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Original Research

Underestimation of pancreatic cancer in the national cancer registry – Reconsidering the incidence and survival rates

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Abstract ***Background:*** In the Netherlands, like in many other European countries, pancreatic cancer mortality was found to be systematically higher than the incidence. This suggests that there is an underestimation of the reported incidence of pancreatic cancer.
Aim: We aimed to study the incidence of pancreatic cancer in the Rotterdam area and to compare this with the national level.
Methods: This study is embedded in the Rotterdam Study (RS), an ongoing population-based prospective cohort study of people aged 45 years and above, enrolled between 1989 till 2006. Details on incident pancreatic cancer cases were available until 2013. Age-specific incidence rates were calculated and compared with data available in the Netherlands Cancer Registry.
Results: At baseline 14,922 participants were at risk of developing pancreatic cancer. Median follow-up time was 16.4 person years per person. In total, 113 participants developed pancreatic cancer. Rates increased with age with an incidence rate of 109.9 (95% confidence interval [CI]; 85.7–138.8) per 100,000 person years for people older than 75. This is higher than the currently reported 55.9–89.2 per 100,000 person year. Of the 113 cases identified in the RS, only 67.3% was reported as pancreatic cancer in the Netherlands Cancer Registry. Cases that were not registered were significantly older and had significantly poorer survival.

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Conclusion: The incidence of pancreatic cancer, as registered by the Netherlands Cancer Registry, is an underestimation. Patients, not registered by the cancer registry, have a significantly poorer survival. Consequently, we probably overestimate the already poor survival of pancreatic cancer.

1. Introduction

Pancreatic cancer is currently one of the most lethal types of cancer in Europe and has a 5-year survival of around 5% [1]. Due to ageing of populations, the incidence of pancreatic cancer has increased over the past few decades in Europe [1,2]. In the past decade some improvement in survival has been reported, but still [3] it is expected to become the second deadliest cancer by the end of 2020 [2,4].

In line with this European trend, the incidence rate of pancreatic cancer has increased in the Netherlands as well. The estimated incidence rate varies from 0.5 to 3.6 per 100,000 person years for persons younger than 50 years to 55.9 to 89.2 per 100,000 person years for persons older than 75 years [5].

In the Netherlands, cancer incidence is registered nationwide by the Netherlands Comprehensive Cancer Registration (IKNL). Cause of death, however, is registered by a different body: Statistics Netherlands (CBS). They collect death certificates from the Municipal Personal Records Database (BRP) with date and cause of death as assigned by treating physicians.

Between 2010 and 2014, the number of new cases diagnosed ranged from 2198 to 2326 [6]. Interestingly, in those same years, fewer patients were diagnosed with pancreatic cancer than those died of this cancer (2481–2682) [7]. In fact, the rate of pancreatic cancer mortality has been systematically higher than the incidence rate, since the start of the Netherlands Cancer Registry (NKR) in 1989 [6]. Above numbers suggest an underestimation of the true incidence of pancreatic cancer or an overestimation of pancreatic cancer mortality, which could be important for several reasons. Firstly, because these numbers are supposed to inform clinicians and their patients. Secondly because incidence and mortality rates largely influence the way we prioritise our focus in studying different diseases and lastly because these numbers are used to advise health care and insurance company policy makers.

The objectives of this study were to establish the incidence rate of pancreatic cancer and its mortality in a large and long-standing population-based prospective cohort study and to extrapolate this number to a national level to get insight into this discrepancy in figures from national registries.

2. Patients and methods

2.1. Study population

The study was embedded in the Rotterdam Study (RS), an ongoing population-based prospective cohort study in the Netherlands. The rationale and design have been described extensively previously [8,9]. Briefly, in 1989 inhabitants of the suburb Ommoord, aged 55 years and older, were invited to participate. The original cohort was enrolled between 1989 and 1993. Of 10,275 invited subjects, 7983 entered the study (78%). A second cohort of 3011 persons (67% response) was enrolled between 2000 and 2001. In 2006, a third cohort with 3932 persons of 45 years and older were enrolled (65% response). This resulted in an overall study population of 14,926 individuals aged 45 years and above.

The RS has been approved by the institutional review board (Medical Ethics Committee) of the Erasmus Medical Center and by the review board of The Netherlands Ministry of Health, Welfare and Sports.

2.2. Assessment of cancer cases

2.2.1. Rotterdam Study

In this study, cases of pancreatic cancer were identified through follow-up of medical records of the general practitioners, by hospital discharge letters and furthermore through linkage with the Dutch Hospital Data (Landelijke Basisregistratie Ziekenhuiszorg, previously Landelijke Medische Registratie) and registries of histo- and cytopathology. Cases were classified according to the International Statistical Classification of Diseases, 10th revision (ICD-10) and the International Classification of Primary Care, 2nd edition (ICPC-2) [10,11].

All potential cases of pancreatic cancer and level of certainty, thereof, were independently adjudicated by two physicians (JF, RR). In case of disagreement, consensus was sought through consultation of an experienced pancreatic surgeon (CvE).

Level of certainty of diagnosis was established as: certain (pathology confirmed), probable (clinical diagnosis based on a mass in the pancreas and/or liver metastases on CT-scan, ultrasound or endoscopic ultrasonography and/or increased levels of CA19.9), or possible (e.g. an uncircumscribed mass by physical

examination or a clinical presentation with painless jaundice and weight loss).

Date of death was obtained through the mortality registry of the BRP (Basisregistratie Personen, previously Gemeentelijke Basisadministatie) and the cause of death was obtained through follow-up of records of general practitioners or hospital discharge letters. The cause of mortality was coded similarly as morbidity, independently by two physicians according to the ICD-10 and the ICPC-2 [10,11]. All potential cases of pancreatic cancer were provided to the Netherlands Cancer Registry for matching.

2.2.2. Netherlands cancer registry

The Netherlands Cancer Registry started registering cancer incidence in 1989. Newly diagnosed malignancies are notified to the Netherlands Cancer Registry by the automated pathological archive (PALGA), supplemented with data from the Dutch Hospital Data. Unlike many other cancer registries, the Netherlands Cancer Registry has no access to notification by death certificates. Information on vital status is regularly obtained from the BRP by using a data linkage procedure.

Trained registrars verify all notifications and routinely collect data on patient characteristics, tumour type and primary treatment from medical records in all Dutch hospitals. Tumour location and histology are registered according to the International Classification of Diseases for Oncology (ICD-O-3) [12].

2.3. Covariables

The following covariables were considered as potential confounding factors: age, sex, socioeconomic status (high/middle/low), smoking status (current/former/never), alcohol use (heavy [three or more glasses a day]), moderately [more than once a week, but less than three glasses a day], and minor [less than one glass a week]), body mass index (kg/m^2) and incident diabetes mellitus (fasting glucose $\geq$ 7.0 mmol/L or use of glucose-lowering medication) [13]. Patient characteristics were determined at baseline by interview or during visits at the examination centre.

2.4. Statistical analysis

For each participant, follow-up started at the day of inclusion in the study, until date of cancer diagnosis, death or end of study period (1st of January 2013), whichever came first. To assess differences between cases and the remaining cohort and subsequently between registered and unregistered cases, we used Mann–Whitney tests for continuous variables and χ^2 tests for categorical data.

Incidence and mortality rates with 95% confidence intervals (CIs) were calculated, both overall and per age category, as described by Rothman *et al.* [14] Differences in survival between cases from the RS and the Netherlands Cancer Registry were assessed by Kaplan–Meier curves and tested with a Log-Rank test and a Wilcoxon test. Significance of associations was accepted at a P-value < 0.05. All analyses were performed using SPSS software (Version 21.0).

3. Results

3.1. General characteristics cohort

We used data from all participants of the RS with the exception of four participants who had a history of pancreatic cancer at baseline. At the start of the study, 14,922 participants were at the risk of developing pancreatic cancer, of whom 6101 were men (40.9%) and 8821 were women (59.1%), with a mean age of 66.0 years (SD 10.5) at baseline. The total follow-up time was 160,071 person years with a median follow-up time of 16.4 person years (SE 0.2 person years) per person. Completeness of follow-up until 1st January 2013 was 98.5%.

3.2. Risk of pancreatic cancer

In total, 113 participants developed pancreatic cancer: 38.9% male and 61.1% female. Almost all cases were diagnosed above the age of 65 (92.0%) with a mean age of 77.3 years at diagnosis (SD 8.8). In only 44.2% of the cases, diagnosis was confirmed through pathology. Further baseline characteristics can be found in Table 1.

At the end of the study period, all patients with pancreatic cancer had died; 94.7% attributable to pancreatic cancer. The median survival was 71.0 d (SE 11.6) with 1-year survival of 11.4% and no patient survived more than 5 years. Most patients (86.8%) did not receive any form of treatment for their pancreatic cancer. Out of the 18 patients undergoing surgery, only eight had a complete resection of the cancer (7.1%).

The incidence rate and mortality rate for pancreatic cancer in this study population, aged 45 years and above, were calculated at 70.6 and 66.8 per 100,000 person years, respectively. Incidence and mortality rates were also calculated per age category separately (Tables 2 and 3), the rates increased with age.

3.3. Analyses of matching

Of the 113 cases provided to the Netherlands Cancer Registry for matching, 76 cases were registered as cases of pancreatic cancer (67.3%). Seventeen other cases were also registered; however, with an unknown primary tumour (n = 6, 5.3%) or for a different cancer (n = 11, 9.7%). For the latter, most cases were confirmed as patients with double or multiple tumours in the RS. These cancers were non-melanoma skin cancers (n = 4), prostate (n = 2), breast (n = 1), lung (n = 1) or colon

Table 1
General characteristics for cases stratified by registration in the Netherlands Cancer Registry.

General characteristics		Total				Registered				Unregistered				P-value
		N	%	Mean	SD	N	%	Mean	SD	N	%	Mean	SD	
Total		113				82				31				
Sex	Male	44	38.9			34	41.5			10	32.3			0.371
	Female	69	61.1			48	58.5			21	67.7			
Age at baseline				68.7	8.4			67.47	8.4			72.1	7.4	0.004
Age at diagnosis				77.3	8.8			75.8	9.1			81.0	6.8	0.005
Follow-up in years (median, SE)				9.2	0.7			9.2	0.9			9.1	1.1	0.666
Survival in days (median, SE)				71.0	12.0			90.0	15.0			47.0	13.0	0.009
Socioeconomic status[b]	High	13	11.8			10	12.3			3	10.0			0.344
	Middle	38	34.2			24	29.6			14	46.7			
	Low	60	54.1			47	58.0			13	43.3			
Smoking[c]	Current	32	29.4			27	33.8			5	17.2			0.076
	Former	43	39.4			33	41.3			10	34.5			
	Never	34	31.2			20	25.0			14	48.3			
Alcohol[d]	Heavy	16	19.0			13	30.3			3	15.8			0.110
	Moderately	33	39.3			26	49.4			7	36.8			
	Sometimes	35	41.7			27	40.9			8	44.4			
BMI[a]				26.9	3.8			26.8	3.8			27.1	3.9	0.821
DM-II		26	23.0			18	22.0			8	25.8			0.664
Certainty of diagnosis	Certain	50	44.2			45	54.9			5	16.1			<0.001
	Probable	59	52.2			36	43.9			23	74.2			
	Possible	4	3.5			1	1.2			3	9.7			

[a] BMI: unknown; registered 7, unregistered 6.
[b] SES: unknown; registered 1, unregistered 1.
[c] Smoking: unknown; registered 2, unregistered 2.
[d] Alcohol: unknown; registered 16, unregistered 13.

Table 2
Incidence rates of pancreatic cancer per age category.

Age category	Cases	Percent of cases	Follow-up (person years)	Incidence rate (per 100,000 person years)	95% Confidence intervals (Poisson)
45–54	1	0.9	5767	17.3	0.4–96.6
55–64	8	7.1	35,060	22.8	9.9–45.0
65–74	34	30.1	55,537	61.2	42.4–85.5
75–84	49	43.4	45,305	108.2	80.0–143.0
≥85	21	18.6	18,405	114.1	70.6–174.4
Overall	113	100	160,074	70.6	58.2–84.9

Table 3
Mortality rates of pancreatic cancer per age category.

Age category	PDAC-specific mortality	Follow-up (person years)	Mortality Rate (per 100,000 person years)	95% Confidence intervals (Poisson)
45–54	1	5769	17.3	0.4–96.6
55–64	8	35,067	22.8	9.8–45.0
65–74	30	55,549	54.0	36.4–77.1
75–84	47	45,327	103.7	76.2–137.9
≥85	21	18,409	114.1	70.6–174.4
Overall	107	160,121	66.8	54.8–80.8

PDAC = pancreatic ductal adenocarcinoma.

cancer (n = 1). The remaining 20 cases were unknown to the Netherlands Cancer Registry (17.7%).

Patients who were not registered by the Netherlands Cancer Registry were significantly older at time of cancer diagnosis (Mann–Whitney: P = 0.005) and were significantly less likely to have had their diagnosis confirmed by pathology (χ^2: P < 0.001). Cases from the RS had a significantly poorer overall survival than the cases in the general population as registered by the Netherlands Cancer Registry (Log-Rank: 0.013; Wilcoxon: P = 0.017), Fig. 1. Within the RS Study, cases that were not registered by the Netherlands Cancer Registry had a significantly lower cancer-specific survival than those that were registered (Log-Rank: P = 0.018; Wilcoxon: P = 0.009), Supplementary Fig. 1.

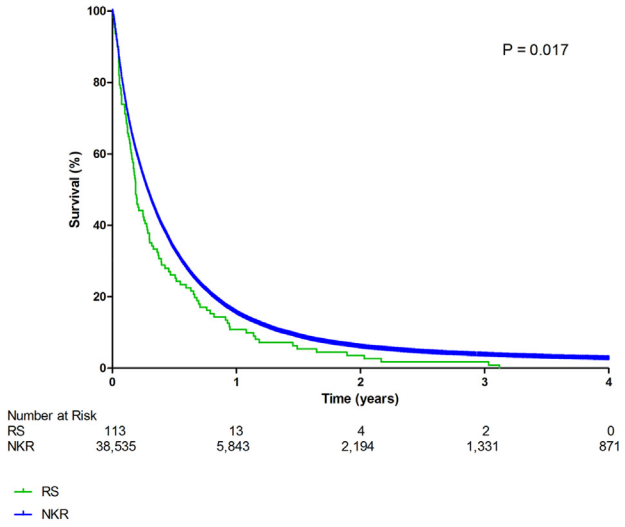

Fig. 1. Overall survival curves from cases in the Rotterdam Study (RS) versus cases in the general population as registered by the Netherlands Cancer Registration (NKR).

4. Discussion

In the RS, of the approximately 15,000 individuals aged 45 years and older who were followed during 160,071 person years, 113 patients developed pancreatic cancer. We calculated the overall incidence rate at 70.6 per 100,000 person years for this specific population and showed that the rate increased with age. They parallel the age-specific incidence rates as reported by Coupland *et al.*, but are higher [15]. We expect that in the Netherlands around 3000–3750 people develop pancreatic cancer annually. This is far more than the approximately 2500 that are currently registered [6].

We showed that of the 113 patients who developed pancreatic cancer, only 67.3% was registered by the Netherlands Cancer Registry as pancreatic cancer. This confirms our assumption that there is an underestimation of the incidence rate as registered by the Netherlands Cancer Registry. This does not only hold true for the Netherlands. In multiple other European countries, amongst which Belgium, Iceland and Sweden, the reported incidence rate is lower than the mortality rate of pancreatic cancer [16].

Another part of the discrepancy between the national incidence and mortality might be explained by misclassification of cause of mortality. Compared with the European mean, the mortality of pancreatic cancer is higher in the Netherlands, whereas the mortality of cholangiocarcinoma is lower [6]. However, this is provides no explanation for the grove under registration we showed in this study.

Most cases that were not registered by the cancer registry did not have pathological confirmation of the cancer, suggesting that the cancer registry relies heavily on pathological verification [17]. This might be particularly problematic for pancreatic cancer. Pathological confirmation for all cases in this cohort was 44.2%, compared with 54.9% when only analysing cases registered by the Netherlands Cancer Registry. This last number is more in line with earlier-reported verification rates of 57.0% and 62.7% [18,19]. Histopathological confirmation rates have significantly risen over the past years, so the relatively low rate in this study can be partly explained by the long follow-up period of this study [19]. Even though pancreatic cancer has one of the lowest verification rates of all cancers, our data suggest that potential inflation of these percentages occurred [17–19]. Patients who had had their diagnosis confirmed by pathology were significantly younger (data not shown). It is plausible that in elderly patients, in the light of a poor prognosis or a poor clinical condition, prohibiting any palliative treatment, patients and their treating physicians consider additional invasive diagnostics too burdensome.

Indeed, we showed that pancreatic cancer is a disease of the elderly, with the highest incidence and mortality figures in the age category of 85 years and above.

Lastly, we showed that cases that were not registered had a significantly poorer survival than those that were. This means we do not only underestimate the incidence of pancreatic cancer, but also overestimate the survival. The overall survival in this cohort is dramatic: the 1-year survival was only 11.4% and no patient survived more than 5 years. In 94.7% death was attributable to pancreatic cancer. This can partly be explained by the stage of disease at presentation, as the stage of disease heavily influences survival [20]. Only 7.1% was able to undergo successful surgery. All surgeries were performed after 2000. Most patients were treated by oncologists from one local hospital and were unlikely to be referred to a tertiary centre, once the disease was locally advanced or metastasized, to undergo any form of palliative treatment. Almost 25% of the patients died within a month after diagnosis and were unlikely to be candidates for palliative chemotherapy such as Gemcitabine or FOLFIRINOX (folinic acid, fluoracil, irinotecan, oxaliplatin). Furthermore, FOLFIRINOX was only introduced at the very end of the study period and, although it might improve survival, it is unlikely that it had much impact on survival in this study [21,22].

4.1. Strengths and limitations

Strengths of this study are the prospective design, the duration and completeness of follow-up and, most importantly, the completeness of the registration of cancer cases. What sets apart cancer registration in the RS is the additional information that is obtained from follow-up of medical records of general practitioners. For pancreatic cancer, there is a considerable group of patients for whom diagnosis is not pathologically confirmed or who are not admitted to hospital. These patients are therefore missed by the currently available

notification sources of the Netherlands Cancer Registry. Completeness of the Netherlands Cancer Registry could be enhanced by information on cause of death, as collected by Statistics Netherlands. However, if patients die from another cause, either truly or as documented, while diagnosed with pancreatic cancer, chances are that these patients will still be missed by the Netherlands Cancer Registry. Therefore, investment in the gathering of more detailed information on cancer morbidity is probably most effective in ensuring better coverage.

The RS consists of individuals of 45 years and older, the age groups in which pancreatic cancers occurs most frequently. However, as a consequence we were not able to calculate an age standardised incidence rate. Another limitation is that a long follow-up period automatically means that part of the data is old, therefore, not always reflecting the effects of new insights, diagnostics and therapies. This holds for pathological verification of disease, but also for treatment of pancreatic cancer with palliative chemotherapy. However, our data were compared with national data from the same time period. The observed differences therefore cannot be explained by these limitations.

In conclusion, the incidence of pancreatic cancer, as registered by the Netherlands Cancer Registry, is an underestimation. Patients who are not registered by the cancer registry are significantly less likely to have had their diagnosis confirmed by pathology, are significantly older and have a poorer survival. Consequently, besides underestimation of the incidence, we are also likely to overestimate the already poor survival of pancreatic cancer.

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Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2016.11.026.

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