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Factors influencing the diagnostic basis in pancreatic cancer. A study within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort

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ABSTRACT

Background and aims: Substantial differences have been reported in risk estimates for etiologic factors of pancreatic cancer among subjects with different degrees of diagnostic certainty. The aim of the study was to

Abbreviations: BMI, Body mass index; CI, Confidence interval; PDAC, Pancreatic ductal adenocarcinoma; EPIC, European Prospective Investigation into Cancer and Nutrition Cohort; MC, Microscopic confirmation; OR, Odds ratio.

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assess the influence of some personal and social characteristics on the diagnostic basis in individuals with pancreatic cancer.
Methods: We analyzed 393 participants from the EPIC cohort with a diagnosis of pancreatic cancer and information on the basis of diagnosis. Two main groups of cases were compared: one in which microscopic confirmation (MC) was available to diagnose pancreatic cancer (including autopsy, histology, cytology or hematology), and one in which non-microscopic methods were used (biochemical, immunological or image tests, exploratory surgery, clinical observation, self-report, or death certificate).
Results: The diagnosis of pancreatic cancer of 73% of participants was achieved through MC. While, overall, over 82% of men had MC, this figure was 65% in women ($p<0.001$). Subjects with MC, both men and women, were younger at diagnosis than participants diagnosed by non-microscopic methods. Younger women (<60 years) had a higher probability of having their cancer diagnosed with MC (OR=2.54, 95% CI 1.04-6.17) than women ≥70 years. After the year 2000 the chances of having the disease diagnosed through MC increased more than 2-fold in women and more than 5-fold in men. No significant differences in diagnostic basis were observed by educational level, comorbidities or established risk factors for pancreatic cancer.
Conclusion: The rates of MC in subjects diagnosed with pancreatic cancer continued to be relatively low. Age and sex are the two main factors that powerfully influence MC. Hence, age and sex must be considered when designing and analyzing clinical and epidemiological studies, as well as in clinical practice. The consistently lower rates of MC in female patients suggest an ingrained sex-related diagnostic bias, which may require specific policies to be counterbalanced.

Introduction

Despite its relatively low incidence, pancreatic cancer is the fourth leading cause of cancer-related deaths in Europe. Over the last years, its incidence and mortality rates have been stable or even increased. The prognosis of exocrine pancreatic cancer continues to be poor, with mortality rates almost paralleling incidence [1–3].

The diagnosis of deep abdominal neoplasms such as pancreatic cancer can be challenging [2–8]. The need for better ways to detect the disease at earlier stages is unquestioned. Yet, large variations exist in the detection and diagnostic strategies. Therefore, there are significant differences worldwide in the diagnostic basis of pancreatic cancer [3, 9–11]. For instance, some cancer registries continue to show relatively low rates of microscopic confirmation (MC). MC is considered an indicator of data quality in registries and research studies, and of clinical quality in healthcare. Nevertheless, lack of MC may sometimes reflect the interests of the patient; e.g., if their clinical status is fragile, and image tests show a pancreatic cancer at an advanced stage, being unresectable [12].

Clinical and epidemiological studies have shown a large heterogeneity in the diagnostic criteria applied in the real world to define *caseness* (i.e., in the diagnostic basis to define a case of pancreatic cancer for study) [7,13–19]. Misclassification of disease status occurs when less valid and reliable techniques, such as non-MC methods, are used. Misclassification of disease may have a substantial impact on etiologic and prognostic estimates of pancreatic neoplasms and other diseases [13–25]. Although disease misclassification has been shown to have relevant implications both in clinical practice and research, it has been less studied than exposure misclassification [22,23,26,27].

The diagnostic basis may be influenced by sociodemographic, clinical, lifestyle, and environmental factors [13–16,22]; therefore, the corresponding disease misclassification may be differential for (i.e., dependent of) such factors. Differential disease misclassification is more likely than nondifferential disease misclassification to severely bias etiologic estimates away from the null [27,28].

In spite of the reasons to conduct research just mentioned, studies on these issues[2,3,7,10,12,14,16,18,22] are scant for pancreatic cancer and other diseases.

Therefore, the main objective of the present study was to assess the influence of a number of personal and social characteristics on the diagnostic basis of 393 subjects diagnosed of exocrine pancreatic cancer within the EPIC cohort.

Methods

Study population

The population of the present study is based on a previous study, whose design has been described in detail [23,24,29]. Briefly, subjects diagnosed with exocrine pancreatic cancer during the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort were selected for inclusion. The EPIC cohort included 521,457 subjects aged 35–70 years old recruited between 1992 and 2000 by 23 collaborating centers from 10 European countries [29]. Three biorepositories from the EPIC study contributed biological samples for the previous study: the repository from Denmark, which centralized samples from the collaborating centers of Aarhus and Copenhagen; the repository from Sweden (Västerbotten county, including Umeå); and the IARC central repository, which centralized the biospecimens of several other countries (see below) [23]. Data from Sweden had to be excluded from the present report due to recent changes in laws on data access in such country.

Participants in the present study were enrolled between 1993 and 1998. At recruitment a questionnaire with baseline information about sociodemographic characteristics, lifestyles (such as lifetime history of alcohol and tobacco consumption, and diet), and medical history was collected for each participant. Anthropometric measures and blood samples were taken at recruitment. Follow-up was performed until cancer diagnosis, death, migration, or end of the follow-up period (2007 and 2010 for Denmark and IARC, respectively), whichever occurred first. The median length of follow-up of participants was 8.9 years [23, 24].

Exclusion criteria for the previous [23,24] and the present study were: a) individuals with endocrine pancreatic cancer; b) occurrence of other malignant tumors before the diagnosis of exocrine pancreatic cancer, except for non-melanoma skin cancer; c) diagnosis of exocrine pancreatic cancer during the first 2 years after blood extraction (5 years for subjects from Denmark) [23,24]; d) subjects with less than 2 straws of plasma available; and e) subjects without information on the basis of cancer diagnosis. A total of 393 participants diagnosed of exocrine pancreatic cancer were included in the present study, of which 135 (28.6 %) came from Denmark, and 258 (54.7 %) from IARC (contributing countries: Germany, 63 participants, United Kingdom, 60, The Netherlands, 47, Italy, 43, Spain, 37, and France 8). Length of follow-up differed between countries [23,24], which was an additional reason to stratify or adjust some analyses by country.

The EPIC study was approved by the Ethical Review Board of the International Agency for Research on Cancer (IARC, Lyon) and by the local Ethical Committees.

Characteristics

Of the 393 participants in the study, 52 % were women and 48 % were men (Table 1). The median age at diagnosis of exocrine pancreatic cancer was nearly 67 years for women, whereas men were only less than one year younger. A higher proportion of men than women had longer education (25 % vs 17 %, respectively), were current smokers (42 % of men vs 26 % of women), drank more than 18 g of alcohol per day (50 % of men vs 20 % of women), and were inactive (24 % of men vs 12 % of women). These differences will be considered when assessing differences in diagnostic basis by sex.

Sixteen different diagnostic methods were registered as the first basis of diagnosis. For the present study they were pooled in two main groups: methods that used microscopic confirmation (MC) of any kind, and methods that only used clinical tests or imaging techniques, among others. Microscopic methods (basically, cytohistological verification), as specified by EPIC, and sorted from higher to lower potential diagnostic validity, included: autopsy ($N = 16$), histology of the primary tumor ($N = 107$), histology of metastasis ($N = 45$), histology/cytology of primary tumor ($N = 76$), histology/cytology of metastasis ($N = 15$), and cytology or hematology ($N = 28$). The non-microscopic methods, sorted from higher to lower potential validity, included: specific biochemical or immunological tests ($N = 1$), exploratory surgery/autopsy ($N = 1$), endoscopy ($N = 4$), magnetic resonance ($N = 1$), computerized

Table 1
Influence of sex, age at diagnosis, birth cohort, and education of participants, stratified by sex, on the probability of having exocrine pancreatic cancer diagnosed by microscopic methods.

	Basis of pancreatic cancer diagnosis								
	Total		Microscopic methods*		Clinical and other tests**				
Characteristic	N	(%)	N	(%)	N	(%)	OR	(95 % CI)	*p*-value[1]
Total	393	(100)	287	(73.0)	106	(27.0)			
Sex[a]									
Women	203	(51.7)	131	(64.5)	72	(35.5)	1.00	–	<0.001
Men	190	(48.3)	156	(82.1)	34	(17.9)	2.37	(1.47–3.82)	
Age at diagnosis of pancreatic cancer (years)									
Women (median)	66.9		65.9		68.9		0.95	(0.91–0.99)	0.019[2]
≥70 years	69	(34.0)	38	(55.1)	31	(44.9)	1.00	–	0.028
60–69 years	97	(47.8)	65	(67.0)	32	(33.0)	1.66	(0.88–3.13)	
<60 years	37	(18.2)	28	(75.7)	9	(24.3)	2.54	(1.04–6.17)	
Men (median)	65.9		65.5		67.9		0.93	(0.87–0.98)	0.045
≥70 years	49	(25.8)	38	(77.6)	11	(22.4)	1.00	–	0.138[3]
60–69 years	101	(53.2)	82	(81.2)	19	(18.8)	1.25	(0.54–2.88)	
<60 years	40	(21.1)	36	(90.0)	4	(10.0)	2.61	(0.76–8.93)	
Birth cohort									
Women									
1919–1938	119	(58.6)	73	(61.3)	46	(38.7)	1.00	–	0.512
1939–1945	63	(31.0)	44	(69.8)	19	(30.2)	1.46	(0.76–2.80)	
1946–1964	21	(10.3)	14	(66.7)	7	(33.3)	1.26	(0.47–3.36)	
Men									
1919–1938	93	(48.9)	69	(74.2)	24	(25.8)	1.00	–	0.026
1939–1945	71	(37.4)	64	(90.1)	7	(9.9)	3.18	(0.10–7.89)	
1946–1964	26	(13.7)	23	(88.5)	3	(11.5)	2.67	(0.73–9.68)	
Year of diagnosis of pancreatic cancer[a]									
Women									
1996–2000	31	(15.3)	16	(51.6)	15	(48.4)	1.00	–	0.056
2001–2005	112	(55.1)	79	(70.5)	33	(29.5)	2.84	(1.21–6.67)	
2006–2009	60	(29.6)	36	(60.0)	24	(40.0)	2.24	(0.86–5.82)	
Men									
1996–2000	21	(11.1)	12	(57.1)	9	(42.9)	1.00	–	0.001[3]
2001–2005	105	(55.2)	88	(83.8)	17	(16.2)	5.54	(1.79–17.13)	
2006–2009	64	(33.7)	56	(87.5)	8	(12.5)	10.90	(2.89–41.08)	
Educational level[a]									
Women									
Longer education	32	(16.8)	20	(62.5)	12	(37.5)	1.00	–	0.467
Secondary school	27	(14.1)	15	(55.6)	12	(44.4)	0.83	(0.29–2.40)	
Technical school	46	(24.1)	32	(69.6)	14	(30.4)	1.46	(0.55–3.86)	
Primary completed	73	(38.2)	52	(71.2)	21	(28.8)	1.71	(0.70–4.21)	
Less than primary completed	13	(6.8)	10	(76.9)	3	(23.1)	2.19	(0.49–9.76)	
Men									
Longer education	47	(24.9)	38	(80.9)	9	(19.1)	1.00	–	0.926
Secondary school	27	(14.3)	24	(88.9)	3	(11.1)	1.43	(0.34–5.99)	
Technical school	43	(22.8)	34	(79.1)	9	(20.9)	0.97	(0.34–2.79)	
Primary completed	64	(33.9)	53	(82.8)	11	(17.2)	1.30	(0.48–3.52)	
Less than primary completed	8	(4.2)	7	(87.5)	1	(12.5)	2.09	(0.22–19.63)	

* Microscopic methods: this category includes cases with the following bases of diagnosis as the first basis: *Autopsy (N = 16), Histology of primary tumour (N = 107), Histology of metastasis (N = 45), Histology/Cytology of primary tumour (N = 76), Histology/Cytology of metastasis (N = 15), and Cytology or haematology (N = 26).*

** Clinical and other test include as the first diagnostic basis: *Specific biochemical or immunological tests (N = 1), Exploratory surgery/autopsy (N = 1), Endoscopy (N = 4), Magnetic resonance imaging (N = 1), Computerized tomography scan (N = 12), Radiological examination (N = 4), Clinical investigation (N = 46), Clinical observation (N = 30), Self-report (N = 2), Death certificate only (N = 5).*

[a] OR adjusted for age at diagnosis of pancreatic cancer.
An OR=1 indicates the reference category. An OR>1 indicates a higher probability of being diagnosed with pancreatic cancer through microscopic methods.

[1] Unless otherwise specified, p value derived from a multivariate Wald's test.

[2] Mann-Whitney's U test (two-tail) on the continuous variable.

[3] Test for linear trend (multivariate analogue of Mantel's extension test).

tomography scan (N = 12), radiological examination (N = 4), clinical investigation (N = 46), clinical observation (N = 30), self-report (N = 2), and death certificate only (N = 5). A second classification of the potential validity of the microscopic diagnosis was also used: it divided cases with MC in two groups: a) cases with autopsy, histology, or histology/cytology of the primary tumor (N = 201); and b) cases with histology or histology/cytology of metastases, and cytology or hematology (N = 86) [13].

We analyzed the role of 20 co-morbidities on the diagnostic basis: hypertension, hyperlipidemia, myocardial infarction, angina, stroke, diabetes, cardiovascular disorders, thyroid disease, asthma, allergic cold, eczema, polyps, gastric/duodenal ulcer, gallstones, kidney stones, urinary infection, oophorectomy, hysterectomy, breast surgery, and fertility problems. We also grouped cardiovascular diseases, and all co-morbidities excluding gynecological diseases.

Information on characteristics of the tumor, such as subsite, stage and grade were collected for a subset of subjects with pancreatic cancer only in some centers [23].

Statistical analyses

Differences in participants' characteristics according to the basis of cancer diagnosis were assessed using the χ^2 test, Student's t-test, and Mann-Whitney's U test, as appropriate. Fisher's exact test for homogeneity was applied to assess the relationship between two categorical variables [23].

The magnitude of the associations between participants characteristics and the basis of cancer diagnosis was estimated with multivariate-adjusted odds ratios (ORs) and their corresponding 95 % confidence intervals (CI), calculated by unconditional logistic regression [23,27]. The final models were either adjusted for age at diagnosis and sex or stratified by sex and, in some instances, country. The level of statistical significance was set at 0.05 and all tests were two tailed. Analyses were conducted using SPSS version 28 (SPSS, Armonk, NY, USA, 2021).

Results

Of the 393 subjects included in the study, 287 (73 %) had MC of their pancreatic cancer diagnosis, and 106 (27 %) were diagnosed by imaging techniques, laboratory tests, clinical symptoms, or physical examination. No significant differences were observed in rates of MC over the study years when adjusting for country of residence (which, as mentioned above, was related to length of follow-up).

Sex and age

While 82 % of men were diagnosed with MC methods, this value was 65 % in women ($p < 0.001$). Adjusting for age, men were 2.4-times more likely to be diagnosed through MC than women (OR = 2.37, 95 % CI: 1.47–3.82) (Table 1).

Men had higher rates of MC than women in every age group. The difference between sexes increased with increasing age: among subjects <60 years, the difference in favor of men was of 14 percentage points, whereas among ≥70 year-olds such advantage was of 22 points (Table 1). Among subjects ≥70 years old, men were over two-times more likely to be diagnosed through MC than women (OR= 2.57, 95 % CI: 1.02–6.47). Even among the younger women MC was slightly lower than among the older men.

Accordingly, the median age of subjects with MC –both men and women– was slightly lower than the median of subjects without MC (Table 1). Yet, the median did not reflect more profound differences. For instance, 76 % of women <60 years were diagnosed of pancreatic cancer by MC methods, a value that was 55 % in women ≥70 years. Younger women were 2.5-times more likely of having their cancer diagnosed with MC than women ≥70 years (OR=2.54, 95 % CI: 1.04–6.17). In fact, the inverse association between age and MC was stronger in women than men: MC was 20.6 percentage points less frequent in the older than in the younger women, whereas this figure was 12.4 in men (Table 1). The sex and age differences were reflected in the birth cohort analysis. Concerning the year of diagnosis of pancreatic cancer: after the year 2000 the chances of having the disease diagnosed through microscopic confirmation increased more than 2-fold in women and more than 5-fold and near 11-fold in men (Table 1).

Educational level

Educational level had a modest or null effect on the diagnostic basis, particularly among men; in women the maximum difference in MC by educational level was of 16 percentage points, highly likely due to chance (Table 1). In each educational category, men had higher rates of MC than women. Men who had attended secondary school were near five times more likely to be diagnosed through MC than women who had attended secondary school (OR=4.84, 95 % CI: 1.08–21.6).

Weight, lifestyle

Body mass index, smoking, and physical activity showed no patterns of association with the diagnostic basis (Table 2). This was also the case for alcohol drinking in women, whereas in men the odds ratios (adjusted for age) suggested that MC might be more likely among pancreatic cancer drinkers.

Tumor characteristics

Among subjects with information on tumor's characteristics, 253 (64 %) had information on the tumor subsite, and 121 (31 %) on tumor stage (Table 2). Neither tumor subsite nor stage were associated with MC.

Country

The percentage of cases with MC ranged from 96 % in Denmark to 22 % in the United Kingdom (Table 3). Differences in MC between men and women were minor in Denmark, Germany, and the United Kingdom; the largest difference was seen in the Netherlands, where 56 % of women and all men had MC (Table 3, Fig. 1).

Co-morbidities

Diabetes was not associated with MC either in women or in men (Table 2). Neither were hypertension and hyperlipidemia (Supplementary Table 1). Subjects who had suffered a myocardial infarction were less likely than disease-free participants of having their pancreatic cancer diagnosed with MC (OR= 0.11, 95 % CI: 0.03–0.47); and so did subjects who experienced angina (OR=0.19, 95 % CI: 0.06–0.66), and gallstones (OR=0.29, 95 % CI: 0.12–0.69) (estimates adjusted by age and sex); however, the number of subjects with such antecedents was small (Supplementary Table 1). Overall, subjects who reported cardiovascular problems were more likely to be diagnosed through MC than those who did not (OR=1.97, 95 % CI: 1.08–3.59).

Concerning the group including all co-morbidities except gynecological disorders: compared to participants with no diseases, the number of diseases by participant was not related to having MC.

Analysis of MC validity: diagnosis from primary tumor or from metastases

Among participants with MC, the pancreatic cancer diagnosis was achieved through the histological or cytological analysis of the primary tumor in 70 % of cases and of metastatic tissue in 30 %. The two groups did not differ significantly in sex and age (Supplementary Table 2). The percentage of diagnoses based on the primary tumor increased with increasing education. It was lower among obese participants, unrelated to smoking and physical activity, and possibly lower among subjects

Table 2
Influence of other characteristics of participants, stratified by sex, on the probability of having exocrine pancreatic cancer diagnosed by microscopic methods.

			Basis of pancreatic cancer diagnosis						
	Total		Microscopic Methods*		Clinical and other tests*				
Characteristic	N	(%)	N	(%)	N	(%)	OR	(95 % CI)	*p*-value[1]
Total	393	(100)	287	(73.0)	106	(27.0)			
Body mass index[a] (kg/m^2)									
Women (median)	25.1		25.3		24.7		1.06	(0.98–1.13)	0.080[2]
Obese	29	(14.6)	23	(79.3)	6	(20.7)	1.00	–	0.094
Overweight	72	(36.4)	45	(62.5)	27	(37.5)	0.42	(0.15–1.16)	
Normal weight	97	(49.0)	59	(60.8)	38	(39.2)	0.38	(0.14–1.03)	
Men (median)	26.5		26.5		26.5		0.98	(0.89–1.08)	0.919[2]
Obese	35	(18.6)	29	(82.9)	6	(17.1)	1.00	–	0.538[3]
Overweight	95	(50.5)	80	(84.2)	15	(15.8)	1.09	(0.38–3.12)	
Normal weight	58	(30.9)	46	(79.3)	12	(20.7)	0.76	(0.25–2.28)	
Smoking status									
Women									
Never	104	(51.7)	64	(61.5)	40	(38.5)	1.00	–	0.192
Former	44	(21.9)	25	(56.8)	19	(43.2)	0.85	(0.41–1.75)	
Current	53	(26.4)	41	(77.4)	12	(22.6)	1.85	(0.86–4.01)	
Men									
Never	42	(22.5)	32	(76.2)	10	(23.8)	1.00	–	0.163[3]
Former	67	(35.8)	54	(80.6)	13	(19.4)	1.30	(0.50–3.36)	
Current	78	(41.7)	68	(87.2)	10	(12.8)	2.00	(0.74–5.37)	
Alcohol intake at recruitment									
Women									
Never and former drinkers	26	(12.9)	16	(61.5)	10	(38.5)	1.00	–	0.789
>0 – 6 g/day	91	(45.0)	56	(61.5)	35	(38.5)	1.17	(0.47–2.93)	
>6 – 18 g/day	46	(22.8)	32	(69.6)	14	(30.4)	1.61	(0.57–4.51)	
>18 g/day	39	(19.3)	26	(66.7)	13	(33.3)	1.36	(0.48–3.90)	
Men									
Never and former drinkers	10	(5.3)	6	(60.0)	4	(40.0)	1.00	–	0.004[3]
>0 – 6 g/day	28	(14.8)	21	(75.0)	7	(25.0)	1.70	(0.35–8.27)	
>6 – 18 g/day	57	(30.2)	44	(77.2)	13	(22.8)	2.39	(0.55–10.29)	
>18 g/day	94	(49.7)	85	(90.4)	9	(9.6)	5.96	(1.35–26.34)	
Physical activity									
Women									
Inactive	23	(11.6)	16	(69.6)	7	(30.4)	1.00	–	0.571
Moderately inactive	50	(25.3)	29	(58.0)	21	(42.0)	0.69	(0.24–2.02)	
Moderately active	111	(56.1)	72	(64.9)	39	(35.1)	0.91	(0.34–2.45)	
Active	14	(7.1)	11	(78.6)	3	(21.4)	1.82	(0.38–8.73)	
Men									
Inactive	45	(23.9)	42	(93.3)	3	(6.7)	1.00	–	0.211
Moderately inactive	62	(33.0)	48	(77.4)	14	(22.6)	0.26	(0.07–0.98)	
Moderately active	65	(34.6)	50	(76.9)	15	(23.1)	0.27	(0.07–1.03)	
Active	16	(8.5)	14	(87.5)	2	(12.5)	0.47	(0.07–3.15)	
Diabetes mellitus									
Women									
No	166	(94.9)	115	(69.3)	51	(30.7)	1.00	–	0.566
Yes	9	(5.1)	7	(77.8)	2	(22.2)	1.60	(0.32–8.05)	
Men									
No	158	(94.0)	139	(88.0)	19	(12.0)	1.00	–	0.157
Yes	10	(6.0)	19	(70.0)	3	(30.0)	0.35	(0.08–1.50)	
Tumour subsite									
Women									
Head of pancreas	88	(70.4)	56	(63.6)	32	(36.4)	1.00	–	0.394
Body of pancreas	22	(17.6)	17	(77.3)	5	(22.7)	2.09	(0.69–6.37)	
Tail of pancreas	15	(12.0)	9	(60.0)	6	(40.0)	0.88	(0.28–2.76)	
Men									
Head of pancreas	88	(68.8)	72	(81.8)	16	(18.2)	1.00	–	0.958
Body of pancreas	23	(18.0)	19	(82.6)	4	(17.4)	0.83	(0.24–2.90)	
Tail of pancreas	17	(13.3)	14	(82.4)	3	(17.6)	0.98	(0.24–3.97)	
Tumour stage									
Women									
Metastatic	45	(83.3)	36	(80.0)	9	(20.0)	1.00	–	0.409
Localised	9	(16.7)	6	(66.7)	3	(33.3)	0.51	(0.10–2.52)	
Men									
Metastatic	62	(92.5)	54	(87.1)	8	(12.9)	–	–	–
Localised	5	(7.5)	5	(100)	0	(0)	–	–	

* See footnotes to Table 1.

OR adjusted for age at diagnosis of pancreatic cancer. An OR=1 indicates the reference category. An OR>1 indicates a higher probability of having the pancreatic cancer diagnosed through microscopic methods.

a Excluding participants with a body mass index <18.5 kg/m^2.

1 Unless otherwise specified, p value derived from a multivariate Wald's test.

2 Mann-Whitney's U test (two-tail).

3 Test for linear trend (multivariate analogue of Mantel's extension test).

Table 3
Influence of sex on the probability of having exocrine pancreatic cancer diagnosed by microscopic methods, by country.

			Basis of pancreatic cancer diagnosis						
	Total		Microscopic Methods*		Clinical and other tests*				
Characteristic		N (%)	N	(%)	N	(%)	OR	(95 % CI)	*p*-value[1]
Total	393	(100)	287	(73.0)	106	(27.0)			
Country									
Denmark	135	(34.4)	129	(95.6)	6	(4.4)			
Women	51	(37.8)	49	(96.1)	2	(3.9)	1.00	–	0.831
Men	84	(62.2)	80	(95.2)	4	(4.8)	0.83	(0.15–4.70)	
Germany	63	(16.0)	50	(71.4)	13	(18.6)			
Women	26	(37.1)	18	(69.2)	5	(19.2)	1.00	–	0.851
Men	44	(62.9)	32	(72.7)	8	(18.1)	1.13	(0.32–4.00)	
United Kingdom	60	(15.3)	13	(21.7)	47	(78.3)			
Women	39	(65.0)	8	(20.5)	31	(76.2)	1.00	–	0.960
Men	21	(35.0)	5	(23.8)	16	(76.2)	1.04	(0.27–4.04)	
The Netherlands	47	(12.0)	31	(65.9)	16	(34.1)			
Women	37	(78.7)	21	(56.3)	16	(43.2)	–	–	–
Men	10	(21.3)	10	(100)	0	(0)	–	–	
Italy	43	(10.9)	29	(67.4)	14	(32.6)			
Women	24	(55.8)	15	(62.5)	9	(37.5)	1.00	–	0.744
Men	19	(44.2)	14	(73.7)	5	(26.3)	1.27	(0.31–5.18)	
Spain	37	(9.4)	32	(86.5)	5	(13.5)			
Women	21	(56.8)	17	(81.0)	4	(19.0)	1.00	–	0.267
Men	16	(43.2)	15	(93.8)	1	(6.3)	3.75	(0.36–38.58)	
France	8	(2.0)	3	(37.5)	5	(62.5)			
Women	8	(100)	3	(37.5)	5	(62.5)	–	–	
Men	0	(0)	0	(0)	0	(0)	–	–	

* See footnotes to Table 1.
Odds ratios (ORs) were adjusted for age at diagnosis of pancreatic cancer.
An OR=1 indicates the reference category. An OR>1 indicates a higher probability of having the pancreatic cancer diagnosed through microscopic methods.
1 Wald's test.

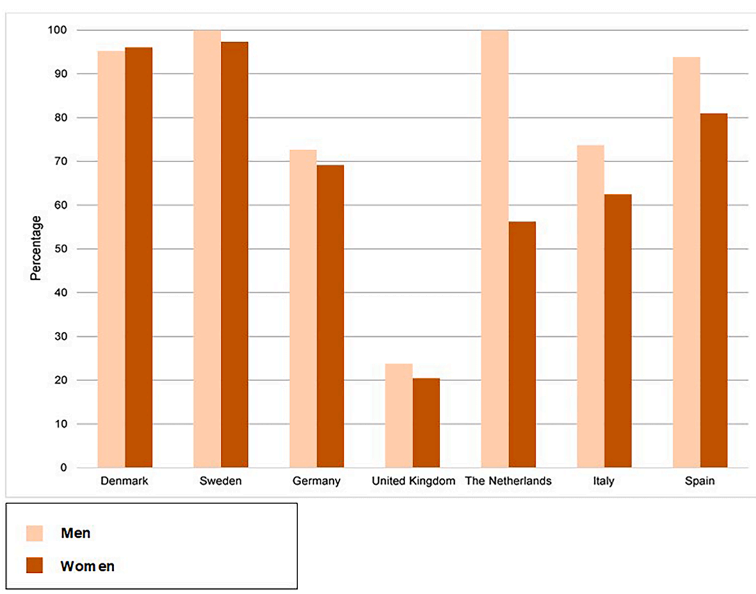

Fig. 1. Participants with microscopic confirmation (%) according to sex for each country (N = 287).

who drank less alcohol.

Over 82 % of participants with longer education had MC from the primary tumor or autopsy. This value was 47 % in participants with less than primary studies (Supplementary Table 2, Fig. 2). Participants with a lower educational level were six times more likely to have MC through metastatic tissue in comparison with participants with longer education; this difference remained unaltered after adjustment for sex and age.

Discussion

In the present study, 73 % of participants had pancreatic cancer diagnosed through microscopic confirmation (MC). This figure is relatively higher than in population-based studies. For instance, in the EUROCARE 5 study, which analyzed data from cancers diagnosed from 2000 to 2007 in 88 population-based cancer registries from 29 European countries, the proportion of diagnoses with MC for pancreatic and liver cancers was 56 % [30]. As most analytic epidemiologic studies, ours did not aim at being representative of the European population. Nevertheless, the extent to which results may be generalizable to other population and clinical contexts should be possible to assess by numerous stakeholders.

Over 82 % of men had diagnosis through MC, while this figure was

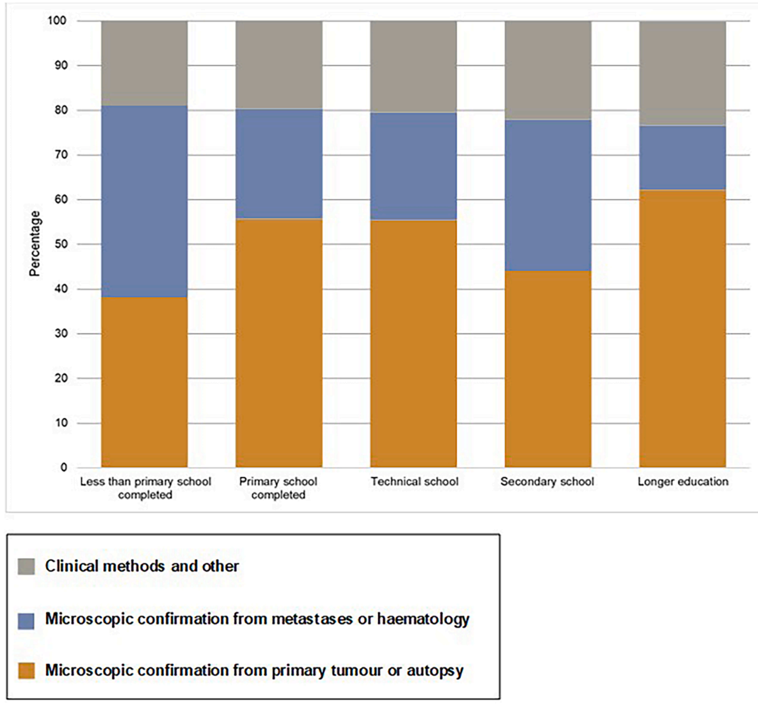

Fig. 2. Proportional distribution of the basis of the pancreatic cancer diagnosis according to educational level ($N = 390$).

nearly 18 percentage points lower in women. Furthermore, men had a higher proportion of MC than women across many of the variables studied; e.g., in each age group. These results are in line with others [31]. There are no clinical reasons why some women might benefit more than men from avoiding procedures enabling MC of their pancreatic cancer. Thus, the lower rates of MC in female participants suggest a substantial sex-related diagnostic bias, which might reflect both influences in clinical decision-making patterns, and broader structural inequities. They may require specific policies to be counterbalanced [2,3,32,33].

Subjects without MC were on average nearly 3 years older at diagnosis than those who had MC. Older participants had the lowest rates of MC, for men and women. In both sexes an inverse relation between age and MC was observed, of greater magnitude in women. This data, consistent with previous studies, highlights the fact that with increasing age fewer invasive procedures are performed [31,34–36]. These findings have implications, since the probability of pancreatic cancer increases with increasing age. While no sex group can benefit *per se* from absence of MC, the increasing avoidance of procedures to achieve a MC with increasing age may partly reflect that clinicians do assess the severity, prognosis and own (patient) interest of older patients; e.g., what may likely be the additional benefit of MC for a patient in whom semiology and image tests suggest they have an unresectable pancreatic cancer [7,14,15,36]. After the year 2000 diagnoses based on microscopic confirmation multiplied by more than 2 in women and by more than 5 and 10 in men, suggesting that a positive trend is ongoing.

Findings on age and sex patterns are interesting not just from epidemiological and methodological perspectives, they are also clinically relevant: attention to maintaining appropriate rates of MC in women and older patients is usually necessary in many real-world clinical settings. Such attention is likely to benefit patient management, and outcomes.

We observed no differences in MC by educational level. Other studies found that subjects with higher socioeconomic status were more likely to have their diagnosis confirmed by MC [36]. Among participants with MC, those with longer education were more frequently diagnosed through tissue samples from the primary tumor, which has greater validity than metastatic tissue [2,3,13]. These findings suggest that participants with MC from a lower educational level may be more frequently diagnosed at later stages, when the disease is disseminated, through the analysis of metastatic tissue. Unfortunately, in our study information on tumor stage was available only for a minority of subjects.

Differences in MC across European countries (Table 3 and Fig. 1) were likely due to slightly different study protocols, and not representative of the general population. Differences between this study and population-based cancer registries can certainly be found. For example, MC for pancreatic cancer in the Danish Cancer Registry from 2003 to 2007 was 79 % [37], whereas in our study it was 96 %. The latter figure was 87 % for Spain; by contrast, in two population cancer registries (in Girona and Murcia), MC was 49 % and 61 %, respectively [31,38].

The high figures of MC in Denmark were accompanied by sex equality, but such sex similarity was also seen in Germany and when MC was low, as in the United Kingdom, whereas in some countries with intermediate rates of MC (Netherlands, Italy, Spain) women had substantially lower MC figures than men. Differences across study centres in some design features (notably, the required diagnostic basis) need to be taken into account by international multicentre studies [23]. Specifically, a systematic collection of detailed diagnostic information may be considered in future studies and cancer surveillance systems, to enable the identification and monitoring of possible diagnostic biases related to sex, age, and socioeconomic status.

Inter-country differences in MC have been reported in population-based studies previously, not only in pancreatic cancer [39]. Although the rates of MC in pancreatic cancer have been increasing over the last decades, considerable differences among European cancer registries still exist to date [11].

Differences on MC between sexes in each country were variable, being of greater magnitude in the Netherlands but also not negligible in Italy and Spain. When assessing the indices of data quality of population-based cancer registries across Europe, higher rates of MC among men were observed in most registries [11].

We observed that men who drank alcohol might be more likely to be diagnosed by MC than never or former drinkers. The pancreatic cancer of individuals with alcohol use disorders may be more likely to be nonmicroscopically confirmed if such persons have concomitant diseases (as chronic pancreatitis) that obscure and delay the diagnosis of pancreatic cancer, or have less access to medical care because of their social position [2,15,40]. Nevertheless, a possible explanation for our results is also that people with alcohol use disorders may be more closely followed than non-alcohol users for other diseases arising from alcohol abuse (such as pancreatitis or cirrhosis), leading to a relative high use of MC-related tests. In fact, through several clinical pathways, MC may be positively related to toxic habits such as alcohol in some populations and studies, and inversely related in other instances.

The central issue to keep in mind when designing, conducting and analyzing studies in humans in the real world is that the diagnostic basis, diagnostic certainty, and the corresponding disease misclassification can seldom be assumed to be nondifferential (and it is necessary to avoid assuming that they are nondifferential unless there is proof that they are nondifferential); e.g., they are rarely similar in the different categories of exposure to the risk factors and confounders of interest [13,15–18,27,28,35,41,42].

Only a subset of 121 subjects with pancreatic cancer had information on tumor stage, and even for these subjects, stage information was limited to "localized" or "metastatic". Previous studies have found higher rates of MC in subjects with metastatic disease in comparison to subjects with non-metastatic disease [36]. Valid information on tumor stage is essential for epidemiologic studies of clinically aggressive diseases as exocrine pancreatic cancer and may be related to the diagnostic basis and to treatment options [2,12,15].

As a result of slightly different study protocols across centers participating in the study, co-morbidities were only asked in few centers. Additionally, no information was available on co-morbidities such as pancreatitis, which would have been of interest in the present study, given the relevance of the differential diagnosis between pancreatic cancer and pancreatitis [10]. But, of course, a large cohort study as EPIC [29] had to select to register a feasible, limited number of co-morbidities. Again, the coexistence of differences across study centres in some design features is of relevance to other multicentre studies.

Participants were enrolled between 1993 and 1998. This is a relatively old inclusion period, and diagnostic imaging and tissue sampling techniques have advanced considerably since then. As shown in Table 1, the probability of MC was higher after the year 2000.

Studies on factors influencing diagnostic basis in cancer remain scarce, and the present study, which includes more than 390 subjects from a European cohort of more than half million people, provides relevant results on such factors in pancreatic cancer.

Conclusions

Sex and age were two powerful factors influencing the diagnostic basis. Thus, they must be considered when designing and analyzing clinical and epidemiologic research, as well as in clinical practice. Differences across study centres in some design features need to be taken into account by international multicentre studies. The consistently lower rates of MC in female patients suggest an ingrained sex-related diagnostic bias, which may require specific policies to be counterbalanced. More studies using state of the art population- and hospital-based cancer registries could assess factors that influence the diagnostic basis of exocrine pancreatic cancer. We continue to need studies on the impact of the diagnostic basis on clinical prognosis and on estimates of etiologic factors.

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Ethics approval

The EPIC study was approved by the Ethical Review Board of the International Agency for Research on Cancer (IARC, Lyon) and by the local Ethical Committees. Participants signed an informed consent before completing questionnaires at baseline. M.P., J.P. and M.G. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. They declare that this manuscript is an honest, accurate and transparent account of the study being reported and that no important aspects of the study have been omitted.

Data availability

The data underlying this article belong to the European Prospective Investigation into Cancer and Nutrition (EPIC). Reasonable requests may be addressed to the corresponding author.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ctarc.2025.101009.

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