Journal of Medical Economics

ISSN: 1369-6998 (Print) 1941-837X (Online) Journal homepage: informahealthcare.com/journals/ijme20

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To cite this article: Stacey DaCosta Byfield, Emily Nash Smyth, Daniel Mytelka, Lee Bowman & April Teitelbaum (2013) Healthcare costs, treatment patterns, and resource utilization among pancreatic cancer patients in a managed care population, Journal of Medical Economics, 16:12, 1379-1386, DOI: 10.3111/13696998.2013.848208

To link to this article: https://doi.org/10.3111/13696998.2013.848208

Published online: 18 Oct 2013.

Journal of Medical Economics Vol. 16, No. 12, 2013, 1379–1386

1369-6998
doi:10.3111/13696998.2013.848208

Article 0049.R1/848208

Original article

Healthcare costs, treatment patterns, and resource utilization among pancreatic cancer patients in a managed care population

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Keywords:
Pancreatic cancer – Costs – Resource use – Retrospective

Accepted: 20 September 2013; published online: 18 October 2013
Citation: J Med Econ 2013; 16:1379–86

Abstract

Background:
Pancreatic adenocarcinoma has few effective treatment options and poor survival. The objective of this study was to characterize treatment patterns and estimate the costs and resource use associated with its treatment in a commercially-insured US population.

Methods:
In this retrospective claims-based analysis, individuals $\geq$18 years old with evidence of pancreatic adenocarcinoma between January 1, 2001 and December 31, 2010 were selected from a managed care database. Treatment phase (either initial non-metastatic or metastatic) was determined using a claims-based algorithm. Patients in the pancreatic cancer population were matched 1:3 to a control population. Resource use (events/person-years), treatment patterns, and healthcare costs (per-patient per-month, PPPM) were determined during a variable length follow-up period (from first pancreatic cancer diagnosis to earliest of death, disenrollment, or study end).

Results:
In this study, 5262 pancreatic cancer patients were matched to 15,786 controls. Rates of office visits, inpatient visits, ER visits, and inpatient stays, and mean total all-cause healthcare costs PPPM ($15,480 vs $1001) were significantly higher among cancer patients than controls (all $p<0.001$). Mean inpatient costs were the single largest cost driver ($9917 PPPM). Also, mean total all-cause healthcare costs were significantly higher during the metastatic treatment phase vs the initial treatment phase of non-metastatic disease ($21,637 vs $10,358, $p<0.001$).

Conclusions:
These results indicate that pancreatic cancer imposes a substantial burden on the US healthcare system, and that treatment of more advanced disease is significantly more costly than initial treatment of non-metastatic disease.

Limitations:
Additional research is needed to validate the accuracy of the claims-based algorithms used to identify the treatment phase.

Introduction

Pancreatic cancer is a highly malignant disease with limited effective treatment options. The lifetime risk of developing pancreatic cancer is 1 in 78 and, based on estimates from the American Cancer Society, there will be

~45,220 new cases of pancreatic cancer in the US in 2013[1,2]. The overall 5-year survival for all stages of pancreatic cancer is poor (~6%)[2]. Pancreatic cancer may spread locally (intra-abdominally or to the liver), and metastasize to the lungs, bone, or brain, which worsens the prognosis[1]. Patients with pancreatic cancer may experience a variety of complications, including obstructive jaundice, pancreatic insufficiency, cachexia, gastric outlet obstruction, and pain[3]. Treatment options vary by stage, and may include surgery (primarily for patients with early stage disease), chemotherapy, and chemoradiotherapy. In the adjuvant or neoadjuvant setting, treatment options include gemcitabine or 5-fluorouracil-based chemotherapy, often administered with concomitant radiotherapy[4,5]. For patients with good performance status and metastatic disease, FOLFIRINOX, or gemcitabine either as a single agent or in combination with nab-paclitaxel, erlotinib, capecitabine, or cisplatin, are among therapies recommended; for patients with poor performance status, gemcitabine given as a standard or fixed-dose rate infusion, capecitabine, or continuous infusion 5-FU are recommended[6–14]. While the anti-EGFR agent erlotinib has gained acceptance in treatment of pancreatic cancer, other targeted agents including cetuximab, bevacizumab, and tipifarnib have not shown significant benefit when added to gemcitabine[15–17].

Pancreatic cancer imposes a substantial burden on the US healthcare system. The annual healthcare costs associated with treating pancreatic cancer in the US were estimated at ~$1.9 billion for 2006[18]. Several studies have reported on patient level costs for pancreatic cancer in the US. In a study comparing pancreatic cancer to six other types of cancer (brain, colorectal, prostate, lung, ovarian, and non-Hodgkin's lymphoma), pancreatic cancer represented the most expensive type of these malignancies, with per patient mean monthly healthcare costs of $7616 (in 1999–2000 US dollars)[19]. Other previous estimates of pancreatic cancer costs were reported by O'Neill *et al.*[20] (mean monthly medical costs of $22,300, adjusted to 2009 US dollars), Du *et al.*[21] (mean annual medical costs of $42,218, adjusted to 1998 US dollars), and Chang *et al.*[22] (mean monthly medical costs of $8228, in 1999–2000 US dollars).

Prior studies of pancreatic cancer healthcare costs and resource use in the US are limited to data from more than 10 years ago, specific demographic groups, and/or specific geographic locations. Therefore, an updated understanding of the burden of pancreatic cancer in the US is needed. In this study, we used a national healthcare claims database to describe resource utilization, treatment patterns, and costs associated with pancreatic cancer in the US from 2001–2010 (as reflected in CPI-adjusted 2010 US dollars).

Methods

Pancreatic cancer population selection

This was a retrospective study using medical claims data, pharmacy claims data, and enrollment information from a large national managed care organization database (Optum Research Database). Study subjects were commercial and Medicare Advantage enrollees. Medical claims were collected from all available healthcare sites for provided services. The database included ~45.5 million enrollees during the identification period and was fairly representative of the US population (US census data 2009), in terms of gender and age with elderly individuals 65+ slightly under-represented. Member coverage was also geographically diverse (10% Northeast, 25% Midwest, 49% South, and 16% West), although the Northeast and West were slightly under-represented relative to the Midwest and South.

To be included in the final study sample, patients were required to have ≥2 claims with a diagnosis of pancreatic adenocarcinoma (ICD-9-CM 157.0x–157.3x, 157.8x, 157.9x in any position on the claim) at least 30 days apart, or ≥1 claim for pancreatic adenocarcinoma and evidence of death within 30 days after cancer diagnosis between January 1, 2001 and December 31, 2010. The index date was the date of first pancreatic cancer diagnosis. Patients were required to be at least 18 years old as of the index year, and continuously enrolled in the health plan with medical and pharmacy benefits for a 12-month period before the index date (defined as the baseline period) and for at least 1 month after the index date (defined as the follow-up period). The follow-up period could be variable in length, and patients were followed until the earliest of death, disenrollment from the health plan, or end of the study period (December 31, 2010). Date of death was identified using a combination of Social Security Administration (SSA) Master Death file data and facility-based discharge codes identifying death; patients who did not have evidence of death had censored survival calculated as the time from the index date until the end of their follow-up period. Patients were excluded if they had evidence of pancreatic neuroendocrine tumors, any other primary cancer (≥2 claims at least 30 days apart with codes indicating the same primary cancer) or evidence of metastatic disease during the baseline period. However, patients with non-melanoma skin cancers were not excluded since these are quite common, usually diagnosed in early stages, and are very rarely metastatic.

Control population selection and matching

The control population included commercial and Medicare Advantage health plan members with at least one medical claim between January 1, 2001 and

December 31, 2010; the service date on the first appearing claim was defined as the index date. Individuals in the control population were required to be continuously enrolled with medical and pharmacy benefits for a 12-month baseline period and for a ≥1-month follow-up period. Individuals were excluded from the control population if they had medical claims with diagnosis codes for cancer in any position during the baseline or follow-up period, or if they had evidence of receipt of any anti-cancer therapy during the baseline or follow-up period. Patients in the pancreatic cancer population were matched at a ratio of 1:3 to individuals in the control population based on age, gender, geographic region, insurance type, baseline Quan-Charlson comorbidity score[23], and index year. Two pancreatic cancer patients that could not be matched were excluded from the analysis.

Healthcare resource utilization and costs

Healthcare resource utilization and costs were measured using claims data during the entire follow-up period for both the cancer and control populations. Healthcare resource utilization was calculated for office visits, hospital outpatient visits, emergency department visits, and inpatient admissions. Total healthcare costs, pharmacy costs, and medical costs (office costs, hospital outpatient costs, emergency room costs, inpatient costs, and other costs) were computed as the sum of reimbursed health plan and patient paid amounts. Costs were adjusted to US dollars for 2010 using the annual medical care component of the Consumer Price Index (CPI) to reflect inflation between 2001 and 2010. Costs were presented as per-patient per-month (PPPM) amounts to account for varying lengths of follow-up time. Sub-sets of treatment-related costs (surgery, radiation therapy, chemotherapy, targeted therapy, laboratory/pathology tests, imaging, management of pancreatic cancer complications, and management of treatment-related side-effects) were also examined in more detail during the follow-up period. The specific treatments for pancreatic cancer complications were selected based on clinical judgment of the authors following consultation with National Comprehensive Cancer Network guidelines[14]. Cancer-related costs were also investigated. These costs were defined as the costs associated with any claims with a diagnosis for primary cancer or metastatic disease. In addition, costs of procedures and drugs related to pancreatic cancer complications and side-effects were included along with drugs for anti-cancer systemic therapy, anti-emetics, antimicrobials, antidepressants, NSAIDs, and opioids.

Phases of care

The follow-up period of pancreatic cancer patients was categorized by phase of care, in order to compare healthcare costs associated with non-advanced disease (initial non-metastatic phase) and costs associated with advanced disease (metastatic phase). Patients with evidence of disease progression during the study, and who initially presented with non-metastatic cancer but later developed metastatic cancer, would contribute monthly costs to the appropriate phase of disease for those time periods. The 'initial phase' was defined as the time from cancer diagnosis (index date) to the end of the initial chemotherapy episode for non-metastatic disease, and included initial cancer treatment (surgery, radiation, chemotherapy, or targeted therapy). The initial phase ended with a change in initial chemotherapy (i.e., start of at least one new agent); a treatment gap of at least 90 days; evidence of metastatic disease (≥2 claims for 'secondary neoplasms' ICD-9-CM codes 196.xx–198.xx, at least 7 days apart); death; disenrollment; or the end of the study period. Patients with ≥2 claims for secondary neoplasm (ICD-9-CM 196.xx–198.xx) at least 7 days apart were included in the 'metastatic phase', and the date of the first claim for metastatic disease indicated the start of the metastatic phase. If the first claim with a metastatic diagnosis occurred within 30 days of the index date, patients were included only in the advanced phase, and the index date was the start date of the advanced phase. In addition, patients with survival of 3 months or less after the index date were considered to have been diagnosed with metastatic disease and were included in the advanced phase, regardless of whether there were claims indicating a metastatic diagnosis. The advanced phase ended at the earliest date of death, disenrollment, or end of the study period. The 'initial phase' and 'metastatic phase' represented two sub-sets of costs for the overall pancreatic cancer population, and patient costs incurred after conclusion of the initial phase but not associated with metastases are also included in the average cost calculations.

Statistical analysis

Categorical and binary variables were compared using chi-square tests. Continuous variables were presented as means with standard deviations and were compared with 2-sided *t*-tests. Rates of healthcare utilization were compared using the exact binomial distribution. Costs across phases of care were compared using PROC GENMOD in SAS with phase as the independent variable. Robust standard errors were used to account for clustering within individuals across phases. Statistical analyses were performed using SAS software (version 9·2; SAS Inc, Cary, NC).

Results

A total of 5262 pancreatic cancer patients were matched to 15,786 control individuals. Statistically significant

differences were not observed between the cancer and control populations for age, gender, geographic region, insurance coverage type, or baseline Quan-Charlson comorbidity index, as these characteristics were used for matching the study population (Table 1). The length of mean time for the follow-up period was significantly shorter among the cancer population than the control population (Table 1). Approximately 62% of pancreatic cancer patients died during the study period compared to ~8% of control patients (Table 1). Using Kaplan-Meier analysis the median survival time of pancreatic cancer patients was estimated to be 9.9 months, and the median survival time of control patients was not reached.

Healthcare resource use and costs were compared between the cancer population and the control population during the follow-up period. The rates (events/person years) of office visits, outpatient visits, ER visits, and inpatient stays were significantly higher among the cancer population than the control population (all $p<0.001$) (Table 2). Mean total all-cause healthcare costs (PPPM) were significantly higher among pancreatic cancer patients vs control individuals ($15,480 [SD = 23,176] vs $1001 [SD = 5591], $p<0.001$) (Table 3). Among pancreatic cancer patients, mean inpatient costs represented the largest category of total healthcare costs ($9917 PPPM [SD = 22,069]) (Table 3). Also, among the pancreatic cancer population, mean total cancer-related costs were $14,243 PPPM (SD = 22,870), indicating that the majority of total all-cause costs among cancer patients were related to cancer. The median costs indicate that there are some expensive outlier patients, but conclusions about differences were not affected (Table 3).

Costs associated with select treatments and procedures were calculated among the pancreatic cancer population ($n = 5262$) during the follow-up period. Of the treatment and procedure categories examined for this study (Table 4), the highest costs were observed for treatments associated with the management of pancreatic cancer complications (average PPPM costs = $2860 among entire pancreatic cancer population [SD = 11,420]). Among the various pancreatic cancer complications, the most costly sub-categories were management of gastric outlet obstruction/GI perforation, management of cholangitis/biliary obstruction, and management of thromboembolic disease (Table 5). Substantial PPPM costs were also observed for surgery of pancreatic cancer ($1419 [SD = 8166]), chemotherapy ($877 [SD = 1583]), and radiation therapy ($699 [SD = 2423]) (Table 4). During the study period 47% of patients received chemotherapy and 13% received targeted therapy. Within the chemotherapy category, the most commonly prescribed agents among the entire pancreatic cancer population were gemcitabine (37%), 5-FU (14%), capecitabine (13%), and oxaliplatin (5%); within the targeted therapy category,

Table 2. All-cause healthcare resource use during follow-up. Cancer population vs control population.

	Cancer population ($n = 5262$)	Control population ($n = 15,786$)	*p*-Value
Office visits			
n	4645	14,789	
%	88	94*	<0.001
Rate[a]	30.1*	10.9	<0.001
Outpatient visits			
n	4639	10,077	
%	88*	64	<0.001
Rate[a]	23.5*	3.4	<0.001
ER visits			
n	3387	5415	
%	64*	34	<0.001
Rate[a]	2.0*	0.8	<0.001
Inpatient stays			
n	4447	2429	
%	85*	15	<0.001
Rate[a]	2.1*	0.2	<0.001
Length[b]	25*	18	<0.001

[a]Events/person-year (compared using the exact binomial test).
[b]Mean length of all inpatient stays in days (compared using 2-sided *t*-test).
Significantly higher results signified by *.

Table 1. Population demographics.

	Cancer population ($n = 5262$)	Control population ($n = 15,786$)	*p*-Value
Age (mean years, SD)	66 (12)	65 (12)	0.205
Gender (*n*, %)			
Male	2682 (51)	8046 (51)	1.000
Female	2580 (49)	7740 (49)	1.000
Coverage type (*n*, %)			
Commercial	3700 (70)	11,100 (70)	1.000
Medicare	1562 (30)	4686 (30)	1.000
Geographic region (*n*, %)			
Northeast	626 (12)	1878 (12)	1.000
Midwest	1846 (35)	5538 (35)	1.000
South	2244 (43)	6732 (43)	1.000
West	546 (11)	1638 (11)	1.000
Baseline Quan-Charlson comorbidity index (mean, SD)	1.50 (1.58)	1.48 (1.59)	0.265
Length of total follow-up (mean days, SD)	347 (443)	608 (588)	<0.001
Mortality (*n*, %)	3239 (62)	1295 (8)	<0.001

Table 3. All-cause healthcare costs (PPPM) during follow-up. Cancer population vs control population.

Costs ($)	Cancer population ($n = 5262$)	Control population ($n = 15,786$)	p-Value
Total costs, mean (SD), median	15,480* (23,176), 9440	1001 (5591), 359	<0.001
Office costs, mean (SD), median	1520* (2500), 319	130 (472), 62	<0.001
Hospital outpatient costs, mean (SD), median	2796* (5468), 813	193 (2100), 14	<0.001
Emergency room costs, mean (SD), median	164* (512), 19	35 (576), 0	<0.001
Inpatient costs, mean (SD), median	9917* (22,069), 3060	344 (4914), 0	<0.001
Other costs, mean (SD), median	393* (1727), 68	101 (540), 7	<0.001
Pharmacy costs, mean (SD), median	689* (1129), 294	197 (312), 104	<0.001

Significantly higher results signified by*.

Table 4. Select treatment/procedure healthcare costs (PPPM) of pancreatic cancer patients during follow-up.

	Total follow-up ($n = 5262$)	Initial phase (non-metastatic disease) ($n = 2651$)	Metastatic phase ($n = 3227$)	p-Value[c]
Pancreatic cancer surgery				
n (%)[a]	1330 (25)	826 (31)	480 (15)	
Mean $ (SD)[b]	1419 (8166)	1871* (6306)	1435 (9871)	0.041
Radiation therapy				
n (%)	1464 (28)	712 (27)	695 (22)	
Mean $ (SD)	699 (2423)	1059* (3173)	593 (2429)	<0.001
Chemotherapy				
n (%)	2496 (47)	1091 (41)	1535 (48)	
Mean $ (SD)	877 (1583)	622 (1409)	1024* (1740)	<0.001
Targeted therapy				
n (%)	669 (13)	94 (4)	496 (15)	
Mean $ (SD)	172 (647)	86 (622)	228* (732)	<0.001
Laboratory/pathology tests				
n (%)	4045 (77)	2067 (78)	2340 (73)	
Mean $ (SD)	69 (217)	41 (118)	94* (267)	<0.001
Imaging				
n (%)	4839 (92)	2425 (91)	2911 (90)	
Mean $ (SD)	496 (4527)	281 (837)	697* (5802)	<0.001
Management of pancreatic cancer complications				
n (%)	4761 (90)	2439 (92)	2816 (87)	
Mean $ (SD)	2860 (11,420)	1639 (4947)	4032* (15,140)	<0.001
Management of treatment-related side-effects				
n (%)	4344 (83)	2300 (44)	2482 (47)	
Mean $ (SD)	534 (1070)	311 (854)	676* (2875)	<0.001

[a]Number of patients in cohort with evidence of treatment or procedure.
[b]Mean cost of treatment/procedure among all patients in cohort.
[c]Comparison of mean costs between initial phase and metastatic phase.
Significantly higher results signified by *.

the most commonly prescribed was erlotinib (11%). When stratified by treatment year, our data did not suggest that the treatment paradigm for pancreatic cancer shifted greatly from 2001–2010, other than the addition of oxaliplatin and erlotinib as treatment options. Mean costs PPPM for treatments associated with managing side-effects of chemotherapy were $534 (SD = 1070) (Table 4).

Healthcare costs and resource use were compared between two different cancer treatment phases: an initial phase in which patients with non-metastatic cancer received treatment, and an advanced phase in which patients with evidence of metastatic pancreatic cancer received treatment. Within the overall pancreatic cancer population, ~50% of patients presented with metastatic disease, and of those not identified as having metastatic disease at index date, ~23% progressed to metastatic disease. The average length of time spent in the initial and advanced phases were 332 and 215 days, respectively. The rates (events/person years) of office visits, outpatient visits, ER visits, and inpatient stays were significantly higher during the metastatic treatment phase vs the initial treatment phase (all $p < 0.001$) (Table 6). Also, mean all-cause PPPM healthcare costs were significantly higher during the metastatic treatment phase vs the initial treatment phase of non-metastatic disease ($21,637 [SD = 29,814] vs 10,358 [SD = 13,026], $p < 0.001$) (Table 7). Among the categories of select procedures and treatments, mean costs (PPPM) for pancreatic cancer surgery ($p = 0.041$) and radiation therapy ($p < 0.001$) were significantly

Table 5. Healthcare costs (PPPM) associated with management of pancreatic cancer complications.

Costs associated with management of	Total follow-up ($n=5262$)	Initial phase (non-metastatic) ($n=2651$)	Metastatic phase ($n=3227$)	p-Value[c]
Cholangitis or biliary obstruction (*costs of ERCP, biliary bypass, and stent placement*)				
n (%)[a]	1914 (36)	955 (36)	988 (31)	
Mean $ (SD)[b]	994 (5467)	760 (2871)	1272* (6789)	<0.001
Intractable ascites (*costs of paracentesis and shunting*)				
n (%)	615 (12)	111 (4)	468 (15)	
Mean $ (SD)	81 (1661)	9 (93)	221* (5329)	0.023
Depression (*costs of antidepressants*)				
n (%)	1507 (29)	698 (26)	816 (25)	
Mean $ (SD)	8 (33)	9 (28)	8 (35)	0.246
Gastric outlet obstruction/GI perforation (*costs of gastric bypass, gastroduodenal stents, nasogastric tube treatment, and repair treatment*)				
n (%)	1371 (26)	643 (24)	696 (22)	
Mean $ (SD)	1010 (8529)	577 (3724)	1403* (10,836)	<0.001
Cachexia (*costs of cyproheptadine HCL, progesterone derivatives, growth hormones, anabolic steroids, nutritional supplementation)*				
n (%)	1188 (23)	442 (17)	704 (22)	
Mean $ (SD)	63 (573)	46 (483)	80* (695)	0.031
Pain (*costs of celiac plexus treatment, splanchnic nerve destruction treatment, epidural injection, opioids, NSAIDs*)				
n (%)	4128 (78)	2109 (80)	2368 (73)	
Mean $ (SD)	254 (1803)	175 (1199)	342* (2299)	<0.001
Pancreatic insufficiency (*costs of replacement pancreatic enzymes*)				
n (%)	1468 (28)	749 (28)	748 (23)	
Mean $ (SD)	29 (93)	32* (99)	26 (92)	0.007
Skeletal metastases (*costs of bisphosphonates*)				
n (%)	70 (1)	7 (0.3)	59 (2)	
Mean $ (SD)	4 (62)	0.2 (6)	7* (92)	<0.001
Thromboembolic disease (*costs of thrombectomy, embolectomy, inferior vena cava filter, low molecular weight heparin, warfarin*)				
n (%)	1228 (23)	402 (15)	791 (25)	
Mean $ (SD)	559 (5136)	127 (1090)	850* (6519)	<0.001

[a]Number of patients in cohort with evidence of treatment for the complication.
[b]Mean cost of treatment among all patients in cohort.
[c]Comparison of mean costs between initial phase and metastatic phase.
Significantly higher results signified by *.

higher during the initial treatment phase vs the metastatic treatment phase (Table 4). However, mean costs for chemotherapy ($p<0.001$), targeted therapy ($p<0.001$), imaging ($p<0.001$), management of pancreatic cancer-related complications ($p<0.001$), and management of chemotherapy side-effects ($p<0.001$) were significantly higher during the metastatic treatment phase vs the initial treatment phase (Table 4).

Discussion

We used a large, nationally diverse, managed care population to estimate the costs and resource use associated with pancreatic cancer in the US. We found that rates of healthcare resource utilization were significantly higher among the pancreatic cancer population than the control population during the follow-up period. Additionally, mean total all-cause healthcare costs (PPPM) were more than 10-fold higher among the cancer population compared with the control population. About two-thirds of all-cause healthcare costs among cancer patients were inpatient costs. The high costs and resource utilization observed in this population of pancreatic cancer patients indicates that pancreatic cancer imposes a substantial burden on the US healthcare system. Among all pancreatic cancer patients in this study, we identified management of complications related to pancreatic cancer as a major cost driver that accounted for mean monthly costs of $2860 per patient. In this study, costs were also compared between non-metastatic and metastatic disease, and mean healthcare costs were ~2-fold higher during treatment of metastatic cancer. These findings indicate that advanced disease is associated with a greater burden on the healthcare system, further supporting the need for improved early detection and more effective therapeutic approaches to prevent pancreatic cancer from progressing to a more advanced stage. Of note, about half of the patients included in this study had metastatic disease at diagnosis.

Previous studies have examined the costs of pancreatic cancer in the US. The mean all-cause healthcare costs among pancreatic cancer patients reported in the present study were higher than some previous estimates, but lower than others. These differences may be attributed to a variety of factors, including study design, study period, inflation, rising healthcare costs, and patient population. For example, Chang *et al.*[22] found that mean unadjusted PPPM direct medical costs among pancreatic cancer patients in a managed care population were $8228 (patients diagnosed 1999–2000), compared to $15,480 in the present study (patients diagnosed 2001–2010). The difference in costs between studies may be related to inflation, advances in diagnostic imaging and non-surgical interventions, increases in costs of delivering medical care, and introduction of certain combination therapy regimens[8–10]. In a more recent study of pancreatic cancer costs (2000–2007), O'Neill *et al.*[20] reported that mean direct medical costs (PPPM) of pancreatic cancer patients were $22,300, which is higher than the estimate reported in the present study. However, O'Neill *et al.* studied a population of elderly Medicare patients aged 66 years or older, whereas the mean age of patients in the present study was ~66 years.

Gemcitabine was the most commonly prescribed chemotherapy agent among pancreatic cancer patients in this population. Although we did observe some shifts in use of other drugs over the study time frame, overall our data suggested that gemcitabine remained the cornerstone of treatment for pancreatic cancer from 2001–2010. Not surprisingly, very few patients received the FOLFIRINOX regimen in our study, as its efficacy was first reported at the 2010 ASCO meeting, and utilization of FOLFIRINOX among advanced pancreatic cancer patients has increased since that time[24,25]. Future studies will be needed to characterize its trajectory of use as well as that of gemcitabine/nab-paclitaxel combination given recent data[26].

Limitations to the claims-based approach used here should be considered when interpreting these results. Presence of a diagnosis code on a claim does not necessarily indicate positive presence of disease, as the diagnosis code may be incorrectly coded or codes may not precisely capture the diagnosis of interest, particularly with regard to metastatic disease. Prior studies have used a similar approach to identify pancreatic cancer patients in administrative claims data, and have provided evidence that claims data can be used to identify metastatic disease in other types of cancer[22,27]. The requirements to have ≥2 claims with a diagnosis of pancreatic adenocarcinoma (as opposed to just 1 claim) for study inclusion and to have ≥2 claims for secondary neoplasm (as opposed to just 1 claim) for inclusion in the metastatic phase likely reduced sensitivity but increased specificity of patient identification. Additional research, such as a medical chart review, is needed to validate the claims-based algorithms used in the present study. Also, certain information is not readily available in claims data that could have an effect on study outcomes (e.g. it is difficult to distinguish between stages of disease) and, when using claims data, one cannot definitively state that procedures or treatment received by a patient were done for a particular reason. Therefore, estimates of costs should be interpreted with caution, as some procedures or medications may have been administered to treat unrelated conditions, while other procedures or

Table 6. All-cause healthcare resource use during follow-up. Initial treatment phase vs metastatic treatment phase.

	Initial phase (non-metastatic disease) ($n=2651$)	Metastatic phase ($n=3227$)	*p*-Value
Office visits			
n	2569	2632	
%	97*	82	<0.001
Rate[a]	24.8	35.7*	<0.001
Outpatient visits			
n	2506	2672	
%	95*	83	<0.001
Rate[a]	19.2	31.2*	<0.001
ER visits			
n	1333	2109	
%	50	65*	<0.001
Rate[a]	1.4	2.8*	<0.001
Inpatient stays			
n	1900	2879	
%	72	89*	<0.001
Rate[a]	1.5	3.4*	<0.001
Length[b]	21	23*	0.002

[a]Events/person-year (compared using the exact binomial test).
[b]Mean length of all inpatient stays in days (compared using 2-sided *t*-test).
Significantly higher results signified by *.

Table 7. All-cause healthcare costs (PPPM) during follow-up. Initial treatment phase vs metastatic treatment phase.

Costs ($)	Initial phase (non-metastatic disease) ($n=2651$)	Metastatic phase ($n=3227$)	*p*-Value
Total costs, mean (SD), median	10,358 (13,026), 5982	21,637* (29,814), 13,611	<0.001
Office costs, mean (SD), median	1317 (2497), 288	1696* (2,781), 338	<0.001
Hospital outpatient costs, mean (SD), median	2862 (4945), 787	3262* (6620), 999	0.006
Emergency room costs, mean (SD), median	65 (176), 0	236* (636), 37	<0.001
Inpatient costs, mean (SD), median	5290 (10,789), 1250	15,130* (29,170), 5545	<0.001
Other costs, mean (SD), median	317 (1340), 52	499* (2199), 71	<0.001
Pharmacy costs, mean (SD), median	508 (844), 242	814* (1299), 323	<0.001

Significantly higher results signified by *.

medications intended to treat these conditions may not have been captured. Additionally, treatments received by patients enrolled in clinical trials may not generate insurance claims and, therefore, might not be included in this claims dataset. Finally, the results of this study are most applicable to a population of patients in a national managed care organization, and may not be applicable to other patient populations.

In conclusion, we found that pancreatic cancer was associated with significantly higher costs and resource use compared with a matched control population of unaffected individuals and, further, that treatment of metastatic pancreatic cancer was associated with significantly higher costs compared with non-metastatic disease. In addition to the clinical burden, our findings indicated that progression to a more advanced disease stage is associated with an increased economic burden, and that this burden results not just from treatment of the cancer itself, but also from the various complications that may arise from pancreatic cancer.

Transparency

Declaration of funding
This study was sponsored by Eli Lilly and Company.

Declaration of financial/other interests
Emily Nash Smyth, Daniel Mytelka, and Lee Bowman are all employees and shareholders of Eli Lilly and Company. Stacey DaCosta Byfield and April Teitelbaum have disclosed that they work for OptumInsight, a company that received funding from Eli Lilly for its role in the development on this study. JME Peer Reviewers on this manuscript have no relevant financial or other relationships to disclose.

Acknowledgments
The authors thank Jesse Potash, PhD, at OptumInsight for assistance with preparation of this manuscript.

References

1. American Cancer Society. Pancreatic Cancer. 2013; http://www.cancer.org/acs/groups/cid/documents/webcontent/003131-pdf.pdf. Accessed August 12, 2013
2. Siegel R, Jemal A, Naishadham D. Cancer statistics, 2013. CA Cancer J Clin 2013;63:11-30
3. el-Kamar FG, Grossbard ML, Kozuch PS. Metastatic pancreatic cancer: emerging strategies in chemotherapy and palliative care. Oncologist 2003;8:18-34
4. Li J, Wientjes MG, Au JL. Pancreatic cancer: pathobiology, treatment options, and drug delivery. AAPS J 2010;12:223-32
5. Gillen S, Schuster T, Meyer Zum Büschenfelde C, et al. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. PLoS Med 2010;7:e1000267
6. Burris 3rd HA,, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997;15:2403-13
7. Cartwright TH, Cohn A, Varkey JA, et al. Phase II study of oral capecitabine in patients with advanced or metastatic pancreatic cancer. J Clin Oncol 2002;20:160-4
8. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007;25:1960-6
9. Louvet C, Labianca R, Hammel P, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. J Clin Oncol 2005;23:3509-16
10. Herrmann R, Bodoky G, Ruhstaller T, et al. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. J Clin Oncol 2007;25:2212-7
11. De Jesus-Acosta A, Oliver GR, Blackford A, et al. A multicenter analysis of GTX chemotherapy in patients with locally advanced and metastatic pancreatic adenocarcinoma. Cancer Chemother Pharmacol 2012; 69:415-24.
12. Tempero MA, Arnoletti JP, Behrman SW, et al. Pancreatic Adenocarcinoma, version 2.2012: featured updates to the NCCN Guidelines. J Natl Compr Canc Netw 2012;10:703-13
13. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817-25
14. National Comprehensive Cancer Network Guidelines. Pancreatic Adenocarcinoma Version 1.2013. 2013; http://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed July 2013
15. Philip PA, Benedetti J, Corless CL, et al. Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: Southwest Oncology Group-directed intergroup trial S0205. J Clin Oncol 2010;28:3605-10
16. Kindler HL, Niedzwiecki D, Hollis D, et al. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). J Clin Oncol 2010;28:3617-22
17. Van Cutsem E, van de Velde H, Karasek P, et al. Phase III trial of gemcitabine plus tipifarnib compared with gemcitabine plus placebo in advanced pancreatic cancer. J Clin Oncol 2004;22:1430-8
18. National Cancer Institute. Cancer Trends Progress Report. 2012; http://progressreport.cancer.gov/doc_detail.asp?pid=1&did=2007&chid=75&coid=726&. Accessed May 29, 2012
19. Chang S, Long SR, Kutikova L, et al. Estimating the cost of cancer: results on the basis of claims data analyses for cancer patients diagnosed with seven types of cancer during 1999 to 2000. J Clin Oncol 2004;22:3524-30
20. O'Neill CB, Atoria CL, O'Reilly EM, et al. Costs and trends in pancreatic cancer treatment. Cancer 2012;118:5132-9
21. Du W, Touchette D, Vaitkevicius VK, et al. Cost analysis of pancreatic carcinoma treatment. Cancer 2000;89:1917-24
22. Chang S, Long SR, Kutikova L, et al. Burden of pancreatic cancer and disease progression: economic analysis in the US. Oncology 2006;70:71-80
23. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005;43:1130-9
24. Conroy T, Desseigne F, Ychou M, et al. Randomized phase III trial comparing FOLFIRINOX (F: 5FU/leucovorin [LV], irinotecan [I], and oxaliplatin [O]) versus gemcitabine (G) as first-line treatment for metastatic pancreatic adenocarcinoma (MPA): preplanned interim analysis results of the PRODIGE 4/ACCORD 11 trial. J Clin Oncol 2010;28(Suppl):abstr 4010
25. Arlen AG, Cartwright TH, Wilfong LS, et al. Use of first-line chemotherapy for advanced pancreatic cancer: FOLFIRINOX versus gemcitabine. J Clin Oncol 2012;30(Suppl):abstr 16536
26. Von Hoff DD, Ervin TJ, Arena FP, et al. Randomized phase III study of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone in patients with metastatic adenocarcinoma of the pancreas (MPACT). J Clin Oncol 2012;30(Suppl 34):abstr LBA148
27. Eichler AF, Lamont EB. Utility of administrative claims data for the study of brain metastases: a validation study. J Neurooncol 2009;95:427-31

