-cancer treatment with curative intent ⩾6 months ago, 1b = patients receiving anti-cancer treatment with curative intent or last treatment less than 6 months ago, 2 = patients receiving palliative anti-cancer treatment and group 3 = treatment not or no longer feasible.
[b] Pain Management Index insufficient meant a negative score on the PMI.
[c] WHO 1, 2, 3 = World Health Organisation 3-step analgesic ladder 1, 2 and 3, co-analgesics included are tricyclic anti-depressants, anti-epileptics and NMDA–receptor antagonists.

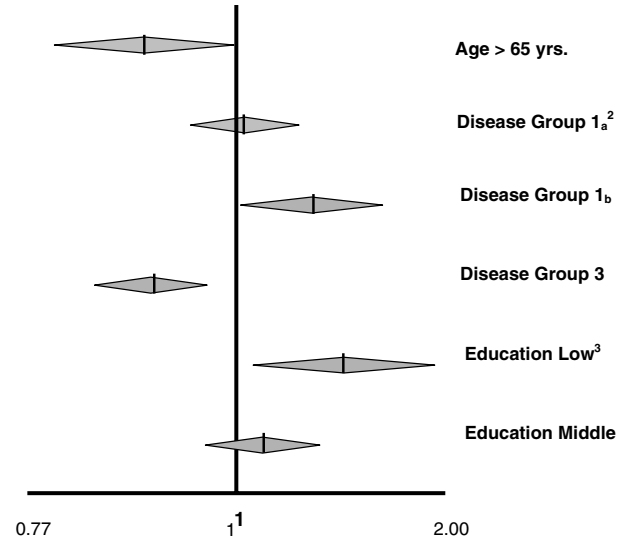

Fig. 3. Predictors of under-treatment of pain in patients with cancer[1] (Odds ratios and confidence intervals). [1]Gender and cancer localisation were not significant factors. [2]Disease group 2 as reference. [3]High education level as reference.

use of co-analgesics [12]. This probably explains why patients with metastatic disease (who make greater use of strong opioids) have the highest pain scores despite their encouraging PMI rates [12,20].

Patients on curative anti-cancer treatment had a significantly higher risk of not being treated adequately for their pain than patients on palliative anti-cancer treatment. This is in agreement with earlier reports in which patients with better performance status [13,58,71] or without metastases [58] were at risk of having negative PMI scores. This suggests that cancer patients experience the well-known barriers against adequate pain relief, such as fear of medication in general and opioids in particular and fear of starting opioids too early so no treatment will be available when the disease progresses [29,34,47,59,96,100].

Our results showed that patients with low education levels were at greater risk of receiving inadequate pain treatment than patients with high education levels. Possible explanations are that people with lower education communicate less effectively with their care providers about their pain, or are more afraid of opioids than people with higher education levels. This should be investigated in further studies. In contrast with our finding that older age protected against undertreatment of pain, earlier reports did not find any age differences in treatment [25,85] or poorer PMI scores in elderly patients 14,52. Gender did not appear to be a predictor of PMI scores. This was in agreement with two recent studies [52,85], whereas Cleeland reported poorer scores in women [13].

There were some limitations in this study. Despite the proper format and effort made to encourage GPs, nursing home physicians and nursing staff at the hospices to recruit patients with advanced disease, the number of patients was small. Therefore, this group may not have been representative of all patients with metastatic/advanced disease. Selection by GPs, nursing home physicians and nursing staff at the hospices could have excluded patients in the most terminal phase of illness. It is not clear how this selection influenced the prevalence of pain. Several studies showed that the prevalence of pain decreased at the very end of life [18,36,49,54], which would mean that we slightly overestimated the prevalence of pain in group 3. However, some studies showed an increase in the prevalence of pain at that phase [51,61].

The fairly broad categories of cancer types make it difficult to translate pain risk to the individual patients.

It was not possible to make more detailed subdivisions into specific types (e.g. pancreas, stomach, oesophagus, etc., instead of gastrointestinal), because of the limited numbers in each group.

5. Conclusion

The number of people who have [37] cancer is growing due to early detection and progress in anti-cancer treatment [16]. In 2005, the 20-year prevalence of cancer in The Netherlands was estimated to be over 450,000 persons (2.8%) and is expected to reach 692,000 in 2015 [16].

Our pain prevalence rate of 55% was far too high. The prevalence of moderate to severe pain in patients treated with curative intent was as high as that of back pain. A quarter of the patients under anti-cancer treatment and more than half of the patients with advanced/terminal disease were suffering from moderate to severe pain. Pain management was insufficient in almost half of the patients in this study. This illustrates the need for better education about pain and pain control in the curricula of medical professionals. Systematic recording of pain intensity in cancer patients, irrespective of the phase of disease, is mandatory.

Acknowledgements

We thank the coordinators at all the institutes for their commitment: A.V.R.J. Bell, F.L.J. Custers, J.J. Jager, J.C.A.H. van de Loo, Ms H.J.M.M. Mertens, Ms B. van Doorn, Ms M. Vromen, Ms L. Ars, Ms W. Habets, M. vandenHoff, R. Persoon, F. Slot, Ms P. Vleugels, Ms R. Palmen.

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