A population-based study of the epidemiology of pancreatic cancer: a brief report

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ABSTRACT

Objective   Administrative data are used to describe the pancreatic cancer (PCC) population. The analysis examines demographic details, incidence, site, survival, and factors influencing mortality in a cohort of individuals diagnosed with PCC.

Methods   Incident cases of PCC diagnosed in Ontario between 1 January 2004 and 31 December 2011 were extracted from the Ontario Cancer Registry. They were linked by encrypted health card number to several administrative databases to obtain demographic and mortality information. Descriptive, bivariate, and survival analyses were conducted.

Results   During the period of interest, 9221 new cases of PCC (4548 in men, 4673 in women) were diagnosed, for an age-adjusted standardized annual incidence in the range of 8.6–9.5 per 100,000 population. Mean age at diagnosis was 70.3 ± 12.5 years (standard deviation). Five-year survival was 7.2% (12.8% for those <60 years of age and 3.6% for those >80 years of age). Survival varied by sex, older age, rural residence, lower income, site of involvement in the pancreas, and presence of comorbidity.

Conclusions   The mortality rate in PCC is exceptionally high. With an increasing incidence and a mortality positively associated with age, additional support will be needed for this highly fatal disease as demographics in Ontario continue to trend toward a higher proportion of older individuals.

Key Words   Pancreatic adenocarcinoma, retrospective analyses, population studies, outcomes

INTRODUCTION

Cancer of the pancreas is rare, and yet it accounts for the 4th largest number of cancer deaths in Canada each year. In 2014, 4700 new cases of pancreatic cancer (PCC) in Canada (9.3 per 100,000 population) were projected. Once a patient is diagnosed, prognosis is poor, with the number of deaths from PCC in 2014 estimated to be 4400 (8.6 per 100,000 population)[1]. The relative survival ratio for PCC is the lowest among the common malignancies and has been estimated to be 21% at 1 year and 6%–8% at 5 years[1,2]. The mortality subsequent to most other cancers has declined since 2000, but no corresponding mortality improvement in PCC has occurred[3].

Because of the absence of symptoms associated with early-stage PCC and a lack of cost-effective screening strategies, the disease is often detected at later stages[4,5]. In most cases, PCC is not discovered until after it has metastasized to adjacent organs, such as the liver. For patients with metastatic PCC, life expectancy approximates 2.5 months with best supportive care[6,7]. New chemotherapy regimens such as FOLFIRINOX and nab-paclitaxel appear to offer longer life expectancy (up to a median of 11 months), but the improvement is accompanied by deleterious side effects and complications[8].

Ontario is the largest province in Canada and has the greatest incidence of PCC patients in the country by virtue of its population size[1]. However, little is known about the overall epidemiology of the disease and the factors influencing survival in this group of patients[9]. In the present analysis, we examined a cohort of patients with a diagnosis of PCC and their survival at 5 years.

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METHODS

This population-based retrospective cohort study used administrative datasets housed at the Institute for Clinical Evaluative Sciences, a prescribed entity under Ontario's *Personal Health Information Protection Act,* which allows use of individual patient-level data for the purpose of research. Approval was obtained from the research ethics board at Sunnybrook Health Sciences Centre.

Incident cases of PCC diagnosed between 1 January 2004 and 31 December 2011 were extracted from the Ontario Cancer Registry (OCR). The OCR captures information about all Ontario residents who have been newly diagnosed with cancer or who have died of cancer. Previous validation studies have demonstrated that the OCR is a valid data source, with high sensitivity and specificity for identifying cancer patients[10]. Malignant neoplasms of the pancreas were identified using International Classification of Diseases version 9 codes (1570, 1571, 1572, 1573, 1574, 1578, and 1579). In the resulting dataset, the pancreatic adenocarcinoma cohort was identified by OCR histology codes (8000, 8001, 8010, 8020, 8021, 8031, 8035, 8140, 8144, 8145, 8255, 8340, 8341, 8344, 8440, 8442, 8470, 8481, 8490, 8500, 8560, 8570, 8574, 8575, 9990). The site of the cancer was determined by International Classification of Diseases version 9 codes: head of the pancreas (1570), tail of the pancreas (1572), and other (or unspecified) locations (1571, 1573, 1574, 1578, 1579).

The patients were linked by encrypted health card number to other administrative datasets housed at the Institute for Clinical Evaluative Sciences. Demographic and mortality information were obtained from the Registered Persons Database, which provides basic demographic information such as birth date, death date, and postal code of residence for all residents with an Ontario health card number. All patients were followed from their date of diagnosis to their date of death, to 5 years after diagnosis, or to 31 December 2013, whichever came first.

Geographic area of residence for the individual patients was linked to Canadian census data by geocoding postal codes into dissemination areas (the smallest unit of census geography), and neighbourhood-level information on median family income (a household size–adjusted measure of household income) was obtained[11].

We further linked the patient cohort to the Canadian Institute for Health Information's Discharge Abstract Database, which provides detailed diagnostic information for each hospital admission. For each patient, we used data from hospitalizations occurring in the 2 years before the PCC diagnosis to calculate a score on Charlson comorbidity index. For patients with a Charlson score of 0, we assigned a comorbidity status of "no"; for those with a score equal to or greater than 1, we assigned a comorbidity status of "yes."

We obtained Ontario population information during the study period from the Ontario Population Estimates and Projections, which are the intercensal and postcensal estimates of the Ontario population by sex, age, and geographic area. Those estimates are produced by Statistics Canada.

Statistical Analysis

We describe patient demographics, disease characteristics, and length of follow-up by patient age at diagnosis. Comparisons between age groups were made using one-way analysis of variance for continuous variables and chi-square tests for categorical variables.

We then calculated the crude incidence rate of PCC for men and women by age group for each year during the study period. For a specific year, the incidence rate was calculated by dividing the number of PCC cases by the yearly population size in each age and sex stratum.

We used the life-table method and dates of death according to the Registered Persons Database as of 31 December 2013 to estimate 5-year survival probabilities. Kaplan–Meier survival analyses were used to describe the survival probability for patients in various age groups, disease site groups, and diagnostic periods. Age at diagnosis was adjusted when computing the survival probability for various disease sites and diagnostic periods.

Cox regression was used to examine factors associated with survival. Variable selection was based on both clinical relevance and influence on risk estimates or statistical significance. The variables examined were sex, age, site of cancer, residence, income, year of diagnosis, and comorbidity. To determine whether the selected variables met the proportional hazards assumption, we generated time-dependent covariates by creating interactions of the predictors and a function of survival time, and included them in the model. If any of the time-dependent covariates were significant, then those predictors were considered not to be proportional[12].

All analyses were performed using the SAS 9.2 software application (SAS Institute, Cary, NC, U.S.A.). Statistical significance was set at $p < 0.05$.

RESULTS

New cases of PCC diagnosed between 2004 and 2011 numbered 9221 (4548 cases in men, 4673 cases in women). During that 8-year period, the age-adjusted standardized annual incidence rate fluctuated in the range 8.57–9.47 per 100,000 population. The most frequent site of PCC was the head of the pancreas (42%); 9.1% of PCCs were reported to have occurred in the tail. The remaining cases (48.9%) were in other locations (including multiple sites) or were not specified in the OCR.

Mean age at diagnosis was 70.3 ± 12.5 years (standard deviation). Women were older (72.3 ± 12.8 years) than men (68.1 ± 11.8 years) at the time of diagnosis. Of these individuals with PCC, 15% were rural residents (rural residents represented 14% of the general population in 2011). Distribution by income quintile was equal across the cohort (Table I). In the younger age groups, the incidence of PCC was lower in women than in men. The female incidence then steadily increased with age and, in 5 of the 8 years, overtook the male incidence in the 81 years and older category (Table II).

In this cohort, 92% died during follow-up. The overall survival within 5 years of follow-up was 7.2%. The mean and median follow-up times were 303 ± 451 days and 113 days (interquartile range: 35–340 days) respectively. At 1 month after diagnosis, 78% of the cohort members were alive; at 1 year, only 23.5% were still living. The probability of survival decreased as age at diagnosis increased. The

TABLE I Demographic details of patients with pancreatic cancer in Ontario, 2004–2011

Variable	Patient group					*p* Value[a]
	≤60 Years	61–70 Years	71–80 Years	≥81 Years	Overall	
Patients (*n*)	2096	2264	2750	2111	9221	
Year of diagnosis [*n* (%)]						
2004	226 (10.8)	273 (12.1)	327 (11.9)	233 (11.0)	1059 (11.5)	0.075
2005	235 (11.2)	281 (12.4)	344 (12.5)	249 (11.8)	1109 (12.0)	
2006	243 (11.6)	270 (11.9)	315 (11.5)	236 (11.2)	1064 (11.5)	
2007	297 (14.2)	255 (11.3)	377 (13.7)	275 (13.0)	1204 (13.1)	
2008	295 (14.1)	268 (11.8)	356 (12.9)	261 (12.4)	1180 (12.8)	
2009	261 (12.5)	293 (12.9)	354 (12.9)	295 (14.0)	1203 (13.0)	
2010	273 (13.0)	279 (12.3)	332 (12.1)	287 (13.6)	1171 (12.7)	
2011	266 (12.7)	345 (15.2)	345 (12.5)	275 (13.0)	1231 (13.3)	
Sex [*n* (%)]						
Women	857 (40.9)	987 (43.6)	1436 (52.2)	1393 (66.0)	4673 (50.7)	<0.001
Men	1239 (59.1)	1277 (56.4)	1314 (47.8)	718 (34.0)	4548 (49.3)	
Rural [*n* (%)]						
Missing	<6	<6	<6	<6	12 (0.1)	0.002
No	1781 (85.0)	1904 (84.1)	2295 (83.5)	1850 (87.6)	7830 (84.9)	
Yes	310 (14.8)	357 (15.8)	453 (16.5)	259 (12.3)	1379 (15.0)	
Income quintile [*n* (%)]						
Missing	13 (0.6)	16 (0.7)	8 (0.3)	15 (0.7)	52 (0.6)	0.466
1 (lowest)	437 (20.8)	460 (20.3)	585 (21.3)	451 (21.4)	1933 (21.0)	
2	426 (20.3)	478 (21.1)	586 (21.3)	426 (20.2)	1916 (20.8)	
3	401 (19.1)	422 (18.6)	537 (19.5)	447 (21.2)	1807 (19.6)	
4	435 (20.8)	454 (20.1)	538 (19.6)	395 (18.7)	1822 (19.8)	
5 (highest)	384 (18.3)	434 (19.2)	496 (18.0)	377 (17.9)	1691 (18.3)	
Site [*n* (%)]						
Head of pancreas	974 (46.5)	1013 (44.7)	1144 (41.6)	744 (35.2)	3875 (42.0)	<0.001
Tail of pancreas	255 (12.2)	236 (10.4)	239 (8.7)	110 (5.2)	840 (9.1)	
Others	867 (41.4)	1015 (44.8)	1367 (49.7)	1257 (59.5)	4506 (48.9)	
Comorbidity[b] [*n* (%)]						
No	1879 (89.6)	1869 (82.6)	2151 (78.2)	1568 (74.3)	7467 (81.0)	<0.001
Yes	217 (10.4)	395 (17.4)	599 (21.8)	543 (25.7)	1754 (19.0)	
Died within 5 years' follow-up [*n* (%)]						
No	286 (13.6)	219 (9.7)	159 (5.8)	82 (3.9)	746 (8.1)	<0.001
Yes	1810 (86.4)	2045 (90.3)	2591 (94.2)	2029 (96.1)	8475 (91.9)	
Follow-up days (*n*)						
Mean	431.72±529.65	351.76±467.22	259.35±405.20	180.21±351.75	303.10±450.51	<0.001
Median	207	159	97	49	113	<0.001
Interquartile range	74–525	51–429	33–279	17–158	35–340	

[a] Reflects significance of variation between age groups.
[b] Based on score on the Charlson comorbidity index (0=no, ≥1=yes) up to 2 years before the diagnosis with pancreatic cancer.

TABLE II Incidence of pancreatic cancer per 100,000 population by year of diagnosis, age, and sex

Year of diagnosis	Sex	Patient age group			
		≤60	61–70	71–80	≥81
2004	Women	1.69	22.31	45.59	69.11
	Men	2.66	35.21	47.26	62.78
2005	Women	1.73	22.07	47.36	70.93
	Men	2.75	35.51	49.93	62.4
2006	Women	1.79	21.46	41.85	60.36
	Men	2.8	32.18	46.89	62.4
2007	Women	2.35	21.13	45.19	72.79
	Men	3.24	27.68	61.09	59.05
2008	Women	2.02	20.51	47.58	61.85
	Men	3.51	27.96	50.53	61.98
2009	Women	2.27	21.5	46.64	68.97
	Men	2.6	28.88	49.75	63.95
2010	Women	2.3	22.5	42.67	66.48
	Men	2.79	25.34	47.95	63.31
2011	Women	2.08	24.98	43.91	61.51
	Men	2.88	34.38	50.35	64.58

FIGURE 1 Probability of survival for patients with pancreatic cancer in Ontario by age at diagnosis.

FIGURE 2 Probability of survival for patients with pancreatic cancer in Ontario by site in the pancreas, adjusted for age.

30-day and 1-year survival rates for affected individuals 60 years of age or less were 88.6% and 34.4% respectively; for those more than 80 years of age, the equivalent rates were 62.2% and 12.1%. Median survival for individuals 60 years of age or younger at diagnosis was 207 days; it was 49 days for individuals more than 80 years of age (Figure 1).
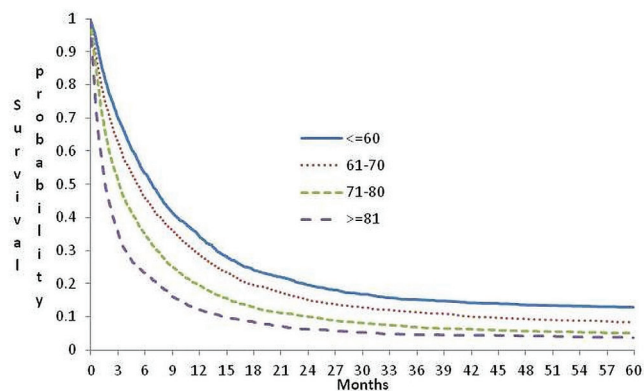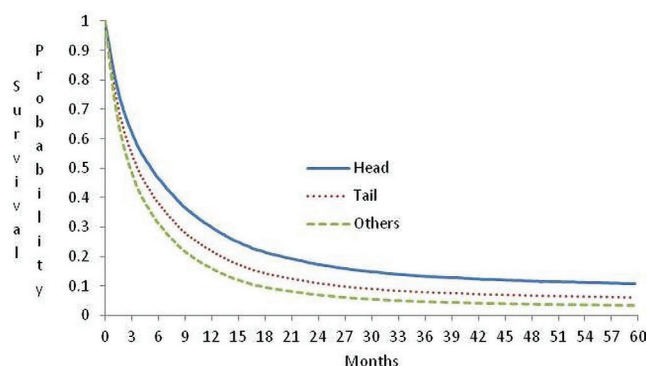
With respect to site of the primary cancer, median survival was 5.0 months in individuals with a diagnosis of carcinoma in the head of pancreas; 3.2 months in those with a diagnosis of carcinoma in the tail of pancreas; and 3.0 months for other sites (Figure 2).

All variables included in the Cox regression met the proportional hazards assumption. Male sex, older age, presence of cancer in sites other than the head of pancreas, rural residence, low income, and presence of comorbidity were associated with lower survival. Survival seemed to improve with more recent diagnosis (Table III, Figure 3).

DISCUSSION

The present work provides an overview of a contemporary cohort of the entire patient population with PCC in Ontario. Survival in that cohort is in line with PCC survival in other jurisdictions, with one quarter still living at 12 months after diagnosis [2] and 7.2% still living at 5 years. Our 5-year survival findings are similar to the survival reported in Ireland (5%) [6] and the relative survival reported in the United States (6%) [4]. A report by Cancer Research UK indicated that the relative 5-year survival was 3.3% for patients diagnosed with PCC during 2010–2011 in England and Wales [13]. All numbers show extremely poor survival with this disease.

Other reports show a relative survival rate of 10.9% for PCC patients in Ontario [14,15]. Cancer Care Ontario [16] and several Canadian government agencies [3] report an 8% 5-year relative survival for PCC in the Canadian population. Because the relative survival is the ratio of the observed survival for a group of persons diagnosed with cancer to the survival expected for people in the entire population, it differs slightly from the result found in an actual 5-year survival analysis, as estimated for the present study.

Health system administrative data was used for patient follow-up. Ontario has a publicly funded single-payer system that covers medically necessary health care costs for all eligible residents. It is unlikely that PCC patients would pursue health care elsewhere; however, the main loss to follow-up in our cohort would have been caused by patients moving out of the province. We had no information on such movements. However, we did ascertain patient eligibility for Ontario Health Insurance Plan coverage at the end of follow-up, and found that only 90 patients (0.98%) had an invalid health card number. It is possible that we lost follow-up for those 90 patients. The proportion of the overall cohort that those patients represent is very low and unlikely to bias our estimates of survival probability.

Our study reports a relatively equal distribution of new PCC cases for the two sexes, but some studies have reported a higher incidence among men [17,18]. In our

TABLE III Multivariate Cox regression survival analysis of risk factors in patients diagnosed with pancreatic cancer in Ontario

Parameter	Reference group	Comparison group	HR	95% CI
Age group	≤60 Years	61–70	1.089	1.043 to 1.138
		71–80	1.196	1.123 to 1.1275
		≥81	1.531	1.44 to 1.627
Sex	Female	Male	2.076	1.943 to 2.217
Rural	No	Yes	1.076	1.005 to 1.152
Income quintile	5 (highest)	1 (lowest)	1.076	1.005 to 1.152
		2	1.086	1.013 to 1.164
		3	1.01	0.943 to 1.083
		4	1.045	0.984 to 1.11
Site	Head	Others	1.424	1.361 to 1.49
		Tail	1.339	1.238 to 1.449
Score on the CCI	0	≥1	1.081	1.023 to 1.143
Year of diagnosis	2004–2006	2007–2009	0.969	0.922 to 1.018
		2010–2011	0.877	0.829 to 0.927

HR = hazard ratio; CI = confidence interval; CCI = Charlson comorbidity index.
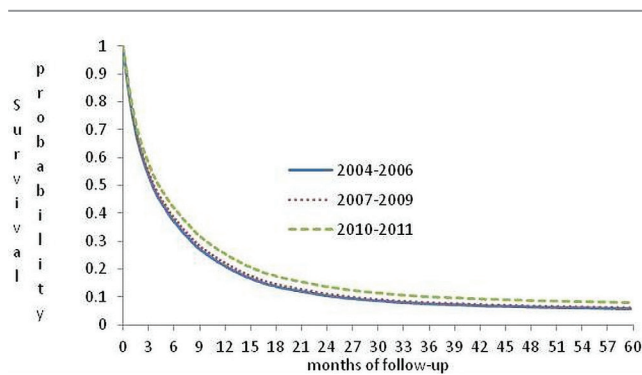
FIGURE 3 Probability of survival for patients with pancreatic cancer in Ontario by year of diagnosis, adjusted for age at diagnosis.

analyses, survival was decreased for men compared with women despite an equal sex distribution. The literature shows that increasing age is associated with a higher incidence of PCC [19]. That association is important in light of an aging population. Our results confirmed the association and also showed that older age at diagnosis is associated with much lower survival.

Our study suggests that tumour location is associated with patient outcomes, which reflects other published data [20,21]. Unfortunately, derivation of tumour location from the administrative data was not possible for 49% of our cohort. The literature suggests that only 10% of pancreatic tumours are multifocal, with 65% being located in the head of the pancreas, and 15% being located in the tail of the pancreas [22]. We assume a similar distribution in Ontario patients.

In a study based in the United States, Mack and Paganini-Hill [23] showed that PCC was not evenly distributed by social class. By contrast, we found rather uniform rates by income quintile. However, we did observe decreased survival in the lowest income quintiles and in patients residing in rural areas, which is consistent with other available data [24]. An American population study published in 2006 by Cress *et al.* [24] showed a relationship of socio-economic status with the proportion of patients receiving surgical resection, with access to high-volume care centres suggested to be the main cause of that disparity. The finding that patients in our cohort from the lowest income quintiles and from rural regions experienced relatively lower survival might indicate that there are barriers to appropriate care in Ontario.

Comorbidity status also appeared to have a significant effect on patient survival in our cohort. That observation supports findings in the existing literature that higher scores on the Charlson comorbidity index might be associated with lower rates of surgical resection [25,26], less-aggressive palliative chemotherapy [27], and relatively worse outcomes with gemcitabine-based chemotherapy [28].

Survival was observed to be greater for patients in our cohort who were diagnosed in 2010–2011 than in 2004–2006. One possible explanation for that finding is the cumulative effect of gradual increases in chemotherapy uptake in the palliative setting [29]. Use of recently developed chemotherapy regimens such as FOLFIRINOX (approved in Ontario in 2011) continues to increase for PCC patients [30], and survival for individuals diagnosed after 2011 is expected to reflect the effect of those regimens.

Although the OCR does not contain full staging information, the literature suggests that at least half of all PCC patients will have metastatic disease at presentation. Consequently, the effects of the newer chemotherapeutic options on survival at a population scale should be investigated.

The strength of our study is its inclusion of all cases of PCC in the province. The single-payer nature of health care in the province, regardless of health care provider, ensures that data are collected for all patients.

Our study is limited because of the type of information available in the administrative databases. Stage and genetic factors provide clinicians with information about appropriate management and can affect survival. Similarly, the availability of information related to treatment regimens would add considerable insight. In some provinces, collaborative staging permits assignment of an American Joint Committee on Cancer stage based on the best available information. Although some collaborative staging information is available in the ocr, staging information was unknown for 70% of the patients in our cohort for 2004; that proportion improved to only approximately 50% for the years 2007–2011. Details of treatment information such as receipt of chemotherapy, radiation therapy, or surgical therapy are also not collected by the ocr. To obtain those details, it would have been necessary establish links with other databases, which was out of scope for the objectives of this epidemiologic report.

Published studies have examined the effect of risk factors for the development of pcc and factors that affect survival (including smoking, caffeine use, alcohol consumption, comorbidity, occupational exposure, and diet [17,19,31–38]), although some of the risks are not clear [39,40]. Unfortunately, information on the foregoing risk factors are not available in provincial administrative databases; however, a review of this cohort's pathology reports to look at the effect of stage on survival is underway.

CONCLUSIONS

Pancreatic cancer, although infrequent, has an exceptionally high mortality rate. Here, we have provided a population-based analysis of pcc from the perspective of patient demographics and survival. Results show the effects of age, sex, income, residence, location of cancer, comorbidity, and year of diagnosis on survival. Future research by anyone using our results as a base case should focus on shifting the survival curve to the right.

CONFLICT OF INTEREST DISCLOSURES
We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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