UNIVERSITY OF SOUTHERN DENMARK

Ph.D. Thesis

CANCER PATIENTS' USE OF OPIOIDS:

A pharmaco-epidemiological view.

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PREFACE

The results presented in this thesis are based on register data and comprise three studies of cancer patients’ use of opioids. The thesis includes an overview and three papers. The structure of the thesis is given by the Faculty of Health Sciences and includes the following main sections: introduction, material, methods, results, discussion, conclusion, perspectives and appendices including the papers. Repetition of text, tables and figures in the overview and the papers will occur.

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Odense, May 2005

Lene Jarlbæk

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THIS THESIS AT A GLANCE

What is already known on this subject?

Until recently, Denmark had the highest consumption of strong opioids per capita in the world and the use continues to increase (1;2).

Around 90% of the opioids consumed in Denmark are prescribed in the primary health care sector (3;4).

Opioids are effective and accepted worldwide as the drugs of choice for pharmacological treatment of moderate to severe cancer pain (5;6).

The prevalence of treatment requiring pain is only known in selected groups of cancer patients. In newly diagnosed patients, in cancer patients undergoing antineoplastic treatment and in terminal cancer patients the prevalence is around 30%, 50% and 60-90% respectively (7-9).

All opioids act via μ-receptors (10), and the pain-relieving effect is a matter of dosage. Dosages of opioids must be individualised and titrated in each patient for the optimal effect (11-13).

Danish doctors are more willing to prescribe higher doses of opioids to cancer patients than doctors in the other Scandinavian countries (14).

What does this study add?

Around 14% of the opioid users in the general population had a cancer diagnosis. In 1998, cancer patients accounted for 22% of the population’s yearly consumption of opioids.

The population’s use of both weak and strong opioids increased during the observation period. Cancer patients accounted for the majority of the increased use of strong opioids, while the increase in use of weak opioids was due to an increased number of users among non-cancer patients.

The 1-year prevalence proportion of opioid users among the cancer patients increased from 17% in 1993 to 20% in 1998.

The proportion of cancer patients, who had received opioids 1, 2 and 5 years after the cancer diagnosis, was 38%, 45% and 55%, respectively. Forty-three percent survived their first treatment episode with opioids, and 60% of those resumed opioids later in their disease course.

The total amount of opioids consumed by the cancer patients increased 85% from 1994 to 1998, while the number of prevalent users per year increased 28%.

Cancer patients, who started treatment with opioids in 1998, seemed to have the treatment initiated earlier in the disease course, compared to patients in 1994. Despite this, 43% of the cancer patients were terminal, when they started their first treatment episode with opioids.

During the observation period, the preference for the first choice opioid changed from strong to weak opioids. The weak opioid, tramadol, became the most frequently used index opioid, even among terminal cancer patients. Half of the incident opioid users received tramadol, while morphine and ketobemidone covered 20% each.

The preference for a strong opioid as first choice was influenced by the patient being terminal at the time of the initiation of the treatment, while old age reduced the odds of a strong index opioid. The first choice was not influenced by cancer type or sex.

ABBREVIATIONS

CPR	central personal registration
DDD	defined daily dose
CI	confidence interval, 95%
WHO	World Health Organisation
OPED	Odense University Pharmacoepidemiological Database
ICD-7	The 7th revision of the International Classification of Diseases
ICD-0	The International Classification of Diseases for Oncology
ATC	Anatomical Therapeutical Classification
INCB	International Narcotics Control Board
NSAIDs	Non steroidal anti-inflammatory drugs

1. CONCEPTUAL PURPOSE OF THE THESIS

“Intractable pain remains one of the complications most feared by patients with cancer, both in itself and as a harbinger of global loss of control and finally, mortality.
In order to plan the cancer care in the society and for the doctors to acknowledge the patients’ different needs during their disease course, epidemiological, physiological and pharmacological knowledge about cancer pain and its treatment is mandatory (15).”

The purpose of this thesis was to apply a pharmaco-epidemiological view to the treatment of cancer pain by focusing on the patients’ use of opioids.

Special emphasis was on

- cancer patients’ share in a population’s use of opioids
- changes in cancer patients’ use of opioids over a 5-year period
- cancer patients’ first treatment episode with opioids

2. INTRODUCTION

The introduction is divided into 4 parts: **Part 2.1** is a brief description of the pharmacology of opioid analgesics, and the rationale for handling the different opioid substances as one entity of drugs based on their pharmacodynamic properties. In **part 2.2** cancer pain and its pharmacological treatment are introduced. **Part 2.3** covers some epidemiological aspects of cancer, cancer pain and the pharmaco-epidemiology of the opioids. In **Part 2.4** the considerations regarding the use of Danish data as a model for studying the use of opioids in cancer pain treatment, and the international implications of this choice, are presented.

2.1 Opioid pharmacology

2.1.1 Opioid analgesics

Opioids are by definition all substances, naturally occurring or synthetically produced, which act via the μ-receptors on the cell surfaces to provide pain relief. Since all opioids share the same pharmacodynamic mechanism of action, the same anti-nociceptive effect can be achieved with different opioids. Taking the opioids’ different affinities for the μ-receptor into account, one opioid can be substituted by another, using equianalgesic dose tables (11).

Morphine and similar strong opioids lack a ceiling (or have a much higher ceiling) to their analgesic efficacy and so are normally administered in increasing doses until pain relief is obtained or unacceptable side-effects occur. There is no fixed “recommended daily dose” or “maximal dose” for a full opioid agonist such as morphine (7), and when given by the oral route doses may vary 1000-fold from 15-30 mg/day to as much as 15 g/day to achieve the same endpoint of pain relief (13).

2.1.2 Weak and strong opioids

Traditionally, the opioid substances are classified as weak or strong opioids depending on their relative efficacy in relieving pain (6;16). **Weak opioids** are: codeine, dextropropoxyphene and tramadol. **Strong opioids** are the remainder group of pure μ-agonist.

The analgesic potency of opioids depends on the affinity for the μ-agonist and the creation of metabolites of varying potency and duration. For oral opioid analgesics the bioavailability also plays a role for the efficacy of the drug (13). The concept of distinguishing weak and strong opioids has been challenged (17;18). If weak opioids are not used, strong opioids are required whenever

non-opioids alone are not adequate to relieve pain. There is a great risk of delaying this step, and weak opioids in step 2 are an important educational instrument for physicians and patients on their way from non-opioid to opioid analgesics (18). The availability of weak opioids offers pain relief to many patients who would otherwise receive no opioids at all or at a later time (18).

The application of pharmaco-epidemiological methods to the use of opioids as one treatment modality is based on the uniform pharmacodynamic effect of these structurally very different substances called opioids.

2.2 Cancer pain and its treatment

2.2.1 Cancer-related pain

Common features of non-cancer and cancer-related pain are plentiful, but distinctive aspects of the latter deserve emphasis because of their clinical implications for patient counseling and therapy (15).

1. Pain from cancer tends to increase in severity with advancing disease. Increase in severity or frequency of pain may herald disease progression or recurrence.
2. Patients with cancer often experience pain at multiple sites concurrently, through multiple mechanisms, and with distinct patterns, such as continuous pain, movement-related pain, and spontaneous breakthrough pain. Addressing only one source and type of pain may be inadequate.
3. A number of cancer pain syndromes have been identified, some of which are tumor-specific patterns of local or distant metastasis whereas others reflect diffuse neuropathies from tumor or treatment.

As many as three-quarters of chronic pain syndromes in cancer patients result from a direct effect of the neoplasm, others are related to therapies administered to manage the disease or to disorders unrelated to the disease or its treatment (19-21).

2.2.2 Pharmacological principles in the treatment of cancer pain

Systemic pharmacotherapy, principally with oral agents, is the foundation for treating cancer pain (22). Patients differ in their acceptance of and responses to specific analgesics or adjuvants, and to different behavioural strategies, and it is essential that treatment is individualized (11;12).

The three principal families of drugs used to manage cancer pain are:

1. NSAIDs (non-steroidal anti-inflammatory drugs) or acetaminophen
2. Opioid analgesics
3. Adjuvant analgesics

Drugs from these three principal families are often given in combination. Adjuvant drugs treat concurrent symptoms that exacerbate pain (e.g., insomnia), enhance the analgesic efficacy of opioids, or provide analgesia for specific types of pain (e.g., neuropathic pain) (22).

In practice, clinical consensus and common sense dictate initial use of the least invasive delivery method and simplest dosage regimen (23). Oral administration of drugs can manage most cancer pain, but different clinical problems or patients’ preferences may indicate the need for other routes of administration.

Despite all the different aspects in cancer pain, pain caused by nociceptive stimuli is very responsive to treatment with opioids, which makes it possible to apply simple guidelines for effective treatment to most of the patients with cancer pain.

A simple, widely applied approach to managing cancer pain, developed by the WHO, is the “three-step analgesic ladder” (or “staircase”) (15);

1. the first tier – for mild to moderate pain, consists of NSAIDs and acetaminophen. As pain escalates or persists, treatment progresses to
2. the second tier – in which a “weak” opioid is added to the NSAID. If pain still persists, treatment progresses to
3. the third tier – with substitution of the “weak” opioid for a “strong” opioid.

Multiple investigators have reported case series in which the WHO method yields satisfactory pain relief in the majority (80–90%) of patients with cancer pain. However, validation trials of the specific choice of agents and the sequence of their application within the WHO ladder have been limited (24;25).

The adequate relief of cancer pain to more than three quarters of patients achieved by opioids justifies its use as a first-line therapy for patients with moderate to severe pain. Since the response

to opioids is highly individual, sequential trials (opioid rotation) may be needed to identify the drug that yields the most favourable balance between analgesia and side-effects (7;26-31). The size of the starting dose varies with the severity of the pain, previous exposure to opioid, and the medical condition of the patient. Mean daily doses of opioids used at time of death vary widely between studies: 52 – 659 mg with a weighed average of 192 mg parenteral morphine equivalents (32).

Pharmaco-epidemiologically, the descriptions of cancer pain and its treatment imply that we could expect:

1. The use of opioids to be more frequent among cancer patients compared to non-cancer patients.
2. A fraction of the cancer patients to present with several treatment episodes. The episodes may vary both with regard to choice of drugs, doses, duration and relation to the disease course of the cancer.
3. Increased use of opioids among patients with metastases or patients, who approach the terminal phase.

Taking the natural history of cancer and the WHO ladder into consideration, we would also expect the first choice of opioid to differ between patients, who have metastases or are terminal, and patients with less advanced disease. The proportion of patients, who start treatment with strong opioids, is expected to be higher among patients with more advanced disease compared to patients with less tumor load.

2.2.3 Implementation of new concepts in cancer patients’ treatment with opioids.

New drugs, new principles and ideas in the treatment of cancer pain have emerged during the last 10 to 15 years, which might have influenced the pattern of opioid use among cancer patients. Tramadol, oxycodone and hydromorphone are opioid substances registered for use in Denmark in 1993, 1996 and 1997, respectively, and transdermal fentanyl as a new form of administering opioids was marketed in 1996. Opioid rotation was launched in the late nineties as a new concept in treatment of severe pain (30) and more focus on the treatment of neuropathic pain and the use of coanalgesics have emerged.

The degree to which these changes have been implemented in the pain treatment of the cancer patients is unknown. Pharmaco-epidemiological studies on the changes in the patients’ opioid use in

this period could indicate whether some of these new concepts have had any impact on the pattern of use.

2.3 Epidemiological aspects

2.3.1 Cancer prevalence

Prevalent cancer patients are a mix of newly diagnosed patients undergoing primary treatment, patients being treated for recurrent disease or in need of palliative care, as well as patients without signs and symptoms of active disease. A major reason for the interest in cancer prevalence is that it provides an overall indication of the demand for cancer-related health care in a population (33).

2.3.2 Cancer pain prevalence

While the prevalence of pain in selected groups of cancer patients is well described, the occurrence and prevalence of pain in the population of cancer patients are unknown. The prevalence of chronic pain is 30-50% among patients with cancer who are undergoing active treatment for a solid tumour and 70-90% among those with advanced disease (7-9). The likelihood of pain is influenced by type of tumor, stage of disease, and extent of metastases (15).

2.3.3 Why care about cancer pain epidemiology?

Cancer has a profound impact on public health and pain is a key dimension in the global degradation of quality of life that patients with cancer may suffer. The critical importance of pain management as part of routine cancer care has been forcefully advanced by WHO, international and national professional organisations, and governmental agencies (19).

In 2001 an evidence report conducted by researchers at the New England Medical Center Evidence-based Practice Center (EPC) was released, summarizing published evidence on the prevalence of cancer-related pain and the efficacy of drug and non-drug therapies for its treatment (15). Of approximately 19,000 studies on the management of cancer pain, only 24 epidemiological surveys qualified for summaries in the report and it was made clear, that:

1. The epidemiological characteristics of cancer-related pain are by large unknown.
2. The national disease burden of cancer-related pain in industrialised nations is probably underestimated, because of studies on selected groups of cancer patients.
3. Population-specific data are needed for advising the healthcare systems, as well as the individual patients and their families.

Population-based follow-up studies are needed to document the incidence and prevalence of symptoms throughout the course of the disease (8).

2.3.4 The pharmaco-epidemiology of cancer patients’ treatment with opioids

2.3.4.1 What is known?

A relationship between high use of opioids in a population and the level of cancer pain management has been hypothesized (34;35).

The International Narcotics Control Board (INCB) survey and update the overall use of opioids in the different countries around the world (1), but data of the cancer patients’ share in this use have never been available because of the difficulties in identifying population-based cohorts of cancer patients. Few publications have dealt with the proportion of cancer patients in populations of opioid users (35-39), and no knowledge of the extension of opioid use among cancer patients in the populations or of the choices of opioids or changes in the use exists. Furthermore epidemiological studies of individual treatment courses are also lacking.

2.3.4.2 Limitations in opioid utility studies.

The study of individualised opioid therapy using prescription databases has limitations to consider. Information of the indication for treatment and the prescribed doses are not present in the databases. The lack of recommended daily or maximum dosages, switches between opioid substances or the frequent use of different substances simultaneously, often combined with fluctuations in pain, imply much care in the performance of the studies and in interpretation of the results.

Usually, in drug utility studies, the amounts of drugs prescribed are provided as the number of defined daily doses (DDDs) or milligrams, and DDDs are the unit of measurement recommended in these types of studies (40). Different opioids vary much in their analgesic potency, which the DDDs do not necessarily take into account. Therefore, neither DDDs nor milligrams are useful in comparisons between treatments unless the same opioid substance and the same route of administration have been used. In individual-based studies of opioid use, the oral morphine equivalent (omeq) is considered to be a more clinically relevant unit of measurement (41-44). Morphine is the prototype and standard of comparison for opioid analgesics (7;12;27). Equianalgesic dose tables with morphine as reference substance are used clinically, when opioid treatments are initiated or changed. Despite the limitations of these tables (45-47), conversion of

consumed amounts of opioids to morphine equivalents is necessary, if individually consumed amounts of opioids are compared (32;44).

2.4 Denmark as a model

2.4.1 Denmark as a model for the study of cancer patients’ opioid use.

As a representative for the industrialised world, Denmark could serve as a model for studying epidemiological issues of pain treatment for several reasons:

1. Some unique possibilities for performing population-based studies exist in Denmark.
2. All Danish citizens have equal access to the services of the health care system, and the primary health care system is anchored by the “family doctor”.
3. The attitude towards use of opioids is more liberal compared with other countries.

2.4.1.1 Population-based research in Denmark

Several social and health-related databases or registries are available for research, where records can be linked by use of the central person registration number (CPR-number), which is a 10-digit code unique to each Danish citizen. The databases often have a high coverage, a long history of data collection, and effective validation procedures for the quality of the data (48).

The Danish Cancer Registry is a population-based registry established in 1943 (49). The registry contains information on the prevalence of cancer patients, but has no information on the patients’ symptoms. In Denmark at 31 December 1992, the cancer prevalence was 2389 persons per 100,000 (all malignant neoplasms excluding non-melanoma skin cancer). During the period from 1988 to 1992, the incidence rate was 263.2 new cases per 100,000 (world standard age-adjusted) and the 5-year relative survival was 38.6% (EUROCARE age-adjusted) (33).

There are several databases in Denmark with a comprehensive recording of all prescriptions of individual patients (50). They provide an opportunity to study aspects of medical treatment of cancer patients in detail by record-linkage with other research registers in Denmark (49;51-53), including longitudinal studies of individual drug use, which have been lacking (54).

Odense University Pharmacoepidemiological Database, OPED, is a population-based database initiated in 1990 (55) and holding information on all subsidised prescription drugs sold in the Danish county, Funen, together with information on residency and death of the citizens in the

county, comprising around 470,000 persons. OPED has had complete coverage of the county since November 1992.

2.4.1.2 Equal access for all citizens to the health-care services

All Danish citizens have equal access to the services of the national healthcare system regardless of their income or social status, since it is tax-funded. The primary health care system is anchored by the “family doctor”, who can be contacted free of charge when a health care problem arises, and more than 97% of the Danish population are listed with a general practitioner.

When a patient is suspected of having cancer, the general practitioner refers the patient to the hospital for further investigation in a surgical or a medical department. Care is provided by the hospital during the diagnostic phase and while active antineoplastic treatment is given. Thereafter, the general practitioner usually takes over the responsibilities of providing the required symptomatic treatment, which can be termed either supportive care or primary palliative care (56), depending on the state and stage of the patient. This arrangement implies that most of the time, during the patients’ disease courses, they are cared for by the general practitioners.

While attention has been given to the role of the general practitioner during the terminal phase of the cancer patient (57), the need for pain treatment provided by the primary care system during other phases of the cancer disease has to our knowledge never been studied.

2.4.1.3 Liberal attitude towards use of opioids

Until very recently, Denmark has had the highest use of strong opioids per capita in the world (1;2) and the use is still increasing. Eighty-seven percent of the opioid use occurs in the primary care sector (35). In Denmark, the indication for use of opioids is nociceptive opioid-sensitive pain, which cannot be relieved satisfactorily by other drugs or precautions (58). The prescribing of opioids for pain treatment has not been hampered by legislative barriers to the same degree in Denmark as in many other countries around the world. Copies of all strong analgesic prescriptions, including telephone prescriptions, are sent from all Danish pharmacies to the National Board of Health for computerized registration. The resulting information is sent to the county public health officers, who are responsible for supervising the prescription of strong analgesics (36). The weak opioids, tramadol and codeine, can be prescribed without special copy request.

From a questionnaire survey, we know that Danish doctors have satisfactory knowledge of the treatment principles for pain from bone metastases and visceral pain (34) and that they are more willing to prescribe strong opioids in higher doses compared to doctors in the rest of Scandinavia (14). Though not directly addressed, this indicates that cultural and attitudinal barriers against using opioids are smaller in the Danish population compared with other countries.

Despite this apparently liberal attitude towards opioids, myths and misconceptions about using opioids (59-62) are also heard among Danish cancer patients, and occasionally among the health care professionals. Longitudinal studies of cancer pain treatment might help to remove some of the concerns that patients may harbour (63), when their doctor suggests treatment with opioids.

The Danish authorities have been concerned by an increasing use of opioids, assuming that the increase has been due to inappropriate use to patients with chronic benign pain. So far, the cancer patients’ share in the Danish population’s use of opioids has been unknown, both with regard to the choices of drugs and to consumption. Knowledge of the cancer patients’ influence on the changes in the overall consumption is required, if a relevant and reliable debate on both cancer patients’ and non-cancer patients’ use of opioids is to be conducted.

2.4.2 International and national use of research in Danish cancer patients’ opioid use

Pain is a significant health problem, and there is considerable need for clinical and epidemiological research on the topic. It has previously been concluded that Danish drug prescription registers form valuable study bases of patients treated with strong analgesics in epidemiological research (37). If the use of opioids is assumed to be related to presence of pain, data from the Cancer Registry and the prescription database can be combined to increase the knowledge of cancer-related pain prevalence.

Though not eliminated, we think that the risk of underestimating the need for opioid treatment in cancer patients is considerably lower in Denmark compared with other countries. Knowledge of Danish cancer patients’ use of opioids adds to the sparse knowledge of cancer pain epidemiology. In Denmark as well as in other countries, the pharmaco-epidemiology of cancer patients’ use of opioids can be used to advise both the national healthcare systems on the organisation of palliative (56) and supportive care, and the individual patients and their families.

3. OPERATIONAL AIMS OF THIS THESIS

This thesis examines cancer patients’ use of opioids by applying pharmaco-epidemiological methods on register-based data.

Aim 1 To assess the use of opioids in a population’s entire cohort of cancer patients:

1. Assess cancer patients’ share in a population’s use of opioids and how much it influences the total use.
2. Analyse trends in the population’s use of weak and strong opioids over a five-year period, during which tramadol and transdermal fentanyl were introduced.

Aim 2 To go into details specifically about the cancer patients’ opioid use and analyse the changes over a five-year period with regard to:

1. Prevalence, incidence and survival of opioid users.
2. First choice of opioid.
3. Consumption of opioids and the drug-use intensity.
4. Different cancer diagnoses’ contribution to the use of opioids.

Aim 3 To analyse the epidemiology of the first episode of opioid treatment in a population-based cohort of cancer patients, by looking at:

1. The incidence of treatment and its relation to the course of disease, type of cancer and characteristics of patients.
2. The choice of drug and the duration of the first treatment episode.

Each of the operational aims corresponds with one of the three papers upon which this thesis is based (appendix[I, II, III]).

4. MATERIALS AND METHODS

The thesis is based on studies dealing with cancer patients in the County of Funen, Denmark.

The County of Funen comprises ~ 470,000 inhabitants; 9% sample of the Danish population. The population on the county is considered representative for the rest of the country with respect to the demographic variables, age and sex (50), cancer epidemiology (64-66) and use of opioids (67).

4.1 Data sources

Person-identifiable data on cancer disease and use of opioids were obtained by linkage of two databases: the Danish Cancer Registry (68;69) and the Odense University Pharmacoepidemiological Database, OPED, (70).

The unique person-identifier in both databases was the central personal registration number, the CPR-number, where information can be drawn on the person’s date of birth and sex.

4.1.1 The Danish Cancer Registry

The Danish Cancer Registry is a population-based registry containing data on the incidence of cancer throughout Denmark since 1943. Reporting of cancer was made mandatory by administrative order in 1987. In the Danish Cancer Registry since 1978 all incident tumours have been coded according to the International Classification of Diseases for Oncology (ICD-O) from the World Health Organization. The classification system rules have been adapted to serve the purposes of the Danish Cancer Registry. In order to maintain comparability with the information in the Registry for the period 1943-77, an electronic conversion programme has been created to generate the modified version of the 7th Revision of the International Classification of Diseases (ICD-7) used by the Danish Cancer Registry until 1977. All tumours in the Registry diagnosed after 1977 are thus classified according to both the ICD-O code and the modified ICD-7 code. A core data set is kept on each individual which includes the CPR-number of the patient, date of cancer diagnosis, method of verification, date of death and cause of death.

When a case of cancer is diagnosed, a notification is forwarded to the Registry, including cases first diagnosed at autopsy. The data are linked to the Danish Registry of Causes of Death and to the

Civil Registration System and a thorough follow-up procedure is carried out each year to obtain further information.

Because of the validation procedures in the Danish Cancer Registry (64), data on cancer patients were only accessible for patients diagnosed 4 years prior to the time when the research database for this project was produced. When data for the first study in the project were analysed, complete and valid data for 1943 to 1997 were available from the Registry. Data on patients from 1998 were added, when study 2 and 3 were performed.

4.1.2 Odense University Pharmacoepidemiological Database - OPED

OPED is a prescription database holding information on all prescribed drugs sold from all the pharmacies in the County of Funen via a link to the County’s refunding system. Prescription refunding applies to all Danish citizens for most of the drugs sold, including opioids. Since the refunds are prepaid by the dispensing pharmacies, with the accounts being refunded monthly by the County, the coverage of these prescriptions is for practical purposes 100%. Coverage has been complete in the County since November 1992. OPED does not contain data on drugs sold without prescription or the few classes of drugs not subsidised by the County.

Every record in OPED contains the CPR-number of the patient, the date of purchase, the pharmacy, the prescriber and a full account of what has been purchased, including brand name, ATC-code, dose unit and quantity (55). The prescribed daily dose and the indication for prescribing are not recorded in the database.

In addition to the prescription records, OPED also contains a demographic module holding information on residency and death of the citizens in the County. This demographic module was used to identify the CPR-numbers of all persons resident in the County of Funen during the 6-year period from 1 January 1993 to 31 December 1998, comprising around 570,000 persons.

4.2 Cancer patients

A cohort of 25,871 cancer patients were identified as residents in the County during the 6-year period from 1 January 1993 to 31 December 1998.

The patients were identified by linkage between the Cancer Registry and a list of CPR-numbers on all inhabitants in the County during the period, obtained from OPED’s demographic module. Migration data showed that 94.4% (N=24,430) of the cancer patients had lived in the County during their entire status as cancer patients, while 5.6% (N=1441) had moved one or several times to or from the County.

A person was defined as a cancer patient from the time of the first cancer diagnosis whether the patient was cured or not (71;72). The 15th was used as the date of diagnosis, since only the month and year of the diagnosis were known (this meant that in the study database 84 patients (0.3%) appeared to have died a few days before the diagnosis of the cancer). In analyses relating to the cancer diagnosis, the patients were categorised according to their first cancer diagnosis. Patients with non-melanoma skin cancer (ICD-7 code: 191) as the only cancer diagnosis, were not included in the analyses.

The number of cancer diagnoses per patient in the cohort is shown in Table 1.

Table 1: The number of cancer diagnoses per patient included in the cohort, 1993 to 1998.

Number of cancer diagnoses per patient	N	%
1	23998	92.8
2	1740	6.7
3	125	0.5
4	8	0.03

4.2.1 Cancer prevalence, incidence and mortality in the County of Funen, 1993 to 1998

The prevalence of cancer patients in the County showed a slight increase during the 6-year period from 1993 to 1998 (Table 2). This could be explained by the stable incidence rates of new cancer patients and a decrease in the mortality rates (Table 3), together with a declining increase in the County’s total population during the period (Table 2).

Table 2: The population and the cancer prevalence in the County of Funen, 1993 to 1998.

	Population in the County of Funen		Prevalent cancer patients 1 July		1-year prevalent cancer patients	
	the 1st of July	% increase per year	patients	% of the population	patients	% of the population
1993	465785		13228	2.84	15055	3.23
1994	466957	0.25	13622	2.92	15555	3.33
1995	468099	0.24	14026	3.00	15994	3.42
1996	470724	0.56	14401	3.06	16345	3.47
1997	471446	0.15	14714	3.12	16657	3.53
1998	471432	0.00	15045	3.19	17021	3.61
1999	471691	0.05				

Table 3: Cancer incidence and mortality in the County of Funen, 1993 to 1998 inclusive

	Incident cancer patients	Person-time at risk for incidence*	Cancer patients incidence rate per 100 years at risk		Cancer patient mortality	Cancer patients’ years at risk of dying	Crude mortality rate per 100 cancer years
		(years)		95% CI			
1993	2027	452557	0.45	(0.43 – 0.47)	1681	13223	12.71
1994	2181	453335	0.48	(0.46 – 0.50)	1760	13597	12.94
1995	2199	454073	0.48	(0.46 – 0.50)	1764	14029	12.57
1996	2115	456323	0.46	(0.44 – 0.48)	1804	14444	12.49
1997	2116	456732	0.46	(0.44 – 0.48)	1823	14720	12.38
1998	2187	456387	0.48	(0.46 – 0.50)	1813	15042	12.05

* the population on Funen at 1 July minus the number of prevalent cancer patients

4.3 Opioid prescriptions

Opioid prescriptions were identified in OPED using the Anatomical Therapeutic Chemical classification system, which characterise drugs by a seven-digit ATC-code (73). Opioids all have N02A as the four first digits in the ATC-code, the remaining three digits indicate the active substance in the drug. As an exception to this, codeine has the ATC-code R05DA04.

The opioids were divided into weak and strong opioids according to the guidelines from the WHO analgesic ladder (6). The weak opioids are codeine, dextropropoxyphene and tramadol. For the weak opioids only consumption of single entity drugs was included in the study. The rest of the drugs in the N02A – group are categorised as strong opioids, including buprenorphine.

Each opioid substance redeemed by a patient has its own record in OPED. In this study, one prescription with opioids is defined as all opioid substances redeemed on the same day by a patient, explaining why several substances occasionally can appear as one prescription.

4.3.1 Defined daily doses (DDD) and oral morphine equivalents (omeq)

Drug use statistics are usually presented by the Defined Daily Doses (DDD) methodology as recommended by WHO (40). The DDD is a technical unit of measurement, established by an expert panel as the assumed average maintenance dose, when the drug is used for its main indication by an adult, and the DDD does not necessarily reflect the prescribed daily dose (also see section 2.3.4.2).

Conventional drug use statistics are made per calendar year both by the Danish Medicines Agency (74;75) and by the International Narcotics Control Board (INCB) (76) and the units of measurement in these statistics are the defined daily doses. Therefore, we chose the same way of presenting our results in study I.

The defined daily doses for the different opioids are shown in the right column in Table 4.

Table 4: Equianalgetic dose table for the calculation of mg oral morphine equivalents

(mg omeq per prescription = the prescribed amount of DDD x meqfac x mg drug/DDD)

Drug	ATC-code	equids	meqfac	mg drug/DDD
morphine IV	N02AA01	10	3	30
morphine IR / PO	N02AA01	30	1	100
morphine SR / PO	N02AA01	30	1	100
morphine suppository	N02AA01	20	1.5	30
ketobemidone comb. PO	N02AG02	15	2	50
ketobemidone comb. PA	N02AG02	7.5	4	50
ketobemidone SR / PO	N02AB01	30	1	50
ketobemidone rectal	N02AG02	10	3	50
methadone PO	N02AC02	7.5	4	25
methadone PA	N02AC02	3.75	8	25
tramadol PO	N02AX02	150	.2	300
tramadol PA	N02AX02	100	.3	300
tramadol rectal	N02AX02	150	.2	300
pethidine PO	N02AB02	300	.1	400
pethidine PA	N02AB02	75	.4	400
pentazocin PO	N02AD01	176	.17	200
pentazocin PA	N02AD01	60	.5	200
oxycodone IR / PO	N02AA05	20	1.5	30
oxycodone SR / PO	N02AA05	20	1.5	30
hydromorphone SR / PO	N02AA03	4	7.5	4
dextropropoxyphene PO *	N02AC04	130	.23	200
dextropropoxyphene PO **	N02AC04	200	.15	300
buprenorphine SL	N02AE01	.4	75	1.2
buprenorphine PA	N02AE01	.3	100	1.2
codeine PO	R05DA04	300	.1	100
nicomorphine PO	N02AA04	30	1	30
nicomorphine PA	N02AA04	10	3	30
nicomorphine rectal	N02AA04	20	1.5	30
fentanyl transdermal 25 ug/hr	N02AB03	.18	167	0.6

IV intravenous IR instant release SR slow release PO per oral PA parenteral SL sublingual

equids: mg opioid equianalgetic with 30 mg oral morphine
meqfac: the potency of the drug in relation to oral morphine
mg drug/DDD: mg opioid per 1 DDD, defined by WHO

* hydrochloride, ** napsylate

For opioids, no assumed average dose exists, because the response to opioids between individuals is particularly variable (7). The dosage needs individual adjustment both with regard to the individual’s response and to the pain intensity.

Morphine is the prototype and standard of comparison for opioid analgesics (27) and we considered oral morphine equivalents (omeqs) to be more easily interpreted by clinicians. We also considered the omeq to be a relevant unit of measurement in future studies of individuals’ use of opioids.

In the second study, we chose to present the drug use both with DDDs and transformed to milligram oral morphine equivalents (omeqs) (7;43;77) using the values in Table 4. Table 4 and the calculation of each prescription's omeq value was based on published equianalgesic doses for different opioids (27;78-84).

4.4 Data handling

We constructed a database holding information on each cancer patient’s with regard to the cancer disease, the patient’s use of opioids and demographic data. The data were obtained by linkage between the Danish Cancer Registry and OPED, using the central person registration number (CPR-number) as the unique person identifier. This database provided the material for the 3 studies: The first two studies were cross-sectional studies on prevalent cancer patients’ use of opioids for each calendar-year in 5-year periods, 1993 – 1997 and 1994 – 1998 respectively. The third study was a cohort study on incident cancer patients from a 2-year period, 1997 – 1998, who were followed until death or 31 December 2003.

The statistical software was Stata ® (85).

Details of the methods used in the three sub-studies are presented below in the sections 4.4.1, 4.4.2 and 4.4.3

4.4.1 Study 1: Cancer patients’ share in a population’s use of opioids. A linkage study between a prescription database and the Danish Cancer Registry [I]

4.4.1.1 Study design and setting

During the 5-year period from 1993 to 1997, yearly, cross-sectional views on the use of opioids were applied to the entire cohort of 23,843 cancer patients and the population in the County of Funen, comprising around 565,000 persons during the study period.

The annual use of opioids in the County was drawn from OPED, both with regard to the number of users and to the consumption of defined daily doses (DDD).

Among cancer patients, the number of opioid users and the consumption of opioids were obtained from the study database.

The non-cancer patients’ use of opioids was calculated by subtraction of the cancer patients’ use from the total values.

4.4.1.2 Variables

Cancer patients – were the persons in the County, who were diagnosed with cancer prior to or during the year of interest. (280 cancer patients (1.2%) received their diagnosis in relation to the time of death).

Opioid users with cancer – were cancer patients who redeemed at least one opioid prescription in the year of interest, even if the cancer diagnosis was established after the date of redemption. (42 of the opioid users with cancer (0.5% of 8,566) were diagnosed with cancer in relation to their time of death).

Non-cancer population – was the number of persons, who remained after subtraction of the cancer patients from the total population in the County on 1 July in the year of interest.

Non-cancer opioid users – was the number of opioid users, who remained after subtraction of the opioid users with cancer from all the opioid users in the County during that year.

Opioid consumption – the amount of DDDs of opioids consumed during the year of interest.

Drug use intensity – the mean amount of consumed DDDs/user/calendar year. The drug-use intensity was calculated for all opioids and for weak and strong opioids separately. If a patient was treated with both weak and strong opioids in the same calendar year, the patient was counted once in each group of users.

4.4.1.3 Analyses

Descriptive statistics were used for presentation of the data and formed the basis for the interpretation of the results.

Users of opioids and consumption of opioids

The annual number of opioid users in the non-cancer population and among cancer patients were presented (Table I-2a), also showing the percentage increase in the absolute numbers during the 5-year period.

Among the opioid users, the percentages of users with cancer were presented (Table I-2a) and the users’ consumption was presented in 1000 DDDs/year for the whole population and for the cancer patients separately (Table I-2b).

Graphic presentations of the annual numbers of users (Fig. I-1) and the consumption of weak and strong opioids (Fig. I-2) were used to visualise the changes during the 5-year period.

Drug use intensity (DI) – was presented graphically showing the overall values in the population and separated into cancer patients’ and non-cancer patients’ DI for weak and strong opioids (Fig. I-3). This enabled the interpretation of the overall use as a function of the changes in the different groups of opioid users.

The number of users and the consumption of the 4 most significant opioids – were presented graphically for the cancer patients only (Fig. I-4).

4.4.2 Study 2: Use of opioids in a Danish population-based cohort of cancer patients [II]

4.4.2.1 Study design and setting

In each calendar year cross-sectional epidemiological views were applied on the entire cohort of 24,190 cancer patients, who were prevalent for shorter or longer periods of time in the County of Funen during the 5-year period from 1994 to 1998.

The cancer patients were ascertained to be residents in the County during the periods of interest and they were followed with respect to death through 2000. Only cancer patients diagnosed while they were alive were included in the population of cancer patients. All opioid prescriptions redeemed by the cancer patients since 1 January 1993 and until 31 December 1998 were retrieved from OPED.

4.4.2.2 Variables

Cancer patients

Prevalent cancer patients – were the persons in the County, who were diagnosed with cancer prior to or during the year of interest.

1-year cancer prevalence proportion – the number of prevalent cancer patients divided by the size of the County’s population on 1 July of the year.

Crude mortality rates per 100 cancer years – the number of deaths among the cancer patients during one calendar year divided by the number of cancer patient-years at risk.

Incident cancer patients per year – the number of patients per year diagnosed with cancer for the first time.

Incidence rate of cancer per 100 person-years – the number of incident cancer patients divided by the total person-time at risk (County’s total population on 1 July minus the number of prevalent cancer patients on 1 July).

Prescriptions

Incident opioid prescription – an opioid prescription, where no opioids 1 year prior to this prescription were redeemed by the patient. The prescription should be redeemed by a patient already diagnosed with cancer or less than 3 months prior to the date of the diagnosis (we assumed these prescriptions to be related to the cancer disease). We used 1993 as run-in period for incident prescriptions in 1994.

Repeated prescriptions were defined as prescriptions to the same patient with less than one year’s interval.

First choice opioid – the opioid substance prescribed on the incident prescription.

Users

Incident opioid user – a cancer patient, who received an incident opioid prescription.

Prevalent opioid user – a cancer patient, who received at least one prescription during a given year.

Consumption of opioid – the amount of opioids consumed per calendar year by the users.

Drug use intensity – the mean amount of consumed opioid/user/calendar year.

4.4.2.3 Analyses

The cancer population

For each year during 1994 to 1998, the cancer epidemiology in the County was accounted for (Table II-1) to see whether the population of cancer patients remained stable or changed. Comparisons between 1994 and 1998 were made by calculating the *incidence rate ratio* for *cancer incidence rate* and *crude mortality rate*, presented with 95% confidence intervals (section 5.2.1).

The use of opioids

The annual numbers of new users of opioids were presented as *incidence rates per 100 cancer-years* (Table II-2). The difference in numbers of *incident opioid users* in 1994 and 1998 was presented as the IRR with 95%CI (section 5.2.2). *Incidence rates* for *users of weak* or *strong opioids* as *first choice* were presented for each calendar year (Table II-2).

The *prevalence* of opioid users was presented as 1-year prevalence proportions, calculated as the number of cancer patients, who received at least one opioid prescription during a calendar year, divided by the number of 1-year prevalent cancer patients (Table II-2).

The *survival* of *opioid users* was presented as *1-year and 2-year survival of incident opioid users*, calculated as the percentages of incident users, who were alive one year and two years after the incident prescription (Table II-2).

1-year mortality proportion among users and non-users was calculated as the number of users or non-users dying during the calendar year divided by the number of 1-year prevalent patients (Table II-2).

The annual *consumption of opioids* was presented both as DDDs and as omeqs (Table II-3).

Drug use intensity (DI) – was calculated as the mean amount of consumed opioid/user/calendar year and presented both as DDDs and as omeqs (Table II-3). The DIs for weak and strong opioids were displayed graphically (Fig. II-3). This enabled the interpretation of the overall use as a function of the changes in the use of *weak* compared to *strong opioids*.

First choice opioid – was presented in Fig. II-1 as the different drugs’ percentages of the *incident prescriptions* for each year, to visualise the changes during the period.

The different drugs’ contributions to the *total consumption of opioids* per year were presented as percentages in Fig. II-2.

The different *cancer diagnoses’* contribution to the use of opioids was presented for 1994 and 1998 in Table II-4, displaying the percentages of *opioid users* with different *diagnoses* and the share the patients with the different *diagnoses* had as percentage of the total *consumption*.

Analyses based on the level of the individual were;

1. The contribution to the consumption of opioids from patients with different diagnoses
2. Incident opioid prescriptions
3. Repeated prescriptions
4. 1- and 2-year survival of the incident opioid users.

4.4.3 Study 3: Cancer patients’ first treatment episode with opioids: a pharmaco-epidemiological perspective [III]

4.4.3.1 Study design and setting

The study was designed as a cohort study, where incident cancer patients from 1997-1998 were followed from the diagnosis to death or to the 31 December 2003 inclusive, with regard to their first episode of treatment with opioids. Only incident cancer patients, who had been inhabitants in the County from at least 1 year prior to the date of the cancer diagnosis and until death or the 31 December 2003, were included in the analyses.

4.4.3.2 Variables

Incident cancer patients

Incident cancer patients – the number of patients, who were diagnosed with cancer for the first time during the 2-year period from 1997 to 1998, and who fulfilled the inclusion criteria.

The *cancer patients* were defined as *terminal* from 6 months prior to their death, which meant that cancer patients, who were still alive on 31 December 2003, could not be categorised with regard to terminal status in the remaining 6 months of their observation period. We assumed that the prescribing doctors could judge *the patients* to be *terminal* if *the patients* had 6 months or less left to live. This assumption was based on clinical knowledge and on the literature, where doctors’

predictions of survival up to 6 months in length have been shown to be reliable, as they are highly correlated with actual survival (86).

Opioid users

Incident opioid users were cancer patients, who redeemed their first opioid prescription, the *index-prescription.*

Prescriptions

The *index prescription* was defined as an opioid prescription, where no opioids were redeemed by the user at least 1 year prior to the date of the index prescription, the *index date*.

The first episode with opioids

Time from diagnosis to the first treatment episode with opioids

The Cancer Registry only provides information of the month and year of the cancer diagnosis, therefore the *date of diagnosis* was defined as the 15th of the months. If the opioid treatment was initiated in the time window from 3 months before the date of diagnosis to 15 days after, the treatment was defined to be initiated simultaneously with the diagnosis, and we made the assumption that it was related to the cancer disease. Start of treatment in this time window was defined as start on day 1 in the Kaplan-Meier analysis of time from diagnosis to start of treatment.

The *first episode* started when the *index prescription* was redeemed. The *last prescription* in the first episode was defined as the prescription in the database, where no opioid prescriptions were redeemed by the user at least for the following 4 months’ (122 days) period. The patient could end the first treatment episode either because of death less than 4 months after the last prescription (*non-survivors*) or for other reasons, which are not recorded in the database (*survivors*).

The *duration of the first treatment episode* was defined as the time-interval between the *index date* and the date of the *last prescription* in the first episode.

4.4.3.3 Analyses

Cancer patients

Descriptive statistics were used to present patient characteristics (Table III-1), the percentages of *incident opioid users* 1, 2 and 5 years after the cancer diagnosis (Table III-2) and the *first choice of opioid* (Table III-3).

5-year survival – was the percentage of patients, who were alive 5 years after the cancer diagnosis.

Opioid users

The time from the cancer diagnosis to the first opioid prescription was presented using the Kaplan-Meier method and the *hazard ratios* were estimated using Cox regression with 95% confidence intervals (Fig. III-2). The *incidence rates of new opioid use* were crude values of *the number of new users* in the observation period divided by *the number of years at risk* for the incident cancer patients with the different cancer types. The different cancer types’ *incidence rates of new opioid use* were presented as a function of the cancer patient’s 5-year survival (Fig. III-3)

The first choice of opioid

The choice of a strong versus a weak index opioid was analysed using logistic regression with diagnosis, sex, age at the index date, stage of the disease at the time of diagnosis (referred to only as “stage” in the following) and terminal status (< 6 months to death) as explanatory variables (Table III-4). *Odds ratios* were presented with 95% confidence intervals (CI). Colorectal cancer was used as comparator for the other cancer types because of the number of cases, frequency of opioid use, no known sex-related confounders and well-described staging procedures. Only sex-unspecific cancers were used to analyse the influence of sex, age and stage on the first choice of opioid, to avoid the influence of the biology of the sex-related cancers. Analyses that included terminal status were performed on the cohort of patients who started treatment before 1 July 2003.

The choices of the different opioid substance were presented as percentages of all users and of patients who were terminal or not terminal, when they started their opioid treatment (Table III-3).

The duration of the cancer patients’ first treatment episodes with opioids – was the time interval between the *index date* and the date of the last prescription in the first treatment episode (Fig. III-4).

5. RESULTS

The results are presented corresponding to the aims and the description in the section; Materials and methods.

5.1 Study 1: Cancer patients’ share in a population’s use of opioids. A linkage study between a prescription database and the Danish Cancer Registry [1]

Aim: To assess the use of opioids in a population’s entire cohort of cancer patients

- To assess cancer patients’ share in a population’s use of opioids and how much it influences the total use.
- To analyse trends in the population’s use of weak and strong opioids over a five-year period, during which tramadol and transdermal fentanyl were introduced.

5.1.1 Opioid users

The total number of opioid users in the County increased 49.6% during the period. The number of opioid users with cancer increased 35% and the number of opioid users without cancer increased 52% (Table I-1). Thus, the proportion of opioid users with cancer in the population’s group of opioid users decreased from 15.4% (CI: 14.8 - 15.9%) in 1993 to 13.8% (13.4 – 14.3%) in 1997.

During the 5-year study period (1993 to 1997), 23,843 cancer patients were identified in the County of Funen, of those 9,516 (40%) received an opioid analgesic. Around 80% of the opioid-using cancer patients had their first opioid prescription after the cancer diagnosis and around 16% used opioids both before and after the diagnosis.

The proportion of opioid users in the cohorts of one-year prevalent cancer patients increased from 17% to 21% during the period (Table I-1).

Table I-1: The proportion of opioid users per calendar year in the non-cancer population and among cancer patients.

Calendar year	Non-cancer population*	Non-cancer opioid users	(%)	Cancer patients	Opioid users with cancer	(%)
1993	450164	14104	3.1	15075	2560	17.0
1994	451007	15829	3.5	15560	2752	17.7
1995	451717	18680	4.1	15978	3064	19.2
1996	454206	19899	4.4	16322	3206	19.6
1997	454820	21481	4.7	16602	3448	20.8
% increase 93-97	*1.0*	*52.3*		*10.1*	*34.7*	

* The County’s total population minus the cancer patients.

The number of patients using weak opioids increased and the number of patients using strong opioids decreased during the period; this trend applied to both cancer patients and non-cancer patients (Fig. I-1).

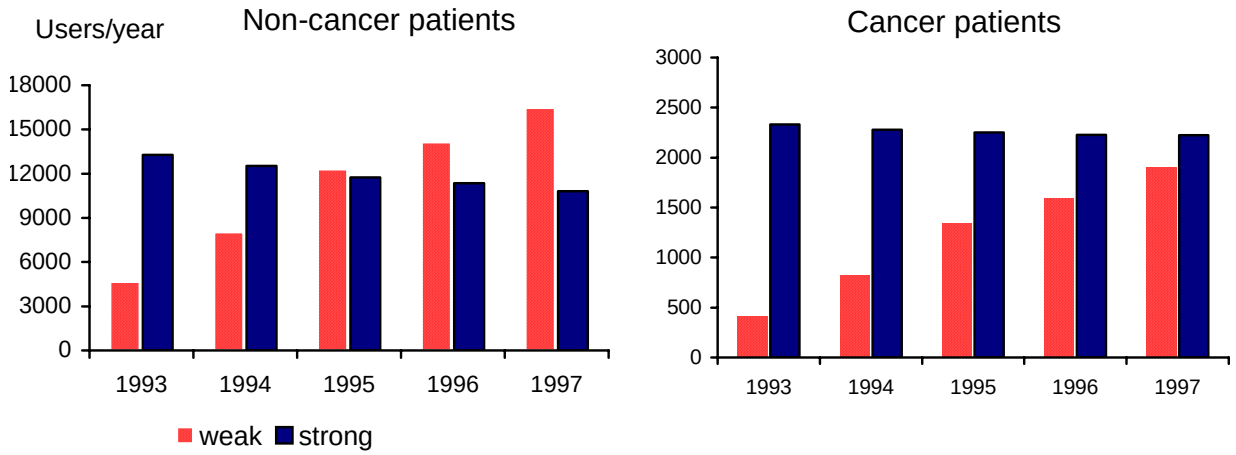


Fig.1. Number of opioid users per year for weak and for strong opioids, presented for non-cancer patients and cancer patients.

The proportion of cancer patients among the users of weak opioids increased from 8.0% (7.3 - 8.8%) to 10.4% (9.9 - 10.8%). The proportion of cancer patients among users of strong opioids increased from 14.9% (14.4 - 15.5%) to 17.1% (16.4 - 17.7%) (Table I-2a). The proportion of cancer patients using both weak and strong opioids in the same calendar year increased from 7% to 20%, and remained stable at 27% among non-cancer patients.

Table I-2a: The annual number of opioid users in the County and the proportion of users with a cancer diagnosis, 1993 – 1997.

	All opioids			Weak opioids			Strong opioids		
Calendar year	All patients	Cancer patients number	%	All patients	Cancer patients number	%	All patients	Cancer patients number	%
1993	16664	2560	15,4	5077	408	8,0	15610	2330	14,9
1994	18581	2752	14,8	8850	825	9,3	14801	2280	15,4
1995	21744	3064	14,1	13649	1339	9,8	14004	2253	16,1
1996	23105	3206	13,9	15743	1594	10,1	13579	2226	16,4
1997	24929	3448	13,8	18385	1906	10,4	13033	2224	17,1
% increase 1993 to 1997	*49,6*	*34,7*		*262,1*	*367,2*		*-16,5*	*-4,5*	

5.1.2 The consumption of opioids

The cancer patients accounted for 18.6% of the population’s opioid consumption in 1993, and after a small decrease in 1994 and 1995 this proportion rose to 22.3% in 1997 (Table I-2b).

The consumption of opioids in the population increased 43.9% during the period 1993 – 1997, reflecting an increase in both groups of patients. Cancer patients’ consumption increased 72% and non-cancer patients’ consumption increased 37.5%. For the non-cancer patients the increase in consumption of all opioids was slowly declining during the period.

Table I-2b: The annual consumption of opioids in the County in 1000 DDD, 1993-1997, for the whole population and for patients with a cancer diagnosis.

	All opioids			Weak opioids			Strong opioids		
Calendar year	All patients	Cancer patients amount	%	All patients	Cancer patients amount	%	All patients	Cancer patients amount	%
1993	1456	271	18.6	374	35	9.2	1082	237	21.9
1994	1574	282	17.9	466	45	9.8	1109	237	21.4
1995	1726	307	17.8	606	61	10.0	1120	246	22.0
1996	1883	360	19.1	720	73	10.2	1163	287	24.7
1997	2095	466	22.3	848	95	11.2	1247	371	29.8
% increase 1993 to 1997	*43.9*	*72.0*		*126.6*	*174.4*		*15.3*	*57.0*	

Cancer patients and non-cancer patients affected the population’s consumption of weak and strong opioids differently (Fig. I-2). The non-cancer patients predominantly influenced the increase in consumption of weak opioids, while the population’s increase in consumption of strong opioids was due to the cancer patients’ use. The cancer patients’ increase in consumption of strong opioids continued throughout the study period, while the non-cancer patients’ consumption remained stable.

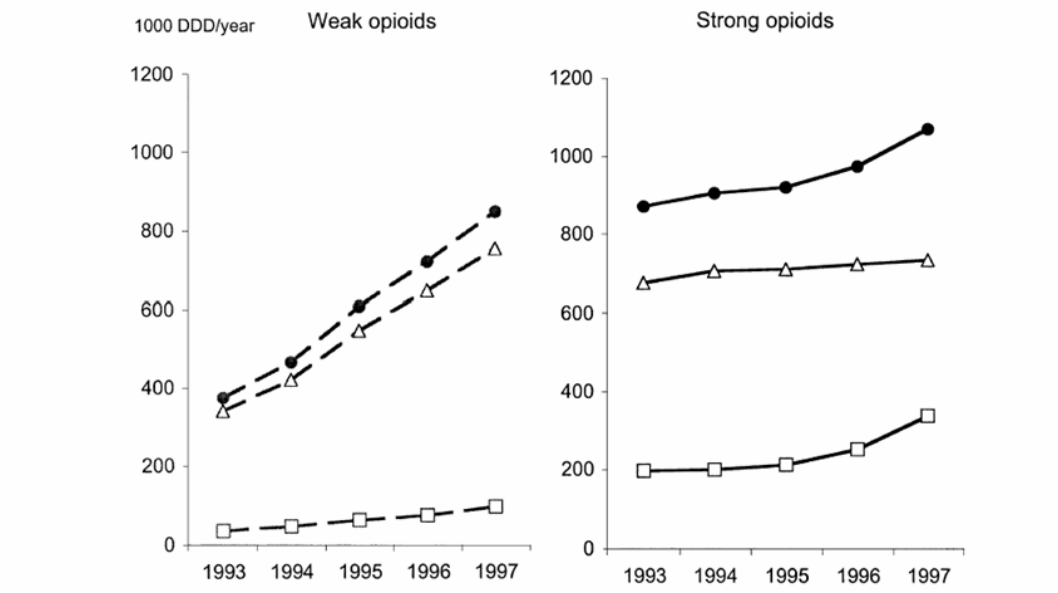


Fig.2. Consumption of weak (---) and strong (—) opioids per year in the population (●) (N ~ 470,000), separated into cancer (□) and non-cancer (△) patients

5.1.3 The drug-use intensity (DI)

The DI in the population remained stable during the whole 5-year period (Fig. I-3). This apparent stability at around 74 DDD/user/calendar year was the result of some rather pronounced, opposite changes, if weak and strong opioids were analysed separately. The DI for the weak opioids declined and then stabilised during the period 1993 – 1997, for both cancer patients and non-cancer patients. The DI of strong opioids increased considerably for the cancer patients, while the non-cancer patients only showed a small and declining increase.

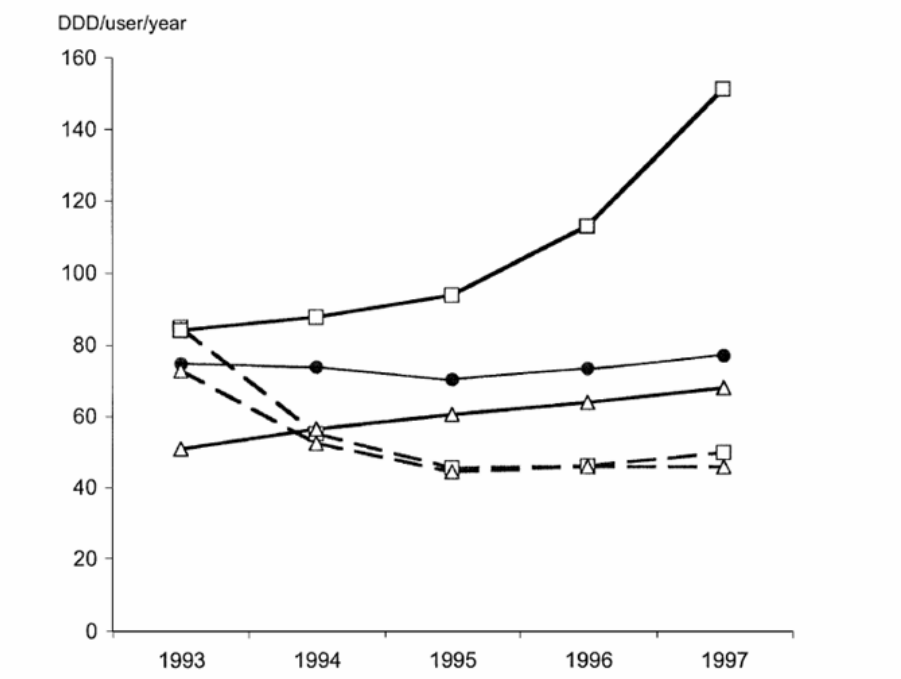


Fig.3. Drug-use intensity per year for all users’ overall opioid use (●), for non-cancer (△) and cancer patients’ (□) use, separated into strong (—) and weak (---) opioids.

5.1.4 Cancer patients’ use of different opioids

The most commonly used opioids by the cancer patients were morphine, ketobemidone, tramadol and transdermal fentanyl (Fig. I-4). Tramadol was introduced onto the market in 1993 and transdermal fentanyl in 1996.

Until 1997, users of ketobemidone and morphine were the most frequent. In 1997 this picture changed, where tramadol became the opioid used by most of the cancer patients, 29.1% (27.9 – 30.3%) compared with 22.1% (21.0 – 23.2%) having used morphine. The transdermal fentanyl was used by 5.9% (5.3 – 6.6%) of the opioid-using cancer patients in 1997.

Throughout the period, morphine was the most consumed opioid. Already the year after its introduction to the market, transdermal fentanyl became the second most consumed opioid (Fig. I-4); in 1997, 26.3% of all consumed opioid was transdermal fentanyl compared with 30.6% morphine.

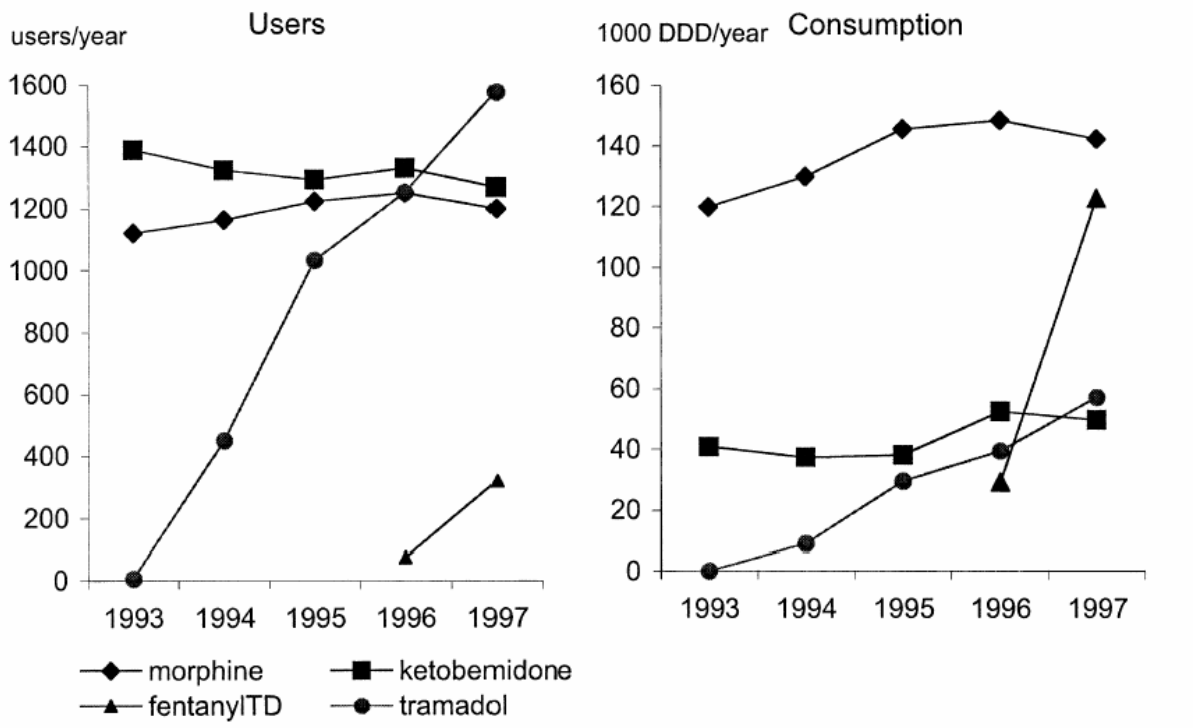


Fig.4. Trends in cancer patients’ use of the four most significant opioids during 1993–1997.

5.2 Study 2: Use of opioids in a Danish population-based cohort of cancer patients [II]

Aim: To go into details specifically about the cancer patients’ opioid use and analyse the changes over a five-year period of

- Prevalence, incidence and survival of opioid users
- First choice of opioid
- Consumption of opioids and the drug-use intensity
- Different cancer diagnoses’ contribution to the use of opioids.

5.2.1 The cancer population, 1994 to 1998

The 1-year cancer prevalence proportion increased during the 5-year period (Table II-1). The cancer incidence rate remained stable with an incidence rate ratio (IRR) = 1.00 (CI: 0.94 - 1.06) for 1998 relative to 1994, while the crude mortality rate decreased from 12.94 to 12.05 deaths per 100 cancer patient-years in the period, IRR = 0.93 (CI: 0.89 - 0.99).

Table II-1: Cancer epidemiology in the County of Funen (n ~ 470,000), 1994 to 1998

	1994	1995	1996	1997	1998
Prevalent cancer patients per year	15555	15994	16345	16657	17021
1-year cancer prevalence proportion (%)	3.33	3.40	3.47	3.53	3.61
Mean age	65.4	65.5	65.5	65.6	65.7
Crude mortality rate per 100 cancer-years	12.94	12.57	12.49	12.38	12.05
Incident cancer patients per year	2181	2199	2115	2116	2187
Incidence rate per 100 person-years	0.48	0.48	0.46	0.46	0.48

5.2.2 Prevalence, incidence and survival of opioid users

We identified 24,190 cancer patients in the County from 1994 to 1998. Of those, 40% (N=9,663) received at least one opioid prescription during the 5-year period. Repeated prescriptions, i.e. prescriptions with less than 1-year interval, were received by 7,133 of the 9,663 patients (74%).

The number of 1-year prevalent opioid users increased by 27.6% with the annual proportion of users increasing from 17.3% (CI: 16.7 – 18.0) to 20.2% (CI: 19.6 – 20.9) during the 5 years (Table

II-2). The proportion of new opioid users among the prevalent users decreased from 60% to 55% during the period.

The incidence rate of opioid users among the cancer patients increased slightly from 13 to 14 per 100 cancer-years. IRR = 1.08 (CI: 1.01 – 1.16) for 1998 relative to 1994. Sixty-eight percent of the incident users received at least two opioid prescriptions during the following year.

Table II-2: Cancer patients' use of opioids, 1994 to 1998: Incidence and prevalence.

	1994	1995	1996	1997	1998
Number of incident users per year	1623	1766	1769	1951	1884
incidence rate, per 100 cancer-years	12.9	13.8	13.5	14.8	14.0
incidence rate for weak opioids	3.9	6.6	7.3	8.6	8.5
incidence rate for strong opioids	9.0	7.3	6.3	6.2	5.6
1-year survival of incident users in%	47.5	53.1	55.2	54.9	59.3
2-year survival of incident users in%	37.9	43.5	44.7	46.3	54.7
Number of prevalent users per year	2698	3004	3157	3394	3443
1-year prevalence proportion of users (%)	17.3	18.8	19.3	20.4	20.2
incidence proportion among users(%)	60.2	58.8	56.0	57.5	54.7
1-year mortality proportion among users (%)	35.5	34.0	33.5	31.6	31.7
1-year mortality proportion among non-users (%)	6.2	5.7	5.7	5.7	5.3

The increase in 1-year and 2-year survival after the first opioid prescription is also shown in Table II-2. The proportion of patients, who were still alive one year after their incident opioid prescription, increased from 48% (CI: 44-51) among the incident users in 1994 to 59% (CI: 56-63) in 1998. More evident though, were the changes for the 2-year survival, which increased from 38% (CI: 35-41) to 55% (CI: 51-58), with two breakpoints on the increase between 1994 and 1995 and especially between 1997 and 1998.

5.2.3 First choice opioid

The first choice opioid changed during the period (Fig. II-1). A strong opioid was chosen in 70% of the cases in 1993 and in 40% in 1998. The incidence rates for “weak” and “strong” opioids are presented in Table II-2. Since the introduction of tramadol in 1993, its share among the incident opioid prescriptions increased to 49%, compared to 17% for ketobemidone and 16% for morphine in 1998.

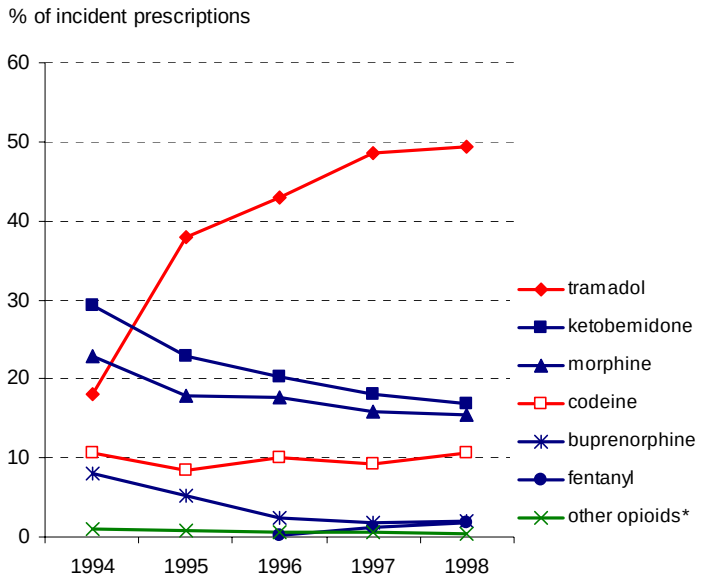


Figure II-1. First choice opioid for incident users, 1994 to 1998.

5.2.4 Consumption of opioids

The cancer patients' consumption of opioids increased with 80%, from 20 kg omeq/year to 37 kg omeq/year (Table II-3). The consumption of transdermal fentanyl increased very rapidly after its registration in 1996 (Fig II-2). Eleven percent of the opioid users in 1998 received the drug, and the consumption of transdermal fentanyl reached 35% of the cancer patients' total opioid consumption, similar to the consumption of morphine.

Table II-3: Cancer patients' use of opioids, 1994 to 1998: Consumption and drug use intensity.

	1994	1995	1996	1997	1998
Opioid consumption per year					
DDD (thousands)	237	264	315	420	437
Kg oral morphine equivalents (omeq)	20.4	22.7	26.6	36.0	36.8
Drug-use intensity per year					
DDD/user/year	87.8	88.0	99.8	123.7	126.9
grams omeq/user/year	7.6	7.5	8.4	10.6	10.7

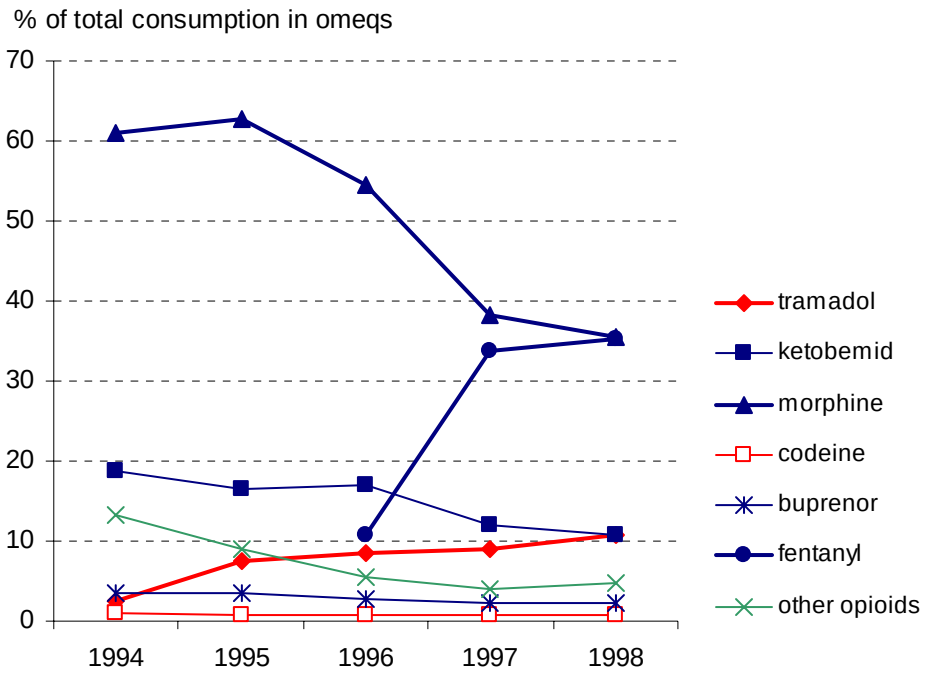


Figure II-2. Different opioids share in percentage of the cancer patients' overall consumption of opioids, 1994 to 1998.

5.2.5 The drug-use intensity

The drug-use intensity increased by 41% from 1994 to 1998, corresponding to an increase from 7.6 to 10.7 g omeq/user/year. The increase in drug-use intensity became steeper after 1996, particularly for patients using strong opioids (Fig. II-3).

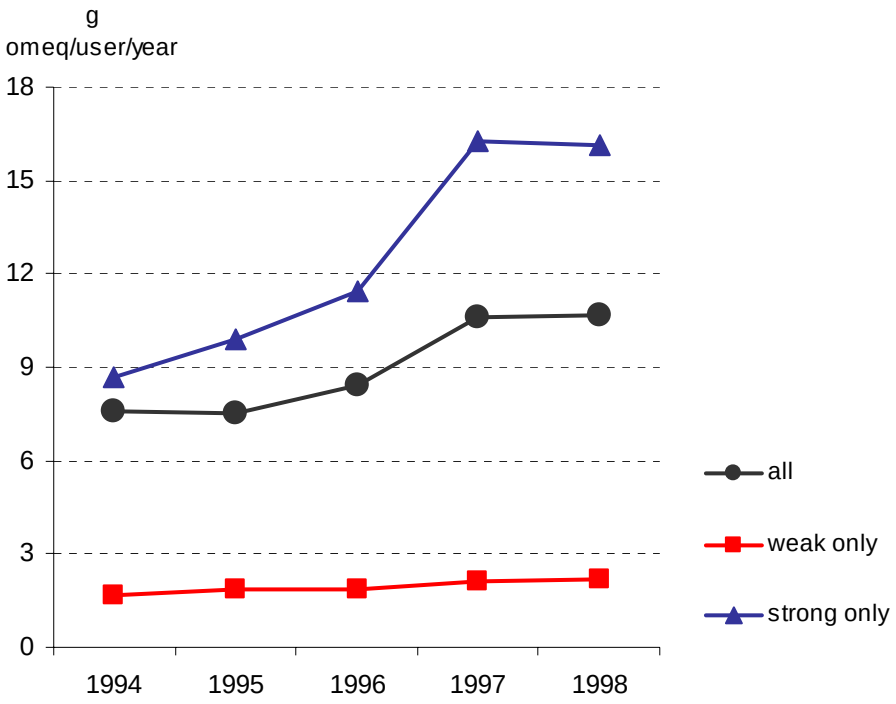


Figure II-3. The drug-use intensity (DI) from 1994 to 1998. DI is the average use of opioid/user per year measured in g oral morphine equivalents.

5.2.6 Different cancer diagnoses’ contribution to the use of opioids

No changes in the distribution between the different cancer diagnoses among the opioid users and their share of the total use of morphine equivalents were seen during the 5-year period, except for a small relative increase in the number of breast cancer patients (Table II-4). Forty-nine percent of the opioid users and 53% of the consumption were related to one of the four cancer diagnoses; breast, colorectal, lung and prostate cancer, which were also the four most frequent cancers.

Table II-4: Different diagnoses' contribution to cancer patients' use of opioids, 1994 and 1998.

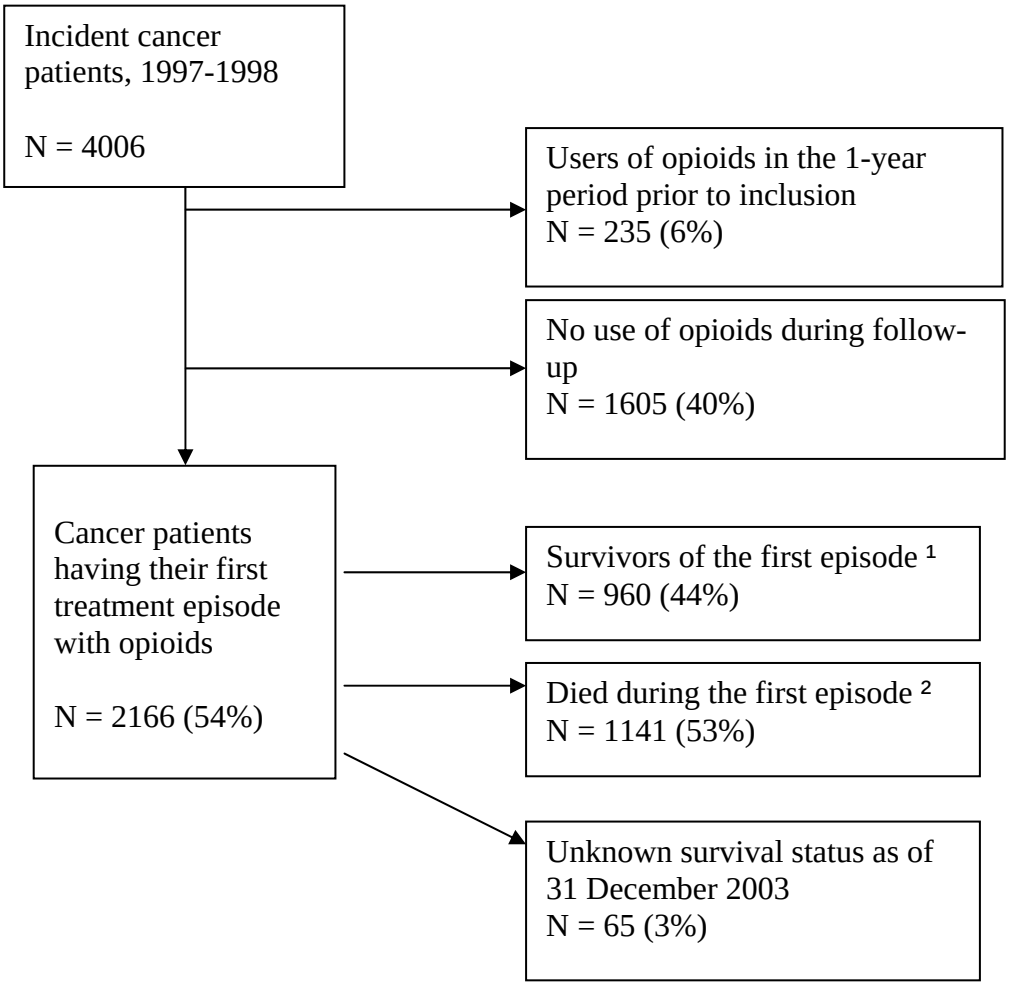
	% opioid users		% of consumption		Number of patients using opioids	
	1994	1998	1994	1998	1994	1998
Breast	17.8	20.9	19.1	18.1	481	718
Colorectal	13.2	12.3	12.4	12.5	356	425
Prostate	7.7	7.0	10.9	10.1	209	242
Lung	10.9	9.1	10.2	12.0	295	315
Hemopoietic	6.6	6.8	7.6	5.0	178	233
Various possibly painful*	3.9	3.6	6.6	5.4	105	125
Other female genital	6.5	7.2	6.5	6.4	175	248
Head and neck	4.9	4.9	5.5	5.7	132	167
Cervix	5.8	5.4	5.4	5.8	157	186
Others **	22.7	22.8	15.8	19.0	610	784
Total	100	100	100	100	2698	3443

* various possible painful cancers include: mediastinal, pleural, sarcomas, oesophageal and liver cancer

** Patients from each group of the following cancers consumed less than 4% of the opioids in 1998: kidney, bladder, pancreas, melanoma, brain, stomach, other male genital, various others, unspecified

Figure III-1: Flowchart study III

Opioid use among incident cancer patients with a follow-up period of 5 to 7 years after the diagnosis (until death or 31 December 2003)**.**



¹ The patients were alive 4 months after the last opioid prescription in the first episode.

² The patients died less than 4 months after the last opioid prescription in the first episode.

5.3 *Study 3: Cancer patients' first treatment episode with opioids: a pharmaco-epidemiological perspective* [III]

Aim: To analyse the epidemiology of the first episode of opioid treatment in a population-based cohort of cancer patients

- Incidence of treatment and its relation to the course of disease, type of cancer and characteristics of patients
- First choice of opioids and the duration of the first treatment episode

5.3.1 Incident cancer patients 1997 and 1998

The characteristics of the 4006 incident cancer patients (diagnosed in 1997 and 1998) fulfilling the inclusion criteria (section 4.4.3.1) are shown in Table III-1. Only 3,771 patients were included in the cohort of incident cancer patients at risk for a first time episode of opioid use, since 235 patients (6%) had already used the drugs in the year prior to cancer diagnosis (Fig. III-1 Flowchart).

Table III-1. Characteristics of incident cancer patients from the County of Funen in 1997 and 1998, N = 4006.

Diagnosis	Females	Males	Age at diagnosis	Cancer stage at the time of diagnosis (%)				5-year survival
			(mean)	local	regional	metastatic	unknown	(%)
Hemopoietic	137	178	64.9	13	6	14	66	41
Breast	689	6	62.0	59	31	6	4	74
Colorectal	238	291	70.9	41	32	17	10	39
Lung	211	311	67.3	28	29	30	12	9
Prostate	0	291	75.1	26	7	25	43	33
Female genital	303	0	63.4	49	23	10	17	54
Other visceral [1]	222	442	68.8	36	16	20	28	28
Head and neck	51	125	64.1	65	28	3	3	51
Others [2]	234	277	57.0	58	12	13	17	56
All	2085	1921	65.7	42	21	16	20	43

[1] Other visceral: cancer diagnoses (number of patients)
bladder (236), pancreas (110), kidney (98), liver (81), stomach (53), oesophagus (51), gallbladder (21), retro- and peritoneal (6), small intestine (6), endocrine glands (2)

[2] Others:
melanoma (170), brain (130), unspecified (50), testis (45), metastases (40) sarcoma (24), peripheral nerves (15), eye (14) , connective tissue (12), other male genital (5), bone metastases (5), bone (1)

5.3.2 Incidence of opioid use

Among the 3,771 patients in the cohort 57% (N=2166) had received a prescription for opioids before the end of the 5-7-year period of follow-up (Fig. III-1 Flowchart). The time to the first episode of opioid use among men and women is shown as Kaplan-Meier plots in Fig. III-2. When sex-related cancers were excluded from the analysis, no statistically significant difference between men and women was observed in time from diagnosis to first opioid prescription.

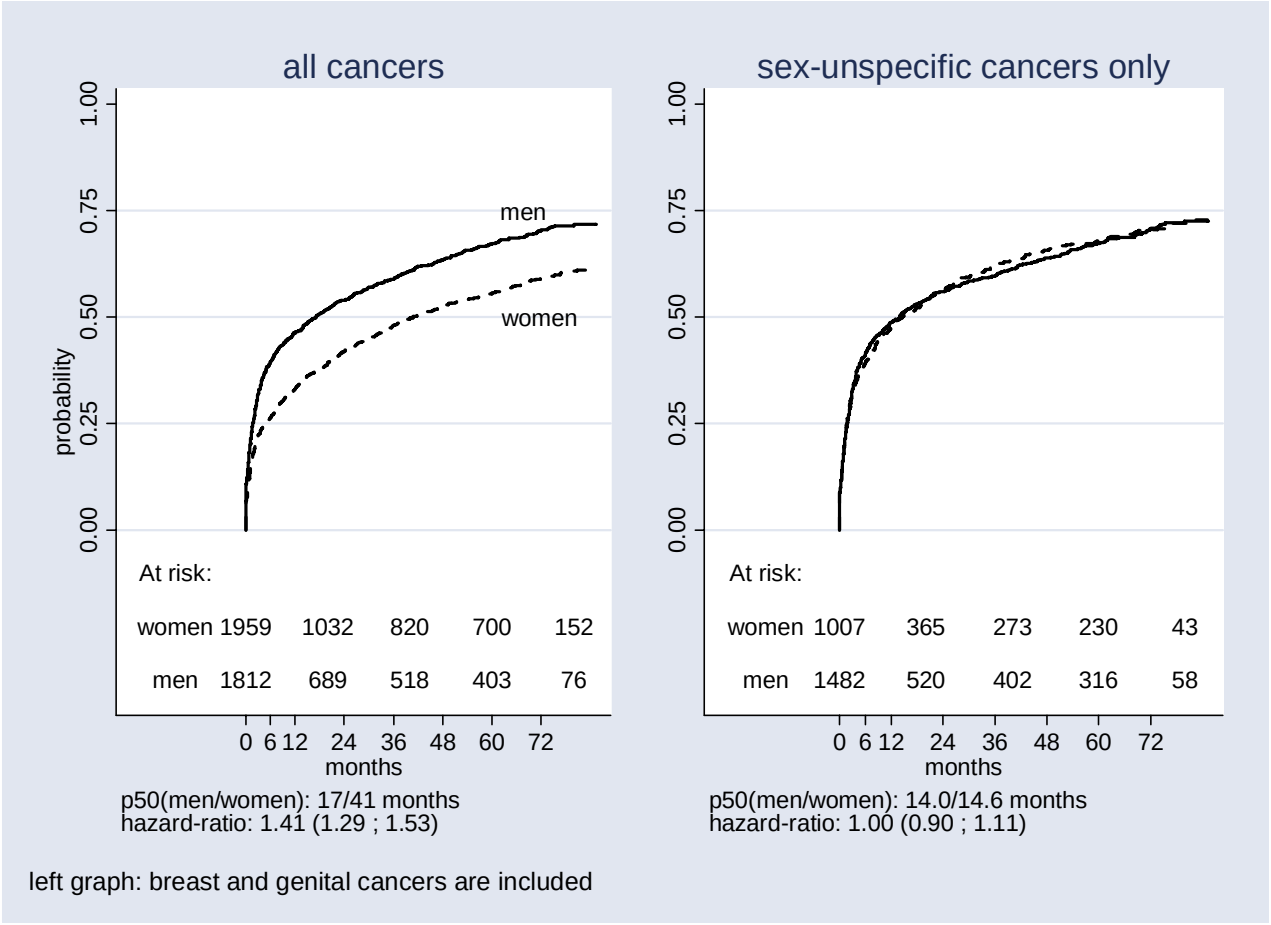


Figure III-2: Incident opioid treatment among cancer patients. Kaplan-Meier estimates of the cumulative probability of opioid use.
p50: the time (months) when half of the cancer patients had received an opioid prescription (correlates to median survival time).

Twenty percent (N=410) of the 2,166 incident opioid users received their first prescription near the time of diagnosis and 50% had been treated within 29 months.

By 1 July 2003 (six months before the end of the follow-up period) the number of incident opioid users was 2,131 and 43% (n = 913) of these patients had started their first treatment episode in the

terminal phase (< 6 months before death). Sixty percent (N=2,409) of the cohort of cancer patients died before the end of follow-up and in this group 70% (N=1,686) had received one or more episodes of opioid treatment while the similar figure for those who were alive was 38%.

Considerable differences between cancers were found in the cumulative probability of opioid use 1, 2 and 5 years after diagnosis (Table III-2).

Table III-2. Percentage of cancer patients becoming incident opioid users after 1, 2 and 5 years of follow-up (N = 3771)

Cancer	Patients at risk	1-year (%)	2-year (%)	5-year (%)
Hemopoietic	297	31	39	48
Breast	671	17	25	39
Colorectal	511	35	45	58
Lung	466	74	77	78
Prostate	279	42	51	70
Female genital	285	25	35	48
Other visceral	611	52	57	63
Head and neck	169	47	51	59
Other	482	26	31	42
Total	3771	38	45	55

The overall incidence rates (new opioid users per 100 cancer years) for patients with local, regional, metastatic and unknown disease stage were 14, 32, 139 and 25, respectively. In patients with head and neck cancer, the highest incidence rate (79 new users per 100 years) for opioid use was found for regional disease, while for all other cancer types metastatic disease was associated with the highest incidence rate.

An inverse relation was demonstrated between the incidence rate and the 5-year survival for the cancer type (Fig. III-3).

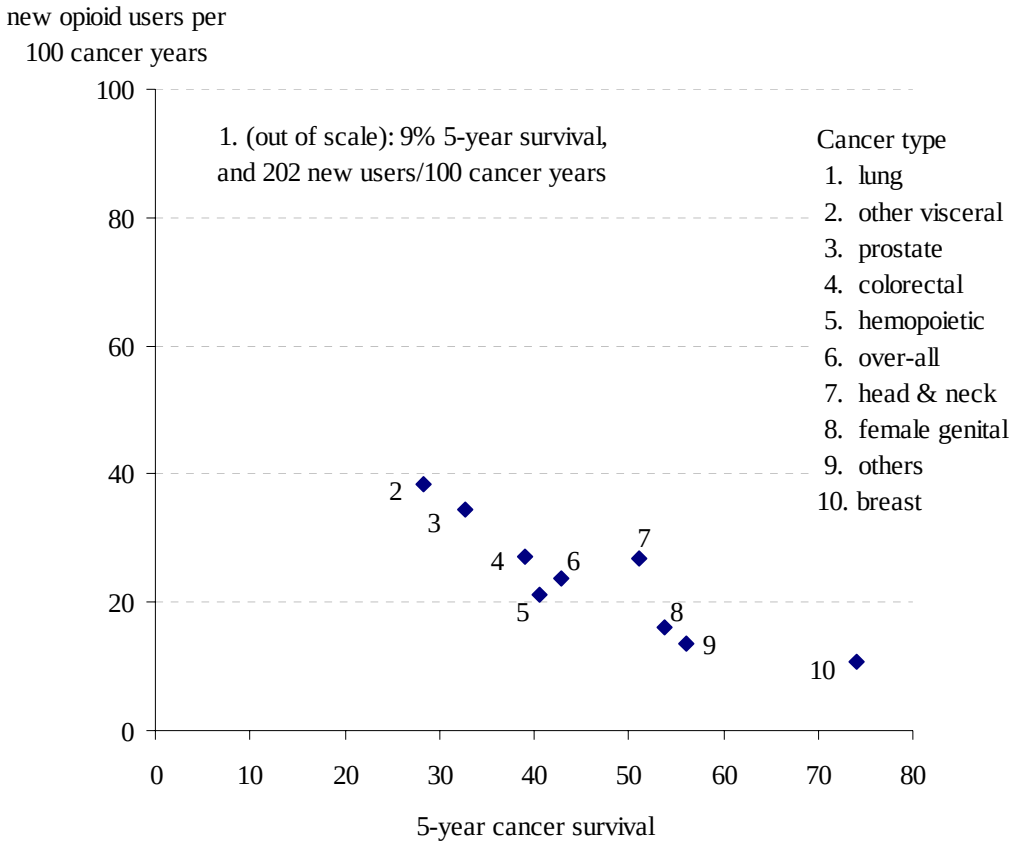


Figure III-3. The incidence rate of new opioid users among incident cancer patients displayed as a function of the 5-year cancer survival.

5.3.3 First treatment episode and choice of opioid

The first choices of opioid are presented in Table III-3. Tramadol was the most frequent choice, regardless of the patient’s disease status. Thirty-three patients received both a strong and a weak opioid in the first prescription and were categorised as patients with a strong index opioid for the analyses. Forty-three percent of the terminal patients were given a weak index-opioid, while 64% of the non-terminal users started treatment with a weak opioid.

Table III-3. First choice of opioid to cancer patients; percentage of patients receiving the substance

	All [1]	**Not terminal**	**Terminal**
Patients	2131	1218	913
% of incident users	%	%	%
Morphine	19	14	25
Fentanyl TD	3	1	5
Ketobemidone	18	16	20
Tramadol	48	55	39
Codeine	7	9	4
Others [2]	6	5	7

[1] Incident users after 1 July 2003 not included

[2] Other "strong" opioids (377 patients) and dextropropoxyphene (2 patients)

The influence of the cancer type on first choice of opioid was analysed for all cancer patients, who became incident opioid users before 1 July 2003 (Table III-4). Except for breast cancer, the preference for a strong index opioid did not seem to be related to the type of cancer, since none of the odds ratios for the other cancer types differed significantly from colorectal cancer (Table III-4). Patients with breast cancer seemed to receive strong index opioids less frequently than patients with colorectal cancer.

The influence of sex, age, disease stage (at the time of the diagnosis) and terminal status (at the time of the first opioid prescription) on first choice of opioid was analysed for non sex-related cancers (Table III-4). Older patients (above 60 years of age) were more likely to receive a weak opioid as first choice, while no statistically significant associations to sex and stage were demonstrated. After adjusting for all other factors, the odds ratio for getting a strong opioid was 1.96 for patients in the terminal phase compared to non-terminal patients.

Table III-4. Characteristics of incident opioid users[1] and the adjusted odds-ratios for choosing a strong versus a weak index opioid.

	Opioid users		Adj. odds-ratios [95% CI] for
	Patients	% women	strong vs weak index opioid
ALL CANCERS			
All	**2131**	**49**	**adj. for stage, sex, age, terminal st**
Colorectal	301	47	1.0
Breast	279	100	0.63 [0.43 , 0.92]
Hemopoietic	145	44	0.70 [0.45 , 1.10]
Lung	365	40	1.34 [0.97 , 1.84]
Prostate	196	0	0.76 [0.51 , 1.13]
Female genital	139	100	0.93 [0.60 , 1.44]
Other visceral	393	35	1.13 [0.83 , 1.55]
Head and neck	101	29	1.40 [0.88 , 2.24]
Others	212	47	0.89 [0.61 , 1.29]
SEX-UNSPECIFIC CANCERS ONLY			
Sex	**1506**	**41**	**adj. for diagnosis, stage, age, term**
Women			1.0
Men			1.17 [0.94 , 1.44]
Cancer-stage at diagnosis			**adj. for diagnosis, sex, age, term**
Local	510	43	1.0
Regional	368	38	1.05 [0.79 , 1.39]
Metastases	331	41	0.94 [0.70 , 1.28]
Unknown	297	41	1.05 [0.75 , 1.45]
Age at index-date			**adj. for diagnosis, sex, stage, term**
50-59	248	41	1.0
0-49	142	41	0.82 [0.54 , 1.26]
60-69	404	34	0.72 [0.52 , 1.0]
70-79	429	43	0.59 [0.43 , 0.82]
>=80	283	47	0.63 [0.44 , 0.91]
Terminal status			**adj. for diagnosis, sex, age, stage**
Not terminal			1.0
Terminal			1.96 [1.56 , 2.46]

[1] Incident users after 1 July 2003 not included

5.3.4 Survivors and non-survivors of first episode

Forty-four percent (N=960) of the incident opioid users survived the first treatment episode, and 60% (N=575) of these patients had one or more later episodes of opioid treatment within the follow-up period (after a median of 351 days (25 percentile: 189 days; 75 percentile: 718 days, range 124 – 2333 days)).

The duration of treatment, defined as the time from the index-prescription to the last prescription (see section 4.4.3.2) in the first episode is shown in Fig. III-4. The proportion of patients with only 1 prescription in the first episode was 50% in the survivors’ group and 17% in the non-survivors’ group.

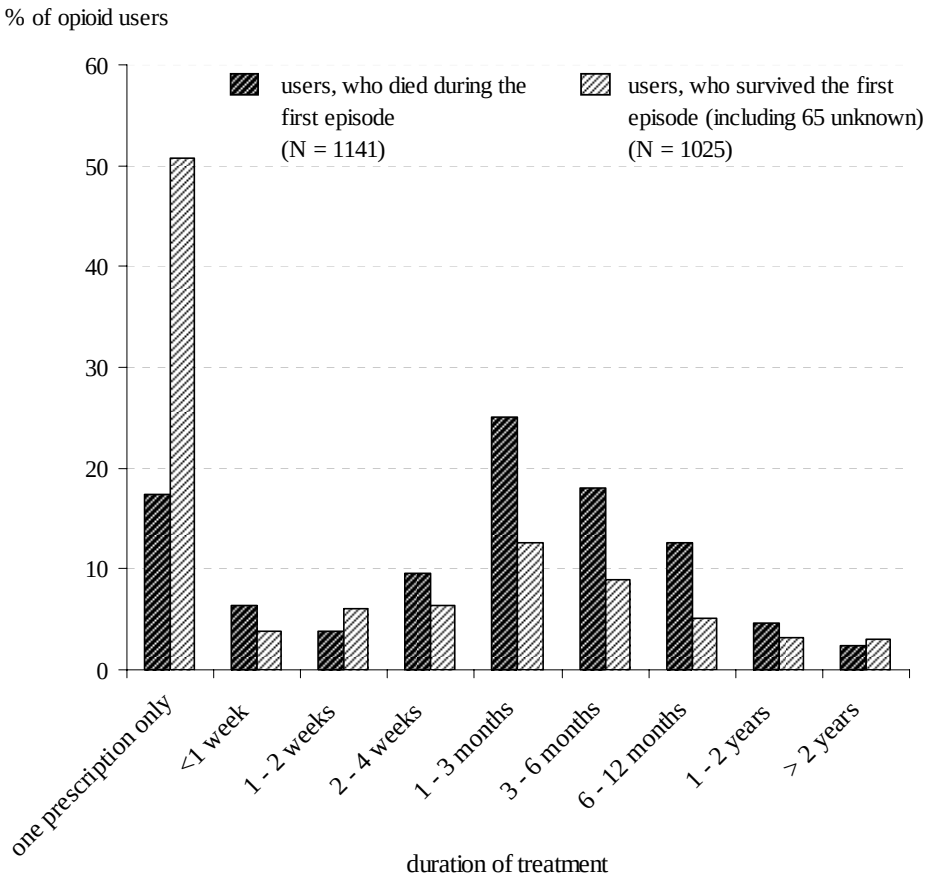


Figure III-4. Duration of cancer patients' first treatment episode with opioids; the time between the first and the last prescription.

Fifty-three percent of the patients (N=1141) died during the first treatment episode, i.e. less than 4 months between the last prescription and death. The median time from the last prescription to death was 10 days or less.

6. DISCUSSION

6.1 Principal findings

The cancer patients accounted for the majority of the population’s increased use of strong opioids, while the increase in the use of weak opioids mainly was due to an increased number of users among non-cancer patients. Among the cancer patients, the proportions of patients who received opioids were 20% and 40% if analysed over a 1-year period or a 5-year period, respectively. During the 5-year period from 1994 to 1998, the cancer patients’ use of opioids changed. The weak opioid tramadol was increasingly used as first choice opioid, the average consumption of strong opioids per patient increased and the opioid treatment seemed to be introduced at an earlier stage in the patients’ disease courses. After 5 to 7 years of observation more than half of all incident cancer patients had their first treatment episode with opioids. Whether a weak or a strong opioid was the first choice, when a cancer patients started treatment with opioids, seemed to be influenced by the disease stage and the age of the patient, but tramadol continued to be the most used first choice opioid.

6.2 Methodological considerations

The factors affecting the value of using secondary data sources and the epidemiological research methods used in the 3 studies are discussed in this section. The first part deals with the limitations and advantages of using routine-collected data, the second part with the introduction of biases, the third part with the designs chosen for the 3 studies and the fourth part with the interpretation of the results in relation to the data used.

6.2.1 Limitations and advantages of routine-database studies

The thesis is based on 3 observational studies which are all routine-data-based studies (87) characterized by the fact that data on both the exposure (cancer) and outcome (opioid use) are obtained from routine data-collection systems, as in this case the Cancer Registry and the prescription database OPED. The main limitations in this type of studies are the limited number of variables available (87) and the lack of control over the collection of data (88). In our project, we were also limited by the delay in update of cancer cases due to the validation procedures in the Cancer Registry. When the database for this project was produced by linkage between the Cancer Registry and OPED, we could only receive validated data on cancer patients until 31 December 1998.

6.2.1.1 Limited number of variables.

Only incident cancer cases are registered in the Cancer Registry and there are no data on recurrence or progression of the cancer disease, neither do we have any knowledge of the patients’ pain episodes. For the opioid prescriptions we had no knowledge of dosage instructions or indications for treatment. We assumed that the use of opioids among cancer patients was mainly related to the cancer disease. Thereby we introduced an information bias because some of the opioids may have been prescribed for incidental conditions, unrelated to the cancer diagnosis. In our study, we found the incidence of opioid use among incident cancer patients to lie between 11 - 202 new users per 100 years of risk (mean value: 24 new users per 100 years). The crude incidence of opioid use in the background population (including cancer patients) was 4 per 100 years of risk in year 2000 (3). The assumption is also supported by some studies showing that pain in cancer patients is related to the cancer in most of the cases (20;21). In a open prospective study of 2266 cancer patients referred to a pain service, the majority of patients had pain caused by cancer (85%) or antineoplastic treatment (17%); 9% had pain related to cancer disease and 9% due to aetiologies unrelated to cancer (21).

6.2.1.2 Advantages.

The advantages of using the secondary data sources (88) in a project like this include the size of the sample, the representativeness of the population, the elimination of recall bias and the elimination of an effect on the prescribing behaviour due to attention caused by the research question.

6.2.2 Introduction of biases

6.2.2.1 Information biases

Both the Cancer Registry and OPED have previously been shown to be of high validity and coverage (49;50;55), and the records provide near-complete data on the entire population in the County. The Cancer Registry has been found to be 96-98% complete for the different cancer types, the diagnosis is based on histology in 90% of the cases and on death certificate only in less than 2% of the cases (64). Data to OPED were delivered directly from all pharmacies in the county. The precise amount of opioids bought outside the county is unknown, but in another drug class, the lipid-lowering drugs, it was found that less than 1% of the prescriptions were filled outside the county (89). In 1994, less than 0.5% of the total quantity of medication reimbursed by the county was purchased at pharmacies outside the county (50). We assume the problem to be of minor importance.

Only data on the opioid use from the primary care sector were included, which represents around 90% of the total use in the country (4;35). Patient-specific data on in-patient care could not be retrieved. We assumed that cancer patients only consumed a small proportion of the opioids used in the secondary health care sector, and the information bias introduced because of this is likely to be minimal.

6.2.2.2 Selection biases

By choosing the population in the County of Funen we introduced a risk of selection bias. We found it justifiable to extrapolate the results to the whole of the Danish population, because Funen covers 9% of the total population and it is considered to be representative of the whole country, both with regard to demographic variables (50), cancer epidemiology (64-66) and consumption of opioids (in the County of Funen in 2000 and 2003 the total use of N02A and of tramadol was 9.5% of the total consumption in Denmark) (67). One caveat to the risk of selection bias was the introduction of mammography screening in the County of Funen in November 1993 for women 50-79 years of age. Apart from Funen, Copenhagen County was the only other location in Denmark, where mammography screening was introduced. The screening resulted in a mean increase in the number of patients with invasive breast cancer aged 50-79, from 129 patients/year before the screening started to 168 patients/year after the introduction of the screening (90). By using the figures from the medical technology assessment report (90) less than 8% of the patients with invasive breast cancer included in study III were estimated to be found specifically due to the screening procedure.

We only included patients, who were living in the County in the specific time of interest to the study question. Therefore we introduced a small risk of selection bias, by excluding cancer patients who migrated in and out of the County. Less than 5% of the patients in the research database had a potential migration problem to consider, and this proportion became even smaller when the specific study periods for the three studies were considered.

6.2.2.3 Misclassification

During the data reduction process necessary for presentation of data related to the cancer diagnosis, we introduced a risk of misclassification. The patient’s first cancer diagnosis and time of diagnosis were used as reference for the analyses. Around 7% of the cancer patients in the research database had more than one cancer diagnosis, but in the cohorts selected for the different analyses, this proportion was smaller, reducing the risk of misclassification.

6.2.3 Design of the 3 studies

As data source in the 3 studies, a research database was produced by record linkage between the data from the Cancer Registry and OPED. The CPR-numbers were used as personal identifiers implying that all data could be drawn on the individual level.

In the first two studies, compromises between the cohort study method and the cross-sectional survey method were used. The 5-year cohorts of cancer patients in study I and II were sliced in cross-sections of 1 year’s duration. This method allowed both incident and prevalent cancer patients’ pain treatments to be analysed, but the results had to be interpreted in relation to the duration of the period chosen for observation. The third study was a pure cohort study of incidence of pain treatment among incident cancer patients. Naturally, this design only allowed conclusions for incident cancer patients, only reflecting a proportion of the pain treatment in the prevalent group of cancer patients, which the general practitioner is presented with in daily clinical life. Therefore, the strength of the method used in study III is the ability to predict the use of opioids among new cancer patients, given the surrounding premises are similar to the study, but the weakness is the lacking ability to extrapolate to the situation for the prevalent cancer patients.

In our analyses of the initiation, duration and the ending of an opioid treatment episode we had to make some assumptions based on the general knowledge of cancer patients’ frequent fluctuations in pain, the lack of recommended daily or maximum dosages, switches between opioid substances or the frequent use of different substances simultaneously. Assumptions instead of knowledge weaken the conclusions in the studies, but this is the price to pay in routine-data-based studies.

Judged by the cross-sectional studies, the prescribing practices regarding pain treatment seemed to stabilise in 1997 and 1998, but we do not know to what degree prescribing practices have changed after 1998. In the cohort study (Study III) we were able to follow the cancer patients’ use of opioids until the 31 December 2003, and this study did not indicate major changes in the first choice of opioid among the incident cancer patients compared with the first choice of opioid among the prevalent cancer patients in 1997 and 1998 in study II.

6.2.4 Interpretation of the results

The 3 studies all analyse the cancer patients’ use of opioids. Because data on the presence of pain among the cancer patients are lacking, it is not possible to know, if the patients’ use of opioids are related to pain. Interpretations of the results in the thesis are built on the main assumption that there is a strong association between the use of opioids and the presence of pain. Even though Danish doctors are more willing to prescribe opioids to patients compared with the doctors in the other Scandinavian countries, and even though Denmark has had the highest use of opioids per capita in the world, we have not been able to identify any indication in the literature or from daily clinical experience that Danish cancer patients are prescribed opioids without having pain.

Pharmaco-epidemiological routine-data-based studies of opioid use will not eliminate the risk of underestimating the national disease burden of cancer-related pain (15). We think that the magnitude of underestimating the need for opioid treatment in Denmark is considerably less compared with other countries, because of: 1) equal access to the services of the health care system through the general practitioner, and 2) the liberal attitude towards use of opioids, and 3) the unique possibilities of performing population-based studies (88).

6.3 Relations to other studies

Few studies have dealt with the use of opioids in Denmark pharmaco-epidemiologically (4;35-37;91;92). In 1992, the general practitioners’ stated that 17% of their patients, to whom they prescribed opioids, were cancer patients (36), and in another study of 1854 prescriptions of strong opioids, the doctors stated the indication for the prescriptions to be due to malignancy in 9.5% (35). In our material 16% of the strong opioid prescriptions redeemed in 1993 were prescribed to cancer patients (data not shown). In a German study the computerised patient records of 330 practices, which treated a total number of 1,104,435 patients over a 3-year period, were analysed (38). Strong opioids were prescribed to just 322 of 16,630 cancer patients (1.9%) and only 99 (0.6%) patients received more than three prescriptions. In our studies, the proportion of cancer patients, who received opioids were 20% and 40% if analysed over a 1-year period or a 5-year period, respectively. Germany was considered one of the opioiphobic countries in Europe (93) in that period. A comparison between these data and ours would more likely reflect different political and cultural attitudes towards treatment with opioids, laws and prescribing regulations. We are not aware of any studies analysing cancer patients’ consumption of opioids in relation to a whole population’s use of opioids. The only other study we found concerning cancer patients’

consumption of opioids was a study of the trend in morphine consumption in Italy and Sicily (39), using sales of sustained-release formulations as an indicator.

Differences in men’s and women’s experience of pain (14;94) and in related health care seeking behaviour have been increasingly discussed. Only few studies have concentrated on cancer patients (95-98), not finding differences related to gender, as in those reported for patients without cancer. The patients in these studies all seemed to have advanced cancer. Our study supports these findings of no differences between male and female cancer patients with regard to use of opioids, even for non-terminal patients.

The results of the studies reflect the willingness described among Danish doctors to prescribe opioids to cancer patients (14;34;99). The quality of the pain treatment for the individual patients cannot be studied in prescription databases and registries. Neither can any conclusions be drawn, whether the patients’ use of opioids represents sufficient treatment with regard to the frequency of treated patients or to the reduction of pain symptoms, because the prevalence of pain is unknown in an unselected cohort of cancer patients identified in a population. Among the terminal cancer patients we identified in study III, the frequency of opioid use seemed almost sufficient compared with common knowledge of the pain prevalence in the group of patients with advanced disease. In a study of Danish cancer patients referred for specialised palliative care, 81% received opioid treatment (100). In spite of this the patients’ initial pain scores were high. Whether this insufficient pain relief is a general problem in patients with cancer pain remains to be investigated. The study also showed that patients who were receiving strong opioid treatment on arrival at the department had higher initial pain scores than the patients on steps 1 or 2 (100). The study indicated that pain intensity was a predictor for use of strong opioids, but the group of patients was highly selected.

Opioids should be introduced into the therapeutic regimen to treat pain at an appropriate time and not withheld to the terminal stages because of opioiphobia (101). In our study, 43% of the patients were terminal when they started their first treatment with opioids. We could not identify any studies addressing the appropriateness of these proportions.

7. CONCLUSIONS

The conclusions are presented according to the operational aims of the 3 studies upon which this thesis is based (appendix[I, II, III]).

7.1 Assessment of the use of opioids in a population’s entire cohort of cancer patients.

Twenty percent of the population’s yearly consumption of opioids was used by patients with a cancer diagnosis. If only the strong opioids were considered, this proportion rose to 30%. During the 5-year period investigated, the population’s consumption of both strong and weak opioids increased. Study I demonstrated that it was in fact the cancer patients, who accounted for the population’s increase in strong opioids, while the increase in weak opioids mainly was due to an increased number of users among non-cancer patients. Fourteen percent of the population’s opioid users had a cancer diagnosis. The absolute number of patients using strong opioids decreased, both among cancer patients and non-cancer patients, but the average use of strong opioids per cancer patients increased dramatically, while non-cancer patients’ average use of strong opioids per patients only showed a slight increase. The number of users of weak opioids increased, both among cancer patients and non-cancer patients, while the average use of weak opioids per patient decreased. The results demonstrated the importance of a differentiated view, when a population’s use of opioids is evaluated.

7.2 Cancer patients’ opioid use analysed over a five-year period.

The cancer epidemiology in the County was almost stable during 1993 to 1998 with a very slight increase in the cancer prevalence. Despite this stability there was an increase in prevalence, incidence and survival of opioid users among the cancer patients. The 1- and 2-year survival after the first opioid prescription increased and we interpreted this to be the result of a tendency to initiate pain treatment earlier in the patients’ symptomatic disease courses. This could explain the increase in incidence rates of new opioid users, and together with a decreased mortality rate for the cancer patients it could explain the increase in the prevalence of opioid users.

The preferences for the choice of first opioid were reversed during the period from strong opioids towards weak opioids. In 1998 half of all incident opioid prescriptions were for tramadol. Whether this was due to implementation of the WHO pain ladder guidelines recommending a weak opioid as step 2 treatment or it was due to the remarkably high popularity tramadol achieved after its launch in 1993 cannot be revealed by this register-based study.

There was a considerable increase in the consumption of opioids among cancer patients, and because the number of users only increased slightly the resulting increase in drug-use intensity was prominent, especially for the strong opioids. Apart from earlier initiation of pain treatment, the increase in drug-use intensity was speculated to be a result of an increasing awareness towards using sufficient doses of opioids. The most likely explanation for the steep increase in drug-use intensity for the strong opioids in 1997 seemed to be the extensive use of transdermal fentanyl to a smaller group of opioid users.

The different diagnoses’ contribution to the proportion of cancer patients using opioids seemed very stable except for a relative high increase in the number of opioid users among women with breast cancer.

7.3 The epidemiology of the first opioid treatment episode among incident cancer patients.

Almost 60% of the incident cancer patients received opioids, if they were observed 5 to 7 years after their cancer diagnosis. Around 20% of the opioid users started the treatment in close connection to the time of the cancer diagnosis. The aggressiveness of the cancer, judged by the 5-year survival, and the presence of metastases were characteristics found to be strong determinants of opioid use, while demographic characteristics played a much smaller role. No differences between male and female cancer patients with regard to use of opioids were identified, even for non-terminal patients.

A dynamic pattern of opioid usage was found, with patients who shifted between periods of use and non-use or patients who used opioids throughout the entire disease course. It was shown that patients could stop using opioids, even after longer periods of treatment. They frequently resumed the opioid treatment, implying that the reason for stopping the first treatment episode was not due to patients’ bad experiences with opioids.

The preference of choosing a strong versus a weak opioid as first choice was mainly determined by the patient being terminal and by age. Tramadol has continuously been a popular choice in the treatment of cancer-related pain in Denmark. Tramadol was used as first choice opioid in 40% of those patients, who could be considered terminal when they started their opioid treatment. We found this proportion to be high, but it remains to be investigated if these terminal cancer patients received a sufficient and effective treatment with tramadol (18;102-104), in which case the choice must be termed appropriate.

8. PERSPECTIVES

8.1 Healthcare perspectives

In Denmark as well as in other countries it is not possible to investigate the true prevalence of pain among cancer patients, because it is impossible to identify all prevalent cancer patients in a population at present time due to the delay in the centralised cancer registration. The results from this thesis can be used for conservative minimum estimates of pain prevalence among the cancer patients, and the pharmaco-epidemiology of cancer patients’ use of opioids can be used in the organisation of national health care systems’ palliative (56) and supportive care.

The studies have demonstrated the heterogeneity in opioid treatment of the patients both with regard to the initiation of the treatment in relation to the time of the cancer diagnosis, the duration of the opioid use and the possibility of stopping a treatment episode. For instance, treatment with opioids is not necessarily associated with a terminal disease stage and it is not necessarily a chronic treatment. Hopefully, our studies of the actual use of opioids can help to remove some of the common beliefs about opioid analgesia that may limit patients’ reporting of pain and also their willingness to take potent analgesic medication (105). More longitudinal studies of individual patients’ switches between opioids and studies of dosages might further help to remove the concerns that some patients harbour (63), when their doctor suggests treatment with opioids.

8.2 Scientific perspectives

The prescription pattern of opioids might be used as a quality indicator for treatment of pain at the level of the community but this implies further studies of the agreement between the opioid use and the presence and development of pain conditions in the patients. Considering the need for individualisation when a patient is treated with opioids, development of quality indicators on the individual level in the prescription databases seems unrealistic.

Even though study III seemed to indicate that opioids were prescribed to a reasonable number of terminal cancer patients, our knowledge is still too sparse regarding the sufficiency of the treatment. The timing of the initiation of opioid treatment and the first choice of opioid should be further investigated. In our study, 43% of the incident cancer patients were terminal, when they started their first treatment with opioids. Is this proportion reasonable or has the treatment been delayed in relation to the occurrence of the patients’ pain symptoms?

Studies of the compliance to the pain treatment are needed. Why do such a high proportion of the patients only receive one prescription in their first treatment episode with opioids?

To discuss a proper organisation of the palliative treatment and the allocation of resources we also need to know who takes the responsibility for the pain treatment of cancer patients during their disease course. In the prescription database it is possible to identify to which extent the opioids were prescribed by general practitioners or by hospital departments.

The uses of tramadol and transdermal fentanyl have increased considerably among cancer patients. More effort should be put into analyses of the benefits and disadvantages of using these drugs and their use should be viewed against less expensive drugs like morphine and methadone.

9. SUMMARIES

9.1 Dansk resumé [Danish summary]

Denne Ph.d.-afhandling består af en oversigt og tre artikler til internationale tidsskrifter. Arbejdet blev udført under mine ansættelser på Klinisk Farmakologi, Institut for Sundhedstjenesteforskning, Syddansk Universitet, og på Forskningsenheden for Almen Praksis i Odense, i perioden 2001-2004.

Baggrund Epidemiologisk og farmakologisk viden om cancersmerter og behandlingen heraf er nødvendig for at kunne planlægge palliativ og understøttende behandling af cancerpatienter hensigtsmæssigt og for at kunne erkende de forskellige behov, som patienterne har i forløbet af deres cancersygdom. Den omfattende registrering i Danmark af både cancerpatienter og forbrug af lægemidler giver optimale forudsætninger for at udføre populationsbaserede farmako-epidemiologiske studier af cancerpatienters lægemiddelforbrug.

Formål Formålet med afhandlingen var at studere cancerpatienters forbrug af opioider farmako-epidemiologisk.

Metoder Tre farmako-epidemiologiske studier blev udført fra en populations-baseret forsknings-database, som blev skabt ved kobling på individniveau mellem Cancer Registret og receptdatabasen Odense Universitets Farmakoepidemiologiske Database (OPED).

Studie 1 Formålet var at beskrive anvendelsen af opioider i en populations samlede kohorte af cancerpatienter. Cancerpatienterne var ansvarlige for populationens stigning i forbruget af stærke opioider, mens stigningen i forbruget af svage opioider især skyldtes en stigning i antallet af brugere blandt ikke cancerpatienter.

Studie 2 Formålet var at analysere ændringer i cancerpatienters opioidforbrug over en 5-årig periode. Patienternes forbrug steg betragteligt i perioden 1994 til 1998, hvor der både var stigning i prævalensen, incidensen og overlevelsen af opioid brugere. Præferencen for førstevalgs-opioidet ændredes fra stærke opioider til svage opioider. Både det svage opioid tramadol og det stærke opioid transdermal fentanyl blev anvendt i stigende omfang i perioden.

Studie 3 Formålet var at analysere epidemiologien for den første behandlingsepisode med opioider blandt en kohorte af incidente cancerpatienter. Næsten 60% af alle incidente cancerpatienter havde brugt opioider inden for en observationsperiode på 5-7 år. Tramadol var det mest anvendte førstevalgs-opioid, selv blandt cancerpatienter, der var terminale, når de startede behandlingen.

Konklusion En anseelig andel af alle cancerpatienter vil bruge opioider. Anvendelsen af opioiderne er spredt ud over hele sygdomsforløbet og begrænser sig ikke kun til den terminale del af sygdomsforløbet. Varigheden af behandling med opioider varierer og behandlingen er ikke nødvendigvis kronisk.

9.2 English summary

This PhD dissertation comprises an overview and three papers for international journals. The work was carried out at the Research Unit of Clinical Pharmacology, Institute of Public Health, University of Southern Denmark, and the Research Unit for General Practice in Odense, in the period 2001-2004.

Background In order to plan the palliative and supportive health care of cancer patients in the community and for the doctors to acknowledge the patients’ different needs during their disease courses epidemiological and pharmacological knowledge about cancer pain and its treatment is necessary. The comprehensive registration in Denmark of both cancer patients and use of drugs provides a unique opportunity to perform population-based pharmaco-epidemiological studies on cancer patients’ drug use.

Aim The purpose of this thesis was to study cancer patients’ use of opioids pharmaco-epidemiologically.

Methods Pharmaco-epidemiological analyses were performed on a population-based research database established by linkage between the Cancer Registry and the prescription database Odense University Pharmacoepidemiological Database (OPED) on the level of the individual. Three studies were carried out.

Study 1 Aimed to assess the cancer patients’ use of opioids in a populations’ entire cohort of cancer patients. The cancer patients accounted for the population’s increase in strong opioids, while the increase in weak opioid mainly was due to an increased number of users among non-cancer patients.

Study 2 Aimed to go into details about the cancer patients’ opioid use and analyse changes over a five-year period. Cancer patients’ use of opioids increased considerably from 1994 to 1998 where an increase in prevalence, incidence and survival of opioid users was demonstrated. During the period the preferences for the choice of first opioid were reversed from strong opioids towards weak opioids. Both the weak opioid tramadol and the strong opioid transdermal fentanyl were increasingly used during the period.

Study 3 Aimed to analyse the epidemiology of the first episode of opioid treatment in a population-based cohort of cancer patients. Almost 60% of incident cancer patients had used opioids after 5-7 years of observation. Tramadol was the most used first choice opioid even in cancer patients, who were considered terminal, when they started the opioid treatment.

Conclusion A substantial proportion of cancer patients will use opioids. The use is dispersed throughout the disease courses and not only confined to the terminal stage of the disease. The duration of treatments varies and treatment with opioids is not a chronic condition.

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11. APPENDICES

I : Jarlbaek L, Andersen M, Kragstrup J, Hallas J. Cancer patients' share in a population's use of opioids: A linkage study between a prescription database and the Danish Cancer Registry. Journal of Pain and Symptom Management 2004; 27(1):36-43.

II: Jarlbaek L, Andersen M, Hallas J, Engholm G, Kragstrup J. Use of opioids in a Danish population-based cohort of cancer patients. Journal of Pain and Symptom Management 2005; 29(4): 336-343

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Original Article

Cancer Patients' Share in a Population's Use of Opioids. A Linkage Study Between a Prescription Database and The Danish Cancer Registry

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Abstract
The aim of this study was to 1) assess cancer patients' share in a population's use of opioids and how much it influences the total use, and 2) analyze trends in the population's use of "weak" and "strong" opioids during a five-year period. Person-identifiable data on opioid prescriptions and cancer diagnoses from a Danish county (n ~ 470,000) were retrieved from a prescription database, OPED, and The Danish Cancer Registry from 1993–1997 (identifying 23,843 cancer patients). In a given year, 14% of the population's opioid users were cancer patients, and they received 23% of the total opioid consumption. Over time, the number of patients using weak opioids increased and the number using strong opioids decreased among both cancer patients and non-cancer patients. Cancer patients' consumption of strong opioids increased dramatically in 1996–1997, almost accounting for the entire increase in the whole population's consumption of strong opioids. J Pain Symptom Manage 2004;27:36–43. © *2004 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words
Cancer pain, opioids, consumption, population-based, record linkage, cohort study, OPED, Danish Cancer Registry, pharmaco-epidemiological, morphine, tramadol, transdermal fentanyl

Introduction

Denmark has the highest legal use of strong opioids per capita in the world[1] and the use is still increasing.[2,3] The majority of the opioids is prescribed in the primary health care sector, and the majority of opioid users seems to be patients treated for non-cancer conditions.[4-6] We do not know, however, how the consumption of opioids is distributed among patients with or without cancer, nor the extent to which the use of "weak" or "strong" opioids is related to the diagnosis of cancer.

Cancer patients often develop severe pain,[7] and according to previous studies, Danish doctors seem willing to prescribe opioids to this population.[8,9] The indication for use of strong

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opioids in Denmark is nociceptive, opioid-sensitive pain that cannot be relieved by other drugs or interventions. Apart from chronic pain due to malignancy, severe acute pain and chronic nociceptive nonmalignant pain are mentioned as potential indications for opioid therapy. Restrained use of opioids is recommended for the last category of pain.[10,11] Based on this knowledge, one could assume that cancer patients accounted for a substantial part of the population's consumption of strong opioids, and non-cancer patients accounted for most of the weak opioids consumed.

The aim of this study was to assess the use of opioids in the entire cohort of cancer patients in a population and how it relates to the overall use in this population. The changes in opioid use over a 5-year period, during which tramadol and transdermal fentanyl were introduced, were analyzed, focusing on the use of weak and strong opioids with regard to the diagnosis of cancer.

Methods

Person-identifiable data from the entire population of the County of Funen (~470,000 inhabitants; 9% of the Danish population) on cancer disease and use of opioids were obtained by linkage of two databases, the Danish Cancer Registry (DCR)[12,13] and the Odense Pharmacoepidemiologic Database, OPED,[14] using the central person registration number (CPR-number) as the person identifier. The CPR-number is a 10-digit code unique to each Danish citizen and used in a large number of social and health-related registries.

OPED is a prescription database holding information on all computerized prescriptions sold from all the pharmacies in the County of Funen via a link to the county's refunding system. Prescription refunding applies to all Danish citizens for most of the drugs sold, including opioids. Because the refunds are prepaid by the dispensing pharmacies, with the accounts being refunded monthly by the county, the coverage of these prescriptions is, for practical purposes, 100%. Coverage has been complete since November 1992. OPED does not contain data on drugs sold without prescription or the few classes of drugs not subsidized by the county. Every record in OPED contains the CPR-number of the patient, the date of purchase, the pharmacy, the prescriber, and a full account of what has been purchased, including brand name, ATC-code, dose unit, and quantity.[15] The prescribed daily dose and the indication for prescribing are not recorded in the database.

In addition to the prescription records, OPED also contains a demographic module holding information of residency and death of the citizens in the county. This demographic module was used to identify the CPR-numbers of all persons resident in the County of Funen during the 5-year period from 1 January 1993 to 31 December 1997, comprising about 565,000 persons. Among those, 23,843 cancer patients with 25,609 diagnoses of invasive cancer were identified in the Cancer Registry. Patients only diagnosed with non-melanoma skin cancer (ICD-7 code: 191) were not included in this study. A person was defined as a cancer patient from the time of the first cancer diagnosis, regardless of whether the patient was cured or not.[16,17] The 15th was used as the date of diagnosis, since only the month and year of the diagnosis were known. Both the data from OPED and the DCR were validated for the period of interest.

Information on the prescriptions redeemed by the cancer patients was received from OPED and linked to the data on the patient's cancer diagnoses. By use of the demographic module, we ascertained that the cancer patients were residents in the county during the periods of interest. A patient was counted as a cancer patient in the calendar year of interest if the diagnosis was from that year or from earlier years. A cancer patient was registered as a user of opioids in the calendar year of interest if at least one prescription was redeemed in that year, even if the cancer diagnosis was established after the date of redemption.

The total use of opioids in the county on a yearly basis during the period 1993–1997 was drawn from OPED, both with regard to the number of users and to the consumption of defined daily doses (DDD). Non-cancer patients' use of opioids was calculated by subtraction of the cancer patients' use from the total values.

The description of the use was based on the ATC (Anatomical Therapeutic Chemical) classification system and the DDD, as recommended by the World Health Organization

(WHO) for drug utilization studies.[18] The basic definition of the DDD is the assumed average maintenance dose per day for a drug used for its main indications in adults. The DDDs for the most commonly used opioids in this study are shown in Table 1.

The DDD is a unit of measurement and does not necessarily reflect the recommended or the prescribed daily dose. Opioids are identified by N02A as the four first digits in the seven-digit ATC-code; the remaining three digits indicate the active substance in the drug. As an exception to this, codeine has the ATC-code R05DA04. The opioids were divided into "weak" and "strong" according to the guidelines from the WHO analgesic ladder.[19] The weak opioids are codeine, dextropropoxyphene, and tramadol. For the weak opioids, only consumption of single entity drugs was included in the study. The rest of the drugs in the N02A group belong to the strong opioids.

Because conventional drug use statistics are made per calendar year both by the Danish Medicines Agency[2,3] and by the International Narcotics Control Board (INCB),[1] the analyses in this study were also based on the calendar year. In the period 1993–1997, the number of opioid users, the consumption of opioids, and the drug-use intensity (DI), defined as the mean amount of consumed defined daily doses/user/calendar year, were analyzed both with regard to the total use of opioids and separated into weak and strong opioids. If the same patients were treated with both weak and strong opioids in the same calendar year, they were counted once in each group of users.

Binomial 95% confidence intervals (CI) are given for the proportions of users.

Table 1
Defined Daily Doses for the Four Opioids Most Commonly Used by Cancer Patients

ATC Code	Drug	Administration Route	1 DDD
N02AA01	morphine	P/R	30 mg
N02AA01	morphine	O	100 mg
N02AB01	ketobemidone	P/O	50 mg
N02AB03	fentanyl	TD	0.6 mg
N02AX02	tramadol	P/O/R	300 mg

ATC = anatomical therapeutic chemical; DDD = defined daily dose; P = parenteral; R = rectal; O = oral; TD = transdermal. Adapted from the World Health Organization.[18]

Results

Opioid Users

In the one-year cohorts of cancer patients, the proportion of opioid users increased from 17% to 21% during the period (Table 2). Of the 23,843 cancer patients identified during the 5-year period, 9,516 (40%) received an opioid analgesic. Around 80% of the cancer patients had their first opioid prescription after the cancer diagnosis and about 16% used an opioid both before and after the cancer diagnosis.

The total number of opioid users in the county increased 49.6% during the period 1993–1997, with a 35% increase among cancer patients and a 52% increase among non-cancer patients. Thus, the proportion of cancer patients among the whole group of opioid users decreased from 15.4% (95% CI: 14.8–15.9%) to 13.8% (13.4–14.3%) (Table 3).

The number of patients using weak opioids increased and the number of patients using strong opioids decreased during the period (Figure 1). This trend applied to both cancer patients and non-cancer patients. The proportion of weak opioid users with a cancer diagnosis increased from 8% (7.3–8.8%) to 10.4% (9.9–10.8%) during the period 1993–1997, and the proportion of strong opioid users with a cancer diagnosis increased from 14.9% (14.4–15.5%) to 17.1% (16.4–17.7%) (Table 3). The proportion of cancer patients using both weak and strong opioids in the same calendar year

Table 2
The Proportion of Opioid Users per Calendar Year in the Non-Cancer Population and Among Cancer Patients

Calendar Year	Non-Cancer Population[a]	Non-Cancer Opioid Uses	%
1993	450,164	14,104	3.1
1994	451,007	15,829	3.5
1995	451,717	18,680	4.1
1996	454,206	19,899	4.4
1997	454,820	21,481	4.7
% increase 1993–1997	1.0	52.3	
	Cancer Patients	Opioid Users with Cancer	%
1993	15,075	2,560	17.0
1994	15,560	2,752	17.7
1995	15,978	3,064	19.2
1996	16,322	3,206	19.6
1997	16,602	3,448	20.8
% increase 1993–1997	10.1	34.7	

[a]The county's total population minus the cancer patients.

Table 3
Opioid Users and Opioid Consumption Per Year, 1993–1997

	All Opioids			Weak Opioids			Strong Opioids		
Calendar Year	All Patients	Cancer Patients	%	All Patients	Cancer Patients	%	All Patients	Cancer Patients	%
Opioid Users/Year									
1993	16,664	2,560	15.4	5,077	408	8.0	15,610	2,330	14.9
1994	18,581	2,752	14.8	8,850	825	9.3	14,801	2,280	15.4
1995	21,744	3,064	14.1	13,649	1,339	9.8	14,004	2,253	16.1
1996	23,105	3,206	13.9	15,743	1,594	10.1	13,579	2,226	16.4
1997	24,929	3,448	13.8	18,385	1,906	10.4	13,033	2,224	17.1
% Increase from 1993 to 1997	49.6	34.7		262.1	367.2		−16.5	−4.5	
Consumption of Opioids in 1000 DDD/Year									
1993	1,245	230	18.5	374	35	9.2	871	196	22.5
1994	1,371	245	17.9	466	45	9.8	905	200	22.1
1995	1,527	272	17.8	606	61	10.0	921	211	22.9
1996	1,695	325	19.2	720	73	10.2	975	251	25.8
1997	1,919	432	22.5	848	95	11.2	1,071	337	31.5
%Increase from 1993 to 1997	54.2	87.5		126.6	174.4		23.0	72.1	

DDD = defined daily dose.

increased from 7% to 20%, and remained stable at 27% among non-cancer patients.

Consumption of Opioids

The cancer patients accounted for 18.5% of the population's opioid consumption in 1993, and after a small decrease in 1994 and 1995, this proportion rose to 22.5% in 1997. The consumption of opioids in the population increased 54.2% during the period 1993–1997, reflecting an increase in both groups of patients. Cancer patients' consumption increased 87.5% and non-cancer patients' increased 46.6% (Table 3). For the non-cancer patients, the increase in consumption of all opioids was slowly declining during the period.

Cancer patients and non-cancer patients affected the population's consumption of weak and strong opioids differently (Figure 2). The non-cancer patients predominantly influenced the increase in consumption of weak opioids, whereas the population's increase in consumption of strong opioids was mainly due to the cancer patients' use. The cancer patients' escalating increase in consumption of strong opioids continued throughout the study period, whereas the non-cancer patients' increase in consumption remained almost stable.

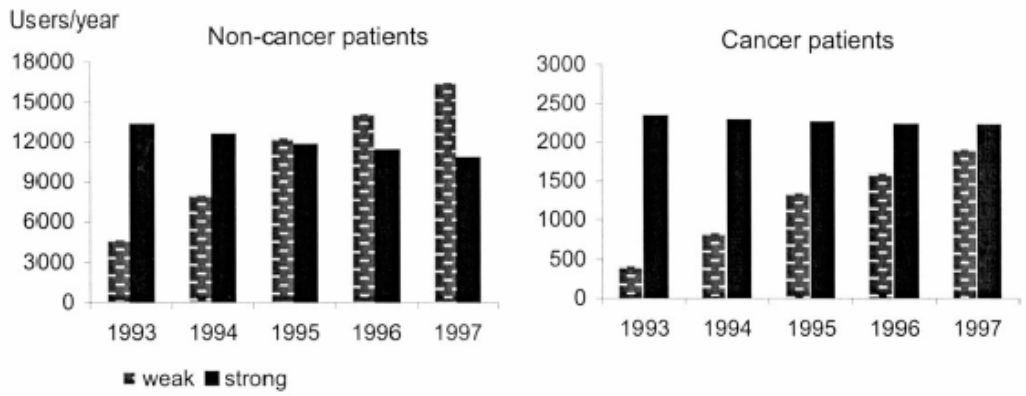

Fig.1. Number of opioid users per year for weak and for strong opioids, presented for non-cancer patients and cancer patients.

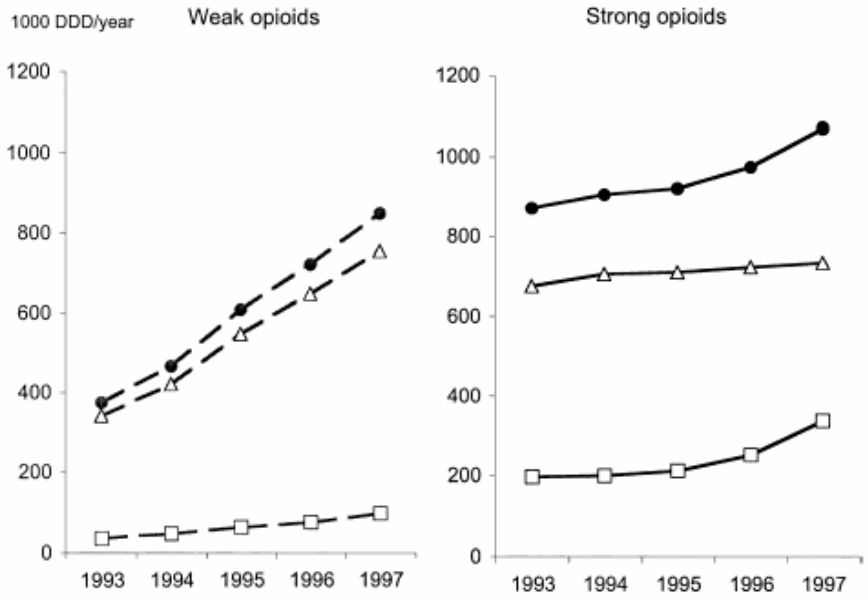

Fig.2. Consumption of weak (---) and strong (—) opioids per year in the population (●) ($n \sim 470{,}000$), separated into cancer (□) and non-cancer patients (△).

Drug Use Intensity

The drug-use intensity (DI) in the population remained stable during the whole 5-year period (Figure 3). This apparent stability, at around 74 DDD/user/calendar year, was the result of some rather pronounced, opposite changes, if weak and strong opioids were analyzed separately. The DI for the weak opioids declined and then stabilized during the period 1993–1997, for both cancer patients and non-cancer patients. The DI of strong opioids increased considerably for the cancer patients, whereas the non-cancer patients only showed a small and declining increase.

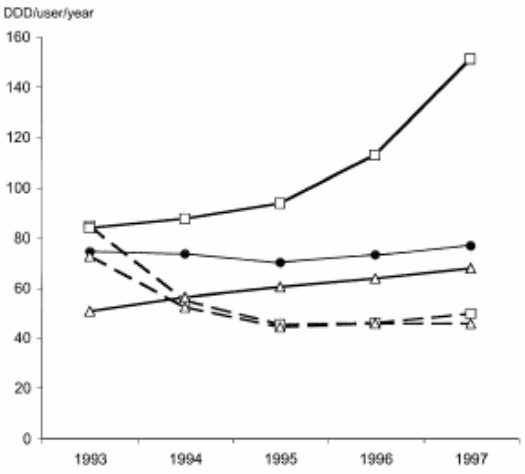

Fig.3. Drug-use intensity per year for all users' overall opioid use (●), for non-cancer (△) and cancer patients' (□) use, separated into strong (—) and weak (---) opioids.

Cancer Patients' Use of Different Opioids

The most commonly used opioids by the cancer patients were morphine, ketobemidone, tramadol, and transdermal fentanyl (Figure 4). Tramadol was marketed in 1993 and transdermal fentanyl in 1996.

Until 1997, users of ketobemidone and morphine were the most frequent. In 1997, this picture changed, when tramadol became the opioid used by most of the cancer patients, 29.1% (27.9–30.3%) compared to 22.1% (21.0–23.2%) having used morphine. The transdermal fentanyl was used by 5.9% (5.3–6.6%) of the opioid-using cancer patients in 1997.

Throughout the period, morphine was the most consumed opioid. The year after its introduction to the market, transdermal fentanyl became the second most consumed opioid (Figure 4). In 1997, 28.4% of all consumed opioid was transdermal fentanyl, compared to 33.0% morphine; tramadol took 13.2%, ketobemidone 11.5%, and other opioids 13.9% of the market.

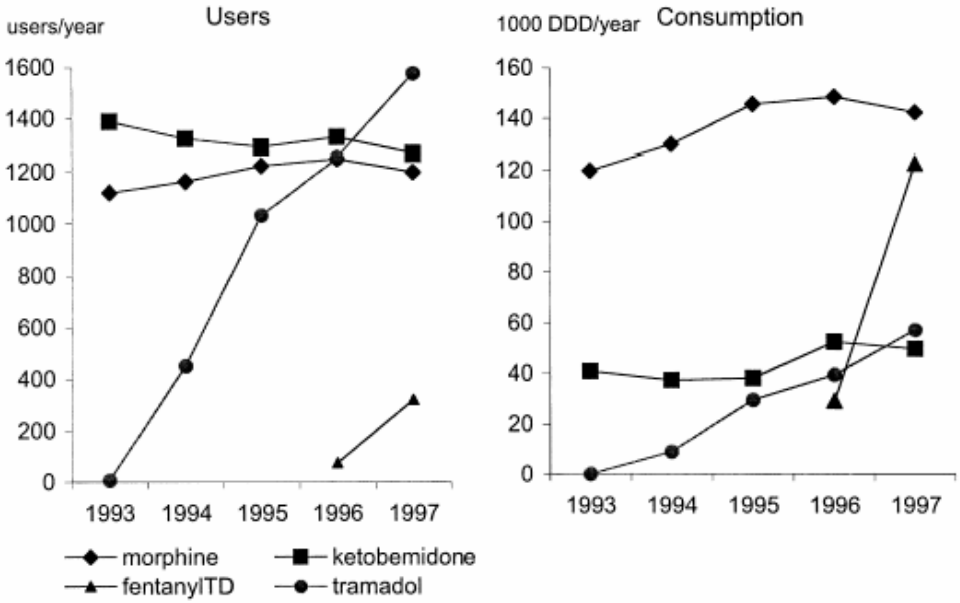

Fig.4. Trends in cancer patients' use of the four most significant opioids during 1993–1997.

Discussion

The cancer patients' share of the population's consumption of all opioids increased from 18.5% to 22.5% during the period 1993–1997, and from 22.5% to 31.5% if only the strong opioids were considered. The population's overall increase in opioid consumption was 54%, and was mainly due to an increasing number of users of weak opioids. The consumption of strong opioids increased 23% and our study demonstrates that it was, predominantly the cancer patients who accounted for the population's increase in consumption of strong opioids. Increasing cancer prevalence could not explain this finding, because, surprisingly, a decreasing number of cancer patients used the strong opioids.

In 1997, the proportion of opioid users was 21% in the cancer cohort and 4.7% in the non-cancer population. It is difficult to view the proportions of opioid users as low or high, because we do not know the frequencies of different disease stages and cured cases in the cancer cohort. Nor do we know the prevalence of moderate and severe pain in the non-cancer population, where treatment with opioids would be appropriate.

The average DI in the population remained very stable throughout the period. By analyzing the DI separately for weak and strong opioids, this stable DI was found to be the result of some rather pronounced and opposite changes. The DI of strong opioids for cancer patients increased dramatically. Whether the concentration of strong opioid in fewer cancer patients was a result of changing prescribing habits due to the introduction of tramadol in 1993, or whether it could be related to the introduction of transdermal fentanyl in 1996, could not be demonstrated in this study. The tendency for increasing dispersion with smaller amounts of weak opioids per individual related to both cancer patients and non-cancer patients. The results demonstrate the importance of a differentiated view, both with regard to the type of opioid and with regard to the users, when a population's use of opioids is evaluated.

This analysis of the opioid use is based on redeemed prescriptions from the pharmacies. We do not know to what degree the sale of drugs represents the doctors' prescriptions[20,21] or the drug intake of the patients.[22] The use of opioids in the primary health care sector represents around 90% of the total use in the country.[4,5] In the remaining 10% consumed in the secondary health care sector, the distribution of the patient categories with regard to cancer is unknown. We do not think these missing data pose a significant bias to the results. In

the prescription database, we cannot see if the opioids given to the cancer patients were prescribed for treatment of malignant pain, but because more than 80% of the cancer patients started their treatment after having the diagnosis, it seems likely in most of the cases.

Consumption of opioids quantified by defined daily doses may not be the best way to evaluate and compare the use of opioids in different populations or to describe individualized pain treatment, since the defined daily dose does not relate unequivocally to the potency of the opioids. If, for instance, comparisons of drug-use intensity between groups of patients or countries are made based on DDDs, it is very important for the interpretation that the composition of the different opioids used is similar.[23] In this article, we have chosen to use defined daily doses to have the opportunity to compare our results with the annual drug statistics of the country, assuming equal prescription behavior all over the country. For individualized descriptions of pain treatment with opioids, the use of oral morphine equivalents would be more clinically relevant.

We are not aware of any other studies analyzing cancer patients' consumption of opioids in relation to a whole population's use of opioids. In a study by Zenz et al., the prescribing pattern among 330 German physicians (general practitioners and internal medicine specialists) regarding the treatment of cancer pain was described, but this study was based on the physicians' own computerized records on disease and medication.[24] In a few studies addressing the use of opioids in Denmark, the proportion of users in the primary sector having a cancer diagnosis has been mentioned.[5,6,25] General practitioners were asked about the indication for prescribing opioids in prescriptions collected during one month in 1992.[6] Malignancy was the reason in 110 of 655 patients (17%). This is in accordance with the 14% we have found. In another study of 1,854 prescriptions of strong opioids from 1991 to 1992, the doctors stated the indication for the prescriptions to be due to malignancy in 9.5%.[4] In our material, 15.9% of the strong opioid prescriptions redeemed in 1993 were prescribed to cancer patients (data not shown). Our study has confirmed the conclusion from the Danish Medical Drug Agency that the increase in the overall use of opioids in Denmark primarily is due to an increase in the amount of users of tramadol in short courses of treatment with small doses.[5]

Whether the declining use of strong opioids to non-cancer patients was due to national, governmental guidelines about restrained use[10,11] or whether other explanations could be given, will have to be addressed in other studies. In our opinion, an opioid consumption due to short treatments with weak opioids does not pose a problem to patients or society, and it could very well represent rational pain treatment. Still, the increase in the number of opioid users during the period was surprisingly high. Whether this represents a change in prescribing habits from nonsteroidal anti-inflammatory drugs towards tramadol for short periods of moderate pain remains to be investigated. Tramadol is presumably a good choice for treatment of pain in many cancer patients[26] and it is recommended as a step II analgesic in the pain ladder.[19] Hopefully, the increase in users of tramadol demonstrated here means sufficient pain treatment to more cancer patients compared to earlier. On the other hand, if treatment with tramadol leads to reluctance in changing to a stronger opioid when the intensity of the pain increases, it is worrying. The unexpected decline in the number of cancer patients using strong opioids during the period must be further explored. The design of the study did not allow us to draw any conclusions regarding the quality of the pain treatment in cancer patients, but some epidemiological issues have been clarified. Analyses of individual treatment courses for cancer patients using opioids will contribute further to the picture of the performance of cancer patients' pain treatment and the doctors' prescribing behavior.

Acknowledgments

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Original Article

Use of Opioids in a Danish Population-Based Cohort of Cancer Patients

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Abstract
Until recently, Denmark has had the highest use of strong opioids per capita in the world. Our aim was to analyze cancer patients' use of opioids in this population by linkage between the Danish Cancer Register and a prescription database. The changes in opioid use from 1994 to 1998 in the entire cohort of cancer patients (n = 24,190) in a Danish county (n ~ 470,000) were analyzed. The overall consumption of opioids increased from 20 kg to 37 kg oral morphine equivalents (omeq) per year. The average consumption increased from 7.6 to 10.7g omeq/opioid user/year. The annual proportion of users increased from 17% to 20%. The proportion of patients who were alive 2 years after their first opioid prescription increased from 38% to 55%. Increased awareness towards pain treatment, with earlier initiation of opioid treatment and higher doses to the cancer patients, could be major explanations for the increase in the cancer patients' use of opioids. J Pain Symptom Manage 2005;29:336–343. *© 2005 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words
Cancer pain, pain treatment, opioids, population-based, OPED, Danish Cancer Register, pharmacoepidemiological, oral morphine equivalents, transdermal fentanyl, tramadol

Introduction

Opioids are the mainstay of management of cancer pain, providing effective pain relief for most patients.[1] Our knowledge of cancer pain epidemiology is sparse and we know even less about how cancer pain is managed in outpatient settings.[2] There are several databases in Denmark with a comprehensive recording of all prescriptions of individual patients.[3] They provide an opportunity to study aspects of the medical pain treatment in detail by record-linkage with other high quality Danish research registers, containing population-based data on the patient level.[4–6] Recently, we analyzed the cancer patients' share in a population's use of opioids over a five-year period[4] and found that cancer patients accounted only for a small proportion of overall opioid use. However, the population's increasing use of strong opioids was

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attributed to a large increase in the cancer patients' use of strong opioids. Using the entire cohort of cancer patients in a Danish county during the period 1994 to 1998, this study aims to go into details specifically about the cancer patients' opioid use. Changes in the patients' use during a five-year period, when tramadol and transdermal fentanyl were introduced to the Danish market, are analyzed.

Methods

Our study population was the inhabitants of Funen County (470,000 inhabitants; 9% of the Danish population) during the period 1994 through 1998. We retrieved data on cancer patients and opioid prescriptions from two sources, the Danish Cancer Register[7,8] and the Odense Pharmacoepidemiologic Database (OPED).[3,4] Both registers have, for all practical purposes, full coverage of the population. Data were linked by use of the central person registration number (CPR-number), a unique identifier for each individual. We ascertained that the cancer patients were residents in the county during the periods of interest and followed the cancer patients with respect to death through 2000 by using OPED's demographic module.

All opioid prescriptions redeemed by the cancer patients since January 1, 1993, were retrieved from OPED. An opioid prescription was defined as incident, if no other opioid prescriptions were redeemed by the patient one year prior to the date of the index prescription, given that the patient had resided in the county. We used 1993 as the run-in period for incident prescriptions in 1994. Repeated prescriptions were defined as prescriptions with less than one year's interval. Each record in OPED contained the CPR-number of the patient, the date of purchase, the pharmacy, the prescriber and a

Table 1
Equianalgesic Dose Table for the Calculation of mg Oral Morphine Equivalents

Drug	ATC	Equids	Meqfac	mg drug/DDD
morphine IV	N02AA01	10	3	30
morphine IR/PO	N02AA01	30	1	100
morphine SR/PO	N02AA01	30	1	100
morphine suppository	N02AA01	20	1.5	30
ketobemidone comb. PO	N02AG02	15	2	50
ketobemidone comb. PA	N02AG02	7.5	4	50
ketobemidone SR/PO	N02AB01	30	1	50
ketobemidone rectal	N02AG02	10	3	50
methadone PO	N02AC02	7.5	4	25
methadone PA	N02AC02	3.75	8	25
tramadol PO	N02AX02	150	0.2	300
tramadol PA	N02AX02	100	0.3	300
tramadol rectal	N02AX02	150	0.2	300
pethidine PO	N02AB02	300	0.1	400
pethidine PA	N02AB02	75	0.4	400
pentazocin PO	N02AD01	176	0.17	200
pentazocin PA	N02AD01	60	0.5	200
oxycodone IR/PO	N02AA05	20	1.5	30
oxycodone SR/PO	N02AA05	20	1.5	30
hydromorphone SR/PO	N02AA03	4	7.5	4
dextropropoxyphene PO[a]	N02AC04	130	0.23	200
dextropropoxyphene PO[b]	N02AC04	200	0.15	300
buprenorphine SL	N02AE01	.4	75	1.2
buprenorphine PA	N02AE01	.3	100	1.2
codeine PO	R05DA04	300	0.1	100
nicomorphine PO	NO2AA04	30	1	30
nicomorphine PA	NO2AA04	10	3	30
nicomorphine rectal	NO2AA04	20	1.5	30
fentanyl transdermal 25 ug/hr	NO2AB03	.18	167	0.6

IV = intravenous; IR = instant release; SR = slow release; PO = per oral; PA = parenteral; SL = sublingual;
equids = mg-opioid equianalgesic with 30 mg oral morphine;
meqfac = the potency of the drug in relation to oral morphine;
mg drug/DDD = mg opioid per 1 DDD, defined by WHO.
(mg omeq per prescription = the prescribed amount of DDD × meqfac × mg drug/DDD)
[a]hydrochloride.
[b]napsylate.

Table 2
Cancer in Funen County (n – 470,000), 1994 to 1998

	1994	1995	1996	1997	1998
Prevalence of cancer patients per year	15,555	15,994	16,345	16,657	17,021
1-year cancer prevalence proportion (%)	3.33	3.40	3.47	3.53	3.61
Mean age	65.4	65.5	65.5	65.6	65.7
Crude mortality rate per 100 cancer-years	12.94	12.57	12.49	12.38	12.05
Incident cancer patients per year	2,181	2,199	2,115	2,116	2,187
Incidence rate per 100 person-years	0.48	0.48	0.46	0.46	0.48

See Appendix for definitions of measures of cancer epidemiology and opioid utilization.

full account of the dispensed product, including substance, formulation, brand name, Anatomical Therapeutic Chemical (ATC)-code, dose unit, and quantity.[9] The dosing instruction and the indication for prescribing were not recorded in the database. The opioids were identified by the seven-digit ATC classification system.[10] N02A are the four first digits in all opioids' ATC-code, except for codeine with ATC-code R05DA04. The last three digits indicate the active substance in the drug. The opioids were divided into weak and strong opioids according to the guidelines from the WHO analgesic ladder.[1] The weak opioids are codeine, dextropropoxyphene, and tramadol. For the weak opioids, only consumption of single entity drugs was included in the study. The rest of the drugs in the N02A group are categorized as strong opioids. Tramadol was registered in 1993 and transdermal fentanyl in 1996 for sale in the primary care sector.

Usually, drug use statistics are presented by the Defined Daily Doses (DDD) methodology as recommended by WHO.[10] The DDD is a technical unit of measurement, established by an expert panel as the assumed average maintenance dose when the drug is used for its main indication by an adult. The DDDs for two closely related drugs should thus in principle be equipotent. However, one DDD for a weak and a strong opioid reflect highly incomparable analgesic doses, as they are formally used for two different indications. Morphine is the prototype and standard of comparison for opioid analgesics.[11] We have chosen to present our analyses by oral morphine equivalents (omeq) to make the patients' use of opioids comparable.[12,13] The DDD does not reflect the prescribed daily dose, which is particularly variable for opioid analgesics. The calculation of each prescription's omeq value was based on commonly used equianalgesic doses[11,14–20] (Table 1).

The results are presented for each calendar year. The drug-use intensity was calculated from the consumed amount of opioid per calendar year divided by the number of 1-year prevalent users. The drug-use intensities and the consumptions are presented both as DDDs and as omeqs to enable comparisons with other opioid use statistics. The remaining results are presented with omeq values.

Incident rate ratios (IRR) for cancer incidence, cancer mortality and opioid user incidence were calculated using STATA. For definitions of the various measures of drug use and cancer epidemiology, see the Appendix.

Results

The Cancer Population, 1994 to 1998

We identified 24,190 cancer patients in the county from 1994 to 1998. Of those, 40% (n = 9,663) received at least one opioid prescription during the 5-year period. Repeated prescriptions, that is, prescriptions with less than a one-year interval, were received by 7,133 of the 9,663 patients (74%).

The cancer incidence rate remained stable, with an IRR = 1.00 (95% CI: 0.94–1.06) for 1998 relative to 1994. The crude mortality rate decreased from 12.94 to 12.05 deaths per 100 cancer patient-years in the period (IRR = 0.93, CI: 0.89–0.99). The number of one-year prevalent cancer patients increased from 15,555 to 17,021 patients (Table 3).

Incidence, Prevalence, and Survival of Opioid Users

The incidence rate of opioid users among the cancer patients increased slightly, from 13 to 14 per 100 cancer-years. The IRR was 1.08 (95%

Table 3
Cancer Patients' Use of Opioids, 1994 to 1998: Incidence, Prevalence and Consumption

	1994	1995	1996	1997	1998
Number of incident users per year	1,623	1,766	1,769	1,951	1,884
Incidence rate, per 100 cancer-years	12.9	13.8	13.5	14.8	14.0
Incidence rate for weak opioids	3.9	6.6	7.3	8.6	8.5
Incidence rate for strong opioids	9.0	7.3	6.3	6.2	5.6
1-year survival of incident users, (%)	47.5	53.1	55.2	54.9	59.3
2-year survival of incident users, (%)	37.9	43.5	44.7	46.3	54.7
Number of prevalent users per year	2,698	3,004	3,157	3,394	3,443
1-year prevalence proportion of users (%)	17.3	18.8	19.3	20.4	20.2
incidence proportion among users (%)	60.2	58.8	56.0	57.5	54.7
1-year mortality proportion among users (%)	35.5	34.0	33.5	31.6	31.7
1-year mortality proportion among non-users (%)	6.2	5.7	5.7	5.7	5.3
Opioid consumption per year					
DDD (thousands)	237	264	315	420	437
kg oral morphine equivalents (omeq)	20.4	22.7	26.6	36.0	36.8
Drug-use intensity per year					
DDD/user/year	87.8	88.0	99.8	123.7	126.9
g omeq/user/year	7.6	7.5	8.4	10.6	10.7

See Appendix for definitions of measures of cancer epidemiology and opioid utilization.

CI: 1.01–1.16) for 1998 relative to 1994. The number of one-year prevalent opioid users increased by 27.6%, with the annual proportion of users increasing from 17.3% (CI: 16.7–18.0%) to 20.2% (CI: 19.6–20.9%) during the 5 years (Table 2). Sixty-eight percent of the incident users received at least two opioid prescriptions during the following year.

The increase in one-year and two-year survival after the first opioid prescription is shown in Table 2. The proportion of patients who were still alive one year after their incident opioid prescription increased from 48% (95% CI: 44–51%) among the incident users in 1994 to 59% (CI: 56–63%) in 1998. More evident, though, were the changes for the two-year survival, which increased from 38% (CI: 35–41%) to 55% (CI: 51–58%), with two breakpoints on the increase between 1994 and 1995 and especially between 1997 and 1998.

First Choice Opioid

The first choice opioid changed during the period. A strong opioid was chosen in 70% of the cases in 1993 and in 40% in 1998. The incidence rates for "weak" and "strong" opioids are shown in Table 2. Since the introduction of tramadol in 1993, its share among the incident opioid prescriptions increased to 49% (Figure 1), compared to 17% for ketobemidone and 16% for morphine in 1998.

Consumption of Opioids and the Drug-Use Intensity

The cancer patients' consumption of opioids in the county increased by 80%, from 20 kg omeq/year to 37 kg omeq/year (Table 2). The drug-use intensity increased by 41% from 1994 to 1998, corresponding to an increase from 7.6 to 10.7 g omeq/user/year (Table 3). The increase in drug-use intensity became steeper after 1996, particularly for patients using strong opioids (Figure 2). The consumption of transdermal fentanyl increased very rapidly after its registration in 1996 (Figure 3). Eleven percent of the opioid users in 1998 received this drug; its consumption reached 35% of the cancer patients' total opioid consumption, similar to the consumption of morphine.

Cancer Diagnoses' Contribution to the Use of Opioids

No changes in the distribution between the different cancer diagnoses among the opioid users and their share of the total use of morphine equivalents were seen during the 5-year period, except for a small relative increase in the number of breast cancer patients (Table 4). Forty-nine percent of the opioid users and 53% of the consumption were related to one of the four cancer diagnoses—breast, colorectal, lung and prostate cancer—which were also the four most frequent cancers.

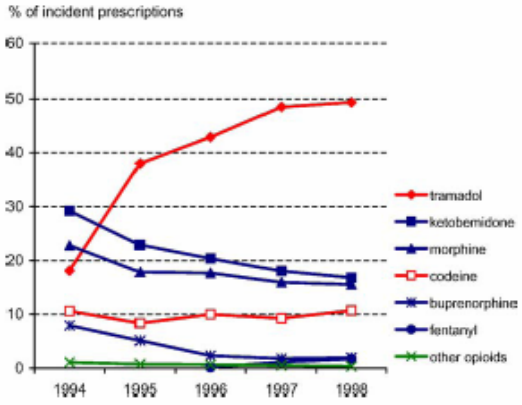

Fig. 1. First choice opioid for incident users, 1994–1998.

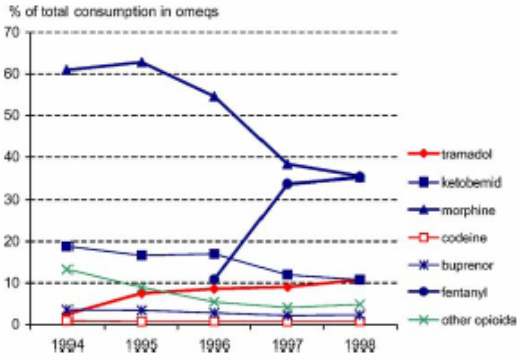

Fig. 3. Different opioids' share in percentage of the cancer patients' overall consumption of opioids, 1994–1998.

Discussion

Although cancer epidemiology in the county seemed very stable, treatment with opioids underwent some major changes from 1994 to 1998. The cancer patients' large increase in opioid consumption was mainly due to an increase in the average amount of strong opioids consumed per patient. We interpret the increasing surviving proportion among patients who started treatment with opioids as a tendency to initiate pain treatment earlier in the patients' symptomatic disease courses. This could explain the slight increase in the incidence rate of opioid users and probably also part of the increase in drug-use intensity. Increasing awareness towards using sufficient doses of opioids might also be an important factor for the observed results. It seemed as if the proportion of cancer patients who were considered candidates for pain treatment was almost constant. This is judged upon the very small changes in the proportions of both users and opioid consumption among the various cancer diagnoses.

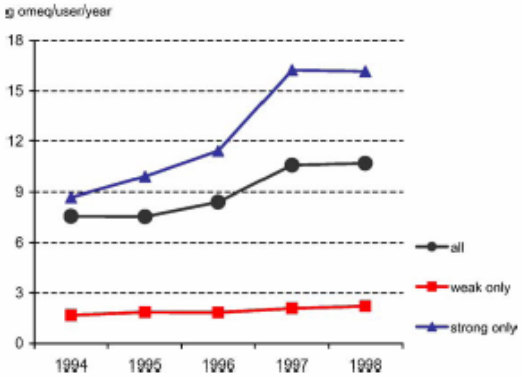

Fig. 2. The drug-use intensity (DI) from 1994 to 1998. DI is the average use of opioid/user per year measured in grams of oral morphine equivalents.

The most likely explanation for the steep increase in drug-use intensity for the strong opioids in 1997 seemed to be the extensive use of transdermal fentanyl to a smaller group of opioid users. Only two years after transdermal fentanyl was introduced to the Danish market, its share of the total opioid consumption became equal to that of morphine. Prior to that, morphine had, without comparison, been the most consumed opioid among the cancer patients.

Our data do not allow any conclusions regarding the high and increasing use of transdermal fentanyl. It seems unlikely that transdermal fentanyl should cover a hitherto unmet need for high doses of opioids, because the analgesic effect of transdermal fentanyl does not differ from equivalently high doses of morphine or other strong opioids. Perhaps transdermal fentanyl has an increased tendency to develop tolerance, compared with other opioids. Animal experimental studies on opioid receptor tolerance have shown differences in the mechanisms of action between fentanyl and morphine. The results are contradictory with regard to which of the two opioids mediate opioid tolerance the most.[21–23] In a clinical study of prolonged treatment with transdermal fentanyl in neuropathic pain, only 1 patient of 8 had developed tolerance after two years' use.[24] Perhaps the treatment with patches is more attractive to

Table 4
Different Diagnoses' Contribution to Cancer Patients' Use of Opioids, 1994 and 1998

	% Opioid Users		% of Consumption		Number of Patients using Opioids	
	1994	1998	1994	1998	1994	1998
Breast	17.8	20.9	19.1	18.1	481	718
Colorectal	13.2	12.3	12.4	12.5	356	425
Prostate	7.7	7.0	10.9	10.1	209	242
Lung	10.9	9.1	10.2	12.0	295	315
Hematopoietic	6.6	6.8	7.6	5.0	178	233
Various possibly painful[a]	3.9	3.6	6.6	5.4	105	125
Other female genital	6.5	7.2	6.5	6.4	175	248
Head and neck	4.9	4.9	5.5	5.7	132	167
Cervix	5.8	5.4	5.4	5.8	157	186
Others[b]	22.7	22.8	15.8	19.0	610	784
Total	100	100	100	100	2698	3443

[a]Various possibly painful cancers include: mediastinal, pleural, sarcomas, esophageal, and liver cancer.
[b]Patients from each group of the following cancers consumed less than 4% of the opioids in 1998: kidney, bladder, pancreas, melanoma, brain, stomach, other male genital, various others, unspecified.

the patients and their caregivers than treatment with tablets. Qualitative research methods would be suitable to address these questions.

The preferences for the choice of first opioid were reversed during the period from strong opioids towards weak opioids. Whether this was due to implementation of the WHO pain ladder guidelines recommending a weak opioid as step 2 treatment or it was due to the remarkably high popularity tramadol achieved after its registration in 1993 cannot be revealed by this register-based study. Half of all incident opioid prescriptions in 1998 were for tramadol. It could be hypothesized that doctors considered treatment with tramadol to be less stigmatizing to the patient than small doses of morphine and, therefore, preferred tramadol as the first choice of opioid. Another possibility could be that an increasing proportion of the incident tramadol users were patients who previously would have been prescribed nonsteroidal anti-inflammatory drugs for their pain. Furthermore, the doctors might have taken the combined effect of tramadol with both the μ-agonistic effect and the inhibition of serotonin and noradrenaline reuptake into consideration when they chose the first opioid for their patient. These questions remain to be answered.

Until recently, Denmark has had the highest use of strong opioids per capita in the world. The population in Funen County is considered to be representative of the Danish population with regard to cancer epidemiology, drug use, and demography. Therefore, we regard our results to be representative of the Danish population. The chosen method allowed us to combine data from two very complete databases of high quality,[3,5,7] thereby reducing the risk of selection bias and information bias to a minimum. Still, there is some uncertainty about the degree to which the redeemed prescriptions represent what was prescribed[25,26] or actually taken by the patients.[27]

To our best knowledge, this is the first study to provide an epidemiological view of opioid use in the entire cohort of cancer patients in a population. Much is known regarding the pain prevalence among selected groups of cancer patients, but the prevalence of pain among cancer patients in a population remains unknown. We found that 20% of the cancer patients used opioids at least once during one calendar year and 40% used these drugs if we considered the whole 5-year period. Because the prevalence of pain is unknown in this unselected cohort of cancer patients, the study does not allow us to conclude whether these figures of opioid use represent sufficient treatment with regard to the number of treated patients or to the reduction of pain symptoms. The results reflect the willingness described among Danish doctors to prescribe opioids to cancer patients with pain.[28–30] During a 3-year period in Germany, from 1990 to 1993, only 1.9% of 16,630 cancer patients received a prescription for a strong opioid and only 99 patients received more than 3 prescriptions from 330 physicians.[31] During that period, Germany was considered one of the countries in Europe with the greatest reluctance to prescribe opioids.[32] A comparison between these data and ours would more likely

reflect different political and cultural attitudes towards treatment with opioids, laws, and prescribing regulations.

In conclusion, increased awareness towards pain treatment, with earlier initiation of opioid treatment and higher doses, could be major explanations for the observed increase in the cancer patients' use of opioids during 1994 to 1998. Knowledge of individual cancer patients' treatment duration, consumed amount of opioids, and changes between drugs in relation to the disease course will improve the understanding of pain treatment in cancer patients. Tramadol and transdermal fentanyl were opioids of increasing importance. Whether their extensive uses are justified compared to the other opioids accessible for treatment of pain should be further explored.

Acknowledgments

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Appendix

Definitions of Measures of Cancer Epidemiology and Opioid Utilization

A cancer patient. A person with at least one diagnosis of invasive cancer, from the date of the first cancer diagnosis, regardless of whether the patient was cured or not. Only the month and year of the diagnosis were known from the Danish Cancer Register, so the date of diagnosis was assigned to the 15th of the month. Patients with non-melanoma skin cancer (ICD-7 code: 191) as the only cancer diagnosis were not included in the study.

The cancer incidence rate. The number of incident cancer cases in one calendar year divided by the total person-time at risk (County's total population on 1 July – prevalent cancer cases on 1 July).

Cancer prevalence. The proportion of individuals in the population at a certain date, who at some stage during their lifetime have been diagnosed with cancer, irrespective of the date of diagnosis.[33]

The 1-year cancer prevalence. The number of cancer patients who had a cancer diagnosis at the beginning of a calendar year or who were diagnosed during the year, divided by the size of the county's population on 1 July of the year.

Cancer patients' crude mortality rate. The number of deaths among the cancer patients during one calendar-year divided by the number of cancer patient-years at risk.

Opioid users. Cancer patients who received at least one opioid prescription within the period of observation. A cancer patient who received an opioid prescription less than 3 months before the first cancer diagnosis was also counted as an opioid user.

Incident opioid users. Cancer patients, who received an opioid prescription after at least one year without opioid prescriptions.

Opioid use incidence rate. The number of incident opioid users in one calendar year divided by the person-years at risk among the non-user cancer cases.

1-year survival of incident opioid users. The proportion of incident opioid users who were alive one year after their incident opioid prescription.

1-year prevalence of users. The number of cancer patients who received at least one opioid prescription during a calendar year divided by the number of 1-year prevalent cancer patients.

Users' 1-year mortality. The number of opioid users dying in the calendar year, divided by the number of 1-year prevalent opioid users.

Cancer patients’ first treatment episode with opioids: a pharmaco-epidemiological perspective

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Abstract

Goals of work: The factors underlying the choice of opioids for cancer patients in primary care are largely unknown. Our aim was to describe cancer patients’ first treatment episode with opioids in relation to disease characteristics and clinical course. *Patients and methods:* During 1997 and 1998, a population-based cohort of 4006 incident cancer patients from a Danish County was identified. The patients were followed from diagnosis to death or 31 December 2003 and data on their use of opioids were obtained from a prescription database. *Main results:* Eventually, 54% of the cancer patients became incident users of opioids. Opioid treatment was initiated close to the diagnosis date in 20% of patients. Most incident users, 57%, were not terminal when they began using opioids, and 44% survived the first treatment episode. Of those who died, 70% received opioids in their terminal phase. The incidence rates of new opioid users were inversely related to the 5-year cancer survival. A weak opioid was the first choice in 64% of the non-terminal users and in 43% of the terminal. No statistically significant differences in opioid use were found between men and women. *Conclusions:* Opioid use in cancer patients was not confined to the terminal course. Treatment with opioids should be viewed as a dynamic condition, with patients shifting between periods of use and non-use. The aggressiveness of the cancer and the presence of metastases were characteristics found to be strong determinants of opioid use.

Keywords: Cancer patients · Opioids · Sex differences · Pain treatment · Cohort study

Introduction

The critical importance of pain management in cancer care has been forcefully advanced by WHO, governmental agencies, and international and national professional organisations [21]. Pain treatment is not only an issue for palliative care of terminal cancer but may also be part of the care to patients in the other stages of disease. Drug therapy is the cornerstone in treatment for pain [18], but not all cancer patients will need treatment. There is, however, little epidemiologic data describing to what degree treatment for pain is given in various phases of cancer disease [10].

The principles in the WHO’s “three-step analgesic ladder” [28] has been internationally recommended [4, 12, 18]. The use of weak and strong opioids as the drugs of choice in step II and III of the ladder are recommended based on the intensity of the pain. Whether the first choice of opioid should be made from a pain intensity perspective or based on the mechanism of pain is a matter of debate, but recent data seem to indicate that the first choice of opioid can be of importance in the efficacy and tolerability of the treatment course [19].

It would be of particular interest to gain information about the first episode of opioid treatment and to analyse patient characteristics and cancer-specific factors associated with the start of treatment. Estimates of the timing and duration of the first episode and the occurrence of new episodes of pain treatment are also important elements for a description of cancer care in the population. Such data may be of value for the care of individual patients and contribute to the planning and discussion of health care to cancer patients [1].

The purpose of this population-based cohort study was to analyse the epidemiology of the first episode of opioid treatment in cancer patients. We described the incidence of treatment in a follow up period (5-7 years) after diagnosis and related the incidence to the course of disease, type of cancer and characteristics of patients. For patients who started opioid treatment we analysed the choice of drug, duration of first treatment episode and the recurrence of treatment.

Patients and methods

A cohort of all incident cancer patients from 1997-1998 in Funen County (n ~ 470.000 inhabitants, 9% of the Danish population) was followed from the diagnosis to death or to 31 December 2003 inclusive, with regard to the patients’ use of opioids.

Data were retrieved from two population-based registries; the Danish Cancer Register [6, 24] and the prescription database, Odense University Pharmacoepidemiologic Database, (OPED) [8, 16]. The Cancer Register has for all practical purposes full coverage of the Danish cancer

population, while OPED has full coverage of all prescriptions redeemed in Funen County. A demographic module in OPED holds information on all citizens in the county including dates of migration and deaths. The CPR numbers (Central Person Registration), which are unique identification numbers provided to every citizen in Denmark, were used to link records from the two databases, enabling identification of all patients in the county with a diagnosis of invasive cancer. If non-melanoma skin cancer was the only cancer diagnosis, the patient was not included. Only incident cancer patients, who had been inhabitants in the county from at least 1 year prior to the date of the cancer diagnosis and until death or 31 December 2003, were included in the analyses.

Apart from the CPR number, each record in OPED contains the date of purchase, a full account of the dispensed product, including substance, formulation, brand name, ATC code, dose unit and quantity [14]. The dosing instruction and the indication for prescribing are not recorded in the database.

The opioids were identified by the seven-digit ATC (Anatomical Therapeutic Chemical) classification system [29]. The opioids were divided into weak and strong opioids according to the guidelines from the WHO analgesic ladder [28]. The weak opioids are codeine, dextropropoxyphene and tramadol, while the remaining opioids are categorised as strong opioids. Except for ketobemidone which is frequently used in combination with an antispasmodic, only consumption of single entity drugs was included in the study.

We defined the index date as the day the patients redeemed their first opioid prescription after at least one year free of opioids. The opioid prescription redeemed on the index day was termed the index prescription.

The Cancer Register only provides information of the month and year of the cancer diagnosis, therefore the date of diagnosis was defined as the 15^{th} of the months. If the opioid treatment was initiated in the time window from 3 months before the date of diagnosis to 15 days after, the treatment was defined to be initiated simultaneously with the diagnosis, and we made the assumption that it was related to the cancer disease. Start of treatment in this time window was defined as start on day 1 in the analysis of time from diagnosis to start of treatment.

In the analysis, we focused on the first episode of opioid treatment. The first episode was defined as ended if no opioid prescriptions were redeemed by the user for a period of more than 4 months (122 days). The duration of the first treatment episode was defined as the time interval between the index date and the date of the last prescription in the first episode.

Doctors’ predictions of survival up to 6 months in length are considered reliable, as they are highly correlated with actual survival [9]. We assumed that the prescribing doctors could judge the patients to be terminal if the patients had 6 months or less left to live, and we defined these patients as terminal. Analyses that included terminal status were performed on the cohort of patients who started treatment before 1 July 2003.

Statistics

Patient characteristics and the first choice of opioid are presented using descriptive statistics. The 5-year survival and the percentage of patients, who had started treatment with opioids after different follow-up times, were calculated as the percentage of patients with the endpoint of interest from the initial number of patients.

The time from the cancer diagnosis to the first opioid prescription is presented using the Kaplan-Meier method and the hazard-ratios are found using Cox regression with 95% confidence intervals. The incidence rates of new opioid use are crude values of the number of new users in the observation period divided by the number of years at risk for the incident cancer patients with the different cancer types.

The choice of a strong versus a weak index opioid was analysed using logistic regression with diagnosis, sex, age at the index date, stage of the disease at the time of diagnosis (referred to only as “stage” in the following) and terminal status (< 6 months to death) as explanatory variables. Odds ratios are presented with 95% confidence intervals (CI). Colorectal cancer was used as comparator for the other cancer types because of the number of cases, frequency of opioid use, no known sex-related confounders and well-described staging procedures. Only sex-unspecific cancers were used to analyse the influence of sex, age and stage on the first choice of opioid, to avoid the influence of the biology of the sex-related cancers.

The statistical software was Stata ®.

Results

The characteristics of the 4006 incident cancer patients (diagnosed in 1997 and 1998) fulfilling the inclusion criteria are shown in Table 1. Only 3,771 patients were included in the cohort of incident cancer patients at risk of a first time episode of opioid use, since 235 patients (6%) had already used the drugs in the year prior to cancer diagnosis (Fig. 1).

Incidence of opioid use

Among the 3,771 patients in the cohort 57% (N=2,166) had received a prescription for opioids before the end of the 5-7-year period of follow-up (Fig. 1). The time to the first episode of opioid use among men and women is shown as Kaplan-Meier plots in Fig. 2. When sex-related cancers were excluded from the analysis, no statistically significant difference between men and women was observed in time from diagnosis to first opioid prescription. Twenty percent (N=410) of the 2,166 incident opioid users received their first prescription near the time of diagnosis and 50% had been treated within 29 months. By 1 July 2003 (six months before the end of the follow-up period) the number of incident opioid users was 2,131 and 43% (n = 913) of these patients had started their first treatment episode in the terminal phase (< 6 months before death). Sixty percent (N=2,409) of the cohort of cancer patients died before the end of follow-up and in this group 70% (N=1,686) had received one or more episodes of opioid treatment while the similar figure for those who were alive was 38%.

Considerable differences between cancers were found in the cumulative probability of opioid use 1, 2 and 5 years after diagnosis (Table 2), and an inverse relation was demonstrated between the incidence rate and the 5-year survival for the cancer type (Fig. 3). The overall incidence rates (new opioid users per 100 cancer years) for patients with local, regional, metastatic and unknown disease stage were 14, 32, 139 and 25, respectively. In patients with head and neck cancer, the highest incidence rate (79 new users per 100 years) for opioid use was found for regional disease, while for all other cancer types metastatic disease was associated with the highest incidence rate.

First treatment episode and choice of opioid

The first choices of opioid are presented in Table 3. Tramadol was the most frequent choice, regardless of the patient’s disease status. Thirty-three patients received both a strong and a weak opioid in the first prescription and were categorised as patients with a strong index opioid for the analyses. Forty-three percent of the terminal patients were given a weak index opioid, while 64% of the non-terminal users started treatment with a weak opioid. Except for breast cancer, the preference for a strong index opioid did not seem to be related to the type of cancer, since no cancer type differed significantly from colorectal cancer (Table 4). Patients with breast cancer seemed to receive strong index opioids less frequently than patients with colorectal cancer. The influence of sex, age, disease stage and terminal status on first choice of opioid was analysed for non sex-related

cancers (Table 4). No statistically significant associations with sex and stage were demonstrated, while older patients (above 60 years of age) were more likely to receive a weak opioid as first choice. After adjusting for all other factors, the odds ratio for getting a strong opioid was 1.96 for patients in the terminal phase compared with non-terminal patients.

Survivors and non-survivors of first episode

Forty-four percent (N=960) of the incident opioid users survived the first treatment episode, and 60% (N=575) of these patients had one or more later episodes of opioid treatment within the follow-up period (after a median of 351 days (p25: 189 days; p75: 718 days, range 124 – 2333 days)).

The duration of treatment, defined as the time from the index prescription to the last prescription in the first episode is shown in Figure 4. The proportion of patients with only 1 prescription in the first episode was 50% in the survivors’ group and 17% in the non-survivors’ group.

Fifty-three percent of the patients (N=1141) died during the first treatment episode, i.e. less than 4 months between the last prescription and death. The median time from the last prescription to death was 10 days or less.

Discussion

Opioids were used by more than half of the cancer patients in the cohort. A dynamic pattern of opioid usage was found, with patients who shifted between periods of use and non-use or patients who used opioids throughout the entire disease course. The study contradicts the belief that initiation of opioid treatment means that the terminal phase has been reached or that the treatment is chronic. Patients can stop using opioids even after longer periods of treatment, and the frequent resumption of the opioid treatment implies that the reason for stopping the first treatment episode was not due to patients’ bad experiences with opioids. The aggressiveness of the cancer and the presence of metastases were characteristics found to be strong determinants of opioid use, while demographic characteristics played a much smaller role. The preference of choosing a strong versus a weak opioid as first choice was mainly determined by the patient being terminal and by age.

To our knowledge, this is the first study to look at the initial treatment episode with opioids in cancer patients. The existence of two population-based databases of high validity and coverage [8, 22, 24] has made longitudinal analyses of cancer patients’ pain treatment possible with a

minimal risk of introducing selection bias and information bias. There are some uncertainties that need to be addressed. We do not know the indication for the prescriptions, and some of the opioids may have been prescribed for incidental conditions, unrelated to the cancer diagnosis. The crude incidence of opioid use in the background population (including cancer patients) was 4 per 100 years of risk in year 2000 [5]. Depending on the cancer type, we found 11 - 202 new users per 100 years of risk (mean value: 24 new users per 100 years), suggesting that the cancer patients’ opioid use is mainly related to their disease. This study only includes data on drug use from primary care, as we could not retrieve patient-specific data on in-patient care. The bias introduced because of this is likely to be minimal. We have no reason to believe that Danish cancer patients differ much in their prevalence of cancer-related pain, compared with other cancer patients in the industrialised part of the world. We also believe that our results provide a reasonable picture of the minimum requirements for opioids in a population of incident cancer patients. With due reservations, the results of this study could give an impression of the need for pharmacological pain treatment in similar populations of incident cancer patients.

Our results seem to corroborate the previous questionnaire-studies [23, 27], confirming Danish doctors’ willingness to prescribe opioids to cancer patients. Admittedly, the extent of treatment or the choice of opioids does not guarantee the quality of the treatment on the level of the patients, but doctors’ willingness to prescribe the medication is a prerequisite for providing effective treatment. The quality of the pain treatment for the individual patients cannot be studied in prescription databases and registries.

Differences in men’s and women’s experience of pain [17, 26] and in related health care seeking behaviour have been increasingly discussed. Only few studies have concentrated on cancer patients [3, 7, 25], not finding differences related to gender, as in those reported for patients without cancer. The patients in these studies all seemed to have advanced cancer. Our study supports their findings of no differences between male and female cancer patients with regard to use of opioids, even for non-terminal patients.

The initial choice of drug seems to be of importance for success later in the disease course [19]. Together with our previous studies [15, 16], this study has shown that tramadol is a popular choice in the treatment of cancer-related pain in Denmark. The discussion whether tramadol is the right choice for treatment of cancer pain is based on sparse evidence [2, 12, 13, 20]. We find that the use of tramadol as first choice opioid in 40% of the patients, who could be considered terminal, seems high, but on the other hand, many cancer patients might receive a sufficient and effective

treatment with tramadol [2, 12, 13, 20]. Based on the widespread use of tramadol and its higher cost compared with low dose morphine it is necessary to obtain more evidence on its use in the treatment of cancer-related pain, before specific recommendations about its use can be given.

Although the frequency of opioid use among the terminal patients seemed almost sufficient compared with our knowledge of their pain prevalence, we still need to investigate whether the treatment is sufficient for the individual patient with regard to pain relief, time of initiation and duration. Opioids should be introduced into the therapeutic regimen to treat pain at an appropriate time and not withheld to the terminal stages because of opioiphobia [11]. In our study, 43% of the patients were terminal when they started their first treatment with opioids. Further studies should investigate whether this figure is too high or appropriate.

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Tables

Table 1 Characteristics of incident cancer patients from Funen County in 1997 and 1998, n = 4006.

Diagnosis	Females	Males	Age at diagnosis (mean)	Cancer stage at the time of diagnosis (%)				5-year survival (%)
				local	regional	metastatic	unknown	
Hemopoietic	137	178	64.9	13	6	14	66	41
Breast	689	6	62.0	59	31	6	4	74
Colorectal	238	291	70.9	41	32	17	10	39
Lung	211	311	67.3	28	29	30	12	9
Prostate	0	291	75.1	26	7	25	43	33
Female genital	303	0	63.4	49	23	10	17	54
Other visceral [1]	222	442	68.8	36	16	20	28	28
Head and neck	51	125	64.1	65	28	3	3	51
Others [2]	234	277	57.0	58	12	13	17	56
All	2085	1921	65.7	42	21	16	20	43

[1] Other visceral: cancer diagnoses (number of patients)

bladder (236), pancreas (110), kidney (98), liver (81), stomach (53), oesophagus (51),
gallbladder (21), retro- and peritoneal (6), small intestine (6), endocrine glands (2)

[2] Others:

melanoma (170), brain (130), unspecified (50), testis (45), metastases (40) sarcoma (24), peripheral nerves (15)
eye (14) , connective tissue (12), other male genital (5), bone metastases (5), bone (1)

Table 2 Percentage of cancer patients becoming incident opioid users after 1, 2 and 5 years of follow-up (N = 3771)

Cancer	Patients at risk	1-year (%)	2-year (%)	5-year (%)
Hemopoietic	297	31	39	48
Breast	671	17	25	39
Colorectal	511	35	45	58
Lung	466	74	77	78
Prostate	279	42	51	70
Vemale genital	285	25	35	48
Other visceral	611	52	57	63
Head and neck	169	47	51	59
Other	482	26	31	42
Total	3771	38	45	55

Table 3 First choice of opioid to cancer patients; percentage of patients receiving the substance

	All [1]	Not terminal	Terminal
Patients	2131	1218	913
% of incident users	%	%	%
Morphine	19	14	25
Fentanyl TD	3	1	5
Ketobemidone	18	16	20
Tramadol	48	55	39
Codeine	7	9	4
Others [2]	6	5	7

[1] Incident users after 1 July 2003 not included

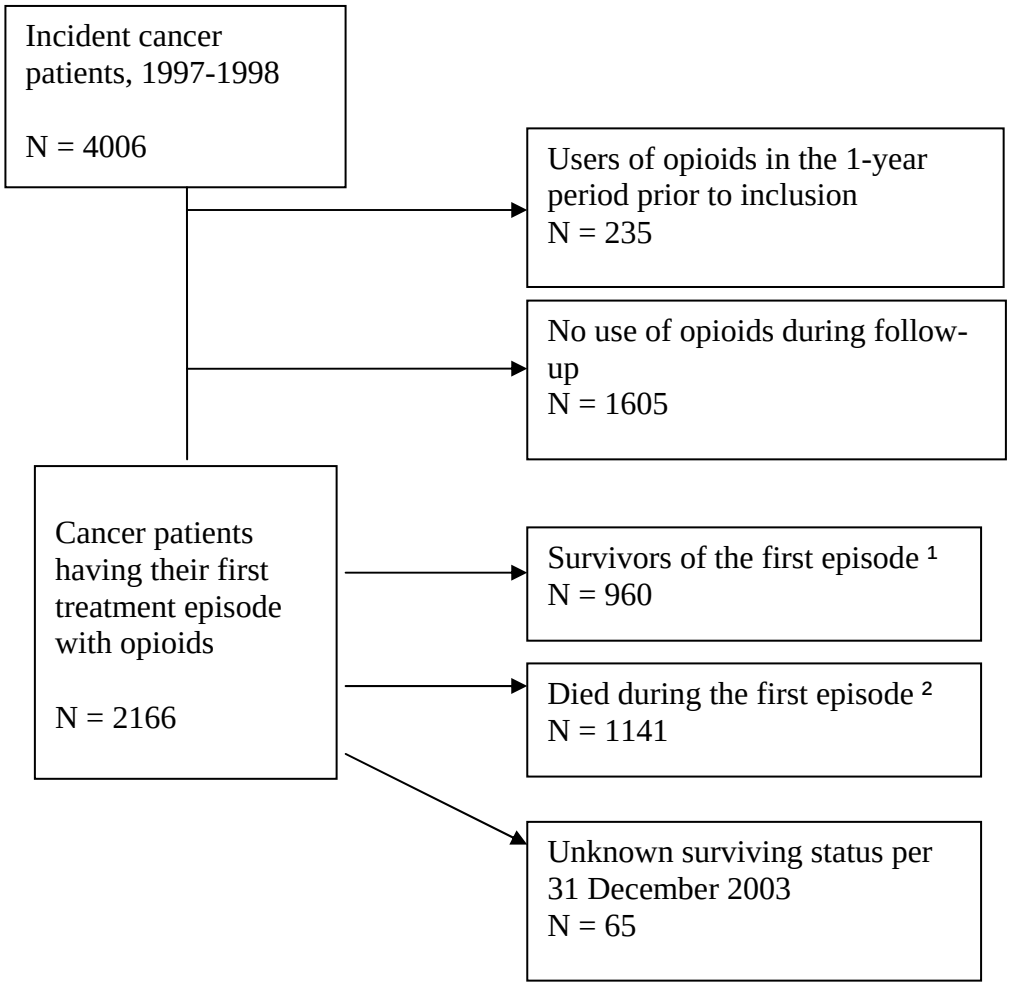
[2] Other "strong" opioids (377 patients) and dextropropoxyphene (2 patients)

Table 4. Characteristics of incident opioid users[1] and the adjusted odds-ratios for choosing a strong versus a weak index-opioid.

	Opioid users		Adj. odds-ratios [95% CI] for
	Patients	% women	strong vs weak index-opioid
ALL CANCERS			
All	**2131**	**49**	**adj. for stage, sex, age, terminal st**
Colorectal	301	47	1.0
Breast	279	100	0.63 [0.435 , 0.919]
Hemopoietic	145	44	0.70 [0.451 , 1.096]
Lung	365	40	1.34 [0.972 , 1.840]
Prostate	196	0	0.76 [0.505 , 1.134]
Female genital	139	100	0.93 [0.604 , 1.441]
Other visceral	393	35	1.13 [0.828 , 1.547]
Head and neck	101	29	1.40 [0.876 , 2.236]
Others	212	47	0.89 [0.610 , 1.285]
SEX-UNSPECIFIC CANCERS ONLY			
Sex	**1506**	**41**	**adj. for diagnosis, stage, age, term**
Women			1.0
Men			1.17 [0.943 , 1.444]
Cancer-stage at diagnosis			**adj. for diagnosis, sex, age, term**
Local	510	43	1.0
Regional	368	38	1.05 [0.785 , 1.392]
Metastases	331	41	0.94 [0.696 , 1.283]
Unknown	297	41	1.05 [0.754 , 1.448]
Age at index-date			**adj. for diagnosis, sex, stage, term**
50-59	248	41	1.0
0-49	142	41	0.82 [0.537 , 1.262]
60-69	404	34	0.72 [0.518 , 0.997]
70-79	429	43	0.59 [0.429 , 0.822]
>=80	283	47	0.63 [0.441 , 0.911]
Terminal status (term)			**adj. for diagnosis, sex, age, stage**
Not terminal			1.0
Terminal			1.96 [1.558 , 2.457]

[1] Incident users after 1 July 2003 not included

Figure 1



[1] The patients were alive 4 months after the last opioid prescription in the first episode.

[2] The patients died less than 4 months after the last opioid prescription in the first episode.

Figure 1. Opioid use among incident cancer patients with a follow-up period of 5 to 7 years after the diagnosis**.**

Figure 2

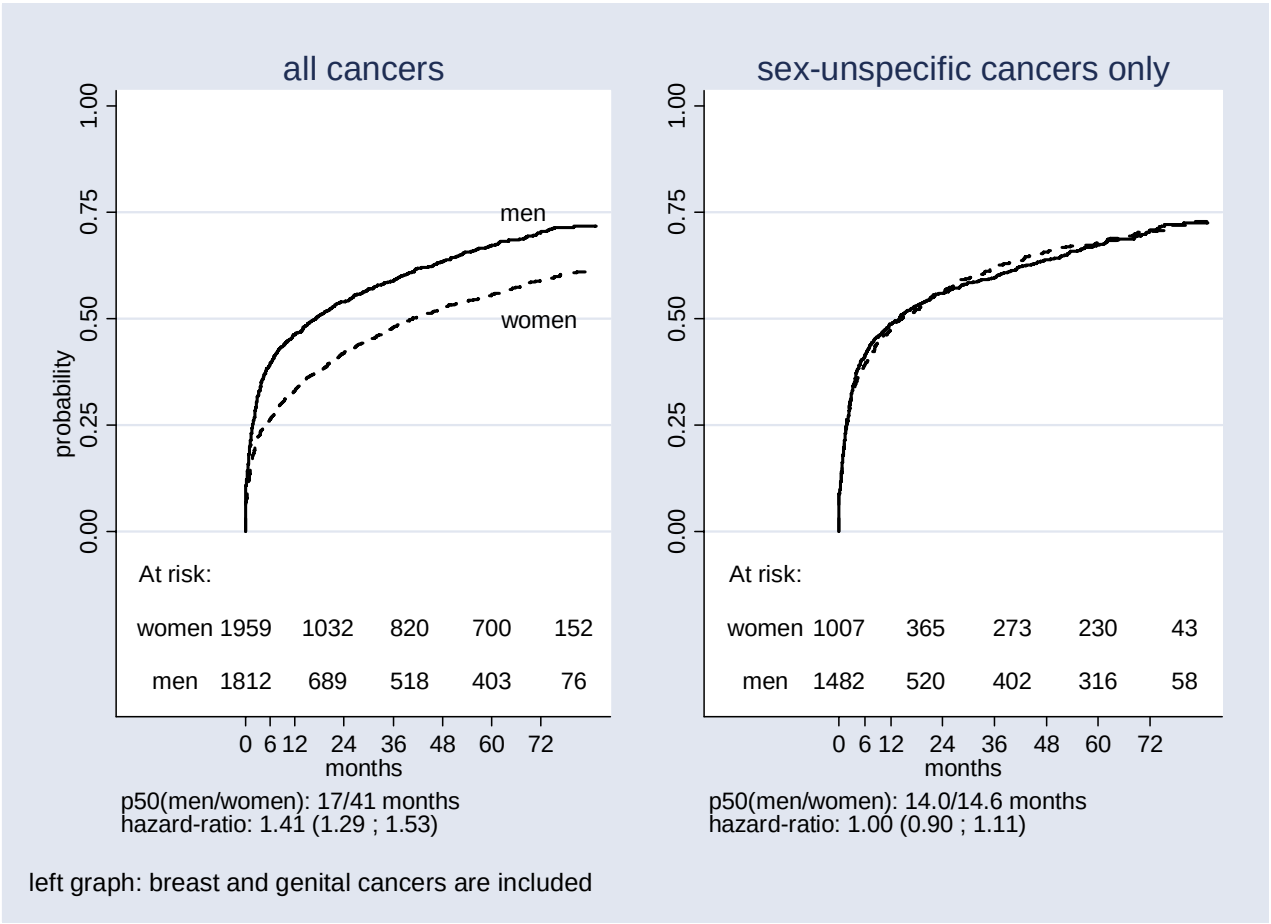


Figure 2: Incident opioid treatment among cancer patients. Kaplan-Meier estimates of the cumulative probability of opioid use. p50: the time (months) when half of the cancer patients have received an opioid prescription (correlate to median survival time).

Figure 3

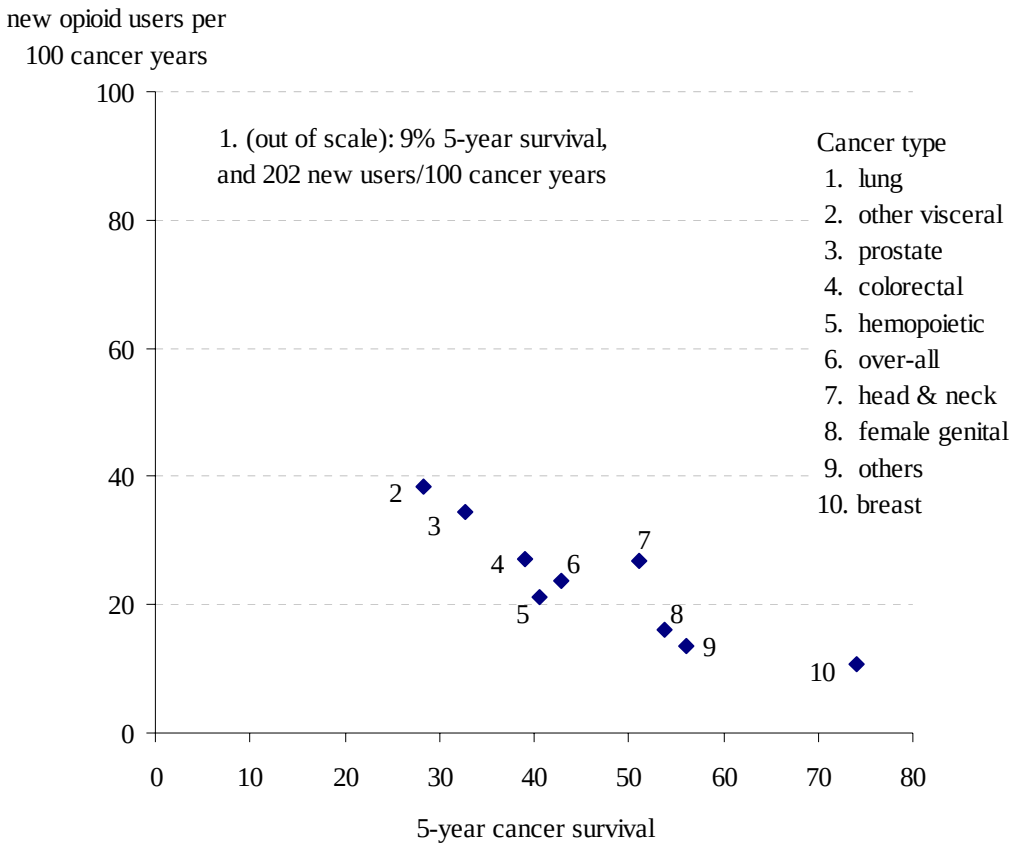


Figure 3. The incidence rate of new opioid users among incident cancer patients displayed as a function of the 5-year cancer survival.

Figure 4

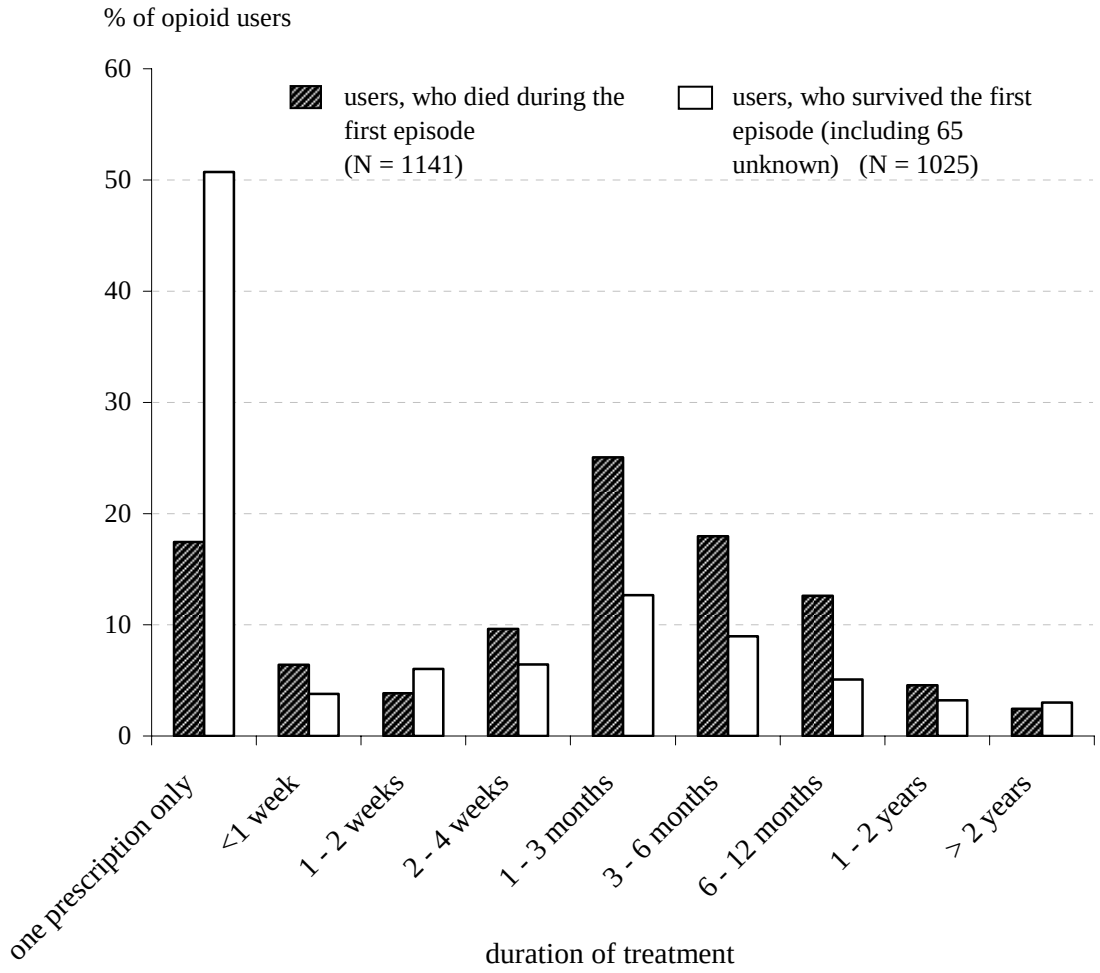


Figure 4. Duration of cancer patients' first treatment episode with opioids; the time between the first and the last prescription.