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Screening for Pancreatic Cancer in High-Risk individuals

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INDICE

L’insegnamento è il più grande atto di generosità e ottimismo.
Ringrazio quindi tutti coloro che sono stati con me generosi e ottimisti!

GENERAL INTRODUCTION AND AIMS OF THE THESIS

Introduction

Pancreatic Ductal Adenocarcinoma (PDAC) is the fourth leading cause of cancer related death in Western countries and it is predicted to become second in the United States by 2030 with an increase up to 70% from 2010 [1, 2] (**Figure.1**) . Likewise, in Italy PDAC has showed, compared to other cancers, an incremental trend in both sex (although more pronounced in the male sex) with a 5-year survival rate less than 10% [3] (**Table.1**). The prognosis of this tumour is dismal because of the delayed diagnosis, biological aggressiveness and poor response to medical treatment [4]. Currently, oncological treatment permits only to extend the survival, therefore, the only potentially curative treatment available nowadays is the radical surgery. Unfortunately, due to the delayed diagnosis and the late onset of symptoms, only 15 to 20% of patients are candidate for surgery[5]. The median survival for an early diagnosed PDAC after surgery ($T \leq 2$ cm, N0,M0) is 38 months (33-43) compared to 15 months (14-16) in patients with positive lymph nodes, even though the rate of Stage IA represents only the 17 % of patents amenable of surgery [6].

Hence, prevention seems to be the only way to decrease pancreatic cancer related death. As far as regard primary prevention, it consists in reduce the modifiable proven risk factors related to PDAC such as obesity and cigarette smoking with the aim to reduce the PDAC incidence [7]. On the other hand, secondary prevention that consists on screening the whole population can't be prosecuted in the setting on PDAC , as happen for other cancers such as breast and colorectal cancer, for two main reasons : firstly, the overall lifetime risk of developing PDAC is relatively low (close to 1%) therefore it doesn't make cost effective such approach , secondly , so far there

are limited data regarding the accuracy of the screening tests available and the interpretations of the test's findings for clinical decisions (surgical treatment/ follow-up) .

Actually, despite it has been recognized that some neoplastic precursor lesions, such as intraductal papillary mucinous neoplasms (IPMNs) or pancreatic intraepithelial neoplasia (PanINs) (**Figure.2**), can be detected at an early stage using currently available imaging techniques[8], they are extremely common findings in healthy subjects, increasing with age. Moreover, the managing of those lesions, when discovered in the general population, is already not well known as well as their exact prevalence.

Since the diagnostic accuracy of a screening test depends also on the prevalence of the disease in a certain population (pre-test probability) there is an accordance between experts about the target population for which screening for PDAC could be feasible. Since a hereditary component has been known for approximately 5-10% of PDAC cases[8], surveillance is therefore currently advised for high-risk individuals (HRIs) with a known elevated risk of developing the disease (i.e., >5% lifetime risk, or five fold increased relative risk) (**Table.2**). The International Cancer of the

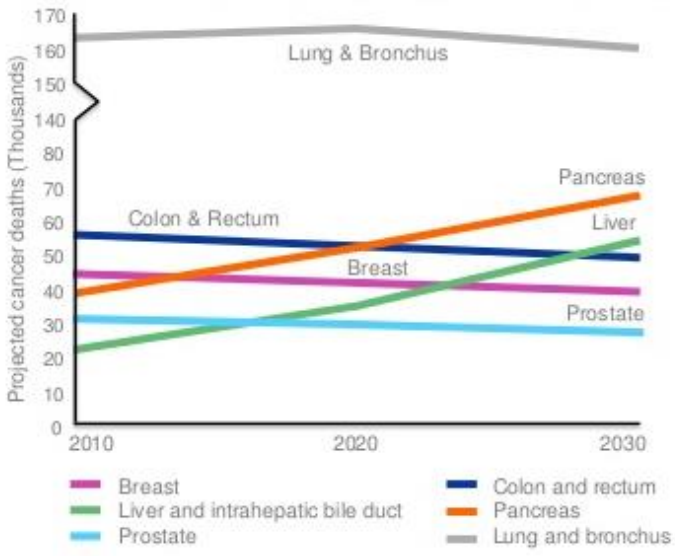

Figure1. Projecting cancer deaths in both sex in USA. As showed, Pancreas is predicted to be the second leading cause of death by 2030 overcame after 2020 cancer related deaths due to colorectal and breast .

Table1. Top five causes of cancer death in Italy and relatively proportion in respect of the total cancer deaths by gender and age range.
*Central nervous system

Rank	Male			Female		
	Age			Age		
	0-49	50-69	70+	0-49	50-69	70+
1st	Lung [14%]	Lung [30%]	Lung [26%]	Breast [29%]	Breast [22%]	Breast [15%]
2nd	CNS* [10%]	Colorectal [10%]	Colorectal [11%]	Lung [9%]	Lung [14%]	Colorectal [13%]
3rd	Colorectal [8%]	Liver [8%]	Prostate [10%]	Colorectal [7%]	Colorectal [10%]	Lung [10%]
4th	Leukemia [8%]	***Pancreas* [7%]**	Liver [7%]	Ovary [6%]	***Pancreas* [7%]**	***Pancreas* [8%]**
5th	Liver [7%]	Stomach [6%]	Stomach [7%]	CNS* [6%]	Ovary [7%]	Stomach [7%]

Pancreas Screening (CAPS) Consortium [9] in 2013 has defined selection criteria for subjects with "familial pancreatic cancer" (FPC) or with hereditary syndromes of which PDAC is one of the phenotypic manifestations for whom surveillance has to be considered in the setting of research protocols.

High-risk individuals

The definition of FPC is not fully established yet, but an individual can be considered at high risk if two or more blood relatives are affected by PDAC, of whom at least one is a 1st degree relative (FDR). The distribution of PC in some families meets the criteria for autosomal dominant transmission with reduced penetrance, although a susceptibility gene for FPC has not been identified yet. The risk to develop PDAC in such a families goes up to 32 folds if ≥ 3 first degree relatives are affected.

Concerning the syndromic pancreatic cancer, they are characterized by a defined gene alteration and a specific transmission. They account for approximately 20% of hereditary pancreatic cancer,

penetrance varies between different syndromes and individuals/families and the cumulative lifetime risk varies between 2 – 3% and 40%. In addition, some studies have found FPC individuals more prone to develop cystic lesions compare to the general population [9].

Surveillance is indicated for all patients with Peutz–Jeghers syndrome (PJS) regardless of family history of PDAC. Furthermore, p16 (familial atypical multiple mole melanoma syndrome, FAMMM syndrome), BRCA2, PALB and mismatch repair gene (hereditary nonpolyposis colorectal cancer, HNPCC) mutation carriers with one FDR or two other family members affected by PDAC should also be considered for surveillance[10] (**Table.2**).

In detail, PJS is an autosomal dominant hereditary disease linked to a mutation of the STK 11 gene increased with an increased risk of developing gastrointestinal and extra-digestive cancer. The most representative phenotype of the syndrome are benign hamartomatous polyps in the gastrointestinal tract in association with a hyperpigmentation on the lips and oral mucosa.

One of those is PDAC with a 132-fold higher in these patients compared to the general population [9].

FAMMM syndrome is due to an alteration of CDKN2A gene and it is characterized by multiple nevi (usually in the hundreds) typically diagnosed 10–20 years earlier than sporadic melanoma and extra-cutaneous tumors. The risk to develop PDAC is up to 25% ranging from 34- to 39-fold higher than in the general population. Moreover, from previous study, it seems that in this setting is more frequent to diagnose directly PDAC during surveillance instead of its precursor.

The mutations of the BRCA1 or BRCA2 genes is typical of breast and ovarian cancer syndrome (HBOC) in which together with the high lifetime risk of developing breast and ovarian cancers there is from 2.3- to 10-fold increased risk of PDAC. The BRCA2 mutation itself was also identified in FPC families in about 13%-17% of the cases.

Hereditary pancreatitis (HP) is characterized by recurrent attacks of acute pancreatitis in childhood, progressing to chronic pancreatitis with time. It is an autosomal dominant condition with 80% penetrance. Different types of HP are described but only HP associated with PRSS1 gene mutation seems liked to an elevated risk to develop PDAC (RR equal to 50-70) mostly in presence of early-onset chronic pancreatitis and a family history of PDAC.

Since the heterogeneity between the different kind of HRIs in terms of hereditary transmission, family history of PDAC, knowing gene alteration, target lesion to diagnose (PDAC or precursor) it seems reasonable that surveillance should be tailored in terms of screening methods and follow up depending on the type of HRIs.

Table.2 Characteristics of the syndrome associated with increased risk of pancreatic cancer and their estimated lifetime risk of pancreatic cancer

Syndrome associated with increased risk of pancreatic cancer		
Syndrome	**Gene**	**Estimated Lifetime Risk of Pancretic Cancer (%)**
Peutz-Jeghers syndrome	STK11	11-36
Familial Atypical Multiple Mole Melanoma syndrome	P16/CDKN2A	10-17
Hereditary breast and ovarian cancer	BRCA1 BRCA2	5 3.6
Hereditary Pancreatitis	PRSS1	40
Familial Pancreatic Cancer 1 FDR 2 FDR ≥ 3 FDR	Majority unknown	 6 8-12 40

Precursor lesions

The ultimate goal of surveillance programs is to decrease PDAC-related mortality. In order to reach this goal, programs should focus on the detection and treatment of high-grade non-invasive precursor lesions of PDAC, such as advanced pancreatic intraepithelial neoplasia (PanINs3) or IPMNs with high grade dysplasia apart from early-stage asymptomatic PDAC still amenable for surgical treatment[11].

PanINs are neoplastic microscopic lesions (<0.5 cm), characterized by flat or papillary epithelium non-invasive duct cell proliferations separated into a group with low-grade (PanIN grade 1 and 2) and high-grade dysplasia (PanIN grade 3). The low grade PanINs are common findings into the pancreatic gland of people affected by chronic pancreatitis or in healthy people aged > 40 years old contrary to high grade PanINs that are associated to PDAC [12, 13]. The accumulation of genetic changes during time is responsible of the histological progression from low-grade to high grade (**Figure.2**)**.** Early genetic alterations include activating KRAS mutation (PanIN 1 by flat or papillary). Subsequent mutations involved inactivation of P16 (PanIN2 more complex architecture with additional nuclear alterations) and in later stages mutation concern inactivation of the tumor suppressor genes TP53 and SMAD4 and rarely BRCA 2 mutation (PanIN3 or carcinoma in situ).

It remains debated if the diagnostic methods available can be able to detect those kind of lesions that are microscopic by definition. In HRIs, some data suggest that PanINs are associated to chronic pancreatitis-like parenchymal changes that could be visualized by EUS as ectasia, irregularity of the duct and/or parenchyma heterogeneityand lobularity despite they cannot be reliably distinguish from non-neoplastic alterations [14].

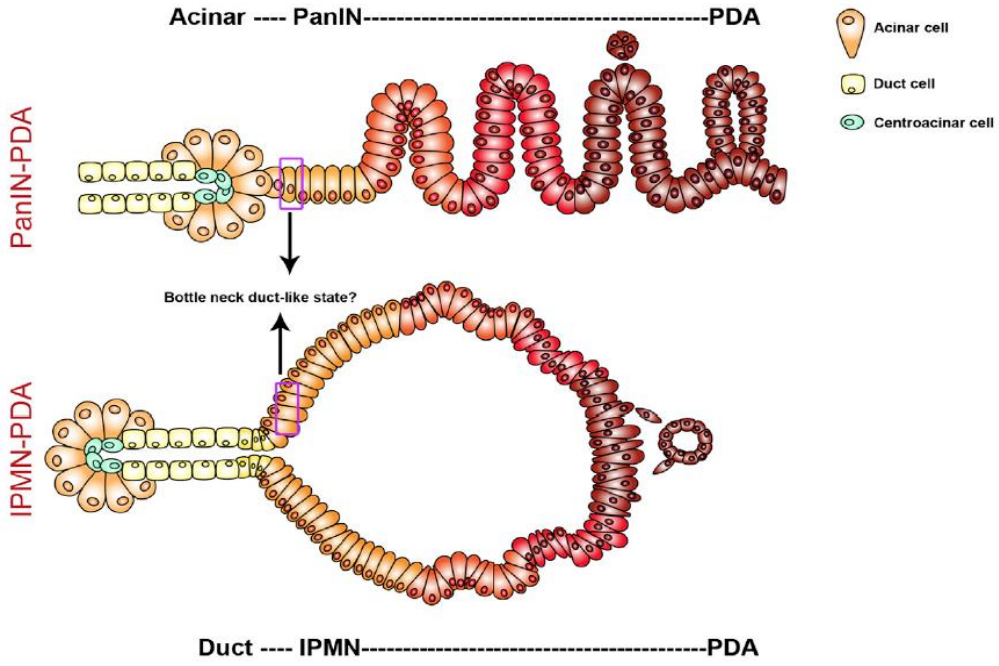

Figure.2 Transition between acinar, ductal or centroacinar normal pancreatic cell into IPMN/PanIN and from those precursors to pancreatic ductal adenocarcinoma (PDA).

IPMNs are nowadays well described neoplasms involving the main pancreatic duct (main duct IPMN or MD-IPMN), the side branches (SB-IPMN) or both (Mixt type IPMN). Those with wall nodules or thickened wall, as called "worrisome features", present a higher risk of progression in adenocarcinoma[15] (**Figure.2**). Currently, due to the widespread use of cross-sectional imaging the incidentally discovered pancreatic cysts are more and more frequent with IPMN being the majority of them. From the histological point of view, IPMNs display a differ types of neoplastic epithelium that can be characterized as gastric, intestinal, pancreatobiliary or oncocytic type[16], with the first type being morphologically and prognostically identical to conventional PC whereas the latter two more indolent. Interestingly, there is a complex relationship between IPMNs and PDAC due to the fact that PDAC can develop not only as a cancerous transformation of the cystic lesions , but often can occur as a synchronous lesion in a different place of the gland topographically separate from the IPMN (mostly gastric type SD-IPMN) [17]. Almost 70% of the pancreatic cysts are discovered incidentally and the prevalence varies among different studies from

3 to 20% depending on the radiological modalities employed. The prevalence seems to increase with the age as showed in autopsy studies where pancreatic cysts were discovered up to 50% in the elderly population[18, 19] . The exactly incidence, prevalence and clinical out-come of the asymptomatic incidentally discovered pancreatic cyst is not well known as far as their clinical behavior in HRIs.

From previous studies about surveillance in HRIs it has emerged that both PanINs and IPMNs are more frequent, with higher grade and most of the time multifocal in this kind of setting than in patients with sporadic disease[10].

Screening modalities

Who can be considered the best imaging modalities to diagnose early PDAC/ high grade precursors in the population of HRIs it is still debated. From previous surveillance programs the imaging methods employed in this setting were: computed tomography scan (CT scan), Endoscopic retrograde cholangiopancreatography (ERCP) , magnetic resonance imaging (MRI) and endoscopic ultrasonography (EUS).

As far as regards CT scan, although it became a widely available not invasive imaging methods with the opportunity to detect intra and extra pancreatic lesions it is not considered an adequate candidate for screening programs mostly because of the radiation exposure that the population should undergo during screening campaigns.

ERCP has been proposed by Brentnall et al. [20] in 1999 as a imaging modalities able to screen a small prospective cohort of a family composed by 14 HRIs. The use of this method has been progressively abandoned for this purpose because of the disadvantages of being an invasive

technique with the risk of post ERCP pancreatitis and the low sensitivity for small pancreatic lesions compared to other radiological tests.

Nowadays, two imaging modalities are considered as a candidate for screening HRIs: MRI and EUS. Both of them have been employed for surveillance of HRIs as first line modalities but no imaging test has gained a univocal evidence based consensus for preferred use.

EUS has the advantages to perform better in the setting of small lesion with a sensitivity for pancreatic lesions less than 2 cm around 93 % with a 100 % of predictive negative value for tumor detection[21]. It has also been described how this technique can early detected "worrisome features" (e.g. mural nodule, thickened of the cystic wall) in the setting of IPMNs and it also carries the advantage to perform guided fine needle aspiration (FNA) that permits to obtain tissue samples for a histopathological evaluation of the lesion with low risk of complications (less than 5%). Although in the setting of surveillance for PDAC the low negative predictive of FNA (value equal to 64%) doesn't allow to a certain exclusion of malignancy when suspected.

This modality has been used as imaging tests , alone or in combination with others screening tests, in several screening studies. Capurso et al .[10] has showed how the diagnostic yield defined as EUS detection of any lesions morphologically suspicious for BD-IPMN or histologically proven (pre) malignant lesion (PanIN≥2, IPMN and pancreatic adenocarcinoma) at baseline evaluation and, when performed, during the follow up of EUS is about 22% with a wide range between all the studies (from 2.6 to 26%) (**Table 3**). Although the number of histologically confirmed target lesions for which surgical treatment could be considered a success of the screening program (resectable PDAC, MD-IPMN or IPMN with dysplasia, PanIN3) was only 2.2% of all the lesions diagnosed. Moreover a considerable amount of HRIs underwent to surgery for a low grade lesions

such as PanIN 1-2 or IPMN with low grade of dysplasia or even a nbenign cystic lesion sich as serocystic adenoma.

Table 3. Summary of diagnostic yields of Endoscopic Ultrasound based based protocols for familiar pancreatic cancer screening in High risk Individuals

Study (reference)	Patients and Syndrome	Diagnostic Yield	Solid lesions (mass or nodule)	Cystic lesions	Chronic Pancreatitis features	Pre/malignant lesions suspected at baseline or FU	Histologically confirmed target lesions (success)**
Brentnall et al.1999	13 (FPC)	46.2%	-	-	10 (77%)	6 (46.2%)	?
Kimmey et al. 2002	46 (FPC)	26%	-	-	24 (52.2%)	12 (26 %)	?
Canto et al 2004	38 (FPC, PJS)	10.5 %	12 (31.5%)	-	17 (44.7%)	6 (15.7%)	2/7 patients who underwent resection (1 PDAC, 1 PanIN3).
Canto et al 2006	78 (FPC, PJS)	10.2%	8 (10.2%)	9 (11.8%)	61 (78.2%)	8 (10.2 %)	3/7 patients who underwent resection (1 IPMN+ca in situ, 1 IPMN + PanIN3, 1 PanIN3).
Poley et al 2009	44 (FPC , PJS, FAMM, FBOC, HP, LFS)	22.7%	3 (6.8%)	7 (16 %)	3 (6.8%)	10 (22.7%)	3/3 patients who underwent resection (3 PDAC).
Langer et al 2009	76 (FPC, FAMM)	2.6 %	7 (9.2%)	3 (3.9%)	17 (22.3%)	7 (11.8%)	0/7 patients who underwent resection.
Verna et al 2010	31 (FPC, FBOC)	22.5%	2 (6.4)	12 (38.7)	9 (29%)	7 (22.6%)	1/5 who underwent surgery (1 PDAC).
Canto et al. 2012	216 (FPC, FBOC, PJS)	37 %	3 (1.4%)	79 (36%)	54 (25%)	79 (37%)	3/5 who underwent surgery (2 MD-IPMN, 1BDIPMN+panIN3)
Total	542	22.2 %	35 (6.5 %)	110 (20.3%)	195 (36%)	135 (25%)	12/542 (2.2%) of total

EUS, endoscopic ultrasonography; FNA, fine-needle aspiration; FPC, familial pancreatic cancer; IPMN, intraductal papillary mucinous neoplasm, PDAC, pancreatic ductal adenocarcinoma; PJS, Peutz–Jeghers syndrome; PanIN, pancreatic intraepithelial neoplasia, FAMMM: Familial atypical multiple mole melanoma; FBOC: Familial breast ovarian cancer; HP: hereditary pancreatitis; LFS: Li fraumeni syndrome
** Treatment is considered a success if any of the following lesions is found at surgery: resectable PDAC, MD-IPMN or IPMN with dysplasia, PanIN3.

As far as regards MRI, it carries the advantages of being a non-invasive and less operator dependent as compared to EUS. Moreover, it is a radiologic modalities that offers the possibility to detect extrapancreatic lesions without radiation exposure and it show an excellent visualization of the ductal system (pancreatic and biliary tree) and provide a good sensibility in characterizing

cystic lesions such as IPMNs that are the most common precursor lesions diagnosed in HRI [22]. In the same review above mentioned[10] , the authors analyzed the

results of seven papers that employed MRI like a screening modalities for detecting pancreatic lesions in HRIs. The diagnostic yield was 26.8 % (ranging from 3.3 to 50.4%) (**Table 4**) . Notably, the MRI methods varies between all the studies with an extremely heterogeneity in terms of using or not contrast agent and/or secretin and the type of MRI scanner used

Table 4. Summary of diagnostic yield of MRI based protocols for familiar pancreatic cancer screening in high risk individuals

Study (reference)	**Patients and Syndrome**	**Diagnostic Yield**	**Solid lesions (mass or nodule)**	**Cystic lesions**	**Chronic pancreatitis features**	**Pre/malignant lesions suspected at baseline or FU**	**Histologically confirmed target lesions (success)****
Langer et al. 2009	76 (FAMMM, MPCS, FBOC)	23.3%	6 (7.8%)	2 (2.6%)	1 (1.3%)	12 (15%)	1/7 who underwent surgery (1 PDAC)
Vasen et al. 2012	77 (FAMMM)	20.7%	7 (9%)	Not specified	9 (11.6%)	7 (9%)	4/5 who underwent surgery (4 R0 PDAC)
Ludwig et al. 2011	109 (FPC)	16.5%	1 (0.9%)	Not specified	2 (1.8%)	18 (17.4%)	4/6 who underwent surgery (2 MD-IPMN, 1 PDAC, 1 PanIn3)
Canto et al. 2012	216 (PJG, FPC, FBOC)	33.7%	1 (0.4%)	71 (32.8%)	-	45 (20.8%)	3/5 who underwent surgery (1 MD-IPMN+ HGD, 1MD IPMN, 1 BD IPMN+ PNET+HGD)
Al-Sukhni et al. 2012	226 (PJG, FPC, FBOC, FAMMM, HP)	50.4%	2 (0.8%)	80 (35.3%)	25 (11%)	5 (2%)	1/4 who underwent surgery (1 PDAC)
Verna et al. 2010	33 (FPC, FAMMM, FBOC, HNPCC)	3.3%	3 (9%)	7 (21.2%)	1 (3%)	5 (15%)	Not specified how may pathological reports had been previously described in MRI
Total	737	34%	20 (2.7%)	160 (21.7%)	38 (5.1%)	92 (12.4%)	13/737 (1.7%) of total

FPC, familial pancreatic cancer; IPMN, intraductal papillary mucinous neoplasm, PDAC, pancreatic ductal adenocarcinoma; PJS, Peutz–Jeghers syndrome; PanIN, pancreatic intraepithelial neoplasia, FAMMM: Familial atypical multiple mole melanoma; FBOC: Familial breast ovarian cancer; HP: hereditary pancreatitis.
** Treatment is considered a success if any of the following lesions is found at surgery: resectable PDAC, MD-IPMN or IPMN with dysplasia, PanIN3.

Few studies compared the diagnostic yield of these two modalities in a pancreatic surveillance program [23, 24]. Some authors have recently suggested that an MRI-based surveillance program,

with additional EUS at baseline and every 3rd year or when changes in MRI occur, appears to be efficient in the surveillance of FPC families[25] .

Aim of the studies

As compared to others screening policies, surveillance for HRIs to develop PDAC still carries various areas of improvement and some issues to be clarified. For this reason, it is indicated only in reference centers as a research protocols.

However so far several screening programs for HRIs has been published all over the world, the results are still difficult to interpret because of different policies employed in terms of HRIs enrolled, screening test chosen, and follow-up intervals so as data on the efficacy of such surveillance programs are still limited and heterogeneous.

Both magnetic resonance imaging (MRI) and endoscopic ultrasonography (EUS) have been employed as first line modalities for HRIs surveillance, but no imaging test has gained a univocal evidence-based consensus.

Furthermore, the results of screening might be different in terms of relevant detected lesions depending on the t HRIs subgroups enrolled. As an example, patients with FAMMM were reported to develop more solid lesions while FPC individuals more cystic ones[26, 27].

No one of the screening studies in literature was conducted in Italy at so that a national protocol for PDAC surveillance was needed, as already reported in a position paper in 2010 written by the Italian Association for the Study of the Pancreas (AISP) [28].

Finally, it is still unknown if some pancreatic parenchymal changes as called *chronic pancreatitis-like features* related to the presence of microscopic PDAC precursor (Pan-INs) and the presence

of IPMNs might show a different risk of progression and characteristics in HRIs compared to the general population.

To improve the knowledge on this field we therefore conducted the subsequent studies:

1) A **systematic review and meta-analysis** of the surveillance studies published aimed to asses in individuals at high risk to develop PDAC: a) the prevalence of solid and cystic lesions and of lesions considered a successful target of the surveillance programs; b) the prevalence of solid and cystic lesions diagnosed by EUS and/or MRI; c) the prevalence of lesions considered a successful target of the surveillance programs in the different HRIs subgroups.
2) A **multicenter surveillance program** included asymptomatic HRIs with familial (FPC) or genetic frailty (BRCA1/2, p16/CDKN2A, STK11/LKB1 and PRSS1 mutations) predisposition to PC published as results of the first screening round of the Italian multicenter program supported by the Italian Association for the study of the Pancreas (AISP).

3) A **Case-control study on pancreatic changes in High-Risk Individuals compare to control** to evaluate the pancreatic parenchyma changes of HRIs and asses if some them (such as cystic lesions or chronic pancreatitis features) occur more often in the setting of a high risk population compared to healthy controls.

4) A **Systematic review and meta-analysis on the prevalence of incidentally detected pancreatic cystic lesions in asymptomatic individuals**, conducted as an ancillary study to better clarify the prevalence Pancreatic cystic lesions (PCLs) in asymptomatic individuals particularly mucinous lesions (PDAC precursors).

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Dig Liver Dis 2010;42:597-605.)

2. RESULTS OF SURVEILLANCE IN INDIVIDUALS AT HIGH-RISK OF PANCREATIC CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background: Data on surveillance for pancreatic ductal adenocarcinoma (PDAC) in high-risk individuals (HRIs) with "familiar pancreatic cancer" (FPC) and specific syndromes are limited and heterogeneous.

Objective: We conducted a systematic review and meta-analysis of PDAC surveillance studies.

Methods: Prevalence of solid/cystic pancreatic lesions and of lesions considered a successful target of surveillance (proven resectable PDAC and high-grade precursors) was pooled across studies. The rate of lesions diagnosed by EUS/MRI and across different HRIs groups were calculated.

Results: Sixteen studies incorporating 1588 HRIs included. The pooled prevalence of pancreatic solid and cystic lesions was 5.8% and 20.2%, respectively. The pooled prevalence of patients with lesions considered a successful target of surveillance was 3.3%, being similar with EUS or MRI and varied across subgroups, being 3% in FPC, 4% in hereditary pancreatitis, 5% in familiar

melanoma, 6.3% in hereditary breast/ovarian cancer and 12.2% in Peutz Jeghers. The pooled estimate rate of lesions considered a successful target of surveillance during follow-up was 5/1000 person-years.

Conclusion: Surveillance programs identifiy successful target lesions in 3.3% of HRIs with similar yield of EUS and MRI and an annual risk of 0.5%. A higher rate of target lesions was reported in HRIs with specific DNA mutations.

Key Summary

1. Summarize the established knowledge on this subject:
    - Surveillance of pancreatic cancer is advised in subjects with "familiar pancreatic cancer" (FPC) and specific genetic syndromes.
    - No evidence-based consensus is available on the imaging test preferred between magnetic resonance imaging (MRI) and endoscopic ultrasonography (EUS).
    - Whether surveillance protocols should be different in the different high-risk individuals subgroups is unknown.
2. What are the significant and/or new findings of this study?
    - The rate of resected lesions considered a successful target of surveillance during pancreatic cancer surveillance programs in HRIs is 3.3% or 0.5% per year.
    - No differences between EUS and MRI in diagnosing "successful" target of the screening.
    - The rate of successful target lesions in FPC is lower compared to specific genetic syndromes, thus surveillance programs might need to be accordingly individualized.

INTRODUCTION

Pancreatic Ductal Adenocarcinoma (PDAC) is an increasing cause of cancer-related death, partially because of delayed diagnosis[1, 2]. Although precursor lesions, such as intraductal papillary mucinous neoplasms (IPMNs) and pancreatic intraepithelial neoplasia (PanINs) can be detected at an early stage [3] , a screening program is not advised for the general population as the overall lifetime PDAC risk is relatively low.

However, since a hereditary component accounts for 5-10% of cases [3] surveillance is advised for high-risk individuals (HRIs). The International Cancer of the Pancreas Screening (CAPS) Consortium [4] defined subjects with "familial pancreatic cancer" (FPC) or with hereditary syndromes of which PDAC is one phenotypic manifestation as candidates for surveillance. FPC definition is not fully established, but an individual can be considered at high risk if ≥ two blood relatives are affected by PDAC, of whom at least one is a 1st degree relative (FDR). Regarding genetic syndromes with a known mutation, surveillance is indicated for all Peutz–Jeghers syndrome (PJS) patients regardless of family history. Furthermore, p16 (familial atypical multiple mole melanoma syndrome, FAMMM), BRCA2, PALB and mismatch repair gene (hereditary nonpolyposis colorectal cancer, HNPCC) mutation carriers with one FDR or two other family members with PDAC should undergo surveillance [5].

The ultimate goal of surveillance is to detect and surgically treat noninvasive precursor lesions, such as advanced PanINs or IPMNs with high-grade dysplasia, or early-stage PDAC, that are considered successful targets of surveillance according to the CAPS Consortium.4 Data on the efficacy of such surveillance programs in HRIs in terms of identification of the above-mentioned lesions are limited and heterogeneous, thus HRI surveillance is generally performed in the setting of research protocols. Both magnetic resonance imaging (MRI) and endoscopic ultrasonography

(EUS) are employed as firstline modalities for HRI surveillance, but no imaging test has gained evidence-based consensus[6,7]. Furthermore, the results of screening might differ in terms of detected lesions in each HRI subgroup. As an example, patients with FAMMM were reported to develop more solid lesions while FPC individuals more cystic ones[8,9].

This systematic review and meta-analysis is therefore aimed to assess in HRIs (a) the prevalence of solid and cystic lesions and of lesions considered a successful target of surveillance, (b) the prevalence of lesions diagnosed by EUS and/or MRI, and (c) the prevalence of lesions considered a successful target of the surveillance in different HRI subgroups.

MATERIALS AND METHODS

Search strategy

A search of PubMed and Scopus databases (see **Appendix 1)** was run until June 2017 to identify studies investigating the prevalence of pancreatic lesions in HRIs in surveillance programs. Duplicates were removed. The methodology was developed from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[10].

The titles of all identified articles were assessed for their relevance, and abstracts and/or full texts of potentially relevant papers screened and evaluated. A manual search of all relevant articles and references was conducted to identify further relevant studies.

Inclusion and exclusion criteria

Inclusion criteria were: English language, inclusion of patients belonging to FPC families and/or with other specific high-risk syndromes or germline mutations carriers, surveillance carried out with MRI and/or EUS, the prevalence and type of diagnosed pancreatic lesions (solid and/or cystic) was reported. In the case of duplicate publications, the most recent or the most informative was

included. Two independent reviewers (MS and GZ) carried out study identification, selection and discussed disagreements with a third reviewer (GC). Excluded studies and the reasons for exclusion were recorded.

Data extraction and quality assessment

Two reviewers (MS and GZ) independently extracted data from each study into a Microsoft Excel spreadsheet (XP Professional Edition; Microsoft Corp., Redmond, Washington, USA). Disagreements were resolved by consulting a third reviewer (GC). Study year, design and location, number of screened subjects and type of high-risk subgroups and of imaging, duration of follow-up, number and type of diagnosed lesions and of patients with an indication for surgery and with an identified lesion considered to be a success of the surveillance or diagnosed with advanced/metastatic PDAC were recorded. A summary table of the relevant studies listing the population characteristics and outcomes was developed. The quality of the studies was evaluated independently by two reviewers (MS and GC) using the Newcastle–Ottawa Scale[11] with a dedicated quality appraisal tool including 7 items. Studies with a score ≥7 were considered of high quality.

Data analysis

We examined 1) the pooled prevalence rate of all solid or cystic lesions 2) the pooled prevalence of lesions being considered a successful target of the surveillance protocols as defined by gold-standard pathology after surgery. Lesions considered as successful target of surveillance were: PanIN3 (or high grade PanIN if not specified), IPMNs with high grade dysplasia or main duct/mixed type IPMN, any resectable PDAC with R0 pathology. This definition is adapted from the CAPS one, as some of the papers did not provide enough information for detailed grouping; 3) the pooled prevalence rate of advanced/metastatic PDAC, not amenable of R0 resection. 4) the

pooled prevalence of the above-mentioned lesions detected either by EUS or by MRI. 5) the pooled prevalence of successful target lesions in each specific HRIs group.

Data were combined to generate a pooled prevalence rate. To better reflect the incidence of detected lesions over time, we also calculated the incidence rates of lesions being a successful target of surveillance by dividing the total number of events by the total number of person-years (pyrs) of follow-up. If these latter data were not provided in a study, it was estimated by multiplying the number of patients who underwent surveillance by the reported mean follow-up time. The corresponding 95% confidence intervals (CIs) were calculated using exact methods and assuming a Poisson distribution. When the number of events was 0, a continuity correction of 0.5 was used for the purpose of calculation, as previously reported[12].

A meta-analysis was performed using the software package Comprehensive Meta-Analysis (Biostat, Englewood, New Jersey, USA) by using a random-effects model[13]. In addition to within-study variance, the random effects model considers heterogeneity among studies and gives more conservative estimates. The quantity of heterogeneity was assessed by means of the I^2 value[32]. The I^2 describes the percentage of total variation across studies that is caused by heterogeneity and not by chance. Publication bias was assessed using the Begg and Mazumdar test. A p-value<0.05 was accepted as statistically significant. We also developed the following *a priori* hypotheses that would explain heterogeneity and planned sensitivity analyses for 1) Area of origin (i.e. USA/Canada or Europe); 2) quality of the study (quality score>7 or ≤ 7).

RESULTS

Search results and study selection and characteristics

The process of study selection is summarized in **Figure 1**. Sixteen studies met the eligibility criteria and were included for qualitative analysis and quantitative synthesis. One of them[15], is a multicenter study whose findings were already reported in three previous single-center studies[9, 16,17]. As the population of this latter study was larger and the results regarding the different HRIs subgroups more detailed, we used this manuscript for the analysis of pooled prevalence of overall lesions. However, as this more recent paper does not report the exact number of cystic/solid lesions diagnosed by either EUS or MRI, we used data from the older studies for the analyses on the role of MRI and EUS.

The descriptive characteristics of the 16 included studies are shown in **Table 1**. Two papers reported only the first surveillance round[18,19] while two other studies did not report the exact follow-up period[20,21]. The mean follow-up in studies reporting>one surveillance round[2, 6-7, 15,22-26] was 32.4 months. The total number of enrolled HRIs was 1588. Considering the 1572 individuals for whom this information was available, the largest group of screened individuals was FPC (1043, 66.3% of total) followed by FAMMM (243, 15.4%) and HBOC individuals or carriers of BRCA1/2 mutations (140, 8.9%). Some of studies also enrolled subjects that did not meet the criteria to be designated as "HRI" according to the CAPS consortium[2, 7,18-20]. There were 4 subjects with Li-Fraumeni syndrome [9,22], 5 with only one affected family member [25], 9 with a family member with early onset PDAC [24], and 6 with>1 relative with a cancer being not pancreatic[2]; all together those subjects accounted for 1.6% of the investigated individuals. Two studies enrolled patients with a very low risk to develop pancreatic cancer based on family history

[19,21] and those subjects therefore were not included in the analysis. Only four[4, 7, 20,25] of the sixteen studies were scored as of 'high quality'.

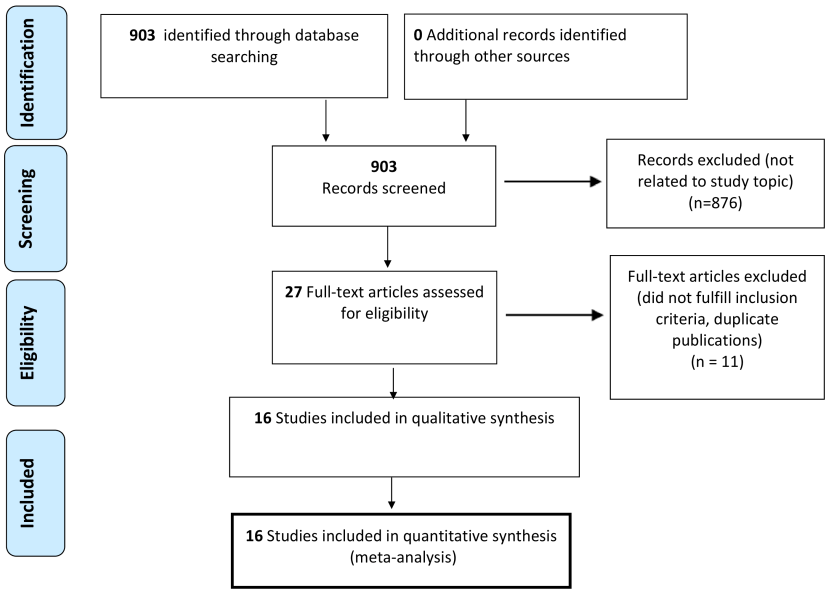


Figure.1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of assessment of studies identified in the preset systematic review.

Prevalence of solid pancreatic lesions in HRIs

A total of 79 pancreatic solid lesions were detected during the surveillance programs, with a pooled prevalence of 5.8% (95%CI 3%–9%; I^2=77.5%) (**Figure 2)**. No publication bias was found (Begg and Mazudmar Kendall's tau=-0.21; p=0.27). When considering only the 7 studies conducted in USA or Canada, the pooled estimate prevalence was 3.8% (95%CI 2-8; I^2=68.8%), compared to 6.8% with similar heterogeneity (95%CI 4-12; I^2=61.2%) in the 6 studies from Europe. The pooled prevalence of solid lesions in studies of high quality [4,7,20,25] was 2.8% (95%CI 1%–6 %)

compared to 7.7% (95%CI 5%–12%) in the eleven studies of lower quality[2,9,16–19,21–24,26], with lower heterogeneity (I^2= 38.2% vs I^2=72.3%) in high quality studies.

Prevalence of Cystic Pancreatic lesions

A total of 340 pancreatic cystic lesions were detected during the surveillance programs with a pooled prevalence of 20.2% (95%CI 14%–28%; I^2 =88.9%) (**Figure 2**). Information on prevalence of pancreatic cystic lesions was not provided in one study[44]. No publication bias was found (Begg and Mazudmar Kendall's tau=-0.34 p=0.09). The pooled prevalence of cystic lesions was 23.4% (95%CI 16%–34%; I^2 =84.1%) in the 7 studies conducted in USA and Canada, and 18.4% (95%CI 8%–37%; I^2 =92.1%) in the studies conducted in Europe. In studies with a high quality score[9, 24, 38, 43], the pooled prevalence of cystic lesions was 33.6% (95%CI 21%–49%; I^2= 90.3%), being higher than the 15.4% (95%CI 10%–24%) of studies with a low quality score [2, 27, 34-37, 39-42, 44] yet with similar heterogeneity(I^2 =83.7%).

Prevalence of successful target lesions of the surveillance

Of 1588 screened HRIs, 95 were considered to have an indication for surgery (pooled prevalence 6.8%; 95% CI 4%–11%; I 2¼ 81%). However, the pooled prevalence of individuals for whom surveillance identified a lesion considered a successful target of surveillance was 3.3% (95% CI 2%–5%; I 2¼ 40.5%) (Figure 3). In high-quality studies, this pooled prevalence was 2.9% (95% CI 1%–8%; I 2 ¼ 69.2%), being 3.4% (95% CI 2%–5%; I 2¼ 23.4%) in studies of lower quality. In the sensitivity analysis by country of origin, the pooled prevalence was 2.7% (95% CI 1%–5%; I 2¼ 43.3%) for studies conducted in the USA or Canada and 4.1% (95% CI 2%–8%; I 2 ¼ 52.2%) for studies conducted in Europe. No publication bias was found (Begg and Mazudmar Kendall's tau ¼ –0.16; p ¼ 0.45). Furthermore, when we repeated this analysis excluding individuals who

were not at high risk according to the guidelines [2,7,18–20] the pooled prevalence was 3.4% (95% CI 2%–5%; I 2¼ 44.7%). As the ideal target of the surveillance programs should be the diagnosis of ‘‘premalignant’’ lesions, the pooled prevalence rate of advanced IPMNs and PanIN3 lesions was also calculated, and resulted in 1.6% (95% CI 1%–2%; I 2¼ 0%) (see Supplementary Figure 1). In detail, 26 (1.6%) patients were diagnosed with a resectable PDAC, 11 (0.7%) with branch duct (BD)- IPMNs with high-grade dysplasia or an MD-IPMN, and four (0.3%) with advanced PanINs. Six individuals were diagnosed with pancreatic neuroendocrine neoplasms (pNENs) [2,6,15,24]. Four of them were resected and all but one2 had a diameter <15 mm. Type and number of histologically confirmed lesions, including those successfully operated on, are summarized in Supplementary Table 1. The pooled estimate rate of lesions considered a successful target of surveillance was calculated for 11 studies in which follow-up length was reported, and resulted in 0.005/pyrs (95%CI 0.001%–0.005%; I 2 ¼ 56%), equal to 5/1000 pyrs (Figure 4).

Prevalence of advanced /metastatic pancreatic adenocarcinoma

During the surveillance programs, nine advanced/metastatic adenocarcinoma were diagnosed. Six metastatic PDAC were diagnosed and histologically confirmed by percutaneous or EUS-guided fine needle aspiration [2,9,19,23] the other three underwent surgical resection but histology showed a positive resection margin [9,15] The pooled prevalence of HRIs for which surveillance identified advanced PDAC was 1.0% (95% CI 1%–2%), without heterogeneity (I 2¼ 0%).

Table 1. Study demographics, population size and characteristics.

First Author of the study	Year	Country	Study design	Number screened	Mean age (range)	Types of High-risk group screened	Mean Months of Follow-up (intervals)	Type of imaging
Kimmey [22]	2002	USA	Single center	46	NR	46 FPC	60	EUS
Canto [23]	2006	USA	Single center	78	52 (32-77)	72 FPC,6 PJS	12 (within one year)	EUS
Poley [18]	2009	The Netherlands	Multicenter	44	Nr (32-75)	21 FPC,3 BRCA1, 2 BRCA2, 2 PJS, 13FAMMM, 2 HP, 1 LFS	Baseline	EUS
Langer [16]	2009	Germany	Multicenter	76	NR	FPC, FAMMM[#]	NR (annualy)	EUS and MRI/MRCP with CE
Verna [19]	2010	USA	Single center	41	52 (29-77)	30 FPC, 6 BRCA1/2, 5 OFMA	Baseline	EUS and MRI (MRCP)
Ludwig [20]	2011	USA	Single center	109	54 (43-65)	93 FPC ,7 BRCA, 9 EOPCF	NR	MRCP
Vasen [15]	2011	The Netherlands	Single center	79	56 (39-72)	79 FAMMM	48 (annualy)	MRI/MRCP with CE
Canto (CAPS3) [4]	2012	USA	Multicenter	216	56 (28-79)	195 FPC,19 BRCA2 ,2 PJS	28.8 (1 to 3 years)	EUS and CT and MRI/MRCP with CE and secretin
Al-Sukhni [2]	2012	Canada	Single center	226	54 (22-89)	146 FPC, 51 BRCA2,5BRCA1, 10 FAMMM, 6 PJG, 2HP, 6 MCFDR	50.4 (annualy)	MRI/MRCP without CE
Sud [24]	2014	USA	Single center	16	NR	FPC, BRCA1, BRCA2, PJS, FAMMM, HNPCC[#]	12(annualy)	EUS
Harinck [7]	2015	The Netherlands	Multicenter	139	51 (20-73)	68 FPC, 3 BRCA1, 20 BRCA2, 38 FAMMM, ,7 PJS,3 LFS	12 (annualy)	EUS and MRI/MRCP with CE
Del Chiaro [25]	2015	Sweden	Single center	40	50 (23-76)	32 FPC, 3 BRCA2, 1 BRCA1, 4 FAMMM	12.9 (annualy)	MRI/MRCP with secretin
Mocci [17]	2015	Spain	Multicenter	41	NR	24 FPC, 12 HBOC, 5 EOPCF	24 (3 to 12 months)	EUS and CT
Joergensen [26]	2016	Danmark	Multicenter	71	51 (27-72)	40 FPC, 31 HP	60 (annualy)	EUS
Vasen [15]*	2016	The Netherlands, Gemany, Spain	Multicenter	411	NR	214 FPC,178 FAMMM, 19 BRCA1/2 PALB2	43.2 (annualy)	EUS and/or MRI
Chang [25]	2017	Taiwan	Single center	151	NR	1 BRCA2, 64 HP, 86 FPC	NR (annauly)	MRI/MRCP with CE

* Includes high risk individuals from Langer 2009, Vasen 2011 and Mocci 2015

The exact number of each HRIs is not provide

FPC: Familial pancreatic cancer; FAMMM: familial atypical multiple mole melanoma syndrome; HBOC: Hereditary breast-ovarian cancer syndrome; PJS: Peutz–Jeghers syndrome ; HP: hereditary pancreatitis LFS: Li-fraumeni syndrome; EOPCF: early onset pancreatic cancer family, MCFDR: multi cancers first degree relatives; OFMA: one family member affected, EUS : Endoscopic Ultrasound ; MRI: Magnetic Resonance Imaging; MRCP: Magnetic resonance cholangiopancreatography ; CE: Contrast Enhancement; CT: Computed Tomography; NR: not reporte

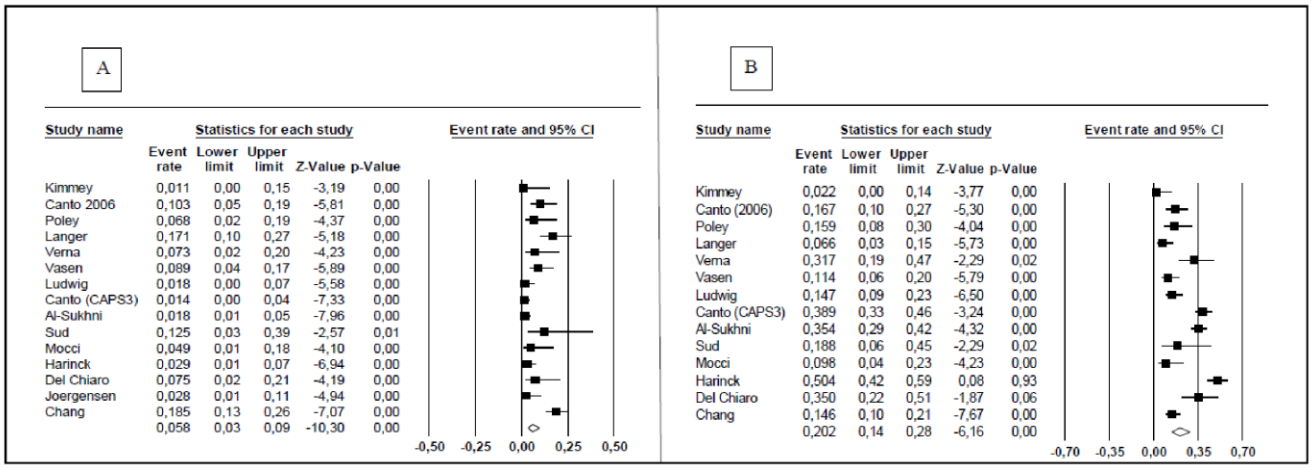


Figure 2. Forest plot showing the pooled prevalence of pancreatic solid lesions (panel A, on the left) diagnosed in high-risk individuals in all the 14 included studies and of the pooled prevalence of cystic lesions (panel B, on the right) diagnosed in high-risk individuals in the 13 studies reporting this information. Random-effects model demonstrating a pooled prevalence of 5.8 % (95% CI 3%–8%) with moderate heterogeneity (I^2=77.5%) for solid lesions and a pooled prevalence of 20.2 % (95% CI 14%–29%) with considerable heterogeneity (I^2=88.9 %) for the cystic ones.

Prevalence of pancreatic lesions diagnosed either by EUS or by MRI

Ten studies employed EUS [6,7,16–19,22–24,26] and nine MRI [2,6,7,9,16,19–21,25] The pooled prevalence of solid lesions was higher in studies employing EUS (5.2%, 95% CI 3%–9%; I 2¼ 60.6%) compared with those using MRI (4.1%, 95% CI 2%–9%; I 2¼ 83%) (Figure 5). The pooled prevalence of cystic lesions was instead 22.4% (95% CI 15%–32%; I 2¼ 89.3%) with MRI and 16.6% (95% CI 10%–27%; 85.7%) with EUS in the eight studies providing this information, which was lacking in two studies.17,26 The pooled prevalence of pancreatic lesions considered a successful target of surveillance was 2.9% with EUS (95% CI 2%–5%; I 2¼ 27.4%) and 2.5% with MRI (95% CI 1%–5%; I 2 ¼ 51.7%) (see Figure 5).

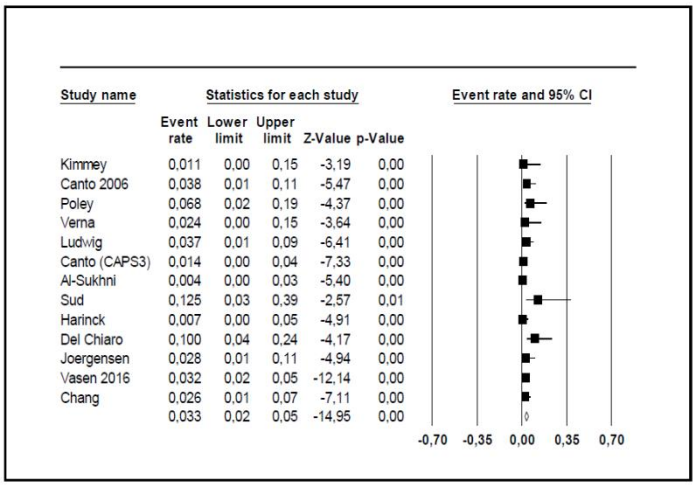


Figure 3. Forest plot showing the overall pooled prevalence of successful target lesions of the surveillance that is equal to 3.3% (95% CI 2%–5%), with moderate heterogeneity (I^2=40.5%).

Prevalence of lesions considered a successful target of surveillance *in different HRIs subgroups*

The pooled prevalence of lesions considered a successful target of surveillance was 3% (95% CI 2%–5%; I 2¼ 22.2%) in FPC individuals. In people with a specific genetic syndrome it was 4% in HP (95% CI 1%–14%), 5% for FAMMM (95% CI 3%–9%), 6.3% in HBOC or BRCA1/2, PALB2 mutation carriers (95% CI 3%–14%), and 12.2% in PJS (95% CI 4%– 32%), without heterogeneity (I 2¼ 0%) in all these subgroups except for people with HP (I 2¼ 12.2%) (Figure 6). We also analyzed the pooled prevalence rate of histologically confirmed solid lesions diagnosed at the baseline examination in each subgroup. These data were available for all studies but one.21 The pooled rate of solid lesions at baseline resulted respectively in: 1.6% (95% CI 1%–3%; I 2¼ 0%) in FPC, 5.8% (95% CI 2%–14%; I 2¼ 0.8%) in HBOC or BRCA1/2 mutation carriers, 4.6% (95% CI 2%–12%; I 2¼ 35%) in FAMM, 12% (95% CI 4%–32%; I 2 ¼ 0%) in PJS, and 7.2% (95% CI 1%–30%; I 2¼ 0.8%) in HP. The number of pancreatic cancer cases and the relative proportion of unresectable/metastatic cases were respectively 12 (25% metastatic) in FPC, 15 (20% metastatic) in FAMMM, four (25% metastatic) in HBOC, and one (0% metastatic) in HP. No PDAC cases were diagnosed in PJS patients.

Table 2. Histologically proven pancreatic lesions diagnosed during the screening programs.

Study	Successfull target lesions			Other lesions				
	Resecable PDAC	IPMN	PanIN3	Advanced/ Metastatic PDAC	IPMN	PanIN 1/2	SCA	pNEN
Kimmey	-	-	-	-	-	15	-	-
Canto(2006)	-	3	-	1	3	1	-	-
Poley	3	-	-	-	-	-	-	-
Verna	1	-	-	1	4	-	-	-
Ludwig	1	2	1	-	-	1	1	-
Canto(CAPS3)	-	3	-	-	2	-	-	3*
Al-Sukhni	1	-	-	2	1	1	-	1
Sud	2	-	-	-	1	-	-	1
Harinck	1	-	-	-	-	2	-	-
Del Chiaro	3	1	-	-	1	-	-	-
Joergensen	2	-	-	-	-	-	-	-
Vasen (2016)	9	1	3	5	7	3	4	1

*one of them was multifocal
PDAC: Pancreatic Ductal Adenocarcinoma; IPMN: intraductal papillary mucinous neoplasms; PanIN: pancreatic intraepithelial neoplasia SCA: Serous Cystadenoma; pNENs: pancreatic neuroendocrine neoplasms

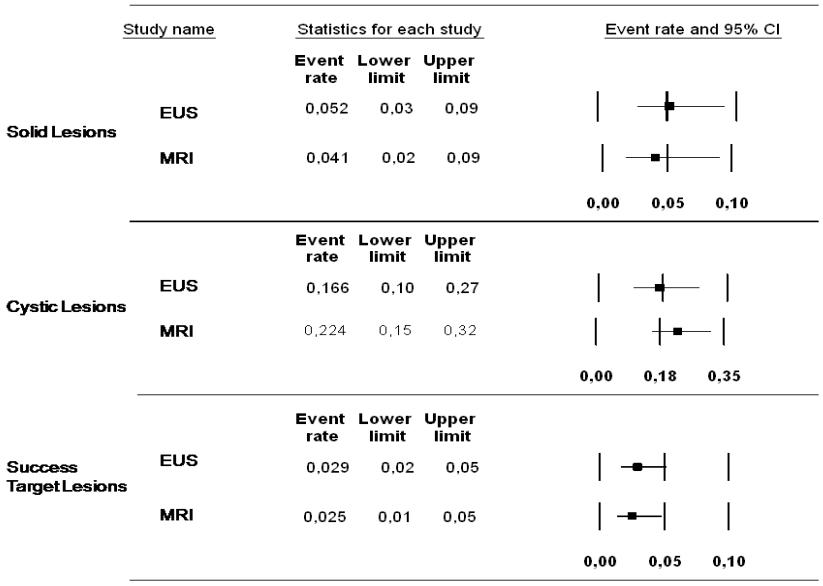


Figure 4. Summary of the pooled prevalence of pancreatic lesions (solid, cystic and successful target lesions of the surveillance) diagnosed either by Endoscopic Ultrasound (EUS) or Magnetic Resonance (MRI)

DISCUSSION

As data on the prevalence of lesions diagnosed during surveillance programs in individuals at high risk of PDAC are scanty and heterogeneous, we conducted a meta-analysis to estimate the pooled prevalence of solid and/or cystic lesions, and more important, whether detected lesions could be considered a successful target of surveillance. We also calculated the pooled estimated rate of detected lesions during the course of subsequent surveillance rounds, the prevalence of lesions diagnosed by either EUS or MRI, and the differential prevalence of lesions among the various HRI subgroups. Data from 1588 enrolled HRIs were included. The pooled prevalence of solid and cystic lesions in these individuals was 5.8% and 20.2%, respectively (Figure 2). The pooled prevalence of lesions considered a successful target of surveillance according to the CAPS definition was 3.3% (Figure 3), while the actual pooled prevalence of ‘‘preneoplastic’’ target lesions (advanced IPMNs and PanIN3 lesions) was 1.6% (see Supplementary Figure 1). The pooled estimated rate of lesions considered a successful target of surveillance during follow-up amounted to five cases per 1000 pyrs, equal to an annual risk of 0.5% (Figure 4). EUS seemed able to diagnose more solid lesions and MRI more cystic ones (Figure 5). Moreover, the rate of lesions considered a successful target of surveillance was much lower in FPC compared to HRI with specific syndromes (Figure 6). This is not surprising as in FPC the causal mutation is unknown despite a clear autosomal dominant inheritance pattern. Therefore, half of FPC individuals undergo surveillance without carrying the causal mutation. Of the 1588 screened HRIs, 6.8% underwent surgery, with histologically confirmed lesions considered a successful target of surveillance in 3.3%. To date, there is little consensus about which lesions detected by surveillance represent an indication for surgery [4]considering the morbidity of pancreatic surgery[27] It is

unknown whether for example in the case of BDIPMNs the same criteria for resection apply in HRIs compared to sporadic cases[28]. A recent study showed that cystic lesions diagnosed in HRIs with a known mutation are more prone to progress compared to those discovered in FPC individuals, although this latter group had a significantly higher prevalence of cystic lesions.29 There is also evidence of a high rate of lymph node involvement and poor prognosis in HRIs with PDAC even with very small lesions [9,18] This might justify a more aggressive attitude toward resecting precursor lesions in this setting. A proportion of patients diagnosed with PDAC (n ¼ 9, pooled prevalence 1%) were identified at an advanced/metastatic stage. Two of them were prevalent cases diagnosed at baseline. The other patients who underwent surgical resection with positive resection margins, or who were diagnosed with an unresectable interval cancer during subsequent follow-up, however, should be considered a failure of surveillance. The proportion of unresectable PDAC was similar in people with FPC, FAMMM, and HBOC. This raises concerns about the validity of currently performed surveillance programs. In four cases the resected lesions were pNENs, only one [2] with diameter >1.5 cm. The European Neuroendocrine Tumours Society guidelines[30] would not recommend surgery for incidentally detected pNENs.

Few studies compared the diagnostic yield of EUS and MRI/magnetic resonance cholangiopancreatography. A high concordance between the two methods was described by Canto et al.[6] while only a 55% agreement was shown by Harinck et al.[7] for the detection of clinically relevant lesions. In the present study, the pooled prevalence of solid lesions detected by EUS was higher compared to MRI (5.2% vs 4.1%), while MRI had a higher yield for cystic lesions (22.4% vs 16.6%). The pooled prevalence of lesions considered a successful target of surveillance was similar for EUS and MRI. A limitation of this analysis is the high heterogeneity between studies in terms of MRI protocols, and the use of radial EUS in some studies, while linear EUS is able to

detect more pancreatic lesions in HRIs [31] The two methods might be considered complementary rather than interchangeable in surveillance programs[7]and their use should be tailored considering local expertise. The yield of surveillance programs in different HRI subgroups is another interesting subject. The pooled prevalence of lesions considered a successful target of surveillance in the present meta-analysis was 3% in FPC individuals, representing the majority of people screened, 4% in HP, 5% in FAMMM, 6.3% in HBOC, BRCA1/2, or PALB2 mutations carriers, and 12.2% in PJS. Notably, while the results obtained in FPC showed a certain heterogeneity, this was not the case in patients with genetic syndromes. It would be attractive to tailor surveillance in terms of age at which to start, modality, and follow-up intervals based on the frequency and growth characteristics of the lesions diagnosed in each HRI subgroup. Vasen et al.[15] recently reported that IPMNs with high-grade dysplasia and multifocal PanINs3 were more frequent in FPC compared to FAMMM patients, while the rate of diagnosed PDAC was higher in this latter group. Further studies into the differential risk and growth characteristics of the various subgroups of HRIs are needed. This is the first study to systematically appraise the available literature evidence from surveillance studies in HRIs for developing PDAC. Although we developed a priori hypotheses for sensitivity analyses considering likely sources of heterogeneity, the observed heterogeneity between studies reflecting differences in surveillance tests, intervals, type of reported lesions, and kind of HRIs enrolled is a potential limitation. The lack of individual patient data limited the possibility of performing any analysis other than that of aggregate data, and the influence of factors such as the age of the individuals enrolled in the surveillance programs, and the relevance of risk factors such as smoking, could not be appropriately considered. In conclusion, the pooled prevalence rate of resected lesions that can be considered a successful target of surveillance during PDAC surveillance programs in HRIs is 3.3% with an annual risk of 0.5%.

The pooled prevalence rate of successful ‘‘premalignant’’ target lesions is, however, lower and equal to only 1.6%. A higher prevalence rate was observed in HRI carriers with a specific DNA mutation compared to HRIs with FPC in whom the mutation is unknown.

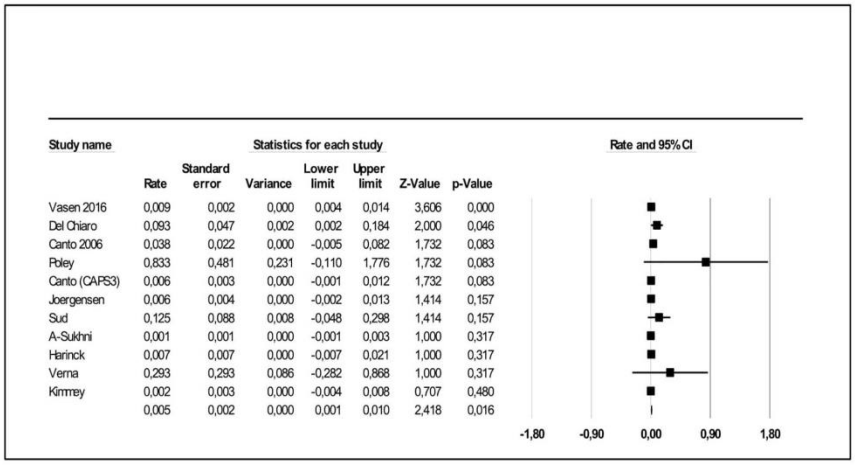
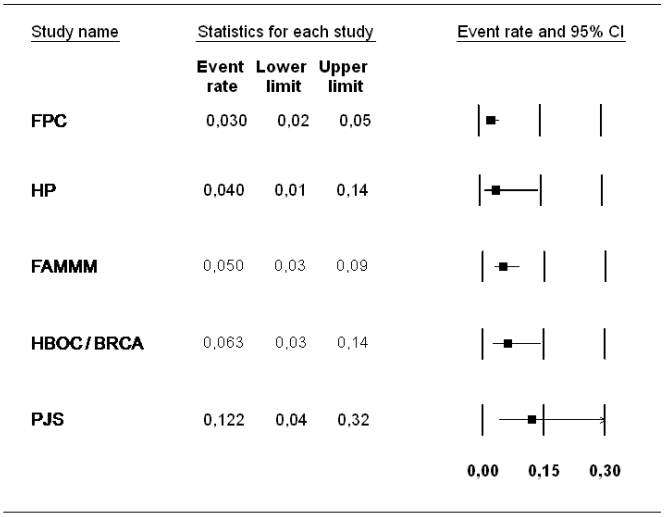


Figure 5. Forest plot showing the pooled estimate rate of successful target lesions of the surveillance in the 11 studies that reported the follow-up length. The pooled estimate rate resulted of 5/1000 person years with moderate heterogeneity (I^2=56%).

Figure 6. Pooled prevalence of lesions considered a successful target of surveillance in the different high risk individuals subgroups. The pooled prevalence of lesions considerable a successful target of surveillance diagnosed in familial pancreatic cancer (FPC) was 3 % (95% CI 2%–5%) with moderate heterogeneity (I2=22.2%). The pooled prevalence in familial atypical multi mole melanoma syndrome (FAMMM) was 5% (95% CI 3%–9%), in hereditary pancreatitis (HP) was 4 % (CI 1%–14%), in hereditary breast-ovarian cancer syndrome (HBOC) or BRCA1/BRCA2 or PALB2 mutation carriers was 6.3% (95% CI 3%–14%), and in Peutz–Jeghers syndrome (PJS) it was 12.2% (95% CI 4%–32%). Notably, in all these genetic syndromes but HP, there was no heterogeneity (I2 equal to 0%).



Appendix 1: Search strategy

(Neoplasm, Pancreatic OR Pancreatic Neoplasm OR Neoplasms, Pancreas OR Pancreas Neoplasm OR Neoplasms, Pancreatic OR Cancer of Pancreas OR Pancreas Cancers OR Pancreas Cancer OR Cancer, Pancreas OR Cancers, Pancreas OR Pancreatic Cancer OR Cancer, Pancreatic OR Cancers, Pancreatic OR Pancreatic Cancers OR Cancer of the Pancreas)
AND (Cancer Early Detection OR Cancer Screening OR Screening, Cancer OR Cancer Screening Tests OR Cancer Screening Test OR Screening Test, Cancer OR Screening Tests, Cancer OR Test, Cancer Screening OR Tests, Cancer Screening OR Early Diagnosis of Cancer OR Cancer Early Diagnosis)
AND (High Risk OR High-Risk individuals OR High-Risk patients OR High-Risk cohort OR High-Risk population OR FPC OR familial pancreatic cancer OR inherited pancreatic cancer OR HBOC OR hereditary breast and ovarian cancer syndrome OR BRCA OR FAMMM OR familial atypical multiple mole melanoma OR PJS OR Peutz–Jeghers syndrome OR HNPCC OR hereditary nonpolyposis colorectal cancer OR PALB OR mismatch repair gene mutation OR Genetic Susceptibility OR Genetic Susceptibilities OR Susceptibilities, Genetic OR Susceptibility, Genetic OR Genetic Predisposition OR Genetic Predispositions OR Predispositions, Genetic OR Predisposition, Genetic)

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3. RESULTS OF FIRST-ROUND OF SURVEILLANCE IN INDIVIDUALS AT HIGH-RISK OF PANCREATIC CANCER FROM THE AISP (ITALIAN ASSOCIATION FOR THE STUDY OF THE PANCREAS) REGISTRY

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Study highlights:

› WHAT IS CURRENT KNOWLEDGE

- Pancreatic cancer surveillance programs may detect malignant and pre-malignant lesions in high-risk individuals.
- Two groups of HRIs can be identified, one with a familial predisposition and one with a known genetic frailty.

› WHAT ARE THE NEW FINDINGS?

- After the first-round of screening of the Italian registry the rate of malignancies was 2.6%.
- Some risk factors for the detection of pre-malignant or malignant lesions were found.

Abstract

Introduction: Surveillance programs on high-risk individuals (HRIs) can detect premalignant lesions or early pancreatic cancer (PC). We report the results of the first screening round of the Italian multicenter program supported by the Italian Association for the study of the Pancreas (AISP).

Methods: The multicenter surveillance program included asymptomatic HRIs with familial (FPC) or genetic frailty (GS: BRCA1/2, p16/CDKN2A, STK11/LKB1 and PRSS1) predisposition to PC. The surveillance program included at least an annual magnetic resonance cholangiopancreatography (MRCP). Endoscopic ultrasound (EUS) was proposed to patients who refused or could not be submitted to MRCP.

Results: One-hundreds eighty-seven HRIs underwent a first-round screening examination with MRCP (174;93.1%) or EUS (13;6.9%) from September 2015 to March 2018.The mean age was 51 years (range 21-80).One-hundreds sixty-five (88.2%) FPC and 22 (11.8%) GF HRIs were included. MRCP detected 27 (21.9%) presumed branch-duct intraductal papillary mucinous neoplasms (IPMN), 1 invasive carcinoma/IPMN and one low-grade mixed-type IPMN, respectively. EUS detected 4 PC (2.1%): 1 was resected, 1 was found locally advanced intraoperatively and 2 were metastatic. Age>50 (OR 3.3, 95%CI 1.4-8), smoking habit (OR 2.8, 95%CI 1.1-7.5), and having >2 relatives with PC (OR 2.7, 95%CI 1.1-6.4) were independently associated with detection of pre-malignant and malignant lesions. The diagnostic yield for MRCP/EUS was 20.3% for cystic lesions. The overall rate of surgery was 2.6% with nil mortality.

Discussion: The rate of malignancies found in this cohort was high (2.6%). According to the International Cancer of the Pancreas Screening Consortium the screening goal achievement was high (1%).

INTRODUCTION

Pancreatic ductal adenocarcinoma (PC) is one of the deadliest solid tumors. It is predicted to become the second cause of tumor-related death by 2030[1]. Surgical resection is the only potential cure and it is possible in less than 20% of patients at the time of diagnosis[50]. PC is usually asymptomatic until the disease has spread outside the gland, causing jaundice or abdominal and back pain. However, similarly to other solid tumors, even PC has precursor lesions, namely pancreatic intraepithelial neoplasia (PanIN), and intraductal papillary mucinous neoplasms (IPMN)[14, 51].

Considering the wide window of opportunity to detect PC at its earlier stages[52] and the low incidence of this tumor (6.3-7.3 per 100,000 people in Europe)[53], it might seem reasonable and advantageous to focus diagnostic efforts to identify precursor lesions or early PC on a selected population of high-risk individuals (HRIs). Population screening is not recommended.

In 2013, the International Cancer of the Pancreas Screening (CAPS) Consortium established that PC screening should be recommended only for HRIs with a lifetime risk of PC greater than 5% or a fivefold increased relative risk, as this would eventually lead to a better prognosis [9].

Guidelines for screening define two groups of HRIs: a) individuals with a defined genetic syndrome (e.g. Hereditary breast and ovarian cancer syndrome, familial atypical multiple mole-melanoma (FAMMM) syndrome, Peutz-Jeghers Syndrome, *PRSS-1* related hereditary pancreatitis, Lynch syndrome) or genetic mutations (*PALB2* gene mutations); b) individuals without a diagnosed syndrome but with familiar pancreatic cancer (FPC)[54]. According to the CAPS Consortium, the goal of a PC surveillance program should be the identification of early (pT1N0M0R0) PC, or advanced precursor lesions such as PanIN3 or high-grade IPMN[9]. However, an internationally standardized protocol for PC surveillance is not available yet, as the

current evidence is based on single- or multi-centric experiences with heterogeneous policies in terms of inclusion criteria, diagnostic methods and frequency of screening being adopted[55, 56]. Three recent meta-analyses reported that the probability of reaching the screening goal is satisfactory[55-57], thus reinforcing the rationale in the pursuit of the early diagnosis of PC.

In 2010, the Italian Association for the Study of the Pancreas (AISP) developed a position paper for the surveillance at high-risk of PC, including both HRI with familial and genetic predisposition[8]. In 2015, an official registry of asymptomatic HRI was created following these guidelines. This manuscript reports the results of the first-round of screening.

METHODS

Definition of Individuals at high risk and surveillance protocol

In 2015, six Italian high-volume centers started the enrollment of HRIs according to the Italian Guidelines (Table 1)[8]. Criteria for entry into the registry as an HRI include being defined as FPC if having: ≥ 3 relatives affected by PC until the third degree of kinship (TDR) or 2 relatives affected if at least one being a first degree relative (FDR); having a known genetic mutation of BRCA 1, BRCA2 or p16/CDKN2a genes with at least a FDR or a second degree relative (SDR) affected by PC; a previous diagnosis of hereditary pancreatitis or Peutz-Jeghers Syndrome (PJS). Whenever possible, the diagnosis of pancreatic cancer in affected relatives had to be verified through medical records evaluation. Demographic, clinical and anamnestic data were prospectively collected by each center involved. HRIs aged > 18 could enter the surveillance registry after having signed a proper informed consent.

Each enrolled subject received an outpatient visit and was offered a baseline MRI with 1.5 T to 3.0 T Cholangio-Wirsung-MRI (MRCP). MRI with MRCP was chosen as a baseline diagnostic method because of no radiation risks, low complication rates and high sensitivity[58-

60]. In case of a normal MRCP the subjects were planned to receive annual MRI for 5 years. Identified lesions were classified as solid or cystic with or without connection to pancreatic ducts. Patients who refused or could not be investigated by means of MRCP were offered endoscopic ultrasound (EUS) as first screening tool. EUS was also proposed to patients with alterations at baseline MRI, according to the local practice at each center. Any indication for surgery was center-based after a multidisciplinary board meeting. Each center received the local ethics committee approval and enrolled subjects signed a proper informed consent. The registry is currently promoted through word of mouth, social networks, YouTube channels, the websites of the individual Institutions, as well as the website of the AISP (http://www.aisponline.it). The potential HRIs contact the involved centers spontaneously or they are referred by the general practitioner or other medical doctors. A genetic testing is not part of the protocol, but can be advised at each Centre based on clinical judgment.

Recorded Variables

The surveillance registry data include age, gender, category of risk (FPC or defined GS), total number of relatives with PC and degree of kinship, age of the youngest relative with PC, smoking and alcohol history, personal medical and oncological history, presence of diabetes and time of its diagnosis.

Statistical analysis

The chi-squared test was performed to test for differences of categorical parameters between subgroups, and t-test for continuous variables. A multivariate logistic regression analysis was performed to identify any risk factor associated with MRCP/EUS detection of pre-malignant or malignant lesion.

RESULTS

Population characteristics

Between September 2015 and March 2018, 245 eligible subjects were offered to enter the registry and accepted, and through March 2018, 187 subjects (76.3%) completed the first round of screening and represent the study population described in the present manuscript. According to the risk categories, FPC and "genetic syndrome" (GS) cases were 165 (88.2%) and 22 (11.8%), respectively. **Table 1** shows the composition of the risk categories as well as their demographics. The population of HRIs included 100 women and 87 men. Mean age was 52±12. The mean number of affected relatives was 2 (range 1-5). Fifty-two (27.8%) HRIs had ≥2 FDR affected and the mean age of the youngest affected relative was 61 (range 28-79). Twenty-five HRIs (13.3%) reported a personal history of previous neoplasms, mostly gynecological cancers. MRCP and EUS were used as initial screening methods in 174 (93.1%) and 13 (6.9%) HRIs. Nine HRIs (4.8%) received EUS as supplementary investigation after MRCP. Of note, the reliability of reported family history of pancreatic cancer was verified in 120 out of 187 HRIs (64.1%) through evaluation of charts or other original documents of affected family members.

MRCP findings and risk categories

Figure 1 depicts the flow chart of screening results. Overall, 44 (25.3%) HRIs had an abnormal finding at MRCP, with pancreatic cystic lesions being the most frequently diagnosed abnormality (n=42, 24.1%). At MRCP the presumed radiological diagnosis of these cysts was mostly branch-duct IPMN (BD-IPMN) (n=27, 61.3% of the cysts detected and 21.9% of the cohort of HRI submitted to MRCP), 14 (51.9%) were multifocal. The mean diameter was 9 mm (range 3-25). Two (1.3%) HRI received a diagnosis of a suspected solid pancreatic mass, which was not further confirmed at EUS. One subject received a diagnosis of mixed-type (M)-IPMN, that was found to

be a BD-IPMN at EUS. One subject with PJS received a diagnosis of malignant main-duct (MD)-IPMN, which was confirmed by EUS with fine-needle aspiration (FNA), and one FPC subject was diagnosed with a M-IPMN, further confirmed by EUS. Surgery revealed an invasive carcinoma/IPMN and a low-grade M-IPMN, respectively in these two cases. No complications related to MRCP were reported. The diagnosis rate of MRCP for pre-malignant (IPMNs) or malignant lesions was 17.2% and 0.6%, respectively. BD-IPMNs and undefined cysts are currently enrolled in Institution-specific follow-up programs for pancreatic cystic neoplasms. The diagnosis rate of MRCP for cystic lesion was 24.1%.

EUS findings

The flow-chart of **Figure 1** reports EUS findings. Thirteen (6.9%) HRIs received EUS as first-line investigation. EUS detected 4 PC (30.8%) (all confirmed by FNA), 1 (7.7%) undefined cyst, 2 (15.4%) EUS features of chronic pancreatitis and one solid pseudopapillary tumor (7.7%). The examination was normal in 5 cases (38.5%). Two tumors were deemed amenable to surgery, the remaining two being metastatic cases that were treated with chemotherapy. In 9 further cases EUS was performed as supplementary diagnostic tool after MRCP, due to suspicious findings. In such cases, EUS confirmed 6 MRCP findings and deemed insignificant 2 suspected solid lesions and 1 suspected M-IPMN found at MRCP, that revealed to be fibrotic areas and a BD-IPMN, respectively. No complications related to EUS were reported. The 2 undefined cysts are currently enrolled in Institution-specific follow-up programs for cystic pancreatic neoplasms.

Risk categories and MRCP/EUS findings

Table 2 reports the MRCP/EUS findings of the cohort, comparing the results obtained in the groups of FPC and GS cases. When comparing the FPC and GS HRIs, there was no difference either in the rate of abnormalities and malignancies detected (27.9% vs 27.3% and 2.5% vs 4.5%,

Fisher's exact p=1 and p=0.469, respectively). No malignant lesions were diagnosed in the BRCA1/2 HRIs subgroup.

Surgery and pathology

After multidisciplinary consultation, surgery was offered to 5 subjects (2.6%). Two total pancreatectomies and 2 distal pancreatectomies with splenectomy were performed. One further PC case deemed resectable was found locally advanced intraoperatively and a bypass surgery was performed. Pathology revealed an invasive carcinoma/IPMN, 1 PC (T1N0M0R0), a pseudopapillary tumor and a low-grade panglandular M-IPMN. No postoperative complications were reported. Considering the CAPS guidelines[9], the diagnostic yield of the present study for success of surveillance with diagnosis of target lesions was 1%. The 90-day postoperative mortality was nil.

Risk factors associated with diagnosis of pre-malignant or malignant lesion

A binary logistic regression analysis was performed with the diagnosis of pre-malignant or malignant lesion as dependent variable (yes/no), to ascertain the effects of age (≤> 50 years), gender, alcohol and smoking habit, number of relatives affected (≤/> 2), number of FDR affected (≤/> 1), previous history of any malignancy (yes/no), medical certification of relatives suffering from PC (yes/no), familial or genetic predisposition. At the multivariate analysis, age > 50 years (OR 3.3, 95%CI 1.4-8), smoking habit (OR 2.8, 95%CI 1.1-7.5) and having >2 relatives with PC (OR 2.7, 95%CI 1.1-6.4) were independent factors associated with the diagnosis of pre-malignant and malignant lesions at MRCP/EUS (Table 3). **Table 4** depicts the detailed individual features of HRIs who received a diagnosis of malignancy.

Follow-up

At the time this manuscript was written 2 out of 5 patients that received a malignant diagnosis were alive (mean follow-up 6.2 months, range 2-12). The two patients submitted to surgery were alive and free of recurrence after a median follow-up of 6.5 months. Of the remaining three patients who were diagnosed with an advanced disease, two died after a median follow-up of 7 months from the diagnosis; one patient died due to cardiovascular disease.

DISCUSSION

This is the first report of the Italian multicenter study on HRIs submitted to surveillance. After the first round of screening (n=53, 28.3%) of subjects were diagnosed with a MRCP/EUS abnormality. Five malignant lesions were detected (2.6%); an unexpectedly high number of PC were identified by EUS (n=4, 2.1% overall), whereas MRCP identified only 1 invasive carcinoma/IPMN (0.6%). Of note, the category of HRIs that reported the greatest number of MRCP/EUS abnormalities was the one made of FPC subjects, however, the small sample size of the non-FPC subcohort does not allow us to make further speculations regarding this difference.

The diagnostic yield for MRCP/EUS was 23.5% for cystic lesions. The great majority of the detected cysts were BD-IPMN (n=28, 60.8% of the cysts detected, 14.9% of the whole cohort). This finding is not surprising, as these lesions are frequent incidental findings in the general population, given the wide use of cross-sectional imaging, and it is debatable whether they should be considered a positive result of the screening process or not. This prevalence is in line with data already reported in a metanalysis by Signoretti et al. in 2018, where the pooled prevalence of cystic lesions in HRI enrolled in surveillance program was around 20%[55].

The rate of malignancies detected (2.6%) in our cohort is one of the highest reported so far [55-57, 61]. Notably, all but one malignancy was detected by EUS. As only 4.8% of probands was

submitted to both MRCP and EUS, it is not possible to speculate about any possible difference in the detection rate of solid or cystic abnormalities with the two techniques. Current literature suggest that the two techniques are complementary with MRCP being able to detect more easily any cystic lesion, whereas EUS is likely more sensitive in the detection of solid ones[55, 62]. Two out of the five (40%) cancers diagnosed in the screening asymptomatic subjects were at a metastatic stage, and one was locally advanced. This rate is higher than in previous reports[55, 56], however this finding is consistent with a calculated pooled prevalence of 1%[55], and it cannot be considered a failure of a surveillance policy as the present results regard fist-screening round only. On the other hand, in the two PC cases who received radical surgery, pathology revealed pT1 disease, thus potentially suggesting that surveillance led to early diagnosis with improved survival. Globally, there were no unnecessary surgical procedures being performed for benign lesions in this series, as the other resections were due to a M-IPMN and a solid pseudopapillary tumor, for whom surgery is the treatment of choice.

Personalization of the surveillance strategy is a key issue in screening protocols for pancreatic cancer. We therefore investigated factors that were associated with an increased risk of diagnosis of pancreatic abnormalities. HRIs aged > 50 years, ever smokers, and subjects with >2 relatives with PC had a significantly increased risk of having a diagnosed pre-malignant or malignant lesion. Previous studies partially explored the association between such factors and the detection of a worrisome abnormality [23, 43, 63]. However, those studies were retrospective and more prone to bias or lack of information, and these three factors were not reported as independently associated with risk of significant abnormalities at a multivariate analysis before. Despite the design of this registry regarding each center discretion on the use of MRCP or EUS as a screening tool based

also on patients' preference, it likely that in such a subgroup of HRIs the combined use of both MRCP and EUS, or their alternate use, possibly at shorter intervals, might be appropriate.

Some limitations, however, should be considered. First, although MRI with MRCP was the first-line examination in most cases, some subjects were investigated by EUS first, due to personal preferences. However, the results obtained by the two diagnostic tools are pooled in the present analysis to reflect the actual rate of significant findings in the whole cohort. Secondly, a quote of the diagnosed small pancreatic lesions considered BD-IPMN at MRCP might be other cystic lesions, despite experienced radiologists have been involved. The present protocol, indeed, did not include the need to perform EUS in all cases of cystic lesions, but this was done in some instances, similarly to what is considered common practice in sporadic cystic lesions. Finally, in our logistic regression analysis we considered as outcome variable the diagnosis of any malignant or pre-malignant pancreatic lesion, including BD-IPMN and not malignant lesions only. This was done due to the relatively low rate of malignant lesions which would not permit a meaningful analysis. Third, compared to current literature[55, 56], our registry differed on the age to initiate the surveillance and this might have been responsible for differences in the detection rate of pre-malignant or malignant lesions. However, the mean age of our cohort is in line with the one other studies[55, 56], giving more strength to the finding that HRI > 50 years are at higher risk to be diagnosed with a worrisome lesion.

Some of the limitations reported might have been addressed by building a proper surveillance program, based on MRCP and EUS imaging, genetic testing and shared among the Institutions involved. The form of the registry, with a high level of center discretion in the diagnostic pathway to follow, had been chosen since no dedicated funds were available and each center draws from personal resources and facilities.

In conclusion, the first-round screening results in Italy report a high rate of pancreatic malignancies (n=5, 2.6%), mostly being advanced at baseline (60%). We identified factors associated with an increased risk of diagnosis of malignant or pre-malignant pancreatic lesions in HRIs (age > 50, smoking habit and > 2 relatives diagnosed with PC). Whether these data will also reflect an increased risk of developing de novo lesions or of progression of initial finding needs to be investigated during the following screening rounds that are planned for a duration of at least five years, with a planned end of enrollment in 2020.

Tables

Table 1. Detail and demographics of HRIs enrolled. Data are expressed as number (%) or as mean (±SD).

Characteristics of asymptomatic HRI who were enrolled in the registry	**n**
FPC	165 (88.2)
HBOC (BRCA1)	5 (2.7)
HBOC (BRCA2)	5 (2.7)
FAMMM (p16/CDKN2A)	3 (2.7)
Peutz-Jegher syndrome (STK11/LKB1)	5 (1.6)
Hereditary pancreatitis (PRSS1)	4 (2.1)

Variable	**All patients (n=187)**	**FPC (n=165)**	**GS (n=22)**	**p-value**
Age, mean (SD)	51±12	51±12	47±11	n.s.
Female, gender	100 (53.4)	67 (54.5)	33 (51.5)	n.s.
Ever smokers/current smokers*	28 (15)	24 (14.5)	4 (18.1)	n.s.
Any regular alcohol intake	16 (8.5)	12 (7.2)	4 (18.1)	n.s.
AYR with PC, median (IQR)	61±10	60±11	66±8	n.s.
Personal history of malignancies, n (%)	25 (13.3)	19 (11.5)	6 (24)	n.s.
HRI with 1 FDR affected	120 (64.2)	110 (66.7)	11 (50)	n.s.
HRI with ≥ 2 FDR affected	53 (28.3)	53 (32.1)	-	<0.05
HRI with family history of malignancies	118 (63.1)	101 (61.1)	17 (77.3)	n.s
Number of relatives affected, median	1	1	1	

HRI: high-risk individual; FPC: familial pancreatic cancer; HBOC: Hereditary breast–ovarian cancer syndrome; FAMMM: Familial Atypical Multiple Mole Melanoma; GS: genetic syndrome; AYR: age of the youngest relative; FDR: first-degree relative.
*: Ever smoker is a person who has smoked 100 cigarettes or more in his/her lifetime.

Table 2. MRCP/EUS findings per categories (p=n.s.). Data are expressed as number.

	Category of risk	
Screening results	**FPC (n=165)**	**GS (n=22)**
Abnormalities	46 (27.9)	6 (27.2)
- PC	4 (2.4)	1 (4.5)
- BD-IPMN	26 (15.7)	1 (4.5)
- Undefined cystic lesions	7 (4.2)	1 (4.5)
- Suspected solid lesions	2 (1.2)	-
- Features of CP	5 (30.3)	2 (18.1)
- M-IPMN	1 (0.6)	-
- Degenerated IPMN	-	1 (4.5)

FPC: familial pancreatic cancer; GS: genetic syndrome; PC: Pancreatic ductal adenocarcinoma BD-IPMN: branch-duct intraductal papillary mucinous neoplasm; CP: chronic pancreatitis; M-IPMN: mixed-type intraductal papillary mucinous neoplasm.

Table 3.. Binary logistic regression analysis for risk factors associated with the diagnosis of a pre-malignant or malignant lesion at MRCP/EUS.

Variable	***Univariate Analysis (OR; 95% CI)***	***p* Value**	***Multivariate Analysis (OR; 95% CI)***	***p* Value**
Male Sex	(1; 0.4-1.1)	0.946		
Age > 50 years	(4.1; 1.7-9.6)	0.001*	OR 3.3, 1.4-8	0.008*
Ever Smoking	(4.6; 1.9-11.1)	0.001*	OR 2.8, 1.1-7.5	0.032*
Alcohol Drinker	(1; 0.2-3.8)	0.951		
Number of relatives affected > 2	(3.6; 1.6-8.1)	0.001*	OR 2.7, 1.1-6.4	0.026*
Number of FDR affected > 1	(1; 0.4-2.3)	0.967		
Previous history of any malignancy	(1; 0.8-1.2)	0.287		
Diagnosis of a defined GS	(0.4; 0.1-1.8)	0.253		
Verified certification of affected family members	(1; 0.4-2.3)	0.954		

FDR: first-degree relative; GS: genetic syndrome.

Table 4. Features of High Risk Individuals who received a diagnosis of malignancy.

Patient	**Category of risk**	**Location**	**Size (mm)**	**Pathology-Stage[64]**	**Treatment**	**F-up**	**F-up (mo)**
1	PJS	Body	20	iCa/IPMN (pT1N0M0R0) Stage 1A	DPS	Alive, FoR	11
2	FPC	Body	25	Stage IV	Chemotherapy	Deceased*	2
3	FPC	Head	40	cT4N1M0, Stage III	By-pass surgery	Deceased	2
4	FPC	Head	30	pT1N0M0R0, Stage 1A	TP	Alive, FoR	4
5	FPC	Head-Body	70	Stage IV	Chemotherapy	Deceased	12

PJS; Peutz-Jeghers syndrome; iCa: invasive carcinoma; DPS: distal pancreatectomy with splenectomy; FoR: free of recurrence; FPC: familial pancreatic cancer; PC: pancreatic ductal adenocarcinoma; LAPC: locally advanced pancreatic cancer; TP: total pancreatectomy; PD: pancreaticoduodenectomy. *due to cardiovascular problems.

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4. THE RATE OF PANCREATIC ABNORMALITIES DETECTED BY MAGNETIC RESONANCE IN HIGH RISK INDIVIDUALS UNDER SURVEILLANCE FOR THE RISK OF PANCREATIC CANCER IS NOT DIFFERENT FROM THAT OF CONTROLS.

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ABSTRACT

Background and Aims: Different pancreatic abnormalities (e.g. chronic pancreatitis like features, cystic lesions, solid lesions) have been reported in in high-risk individuals (HRIs) with "familiar pancreatic cancer" (FPC) and specific syndromes undergoing surveillance protocols for pancreatic ductal adenocarcinoma (PDAC). Previous studies compared pancreatic parenchymal alterations detected by endoscopic ultrasonography (EUS) in HRIs to those seen in controls reporting that abnormal changes occur more frequently in HRIs than in controls. However, while magnetic resonance imaging (MRI) with Magnetic Resonance Cholangiopancreatography (MRCP) is the most frequently employed method for HRI surveillance, no studies compared the rate of abnormal pancreatic finding in HRIs investigated by MRI/MRCP to those seen in controls. We therefore conducted a case-control study enrolling HRIs who underwent surveillance with MRI/MRCP and controls without pancreatic disorders to compare the rate and type of pancreatic abnormalities.

Methods: A single-centre case control study was conducted. Cases were HRIs meeting the CAPS criteria who underwent surveillance for the risk of pancreatic cancer and controls were consecutive patients undergoing MRI/MRCP for benign biliary disease without history of pancreatic disorders.

The rate of pancreatic findings was compared with Fisher extact test and logistic regression analysis was performed to examine factors associated with pancreatic findings.

Results: 28 HRIs and 26 controls were included in the study. HRIs were subjects belonging to FPC families (70%), Peutz-Jeghers syndrome (14%), familial atypical multiple mole melanoma syndrome (7%) , BRCA1/2 mutation carriers (7%) . Cases and controls did not differ in terms of sex distribution and age (male 50% vs 53.6, p=0.5; mean age 55.6 vs 59.6 years p = 0.1). The overall rate of any pancreatic abnormality was similar between cases and controls (64.3% vs 53.8%; p=0.58) and parenchymal atrophy was the most common abnormal finding (32% vs 38%, p= 0.8). Branch-duct IPMNs were diagnosed in 25% of cases and 23% of controls (p= 1)(mean diameter 6.4 vs 5 mm respectively). Notably, however, at the first year of follow-up two further HRIs were diagnosed with IPMNs, bringing this rate to 32%.

Conclusion: The rate of pancreatic changes observed in HRIs at the first round of surveillance with MRI/MRCP does not differ from that of controls. Most abnormalities do not have clinical significance, the most common being parenchymal atrophy and small BD-IPMNs without worrisome features. These results differ from those previously reported regarding EUS, possibly suggesting that EUS might diagnose more frequently subtle pancreatic changes as compared to MRI in HRIs.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer-related death in western countries. Due to the biological aggressiveness, the poor response to medical treatment and delayed diagnosis[1], PDAC is predicted to become second killers in the United States by 2030 also because of the decreasing of cancer-related deaths for colorectal and breast cancer [2]. For colorectal and breast cancer indeed specific screening programs are nowadays available while such approach seems to be not cost effective for PDAC considering the relatively low lifetime risk of developing a sporadic PDAC (close to 1%). The International Cancer of the Pancreas Screening (CAPS) Consortium [3] in 2013 has defined selection criteria for surveillance of subjects with "familial pancreatic cancer" (FPC) or with hereditary syndromes of which the risk of developing PDAC is more than 5-fold greater compared to the general population called high-risk individuals (HRIs). Because of the limited data regarding the accuracy of the screening tests used and the interpretations of the test's findings for clinical decisions (surgical treatment/ follow-up) [4] screening for PDAC in HRIs should take place preferably in high-volume center as a research protocols with a multidisciplinary team [3]. Data on the prevalence of pancreatic abnormalities diagnosed during screening and the lesions considered a successful target that are small resectable PDAC, intraductal papillary mucinous neoplasms (IPMNs) with high-grade dysplasia and advanced pancreatic intraepithelial neoplasia (PanIN3) are heterogeneous. The screening methods include endoscopic ultrasonography (EUS) and/or magnetic resonance imaging (MRI) with the first one able to diagnose more solid mass and MRI more cystic lesions [5]. Cystic lesions are diagnosed in around 20 % during screening HRIs and they are more often discovered in FPC families compared to genetic syndromes [6] . If the risk of developing PDAC from a cancerized cyst (IPMN) as well as if the association between IPMNs and synchronous PDAC (already

described in the general population) is more elevated in HRIs is still debated [7]. PanINs lesions are also frequent findings in pancreatic parenchyma of HRIs who underwent to surgery and more common detected in HRIs with PDAC compared to sporadic pancreatic cancer [8, 9]. They are microscopic lesions (<0.5 cm) with different grade of dysplasia. In HRIs, some data suggest that PanINs and IPMN are associated to chronic pancreatitis-like parenchymal changes that could be visualized as ectasia/irregularity of the pancreatic ducts and/or parenchyma heterogeneity despite they cannot be reliably distinguish from non-neoplastic alterations [10]. Signs of Chronic pancreatitis (CP) were observed in more than 50% of HRIs screened with endoscopic ultrasonography (EUS), although only in 7% those features where consistent with CP according to Rosemont criteria [11 e 12].

Few studies compared pancreatic parenchymal alterations in HRIs to controls by using EUS reporting that abnormal changes occur more often in HRIs than controls. [6, 13]. Canto et al. in 2006 [6] have found more CP changes (60% vs 15% and) in HRIS comparing with controls as well as Mizrahi at al. in the setting of BRCA2 carriers (13 % vs 1 %) [13]. In a recent study ,Thiruvengadam et al.[14] found CP features in 18% of HRIs compared to 2 % in controls ($p< 0.01$) with a significance maintained also after adjusted for confounder factors (such as smoking and drinking habits). Same results were observed for cystic lesions with HRIs more prone to have any kind of cysts compared to control ($p< 0.01$). No one of the above mentioned study categorized the type of cystic lesion detected so that the exact number of precancerous cystic lesions (IPMN) described in HRIs compared to controls is not explicit probably to the lower sensitivity of EUS compare to MRCP to describe a connection between the cyst and the ductal system [5] . Although MRI/MRCP is unable to detect signs of CP in the very early phase, it has showed instead very

sensitive for identifying the relation with the cyst and main pancreatic duct as well as whether the PCN is a single or multiple [15] .

We therefore conducted a case-control study between HRIs who underwent to surveillance with MRI with Magnetic resonance cholangiopancreatography (MRCP) and controls to evaluate and compare the rate of overall parenchymal changes and the presence and type of cystic lesions in both groups.

METHODS

Study design and population

This was a retrospective case–control study. Cases of HRIs were selected among those prospectively enrolled in a dedicated database. The inclusion criteria for the case group were subjects FPC if having: ≥ 3 relatives affected by PC until the third degree of kinship (TDR) or 2 relatives affected if at least one being a first degree relative (FDR); having a known genetic mutation of BRCA 1, BRCA2 or p16/CDKN2a genes or Hereditary nonpolyposis colorectal cancer (HNPCC) with at least a FDR or a second degree relative (SDR) affected by PC; a previous diagnosis of hereditary pancreatitis or Peutz-Jeghers Syndrome (PJS) . HRIs underwent to contrast-enhanced magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) at our Radiology Department. The control group consisted of inpatients admitted to the hospital, who underwent to MRI and MRCP for benign biliary indications such us cholecystitis or evaluation of CBD (e.g. stones, stricture) and pancreas-unrelated indications. Exclusion criteria for the control group were a previous diagnosis or familial history of pancreatic disorders or of gastrointestinal neoplasms. Data on alcohol, tobacco use, or BMI were not available for controls, who were not matched for such variables.

All patients gave written informed consent.

Nuclear magnetic resonance (MR).

MR examination was carried out with 1.5 Tesla equipment with a foursingle phased array coil positioned on the patient's upper abdomen. The MR protocol involved the use of T1-weighted gradient echo (GRE) sequences with in-phase and out-of-phase echotime, T1-weighted fatsuppressed GRE sequences, and T2- weighted halfFourier single-shot turbo spin-echo (HASTETSE). The dynamic study was performed during administration of 0.1 mmol/kg body weight of gadolinium chelates with a four-phase technique: precontrast, pancreatic phase (30–40 s), portal venous phase (80 s) and delayed phase (180 s). The dynamic study used a T1-weighted 3D GRE volumetric interpolated breath-hold examination (VIBE) sequence with chemically selective fat saturation in the axial plane. Magnetic resonance cholangiopancreatography (MRCP). MRCP was performed using a 2D single-slab rapid acquisition in coronal planes and a 3D HASTE sequence with respiratory triggering in a coronal oblique plane depending on the course of the main pancreatic duct as visualized on a 2D sequence acquired in the axial plane. The 3D HASTE source images were analysed and subsequently processed with thin Maximumintensity projection (MIP) algorithm and MPR. The MRI images were reviewed independently by two radiologists (I.M. and E.I.). A template was designed to record the parenchymal changes, ductal alteration and cyst morphology details according to standard radiological criteria.[16-17]. About the parenchymal changes of chronic pancreatitis, they include loss of normal high signal intensity of the pancreas on T1-weighted fat-suppressed image, decreased and heterogeneous enhancement of the pancreas in the arterial phase with progressive enhancement in delayed and atrophy. In addition, abnormalities of the pancreatic duct were recorded. A regards the presence of cystic lesions and cyst morphology details, each reader recorded the number, size and location of each cyst, 'worrisome features' (such as cyst of 3 cm, thickened enhanced cyst walls, non-enhanced

mural nodules, main pancreatic duct size of 5–9 mm, abrupt change in the main pancreatic duct with distal pancreatic atrophy and lymphadenopathy).

Statistics

Statistics Differences between HRIs and controls in terms of prevalence of Parenchymal Features of CP, Ductal alteration or pancreatic cyst were analyzed. The Fisher test was used for comparison of proportions for categorical variables and Student's t-test for continuous variables. Multiple logistic regression analysis was employed to investigate factors associated with the diagnosis of PCLs. Tests of statistical significance and confidence intervals were two-sided; a p value < 0.5 was considered statistically significant. Dedicated software (MedCalc, Mariakerke, Belgium) was used throughout the study.

RESULTS

Thirty-two HRIs fulfilled the defined inclusion criteria for enrolment in surveillance registry according to the study protocol. Between the HRIs the most common subgroups were subjects belonging to Familial Pancreatic Cancer (62.5%) with two family member affected by pancreatic cancer; four patients had a diagnosis of Peutz-Jeghers syndrome (12.5%), two HRIs had Familial Atypical Multiple Mole Melanoma syndrome while two were BRCA1/2 carriers (genes mutations in the Hereditary breast and ovarian cancer syndrome) (see **Table 1**).Three subjects were affected by hereditary chronic pancreatitis thus were excluded from the current study because of the presence of chronic pancreatitis features linked to the disease. One subject, with a diagnosis of Hereditary nonpolyposis colorectal cancer and one first degree relative affected by PDAC, decided to undergo EUS instead of MRI as a screening test. At the end 28 HRIs were enrolled and compared with 26 matched controls. Cases and controls did not differ in terms of sex distribution and age (in both

groups 14 were male, $p = 0.5$; mean age 55,6 and 59.6 years $p = 0.1$) (see **Table 2**). No one of the enrolled subjects had a radiological diagnosis of chronic pancreatitis. The overall prevalence of any pancreatic alterations was similar between the two groups (p= 0.58).

In particular, as regards parenchymal features of CP, parenchymal atrophy was the most common alteration point out from the MRI. It was observed equally between cases and controls (32.1% vs 38.5% , p= 0.8).

No decrease or loss of lobularity were observed. One HRIs presented a delayed enhancement of the pancreatic parenchyma while one control a decreased on contrast T1 signal intensity. The most common ductal alteration was the irregularity of the Wirsung duct due to the presence of a Kinking of the duct (5 cases and 3 controls; 17% vs 11.5%) or a diagnosis of pancreas divisum (2 cases and 1 control). No ductal dilation was detected (neither main pancreatic duct nor side branches).

All the cystic lesions discovered during the radiological tests had a presumptive diagnosis of side branches IPMNs. The prevalence SD-IPMNs was also not different between cases and controls (25% vs 23 %; P= 1). The maximum diameter of the cyst was 15 mm in HRIs and 11 mm in control group (mean diameter 6.4 vs 5 mm respectively). No one of the cystic lesions had worrisome features at MRI.

In order to investigate the factors associated with the pancreatic alteration observed (parenchymal atrophy and SD-IPMNs) , we performed a logistic regression analysis, demographic and clinical were considered as explanatory variables (see **Table 3**).

In the analysis, as expected, only the age at the time of the imaging procedure (OR = 1.25 per increasing year, 95% CI 1.02–1.03, $p = .002$) was associated with the presence of parenchymal atrophy (**Fig 1**). On the other hand, the diagnosis of IPMN was not associated with any of the considered variables (see **Table 4**).

Between the 28 HRIs enrolled, 13 subjects underwent to a follow-up examination after 12 months from the basal MRI as reported into the screening protocols.

Four of them had a diagnosis of presumptive SB-IPMN at the first surveillance round and no modifications of the cysts were observed at the subsequent MRI. In 12 months two HRIs with a negative first test developed new pancreatic cystic lesions multifocal compatible with SB-IPMNs between 3 to 2 mm without any additional pancreatic alteration. A comparable radiological finding was notice for the remaining HRIs with a first negative test.

DISCUSSION

To our knowledge, this is the first study who compared pancreatic parenchymal alterations in HRIs to controls by using MRI. In the present study, few signs of chronic pancreatitis were observed in case and controls without any statistical differences, with parenchymal atrophy being the most common alteration (9 cases and 10 controls). The prevalence of cystic lesion was high (25% vs 23 % between cases and controls; P= 1) all with a clear connection with the pancreatic duct so the most common presumptive diagnosis was small SD-IPMNs.

Previous surveillance programs investigated the use of MRI for the screening HRIs. A small percentage of chronic pancreatitis-like changes have been reported for the detection of chronic pancreatitis-like changes ranging from 1.3 to 11.6 % while pancreatic cystic lesions are diagnosed in a higher percentages of patients (2.6%-35.3%) [4]. Previous published data suggest that PanINs when multifocal are associated to *chronic pancreatitis-like* parenchymal change at EUS (such as ectasia, irregularity of the duct and/or parenchyma heterogeneity and lobularity)[16].

On the other hand, by using EUS as a screening method a higher percentage of pancreatic abnormalities were found around 36 % (from 6.8% to 78.2%). As far as regards cystic lesions, as

reported in a recent meta-analysis [5] EUS showed a lower sensitivity compared to MRI with a pooled prevalence of cystic lesions being 16.6% when EUS was employed and 22.4% when MRI was the screening test.

Few studies compared pancreatic parenchymal alterations in HRIs to controls by using endoscopic ultrasonography (EUS) reporting that abnormal changes occur more often in HRIs than controls. [6, 11]. Canto et al. in 2006 [6] have found more CP changes (60% vs 15% and) in HRIs comparing with controls as well as Mizrahi at al.[11] in the setting of BRCA2 carriers (13 % vs 1 %). Thiruvengadam et al.[14] in a recent study found CP features in 18% of HRIs compared to 2 % in controls ($p< 0.01$) with a significance maintained also after adjusted for confounder factors (such as smoking and drinking habits). Same results were observed for cystic lesions with HRIs more prone to have any kind of cysts compared to control ($p< 0.01$) (11.8% vs 9% [6] 21% vs 6% [13] and 76% vs 1% [14]).

No one of the above mentioned study categorized the type of cystic lesion detected so that the exact number of precancerous cystic lesions (IPMN) described in HRIs compared to controls is not known. It is probably due, as reported many studies [5,18-19] to the lower sensitivity of EUS compare to MRI- MRCP in describing the connection between the cyst and the ductal system [5] . MRI/MRCP is instead very sensitive for identifying the relation with the cyst and main pancreatic duct as well as whether it is a single or multifocal [15] .

In our cohort of HRIs, no major signs of CP were diagnosed. Some ductal irregularity where observed such as kinging of the main duct and the presence of pancreas divisum although those findings did not differ between case and controls. As far as regard the parenchymal alteration, atrophy was the most common and related, as expected, to the age of the patient as showed by logistic regression analysis.

A consistent number of small (from 2 to 15 mm) cystic lesions were observed in case and controls group equal to 25% vs 23%. Those results are in line with those already published between HRIs and also in asymptomatic subjects by using MRI-MRCP [5,20].

All the cystic lesions showed a connection with the PD so that the presumptive diagnosis was BD-IPMN without worrisome features. No one of the demographic characteristics where correlate to the diagnosis of such a lesion at the logistic regression. In HRIs those lesions where stable after 12 months of follow-up while two subjects, with a previous negative examination, showed a new diagnosis of multifocal very small SD-IPMNs.

Those results are limited to the small number of HRIs and controls enrolled and the lack of individual demographic and clinical data such as smoking habits, BMI, alcohol consumption in both groups. Moreover, data of a longer follow-up are need to evaluate the clinical significance of pancreatic alteration detected in HRIs and their correlation with the development of malignancy.

In conclusion, even with the above limitation, our results reported that HRIs were less likely to exhibit CP changes when studied with MRI while the rate of cystic lesions was higher in our cohort compared to previous published paper employed EUS as a surveillance method. No one of the pancreatic changes discovered in a HRIs group were significantly more frequent than in controls. It remains still unclear if IPMNs diagnosed in HRIs are more prone to develop malignant features. Future studies with a long follow-up are needed to clarify this important issue.

Table 1. Type of high-risk individuals (HRIs) that fulfilled the defined inclusion criteria for enrolment

Type of HRIs	Number (32)	% of total
Familial Pancreatic Cancer 1 FDR+ 1SDR 1 FDR+ 2SDR 2 FDR ≥ 3 FDR	20 7 (35%) 5 (25%) 6 (30%) 0	62.5%
Peutz-Jeghers syndrome	4	12.5%
Familial Atypical Multiple Mole Melanoma syndrome	2	6.2%
Hereditary breast and ovarian cancer (BRCA1/2 carriers)	2	6.2%
Hereditary Pancreatitis	3	9.4%
Hereditary nonpolyposis colorectal cancer (HNPCC)	1	3.1 %

Table 2. Demographic and clinical characteristics of HRIs and controls.

Demographic	Controls (26)	HRIs (28)	P value
Age (mean)	59.6 (30-79)	55.6 (36-79)	0.1
Sex (F:M)	12:14	14:14	0.5
History of Diabetes	3 (11.5%)	4/28 (14.2%)	0.6

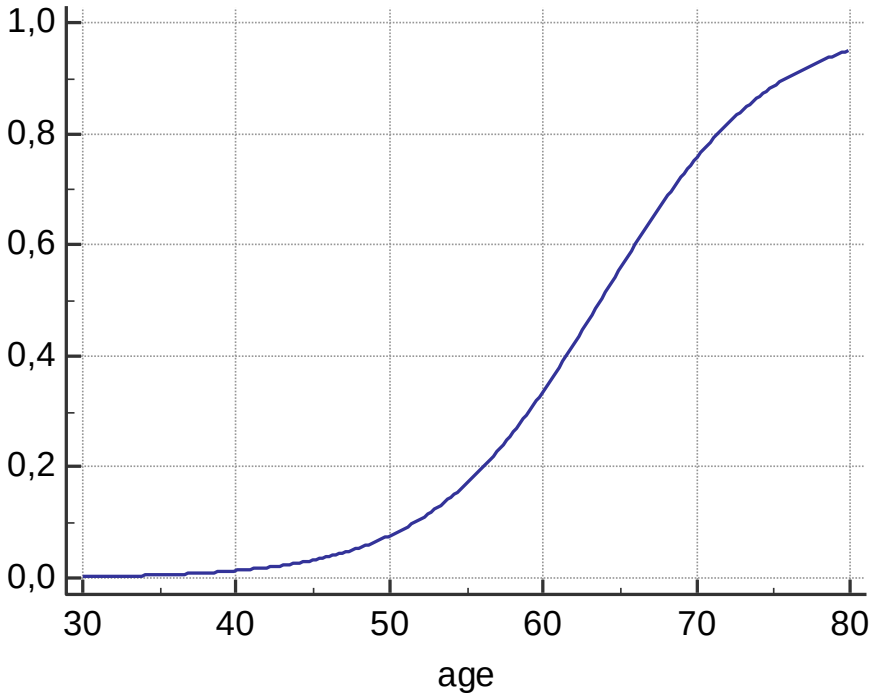

Fig.1 logistic regression curve for age which resulted the only one single independent variable related with the probability of diagnosing atrophy of the pancreatic parenchyma.

Table 3. Prevalence of pancreatic alteration in high-risk individuals (cases) and controls .

Outcome Variable	Controls (n=26)	HRIs (n=28)	P
Any Pancreatic Alteration	14 (53.8%)	18 (64.2%)	0.58
Parenchymal Features of CP:			
Decrease or loss of lobularity	0	0	
Decreased on contrast T1 signal intensity	1	0	0.5
Delayed enhancement	0	1	0.5
Atrophy	10 (38.4%)	9 (32.1%)	0.8
Ductal Alterations:			
Ductal irregularity	4 (15.4%)	7 (25%)	0.5
Ductal narrowing or stricture	0	0	
Ductal dilatation	0	0	
Calculi/filling defect	0	0	
≥3 Dilated side branches	0	0	
Pancreatic cyst:			
IPMN-BD	6 (23%)	7 (25%)	0.5
Multifocal IPMN	5 (2-11)	6.4 (2-15)	1
Max diameter (mm)	11	15	0.3
Worrisome features	0	0	

Table 4. Factors associated with the diagnosis of pancreatic atrophy at the logistic regression analysis

	OR	95% CI	P Value
Case (HRIs)	1.67	1.3-8	0.52
Age (per increasing year)	1.02	1.2-1.3	0.002
Sex (Male)	1.7	0.3-8	0.5
Diabetes	0.6	0.07-4.4	0.6

Table 5. Factors associated with the diagnosis of intraductal papillary mucinous neoplasms in the logistic regression analysis.

	OR	95% CI	P Value
Case (HRIs)	1.3	0.3-4.9	0.7
Age (per increasing year)	1	0.9-1	0.3
Sex (Male)	2.4	0.6-9.7	0.2
Diabetes	1.6	0.3-10.6	0.6

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5. SYSTEMATIC REVIEW AND META-ANALYSIS: PREVALENCE OFINCIDENTALLY PANCREATIC CYSTIC LESIONS IN ASYMPTOMATIC INDIVIDUALS.

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ABSTRACT:

Background & Aims: Pancreatic cystic lesions (PCLs) are frequent incidental findings. As most PCLs require costly diagnostic evaluation and active surveillance, it is important to clarify their prevalence in asymptomatic individuals. We therefore aimed at performing a systematic review and meta-analysis to determine it.

Methods: a systematic search was conducted and studies meeting inclusion criteria were included. The prevalence of PCLs was pooled across studies. A random effect model was used with assessment of heterogeneity.

Results: 17 studies, with 48,860 patients, were included. Only 3 were prospective; 5 studies were conducted in the US, 7 in Europe, 4 in Asia and 1 in Brazil. The pooled prevalence of PCLs was 8% (95% CI 4-14) with considerable heterogeneity (I2=99.5%). This prevalence was higher in studies of higher quality, examining older subjects, smaller cohorts, and employing MRCP (24.8%

vs 2.7% with CT-scan). The pooled rate of PCLs was four times higher in studies conducted in the US than in Asia (12.6% vs 3.1%). 7 studies reported the prevalence of mucinous lesions, with a pooled rate of 4.3% (95% CI 2-10; I2=99.2%), but of 0.7% only for worrisome features or high risk stigmata.

Conclusion: The rate of incidentally detected PCLs is of 8%. Mucinous lesions are the most common incidentally detected PCLs, although they rarely present with potential indication for surgery. The observed different rates in the US and other geographic Areas suggest that different protocols might be necessary to help balancing costs and effectiveness of follow-up investigations in asymptomatic subjects

INTRODUCTION:

Pancreatic cystic lesions (PCLs) are frequent incidental findings diagnosed during abdominal ultrasonography or cross-sectional imaging. The increasingly widespread use and the improved detection accuracy of imaging tests have led to an epidemic of PCLs with prevalence rates reported as high as 40%, in a clinical scenario that might be considered that of a “technology-related disease” [1]. PCLs comprise different entities, each of them with peculiar biological behavior ranging from benign to premalignant or frankly malignant neoplasms [2]. Mucinous pancreatic cystic lesions are associated with a potential risk to develop malignancy and deserve either an active treatment or surveillance [3], while serous cysts are benign lesions [4].

Intraductal Papillary Mucinous Neoplasms (IPMNs) represent the most common PCL. According with current guidelines [5,6,7,8] they should be treated surgically in the presence of major symptoms, morphological changes often defined as high risk stigmata (HRS), or when malignancy is demonstrated by cytology. In the presence of an IPMN of the branch ducts (BD-IPMN) with

size exceeding 30 mm or thickened and enhanced cystic wall or non-enhancing mural nodule or moderate main duct dilatation (5-9 mm) or in presence of abrupt change in pancreatic duct caliber with distal gland atrophy (characteristics usually named worrisome features -WF-), surgery might be considered and endoscopic ultrasound (EUS) with or without aspiration/biopsy is indicated to better analyze the morphology/cytology of the PCL, in order to stratify the risk of malignancy.

However, the vast majority of IPMNs are BD-IPMNs without any of the above mentioned signs and in patients who would be fit for surgery, these lesions require follow-up by means of Magnetic Resonance Imaging (MRI) with contrast medium and cholangio-pancreatography (MRCP) or with EUS with specific time intervals.

In a recent meta-analysis [9] the risk of malignant transformation of these lesions has been calculated to be equal to 7/1,000 per year, and despite the need to maintain surveillance in the long-term is debated [10], recent data suggest that it cannot be stopped after 5 years [11,12,13].

The surveillance of PCLs, and particularly of IPMNs, has become a challenge for health\insurance systems considering their substantial costs and resource burden. Moreover, the sustainability of a surveillance policy depends on the actual prevalence of PCLs in the general population. It is, therefore, important to clarify as accurately as possible the prevalence of PCLs, and particularly of mucinous cystic lesions, in subjects without a history of pancreatic disease.

However, these data are sparse, heterogeneous, with a wide range of prevalence rates, but no systematic and comprehensive analyses examined this issue. The present systematic review and meta-analysis aimed at evaluating the prevalence of incidentally diagnosed PCLs, particularly mucinous lesions.

MATERIALS AND METHODS:

Search strategy

A computerized literature search of the MEDLINE database did not identify any publication related to systematic review on the prevalence of incidentally diagnosed pancreatic cystic lesions in healthy subjects or in asymptomatic population. A MEDLINE search was therefore run until January 2018. Specific search terms were: (pancreatic cyst OR pancreatic cysts OR pancreatic cystic lesions OR intraductal papillary mucinous neoplasia OR pseudocyst OR pancreatic mucinous cyst) AND (radiological technique OR magnetic resonance OR multi-detector OR radiological imaging OR EUS OR ecoendoscopic ultrasound OR tomography OR MRI OR cholangiopancreatography OR abdominal imaging OR US OR MDCT OR CT) AND (occasional OR incidental OR incidence OR prevalence OR accidentally OR asymptomatic). The methodology was developed from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [14]. The titles of all identified articles were screened to ascertain their relevance. Abstracts and/or full texts of selected potentially relevant papers were evaluated. Possible further articles were identified by hand-searching reference

lists in order to identify potentially relevant studies, missed at our search. In the case of duplicate publications, the most recent or the most informative one in terms of number of cases or available data, was included.

Inclusion / exclusion criteria

Studies were considered if they met the following criteria: 1) written in English; 2) inclusion of patients without history of pancreatic disorders or symptoms suggestive for them; 3) all patients underwent second or third level imaging (CTscan, MRI+MRCP or EUS) not to investigate primarily the pancreatic gland; 4) data about prevalence and characteristics of cystic lesions were reported. Studies were excluded if they were available as abstract only because the abstracts did

not allow full data extraction. We also excluded: 1) case reports or small case series of <20 cases; 2) papers investigating the prevalence of pancreatic cystic lesions in specific subset of patient, such as liver/ pancreas transplanted patients or cluster of patients with specific type of neoplastic disease. Two independent reviewers (G.Z. and M.S.) carried out study identification and selection and resolved their disagreements by discussion or by consulting a third reviewer (G.C.). Excluded studies and the reasons for exclusion were recorded.

Data extraction and quality assessment.

Two reviewers (G.Z. and M.S.) independently extracted the data from each study and resolved their disagreements by discussion or by consulting a third reviewer (G.C.).

From the studies that met the eligibility criteria, the following data were collected: 1) study: publication year, study design, study location; 2) patients: total number of asymptomatic patients evaluated, age, sex, risk factors for pancreatic disease; 3) imaging: type of imaging procedure, imaging review, indication for imaging; 4) cases: total number of patients incidentally diagnosed with PCLs, prevalence according with age; 3) cyst features: single cyst, mean/median cyst size, maximum cist size, connection to the main duct, location, calcification, MD dilatation, worrisome features and/or high risk stigmata; 4) Cyst diagnosis: IPMN, pseudocysts, MCN, SCN; 5) extra-pancreatic cysts.

We then developed a summary table of the relevant studies listing the population characteristics and outcomes.

The quality of the studies was evaluated independently by two reviewers (GZ and MS) using the Newcastle-Ottawa Scale with a dedicated quality appraisal tool including 7 items. Studies with a score ≥7 were considered of high quality [15].

Statistical Analysis:

A meta-analysis of all eligible studies identified was planned using the software package Comprehensive Meta-Analysis (Biostat, Englewood, NJ, USA) using a random-effects model. In addition to within-study variance, the random-effects model considers heterogeneity among studies. The corresponding 95% confidence intervals (CI) were calculated using exact methods and assuming a Poisson distribution. We present the random-effect model because we believe that the relevant variation in the risk is most likely a consequence of inter-study differences. The quantity of heterogeneity was assessed by means of the I2 value [16]. The I2 quantity describes the percentage of total variation across studies that is caused by heterogeneity and not by chance. We considered an I2 value of 25% or lower as trivial heterogeneity, and an I2 value of 75% or higher as considerable heterogeneity. Publication bias was assessed using the Begg and Mazumdar test. A p-value <0.05 was accepted as statistically significant. Before performing the analysis, we developed the following a priori hypotheses to examine whether these had any effect on the prevalence of PCLs in asymptomatic

individuals and to explore reasons for any heterogeneity observed: (a) type of imaging employed to investigate the pancreas (MRCP vs MDTC or MRI); (b) sample size (< 1000 or > 1000 individuals); (c) mean age (>55 or <55 years) of the analysed population; (d) area of origin (i.e. United States, European or Asian countries); (e) quality of the studies (quality score<7 or >7/10).

RESULTS:

Search result and study selection

The study selection process is summarized in Figure 1. A total of 1,070 references were identified by the MEDLINE search. After a primary screening of the titles, 1,009 studies were excluded because they did not fit the area of interest.

The remaining 61 records were screened in more detail and 24 were considered potentially appropriate for the analysis. However, only 17 of them fulfilled all inclusion criteria, and were considered both for qualitative analysis and quantitative synthesis.

Study characteristics and quality assessment

The 17 included studies were published between 2008 and 2018 [1,18-33]. Five were conducted in the USA, 7 in Europe (4 in Italy and one respectively in The Netherlands, Germany and Turkey), 4 in Asian countries (two studies both in Korea and in Japan) and one in South America (Brazil). All papers were in English language.

Two studies [29,32] investigated the prevalence of incidental PCLs in a specific subgroup of patients compared with controls and we included in our analysis only data concerning the latter. Overall, 48,860 asymptomatic patients without history or clinical suspect of pancreatic disorders were included.

The descriptive characteristics of the seventeen included studies are summarized in Table 1.

All studies were mono-institutional and the study design was cross-sectional for all of them, being retrospective in 14 and prospective in 3 [18,27,28],respectively. The number of enrolled patients ranged from 110 [29] to 21,745 [30], and the percentage of males ranged from 26% [24] to 65% [21].

The mean age of the enrolled subjects ranged from 47 [24] to 68 years [32], while these data were not available in two studies [25,26]. The performed diagnostic procedures varied considerably among the studies. However, all but one study [32] in which the 192 enrolled patients underwent different investigations (either CT scan or MRI+MRCP), employed a single diagnostic tool.

Abdominal MRI with or without intravenous contrast was the most commonly employed diagnostic procedure (11 studies). MRCP was also performed in 6 of them [1,22,23,31,32,33] with a huge variability: in two studies [1,32] it was employed in a minority of patients (respectively 19% and 15%) and in another one [22] all patients underwent MRCP and only a little part of them (20%) was investigated also with MRI with intravenous contrast.

Few studies reported patients' exposition to well known risk factors for developing pancreatic disorders (such as cigarettes smoking, alcohol consumption, increased BMI and diabetes mellitus) [1,27,31,33] and first degree family history for pancreatic diseases [1,21,31].

While a "pancreatic indication" for the diagnostic procedure was an exclusion criterion for study inclusion, the recent study employing EUS [27] included 6% of cases with a previous acute pancreatitis episode. As it was clarified that the episode occurred at least 3 months before the study enrolment, with pain resolution 8 weeks before the EUS and no evidence of acute fluid collection or pseudocyst at the previous abdominal imaging, this study was not excluded.

As far as regards the quality of the included studies, the Newcastle-Ottawa score ranges from 4/10 to 9/10. Only six studies were scored as "high quality" (>7/10) [1,21,24,27,31,33] .

Pooled Prevalence Rate of Pancreatic Cystic Lesions

The prevalence of incidentally diagnosed pancreatic cystic lesions ranges from 0.2% to 45.9%, with a pooled prevalence of 8% (95% CI 4-14), as detailed in Figure 2. No publication bias was found (Begg and Mazudmar Kendall's tau=-0.07, p=0.64). There was however a considerable heterogeneity between the studies (I2=99.5%).

In order to explore possible reasons for this substantial heterogeneity, we repeated the analysis based on our a priori hypothesis considering different covariates (see Figure 3). Studies with mean age of the enrolled subjects >55 years old [1,18,19,22,23,27,31,32,33] had a pooled prevalence of 11.3%, while those with mean age <55 years [20,21,24,28,29,30] of only 5.7%. In both cases, however, the heterogeneity was very high (I2>99% for both).

When we analyzed the results taking into consideration the performed diagnostic procedure, the pooled prevalence of PCLs resulted 2.7% (95% CI 2-4) in the studies employing MDCT+ c.e.[18,19,25,26,30,32], without a reduction of heterogeneity (I2=93.7%). In the four studies using MRCP [22,23,31,33] the prevalence of PCLs was instead as high as 24.8% (95% CI 10-48), with similar heterogeneity (I2=99.5%).

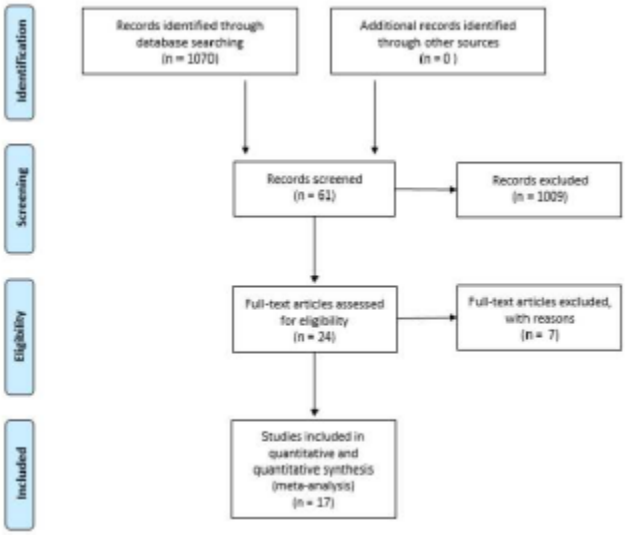

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of assessment of studies identified in the systematic review

When the sample size of the studies (<1,000 or >1,000) nwas considered, a higher pooled prevalence was seen in studies with <1,000 enrolled subjects [1,20,22,25,27,28,29,32] (13.9%, 95% CI 7-25; I2=97.4%) compared to those enrolling >1,000 people [18,19,21,23,24,26,30,31,33] (4.7%, 95% CI 2-11; I2=99.7%).

When considering the country of origin, the pooled prevalence of PCLs resulted 3.1% (95% CI 1-10; I2=99.7%) in studies conducted in Asia [18,23,30,31], 12.6% (95% CI 5-27; I2=99%) for those carried out in the Americas (either US or South America) [1,19,20,24,27,29], and 8.6% (95% CI 2-27; I2=99.6%) for those conducted in Europe [21,22,25,26,28,32,33].

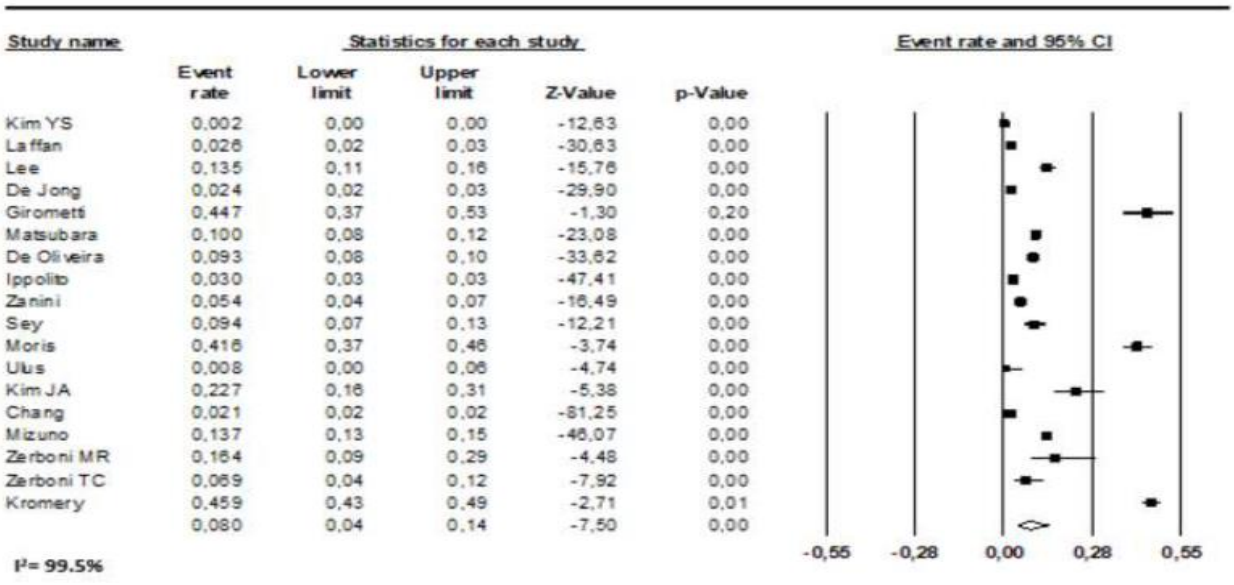

Figure 2. Pooled prevalence of all pancreatic cystic lesions (PCLs) in the 17 examined studies. The pooled prevalence resulted of 8% (95% CI 4%-14%), with considerable heterogeneity (I_2= 99.5%).

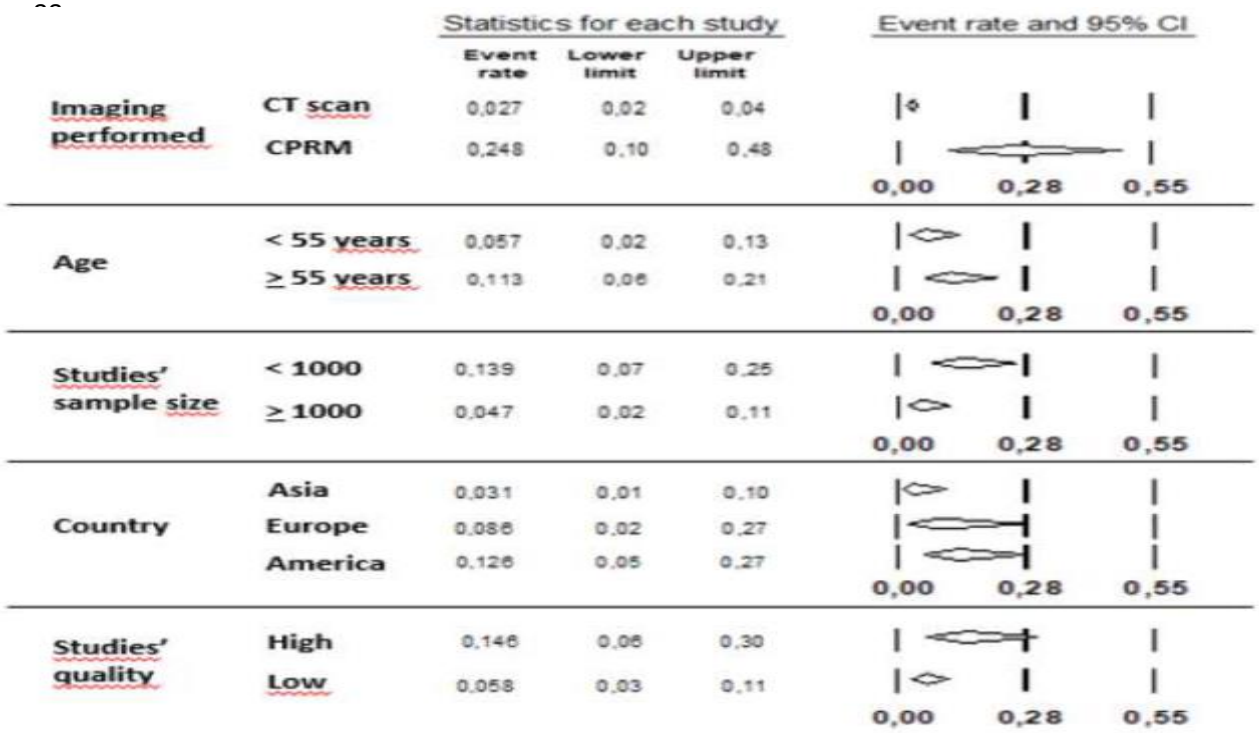

Figure 3. Prevalence of PCLs according to variables considered a priori for sensitivity analysis: A) age (studies with mean/median population age >55 years compared with those with mean/median age <55 years); B) different diagnostic procedures [studies using CT scan + medium contrast vs Magnetic Resonance Cholangio-Pancreatography (MRCP) with or without MRI]; C) sample size (<1,000 vs >1,000 cases); D) geographic area in which the studies were conducted (Asia, Americas and Europe); E) quality of the study (high vs low quality).

As far as regards the quality of the studies, the six studies of "high quality" [1,21,24,27,31,33] score had a higher pooled prevalence of PCLs of 14.6% (95% CI 6-30), with I2= 99.5%, when compared to the 11 studies with a "lower quality".

Pooled Prevalence Rate of Mucinous Cystic Lesions and of lesions harbouring clinically relevant features.

Seven of the 17 studies reported data on the specific type of PCLs. In these studies, the pooled prevalence of all PCLs was 7% (95% CI 2-19), with substantial heterogeneity (I2=99.6%) and the pooled prevalence of lesions diagnosed as of likely "mucinous nature" was 4.3% (95% CI 2-10; I2 = 99.2%) (see Figure 4). Most of these PCLs were considered IPMNs.

Of the included 17 studies, 5 did not provide details about the morphology of the PCLs [18,29,30,31,33]. Of the remaining studies, 4 did not report cases with morphological aspects suggestive of "worrisome features" or "high risk stigmata" [1,19,21,22], whereas in eight studies [20,23,24,25,26,27,28,32] these characteristics were mentioned. The rate of lesions with worrisome features (WF) or high risk stigmata (HRS) such as solid nodules, thickening of the wall and main duct calibre > 5 mm ranged from 0.1% to 3.6%. The pool prevalence of either WF and/or HRS at diagnosis resulted of 0.7% (95% CI 0-1) with considerable heterogeneity (I2 =85.3%) (see Supplementary Figure 1).

DISCUSSION:

To our knowledge, this is the first meta-analysis investigating the prevalence of incidentally diagnosed PCLs in individuals asymptomatic for pancreatic disorders. In the present study, data from seventeen publications were analysed, resulting in a pooled prevalence rate of 8%, with a wide range (0.2% to 45.9%) and considerable heterogeneity.

Only seven of the included studies provide sufficient data to define the nature of the PCLs. In these studies, the pooled prevalence of PCLs was of 7% and that of mucinous lesions was 4.3%, representing 60% of all incidentally diagnosed PCLs. However, at the time of incidental diagnosis, a minority of these lesions (0.7%) harboured features that might pose the suspicious of malignancy and an indication for surgery, such as main pancreatic duct dilation, thickened wall and mural nodules. The strengths of the present study include an exhaustive literature search, rigorous statistical methods, and pooling of data to allow synthesis of all the available evidence examining the possible yield\burden of testing for pancreatic cysts in asymptomatic individuals. Nevertheless,

the most relevant weaknesses of the study, as concerns many systematic review and meta-analysis, arise from the limits of the available evidence.

Most of the studies eligible for the current analysis were retrospective and for five of them the past medical history was not available; however, they include patients that were asymptomatic at the time of examination, without known health co-morbidities.

Moreover, since the included studies evaluated the radiological results collected during a long time span (up to 10 year), imaging were obtained with different machines and protocols. The authors of the studies with a longer time of recruitment considered, however, the effect of the different distribution of radiological modalities on the PCLs' rate.

Moris et al.[1] tried to objectify this correlation performing an adjusted multivariate-analysis, that showed a very strong relationship between PCLs detection and both the MRI hardware and the software versions. Therefore, they confirmed the direct relationship between the number of PCLs detected and the newer MRI version used. On the other hand, Kim J.A. and colleagues [29] matched cases and controls (respectively patients affected by autosomal dominant polycystic kidney disease -ADPKD- and patients who underwent abdominal MRI imaging without history or suspect of both ADPKD and pancreatic disorders) not only for demographic characteristics but also for the timing of abdominal procedures (within 1 year of each other), in order to reduce the "technology influence" on the results.

The highest [33] and one of the lowest [28] rates of PCLs were surprisingly reported by two studies using the same radiological procedure, such as whole body MRI. Paramagnetic contrast was not administrated in both, but, probably, the complementary use of MRCP in one of them [33] could explain the increasing rate of pancreatic findings, although the difference remains huge.

As mentioned before, a considerable degree of heterogeneity was present in all the conducted analyses. A number of a priori hypotheses were made to explain heterogeneity, such as age, country of origin, number of enrolled subjects, different type of abdominal cross-sectional imaging and quality of the study. However, while some of these factors influence the rate of PCLs, they could not explain heterogeneity.

The pooled estimate rate of occasional PCLs was higher in older subjects, in studies enrolling a lower number of patients, in those with a higher quality score and in patients undergoing MRCP. As far as concerns the country of origin, the pooled rate of PCLs was four times higher in studies conducted in the US than in those conducted in Asia

(12.6% vs 3.1%), with roughly intermediate results in Europe (see Figure 3).

Despite the limitations listed above, there are a good similarity between the result from our meta-analysis and the only prospective study performed with EUS available on this topic [27] (respectively pooled rate of 8% and 9.4%), strengthening the reliability of the present data.

In conclusion, the findings of this meta-analysis highlight the considerable high prevalence of PCLs in asymptomatic and/or apparently healthy individuals. On the light of these data there is an impingent need to redefine the surveillance strategy proposed by international consensus guidelines, according with a new scale of clinical risk.

Indeed, taking into account both the higher prevalence of PCLs in older and asymptomatic subjects and the presence of comorbidities and the low rate of potential malignant features, radiological follow-up in this group of patients is expected not to be cost-effective [34]. Furthermore, the observed different rates observed in the US and in other geographic Areas might suggest that different protocols might be necessary in different Countries.

Table 1. General features of the 17 studies included in the quantitative analysis

Author (year)	Country	Study Setting	Study design	Patients	Male (%)	Mean Age	Diagnostic procedure(s)	Imaging revision	Indication	Patients with PCLs (%)	Age of patients with PCLs	Patients with Mucinous lesions (%)
Kromery (2018) [40]	Germany	Single center	Retrospective	1077	521 (48.4)	55.8	WB-MRI (1.5T) +MRCP	Yes	Healthy population	494 (45.9)	60.5 (SD ± 11.6)	NR
Zerboni (2017) [39]	Italy	Single center	Retrospective	192	118 (61)	68	MDCT + c.e.; or MRI 1.5T ± c.e.; or MRCP	Yes	Not pancreas related	19 (10)	73 (95% CI 68.1–78.7)	14 (74)
Mizuno (2017) [38]	Japan	Single center	Retrospective	5296	3189 (60.2)	55.7	MRI + MRCP 3T, (thickness 3–5 mm)	Yes	No medical indication	724 (13.7)	62.6 (SD ± 10.7)	393 (54)
Chang (2016) [37]	South Korea	Single center	Retrospective	21,745	13,046 (60)	51.8	MDCT + c.e. (thickness 3 mm)	Yes	Not pancreas related	457 (2.1)	58 (SD ± 10)	383 (84)
Kim J.A. (2016) [36]	USA	Single center	Retrospective	110	49 (44.5)	47.5	MRI 1.5T (thickness 6–10 mm)	Yes	Not pancreas related	25 (22.7)	NR	NR
Ulus (2016) [35]	Turkey	Single center	Prospective	118	71 (60)	47.4	WB-MRI 1.5T	No	Healthy population	1 (0.8)	NR	1 (100)
Moris (2016) [1]	USA	Single center	Retrospective	500	252 (50)	60	MRI ± c.e. (1.5 or 3 T); MRCP 19%	Yes	Not pancreas related	208 (41.6)	63.8 (SD ± 11.2)	72 (35)
Sey (2015) [34]	USA	Single center	Prospective	341	154 (45)	59	EUS ± FNA	No	Not pancreas related	32 (9.4)	NR	NR
Ippolito (2015) [33]	Italy	Single center	Retrospective	6389	NR	NR	MDCT + c.e. (thickness 2–5 mm)	Yes	Not pancreas related	192 (3)	63 (SD ± 11)	NR
Zanini (2015) [32]	San Marino (Italy)	Single center	Retrospective	650	355 (55)	NR	16-MDCT ± c.e. (thickness 2.5 mm)	Yes	Not pancreas related	35 (5.4)	77 (53–93)	NR
de Oliveira (2015) [31]	Brazil	Single center	Retrospective	2583	672 (26)	47	MRI (3T) + c.e.	No	Not pancreas related	239 (9.3)	61 (SD ± 12.4)	NR
Matsubara (2012) [30]	Japan	Single center	Retrospective	1226	686 (56)	62	MRI (1.5T, thickness 5 mm) and MRCP	Yes	Not pancreas related	123 (10)	69 (38–88)	NR
Girometti (2011) [29]	Italy	Single center	Retrospective	152	87 (57)	57	MRCP (1.5 T); MRI + c.e. (20%)	Yes	Not pancreas related	68 (44.7)	NR	48 (71)
de Jong (2010) [28]	Holland	Single center	Retrospective	2803	1822 (65)	51	MRI + c.e. (1.5 T)	Yes	Without medical indication	66 (2.4)	60 (SD ± 10.9)	NR
Lee (2010) [27]	USA	Single center	Retrospective	616	259 (42)	54	MRI (1.5T, thickness 4 mm)	Yes	Not pancreas related	83 (13.5)	69 (SD ± 13)	NR
Laffan (2008) [26]	USA	Single center	Retrospective	2832	1445 (51)	58.2	16-MDCT + c.e.	Yes	Not pancreas related	73 (2.6)	NR	NR
Kim Y.S. (2008) [25]	South Korea	Single center	Prospective	2230	1338 (60)	57.5	16-MDCT + c.e.	Yes	Asymptomatic patients, CRC screening with CTC	4 (0.2)	NR	4 (100)

PCL = pancreatic cystic lesion; NR = not reported; MDCT = multidetector computed tomography, MRI = magnetic resonance imaging, T = tesla; MRCP = magnetic resonance cholangio-pancreatography, WB-MRI = whole body magnetic resonance imaging, EUS = endoscopic ultrasound, FNA = fine needle aspiration; CTC = computed tomography colonoscopy; CRC = colorectal cancer; c.e. = contrast-enhanced.

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6. SUMMARY, GENERAL DISCUSSION AND FUTURE PERSPECTIVES

This thesis deal with surveillance for HRIs to develop PDAC with the aim to improve the knowledge on this field that still carries various areas of improvement and some issues to clarify. Firstly, both EUS and MRI were considered the most accurate test for pancreatic imaging within the screening setting [1-3] but no imaging test has gained evidence-based consensus [4]. In order to reach the screening goal (reduction of pancreatic cancer related mortality) the best imaging test should diagnose the lesions considered a successful target of surveillance that are high-grade precursors or small PDAC amenable of curative surgical treatment. The exact prevalence of solid and/or cystic lesions, and more important, whether detected lesions could be considered a successful target of surveillance are still debated.

Therefore, we conducted and published on UEG journal a **systematic review and meta-analysis** [5] of the surveillance studies available at that time (see at the end of the thesis). Our results, reporting data from 1588 HRIs, showed a high prevalence of cystic lesions (20.2%) but only 1.6% was considered a pre neoplastic relevant lesion (advanced IPMNs and PanIN3 lesions) as well as of the 5.8% solid lesion discovered only 1.6% patients were diagnosed with a resectable PDAC. Moreover, from our results EUS seemed able to diagnose more solid lesions and MRI more cystic ones. Higher prevalence rate was observed in HRIs carriers with a specific DNA mutation compared to HRIs with FPC in whom the mutation is unknown. From This study we can conclude that both EUS and MRI should be considered for screening HRIs since both solid and cystic lesions are considered a target of the screening. However, we still need to clarify of the total premalignant lesion diagnosed in HRIs, which will progress to advanced neoplasia or early cancer and the

influence of individual factors such as the age of the subjects enrolled in the surveillance programs, and the relevance of risk factors such as smoking, can play a role for the progression.

No one of the screening studies considered for the above systematic review and meta-analysis was conducted in Italy. Therefore, we carried out **multicenter surveillance program** included asymptomatic HRIs with familial (FPC) or genetic frailty (BRCA1/2, p16/CDKN2A, STK11/LKB1 and PRSS1 mutations) predisposition to PDAC.

The paper was published on the American Journal of Gastroenterology (see at the end of the thesis), and reported the results of the first screening round of the Italian multicenter program supported by the Italian Association for the study of the Pancreas (AISP). After the first round of screening of the Italian registry the rate of malignancies was 2.6%. The diagnostic yield for MRCP/EUS was 23.5% for cystic lesions. The great majority of the detected cysts were BD-IPMN (n=28, 60.8% of the cysts detected, 14.9% of the whole cohort). The present study aimed also to answer one of the most important question that is if subjects related factors (familial or clinical) are associated with an increased risk of diagnosis of pancreatic abnormalities. We found that age > 50, smoking habit and > 2 relatives diagnosed with PC increased risk of malignant or pre-malignant pancreatic lesions. Whether these data will also reflect an increased risk of developing de novo lesions or of progression of initial finding needs to be investigated.

Moreover,till now, it is still unknown if some pancreatic parenchymal changes as called *chronic pancreatitis-like features* related to the presence of microscopic PDAC precursor (Pan-INs) and the presence of IPMNs might show a different risk of progression and characteristics in HRIs compared to the general population.

Few studies compared pancreatic parenchymal alterations in HRIs to controls by using endoscopic ultrasonography (EUS) reporting that abnormal changes occur more often in HRIs than controls

[2, 6-7] without categorized the type of cystic lesion detected so that the exact number of precancerous cystic lesions (IPMN) described in HRIs compared to controls is not known. Therefore, we decided to conduct a **case-control study on pancreatic changes in High-Risk Individuals compare to control** to evaluate the pancreatic parenchyma changes of HRIs and asses if some them (such as cystic lesions or chronic pancreatitis features) occur more often in the setting of a high risk population compared to healthy controls. Our study is the first who compare pancreatic changes diagnosed by MRI-MRCP to controls. We were able to enroll and analyzed the MRI findings of the first round of screening of 28 HRIs compared to 26 controls.

The majority pancreatic changes observed in HRIs were parenchymal atrophy and cystic lesions (small SB-IPMNs) without worrisome features. The presence of those pancreatic features did not differ between cases and controls; in particular, it was high even in HRIs (25%) than controls (23%). This study presents some limitations such as the small number of HRIs enrolled, majority of them belonging to FPC group. Those group of HRIs indeed, are more prone to present cystic lesions 10 mm or greater with a lower probability of progression compared to HRIs with a known mutation [8]. A large cohort of subjects and longer follow-up are needed to clarify if the clinical value of small SB-IPMN and /or signs of chronic pancreatitis can predict the development of advanced neoplasia or early cancer in HRIs compared to controls. In particular, we still not know if lesions that arise in HRIs have the same biological behavior as lesions seen in sporadic cases.

Nowadays, we still need to clarify the exact prevalence of mucinous lesions even in the general population of asymptomatic subjects as well as the actual risk of progress of those kind of lesions. Therefore, we finally conducted a **systematic review and meta-analysis on the prevalence of incidentally detected pancreatic cystic lesions in asymptomatic individuals**, paper published on Pancreatology (see at the end of the thesis) . The prevalence of incidental diagnosed mucinous

lesions was 4.3% with 0.7% of worrisome features that might pose the suspicious of malignancy by using different type of abdominal cross-sectional imaging. The four studies using MRCP the prevalence of PCLs was as high as 24.8% (95% CI 10-48), compared to what we found in the case and control groups of the previous mentioned study. The findings of this meta-analysis highlight the considerable high prevalence of PCLs in asymptomatic and/or apparently healthy individuals with low rate of potential malignant features.

On the light of these data, we still not answer to the ultimate question whether screening HRIs is effective or not. However, we have improved the knowledge of this topic for better designed the future surveillance policy.

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Results of surveillance in individuals at high-risk of pancreatic cancer: A systematic review and meta-analysis

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Abstract

Background: Data on surveillance for pancreatic ductal adenocarcinoma (PDAC) in high-risk individuals (HRIs) with ''familial pancreatic cancer'' (FPC) and specific syndromes are limited and heterogeneous.

Objective: We conducted a systematic review and meta-analysis of PDAC surveillance studies in HRIs.

Methods: Prevalence of solid/cystic pancreatic lesions and of lesions considered a successful target of surveillance (proven resectable PDAC and high-grade precursors) was pooled across studies. The rate of lesions diagnosed by endoscopic ultrasonography (EUS)/magnetic resonance imaging (MRI) and across different HRI groups was calculated.

Results: Sixteen studies incorporating 1588 HRIs were included. The pooled prevalence of pancreatic solid and cystic lesions was 5.8% and 20.2%, respectively. The pooled prevalence of patients with lesions considered a successful target of surveillance was 3.3%, being similar to EUS or MRI and varying across subgroups, being 3% in FPC, 4% in hereditary pancreatitis, 5% in familial melanoma, 6.3% in hereditary breast/ovarian cancer, and 12.2% in Peutz-Jeghers syndrome. The pooled estimated rate of lesions considered a successful target of surveillance during follow-up was 5/1000 person-years.

Conclusion: Surveillance programs identify successful target lesions in 3.3% of HRIs with a similar yield of EUS and MRI and an annual risk of 0.5%. A higher rate of target lesions was reported in HRIs with specific DNA mutations.

Keywords

Pancreatic cancer, meta-analysis, family history, screening

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Key summary

1. Summarize the established knowledge on this subject.
- Surveillance of pancreatic cancer is advised in individuals with ''familial pancreatic cancer'' (FPC) and specific genetic syndromes.
- No evidence-based consensus is available on the imaging test preferred between magnetic resonance imaging (MRI) and endoscopic ultrasonography (EUS).
- Whether surveillance protocols should be different in different high-risk individual (HRI) subgroups is unknown.

2. What are the significant and/or new findings of this study?
- The rate of resected lesions considered a successful target of surveillance during pancreatic cancer surveillance programs in HRIs is 3.3% or 0.5% per year.

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- There are no differences between EUS and MRI in diagnosing a "successful" target of screening.
- The rate of successful target lesions in FPC is lower compared to specific genetic syndromes, thus surveillance programs might need to be individualized accordingly.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is an increasing cause of cancer-related death, partially because of delayed diagnosis.[1,2] While precursor lesions, such as intraductal papillary mucinous neoplasms (IPMNs), can be detected at early stages, whether this is possible for pancreatic intraepithelial neoplasia (PanINs)[3] is a matter of debate. At any rate, general population screening is not advised as the overall lifetime PDAC risk is relatively low.

However, since a hereditary component accounts for 5% to 10% of cases,[3] surveillance is advised for high-risk individuals (HRIs). The International Cancer of the Pancreas Screening (CAPS) Consortium[4] defined individuals with "familial pancreatic cancer" (FPC) or with hereditary syndromes of which PDAC is one phenotypic manifestation as HRIs. The FPC definition is not fully established, but an individual can be considered at high risk if ≥two blood relatives are affected by PDAC, of whom at least one is a first-degree relative (FDR). Regarding defined genetic syndromes, surveillance is indicated for all Peutz-Jeghers syndrome (PJS) patients regardless of family history. Furthermore, p16 (familial atypical multiple-mole melanoma syndrome, FAMMM), breast cancer type 2 susceptibility gene (*BRCA2*), partner and localizer of BRCA2 (*PALB*), and mismatch repair gene (hereditary nonpolyposis colorectal cancer, HNPCC) mutation carriers with one FDR or two other family members with PDAC should undergo surveillance.[5]

The ultimate goal of surveillance is to detect and surgically treat noninvasive precursor lesions, such as advanced PanINs or IPMNs with high-grade dysplasia, or early-stage PDAC, that are considered successful targets of surveillance according to the CAPS Consortium.[4] Data on the efficacy of such surveillance programs in HRIs in terms of identification of the above-mentioned lesions are limited and heterogeneous, thus HRI surveillance is generally performed in the setting of research protocols.

Both magnetic resonance imaging (MRI) and endoscopic ultrasonography (EUS) are employed as first-line modalities for HRI surveillance, but no imaging test has gained evidence-based consensus.[6,7] Furthermore, the results of screening might differ in terms of detected lesions in each HRI subgroup. As an example, patients with FAMMM were reported to develop more solid lesions while FPC individuals more cystic ones.[8,9]

This systematic review and meta-analysis is therefore aimed to assess in HRIs (a) the prevalence of solid and cystic lesions and of lesions considered a successful target of surveillance, (b) the prevalence of lesions diagnosed by EUS and/or MRI, and (c) the prevalence of lesions considered a successful target of the surveillance in different HRI subgroups.

Materials and methods

Search strategy

A PubMed and Scopus databases search (see Appendix 1) was run until June 2017. Duplicates were removed. The methodology was developed from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[10]

The titles of all identified articles were assessed for their relevance, and abstracts and/or full texts of potentially relevant papers screened and evaluated. A manual search of all relevant articles and references was conducted to identify further relevant studies.

Inclusion and exclusion criteria

Inclusion criteria were English language, patients belonging to FPC families and/or with other specific high-risk syndromes or germline mutation carriers, and surveillance carried out with MRI and/or EUS, with the prevalence and type of diagnosed pancreatic lesions (solid and/or cystic) being reported. In the case of duplicate publications, the most recent or most informative was included. Two independent reviewers (MS and GZ) carried out study identification and selection and discussed disagreements with a third reviewer (GC). Excluded studies and reasons for exclusion were recorded.

Data extraction and quality assessment

Two reviewers (MS and GZ) independently extracted data from each study into a Microsoft Excel spreadsheet (XP Professional Edition; Microsoft Corp, Redmond, WA, USA). Disagreements were resolved by consulting a third reviewer (GC). Study year, design and location, number of screened individuals, and type of high-risk subgroups, and of imaging, follow-up duration, number, and type of diagnosed lesions, and of patients with an indication for surgery and with an identified lesion considered to be a success of the surveillance or diagnosed with advanced/metastatic PDAC were

recorded. A summary table of the relevant studies listing the population characteristics and outcomes was developed. The quality of the studies was evaluated independently by two reviewers (MS and GC) using the Newcastle-Ottawa Scale[11] with a dedicated quality appraisal tool including seven items. Studies with a score ≥ 7 were considered of high quality.

Data analysis

We examined (a) the pooled prevalence rate of all solid or cystic lesions, and (b) the pooled prevalence of lesions being considered a successful target of surveillance as defined by gold-standard pathology after surgery. Lesions considered as successful targets of surveillance were: PanIN3 (or high-grade PanIN if not specified), IPMNs with high-grade dysplasia or main duct (MD)/mixed-type IPMN, and any resectable PDAC with R0 pathology. This definition is adapted from the CAPS one, as some of the papers did not provide enough information for detailed grouping; the pooled prevalence rate of advanced IPMNs and PanIN3 lesions was also calculated, considering them as "premalignant" target lesions; (c) the pooled prevalence rate of advanced/metastatic PDAC, not amenable to R0 resection; (d) the pooled prevalence of the above-mentioned lesions detected either by EUS or by MRI; and (e) the pooled prevalence of successful target lesions in each specific HRI group.

Data were combined to generate a pooled prevalence rate. To better reflect the incidence of detected lesions over time, we also calculated the incidence rates of lesions being a successful target of surveillance by dividing the total number of events by the total number of person-years (pyrs) of follow-up. If these latter data were not provided in a study, it was estimated by multiplying the number of patients who underwent surveillance by the reported mean follow-up time. The corresponding 95% confidence intervals (CIs) were calculated using exact methods and assuming a Poisson distribution. When the number of events was 0, a continuity correction of 0.5 was used for the purpose of calculation, as previously reported.[12]

A meta-analysis was performed using the software package Comprehensive Meta-Analysis (Biostat, Englewood, NJ, USA) by using a random-effects model.[13] In addition to within-study variance, the random-effects model considers heterogeneity among studies and gives more conservative estimates. The quantity of heterogeneity was assessed by means of the I^2 value.[14] The I^2 describes the percentage of total variation across studies that is caused by heterogeneity and not by chance. Publication bias was assessed using the Begg and Mazumdar test. A p value < 0.05 was accepted as statistically significant. We developed the following a priori hypotheses that would explain heterogeneity and planned sensitivity analyses for (a) area of origin (i.e., United States (US)/Canada or Europe) and (b) quality of the study (quality score >7 or ≤ 7).

Results

Search results and study selection and characteristics

The study selection process is summarized in Figure 1. Sixteen studies met the eligibility criteria and were included for qualitative analysis and quantitative synthesis. One of them[15] is a multicenter study whose findings were already reported in three previous single-center studies.[9,16,17] As the population of this latter study was larger and results regarding the different HRIs subgroups more detailed, we used this manuscript for the analysis of pooled prevalence of overall lesions. However, as this more recent paper does not report the exact number of cystic/solid lesions diagnosed by either EUS or MRI, we used data from the older studies for the analyses on the role of MRI and EUS.

Table 1 summarizes the characteristics of the 16 included studies. Two papers reported only the first surveillance round[18,19] while two other studies did not report the exact follow-up period.[20,21] The mean follow-up in studies reporting $>$ one surveillance round[2,6,7,15,22–26] was 32.4 months, and the total number of enrolled HRIs 1588. Considering the 1572 individuals for whom this information was available, the largest group of screened individuals was FPC (1043, 66.3% of total) followed by FAMMM (243, 15.4%) and hereditary breast and ovarian cancer (HBOC) syndrome individuals or *BRCA1/2* mutation carriers (140, 8.9%). Some studies also enrolled individuals who did not meet the criteria to be designated as "HRI" according to the CAPS consortium.[2,7,18–20] There were four patients with Li-Fraumeni syndrome,[9,22] five with only one affected family member,[25] nine with a family member with early-onset PDAC,[24] and six with >1 relative with non-pancreatic cancers;[2] all together these people accounted for 1.6% of the investigated individuals. Two studies enrolled patients with a very low risk of developing pancreatic cancer based on family history[19,21] and those individuals therefore were not included in the analysis. Only four[4,7,20,25] of the 16 studies were scored as of "high quality."

Prevalence of solid pancreatic lesions in HRIs

A total of 79 pancreatic solid lesions were detected, with a pooled prevalence of 5.8% (95% CI 3%–9%;

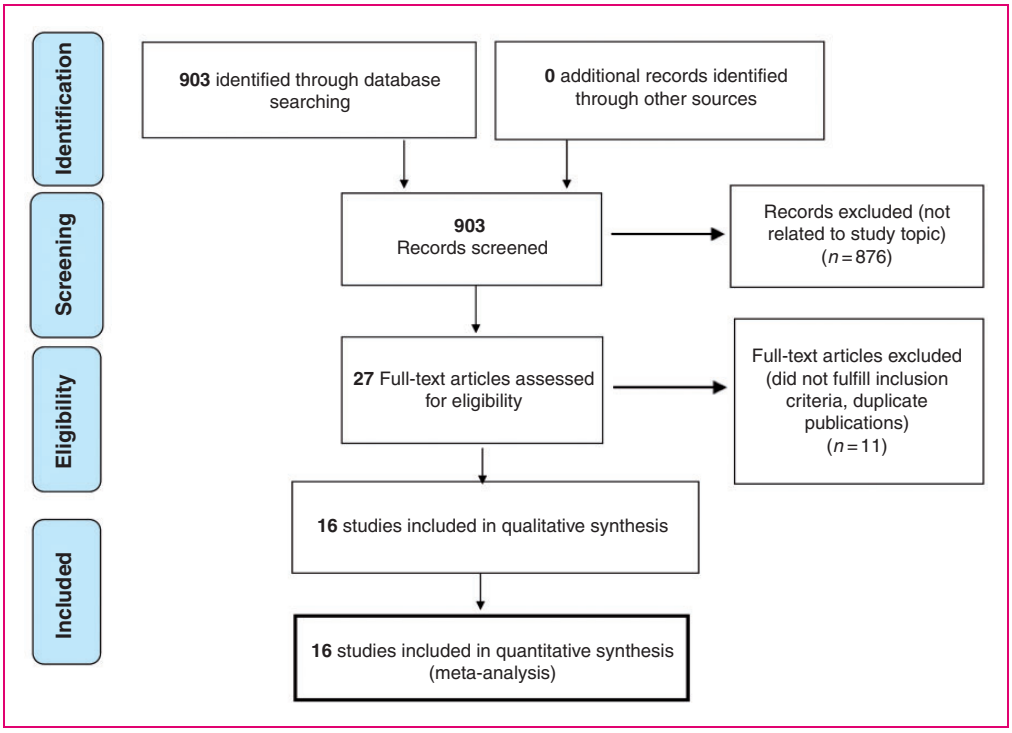

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of assessment of studies identified in the preset systematic review.

$I^2 = 77.5\%$) (Figure 2). No publication bias was found (Begg and Mazudmar Kendall's tau = –0.21; $p = 0.27$). When considering only the studies conducted in the USA or Canada, the pooled estimate prevalence was 3.8% (95% CI 2%–8%; $I^2 = 68.8\%$), compared to 6.8% with similar heterogeneity (95% CI 4%–12%; $I^2 = 61.2\%$) in the studies from Europe. The pooled prevalence of solid lesions in studies of high quality[4,7,20,25] was 2.8% (95% CI 1%–6%) compared to 7.7% (95% CI 5%–12%) in the 11 studies of lower quality,[2,9,16–19,21–24,26] with lower heterogeneity ($I^2 = 38.2\%$ vs $I^2 = 72.3\%$) in high-quality studies.

Prevalence of cystic pancreatic lesions

A total of 340 pancreatic cystic lesions were detected, with a pooled prevalence of 20.2% (95% CI 14%–28%; $I^2 = 88.9\%$) (Figure 2). Information on prevalence of pancreatic cystic lesions was not provided in one study.[26] No publication bias was found (Begg and Mazudmar Kendall's tau = –0.34; $p = 0.09$). The pooled prevalence of cystic lesions was 23.4% (95% CI 16%–34%; $I^2 = 84.1\%$) in the studies conducted in the USA and Canada, and 18.4% (95% CI 8%–37%; $I^2 = 92.1\%$) in the studies conducted in Europe. In studies with a high-quality score, the pooled prevalence of cystic lesions was 33.6% (95% CI 21%–49%; $I^2 = 90.3\%$), being higher than the 15.4% (95% CI 10%–24%) of studies with a low-quality score, yet with similar heterogeneity ($I^2 = 83.7\%$).

Prevalence of successful target lesions of surveillance

Of 1588 screened HRIs, 95 were considered to have an indication for surgery (pooled prevalence 6.8%; 95% CI 4%–11%; $I^2 = 81\%$). However, the pooled prevalence of individuals for whom surveillance identified a lesion considered a successful target of surveillance was 3.3% (95% CI 2%–5%; $I^2 = 40.5\%$) (Figure 3). In high-quality studies, this pooled prevalence was 2.9% (95% CI 1%–8%; $I^2 = 69.2\%$), being 3.4% (95% CI 2%–5%; $I^2 = 23.4\%$) in studies of lower quality. In the sensitivity analysis by country of origin, the pooled prevalence was 2.7% (95% CI 1%–5%; $I^2 = 43.3\%$) for studies conducted in the USA or Canada and 4.1% (95% CI 2%–8%; $I^2 = 52.2\%$) for studies conducted in Europe. No publication bias was found (Begg and Mazudmar Kendall's tau = –0.16; $p = 0.45$). Furthermore, when we repeated this analysis excluding individuals who were not at high risk according to the guidelines,[2,7,18–20] the pooled prevalence was 3.4% (95% CI 2%–5%; $I^2 = 44.7\%$). As the ideal target of the surveillance programs should be the diagnosis of "premalignant" lesions, the pooled prevalence rate of advanced IPMNs and PanIN3 lesions was also

Table 1. Study demographics, population size, and characteristics.

Study first author	Year	Country	Study design	Number screened	Mean age (range)	Types of high-risk group screened	Mean months of follow-up (intervals)	Type of imaging
Kimmey[22]	2002	USA	Single center	46	NR	46 FPC	60	EUS
Canto[23]	2006	USA	Single center	78	52 (32–77)	72 FPC, 6 PJS	12 (within one year)	EUS
Poley[18]	2009	The Netherlands	Multicenter	44	NR (32–75)	21 FPC, 3 *BRCA1*, 2 *BRCA2*, 2 PJS, 13 FAMMM, 2 HP, 1 LFS	Baseline only	EUS
Langer[16]	2009	Germany	Multicenter	76	NR	FPC, FAMMM[b]	NR (annual)	EUS and MRI/MRCP with CE
Verna[19]	2010	USA	Single center	41	52 (29–77)	30 FPC, 6 *BRCA1/2*, 5 OFMA	Baseline only	EUS and MRI (MRCP)
Ludwig[20]	2011	USA	Single center	109	54 (43–65)	93 FPC ,7 *BRCA*, 9 EOPCF	NR	MRCP
Vasen[15]	2011	The Netherlands	Single center	79	56 (39–72)	79 FAMMM	48 (annual)	MRI/MRCP with CE
Canto (CAPS3)[4]	2013	USA	Multicenter	216	56 (28–79)	195 FPC, 19 *BRCA2*, 2 PJS	28.8 (one to three years)	EUS and CT and MRI/MRCP with CE and secretin
Al-Sukhni[2]	2012	Canada	Single center	226	54 (22–89)	146 FPC, 51 *BRCA2*, 5 *BRCA1*, 10 FAMMM, 6 PJG, 2HP, 6 MCFDR	50.4 (annual)	MRI/MRCP without CE
Sud[24]	2014	USA	Single center	16	NR	FPC, *BRCA1*, *BRCA2*, PJS, FAMMM, HNPCC[b]	12 (annual)	EUS
Harinck[7]	2016	The Netherlands	Multicenter	139	51 (20–73)	68 FPC, 3 *BRCA1*, 20 *BRCA2*, 38 FAMMM, 7 PJS, 3 LFS	12 (annual)	EUS and MRI/MRCP with CE
Del Chiaro[25]	2015	Sweden	Single center	40	50 (23–76)	32 FPC, 3 *BRCA2*, 1 *BRCA1*, 4 FAMMM	12.9 (annual)	MRI/MRCP with secretin
Mocci[17]	2015	Spain	Multicenter	41	NR	24 FPC, 12 HBOC, 5 EOPCF	24 (3 to 12 months)	EUS and CT
Joergensen[26]	2016	Denmark	Multicenter	71	51 (27–72)	40 FPC, 31 HP	60 (annual)	EUS
Vasen[a15]	2016	The Netherlands, Germany, Spain	Multicenter	411	NR	214 FPC, 178 FAMMM, 19 *BRCA1/2 PALB2*	43.2 (annual)	EUS and/or MRI
Chang[25]	2017	Taiwan	Single center	151	NR	1 *BRCA2*, 64 HP, 86 FPC	NR (annual)	MRI/MRCP with CE

[a]Includes high-risk individuals from Langer et al.,[16] Vasen et al.[15] and Mocci.[17]

[b]The exact number of high-risk individuals was not provided.

FPC: familial pancreatic cancer; *BRCA*: breast cancer susceptibility gene; PALB2: partner and localizer of BRCA2; CAPS: International Cancer of the Pancreas Screening; FAMMM: familial atypical multiple-mole melanoma syndrome; HNPCC: hereditary nonpolyposis colorectal cancer; HBOC: hereditary breast-ovarian cancer syndrome; PJS: Peutz-Jeghers syndrome; HP: hereditary pancreatitis; LFS: Li-Fraumeni syndrome; EOPCF: early-onset pancreatic cancer family; MCFDR: multicancers first-degree relatives; OFMA: one family member affected; EUS: endoscopic ultrasonography; MRI: magnetic resonance imaging; MRCP: magnetic resonance cholangiopancreatography; CE: contrast enhancement; CT: computed tomography; NR: not reported; USA: United States of America.

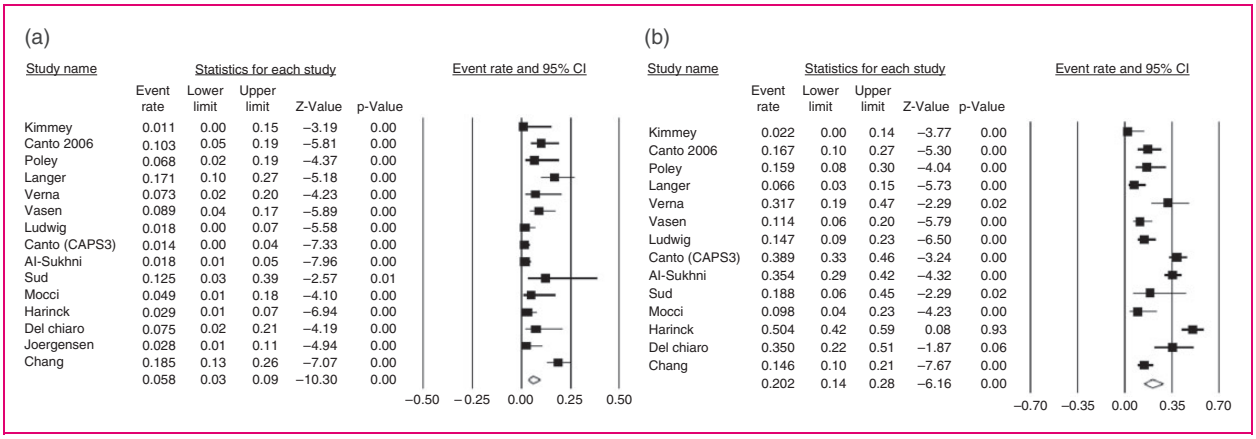

Figure 2. Forest plot showing the pooled prevalence of pancreatic solid lesions (panel (a), on the left) diagnosed in high-risk individuals in all the 14 included studies and of the pooled prevalence of cystic lesions (panel (b), on the right) diagnosed in high-risk individuals in the 13 studies reporting this information. Random-effects model demonstrating a pooled prevalence of 5.8% (95% confidence interval (CI) 3%–8%) with moderate heterogeneity ($I^2 = 77.5\%$) for solid lesions and a pooled prevalence of 20.2% (95% CI 14%–29%) with considerable heterogeneity ($I^2 = 88.9\%$) for cystic ones.

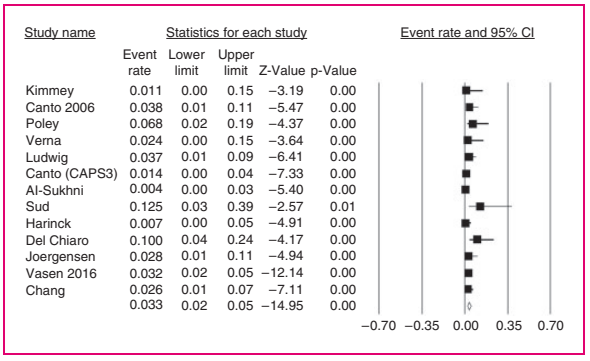

Figure 3. Forest plot showing the overall pooled prevalence of successful target lesions of the surveillance that is equal to 3.3% (95% confidence interval (CI) 2%–5%), with moderate heterogeneity ($I^2 = 40.5\%$).

calculated, and resulted in 1.6% (95% CI 1%–2%; $I^2 = 0\%$) (see Supplementary Figure 1).

In detail, 26 (1.6%) patients were diagnosed with a resectable PDAC, 11 (0.7%) with branch duct (BD)-IPMNs with high-grade dysplasia or an MD-IPMN, and four (0.3%) with advanced PanINs. Six individuals were diagnosed with pancreatic neuroendocrine neoplasms (pNENs).[2,6,15,24] Four of them were resected and all but one[2] had a diameter <15 mm. Type and number of histologically confirmed lesions, including those successfully operated on, are summarized in Supplementary Table 1. The pooled estimate rate of lesions considered a successful target of surveillance was calculated for 11 studies in which follow-up length was reported, and resulted in 0.005/pyrs (95% CI 0.001%–0.005%; $I^2 = 56\%$), equal to 5/1000 pyrs (Figure 4).

Prevalence of advanced/metastatic pancreatic adenocarcinoma

During the surveillance programs, nine advanced/metastatic adenocarcinoma were diagnosed. Six metastatic PDAC were diagnosed and histologically confirmed by percutaneous or EUS-guided fine needle aspiration;[2,9,19,23] the other three underwent surgical resection but histology showed a positive resection margin.[9,15] The pooled prevalence of HRIs for which surveillance identified advanced PDAC was 1.0% (95% CI 1%–2%), without heterogeneity ($I^2 = 0\%$).

Prevalence of pancreatic lesions diagnosed either by EUS or by MRI

Ten studies employed EUS[6,7,16–19,22–24,26] and nine MRI.[2,6,7,9,16,19–21,25] The pooled prevalence of solid lesions was higher in studies employing EUS (5.2%, 95% CI 3%–9%; $I^2 = 60.6\%$) compared with those using MRI (4.1%, 95% CI 2%–9%; $I^2 = 83\%$) (Figure 5). The pooled prevalence of cystic lesions was instead 22.4% (95% CI 15%–32%; $I^2 = 89.3\%$) with MRI and 16.6% (95% CI 10%–27%; 85.7%) with EUS in the eight studies providing this information, which was lacking in two studies.[17,26] The pooled prevalence of pancreatic lesions considered a successful target of surveillance was 2.9% with EUS (95% CI 2%–5%; $I^2 = 27.4\%$) and 2.5% with MRI (95% CI 1%–5%; $I^2 = 51.7\%$) (see Figure 5).

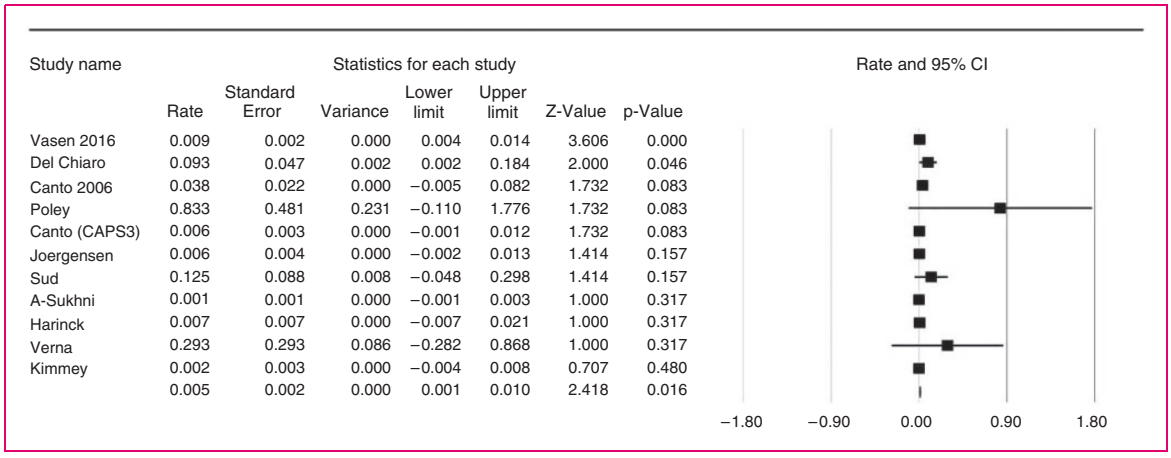

Figure 4. Forest plot showing the pooled estimate rate of successful target lesions of the surveillance in the 11 studies that reported the follow-up length. The pooled estimate rate resulted of 5/1000 person years with moderate heterogeneity ($I^2 = 56\%$).

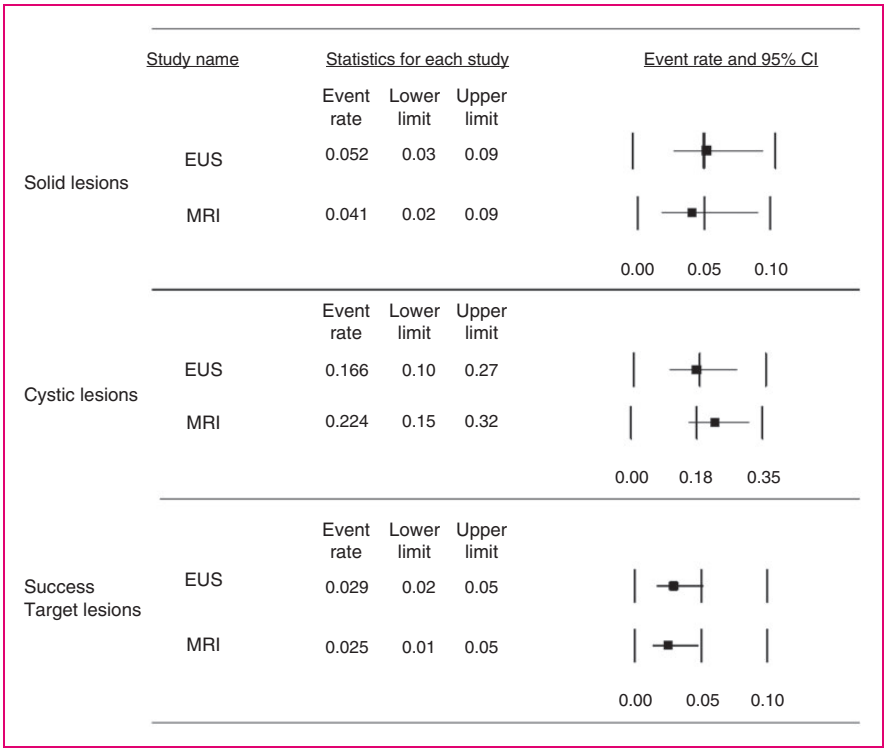

Figure 5. Summary of the pooled prevalence of pancreatic lesions (solid, cystic and successful target lesions of the surveillance) diagnosed either by endoscopic ultrasonography (EUS) or magnetic resonance imaging (MRI). CI: confidence interval.

Prevalence of lesions considered a successful target of surveillance in different HRI subgroups

The pooled prevalence of lesions considered a successful target of surveillance was 3% (95% CI 2%–5%; $I^2 = 22.2\%$) in FPC individuals. In people with a specific genetic syndrome it was 4% in HP (95% CI 1%–14%), 5% for FAMMM (95% CI 3%–9%), 6.3% in HBOC or *BRCA1/2*, *PALB2* mutation carriers (95% CI 3%–14%), and 12.2% in PJS (95% CI 4%–32%), without heterogeneity ($I^2 = 0\%$) in all these subgroups except for people with HP ($I^2 = 12.2\%$) (Figure 6). We also analyzed the pooled prevalence rate of histologically confirmed solid lesions diagnosed

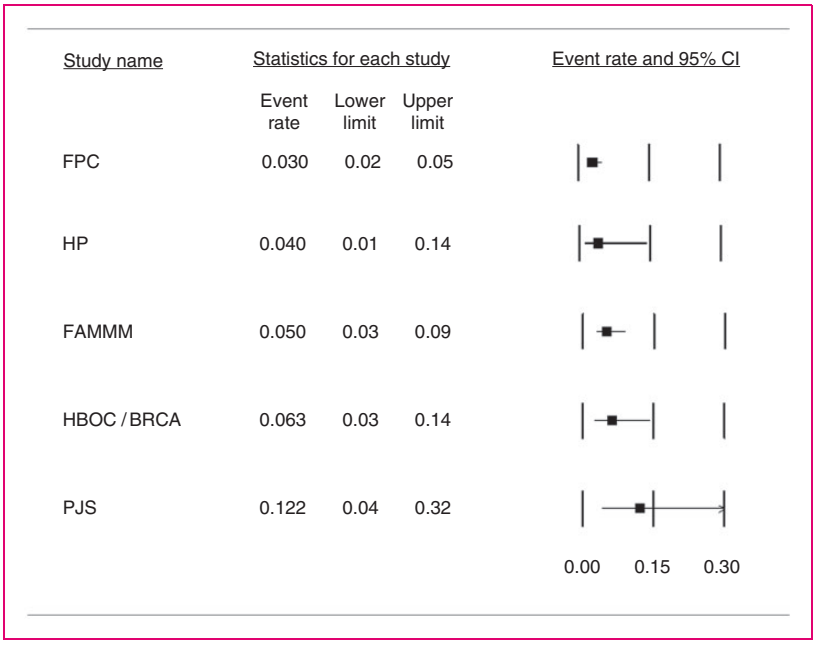

Figure 6. Pooled prevalence of lesions considered a successful target of surveillance in the different high-risk individual subgroups. The pooled prevalence of lesions considered a successful target of surveillance diagnosed in familial pancreatic cancer (FPC) was 3% (95% confidence interval (CI) 2%–5%) with moderate heterogeneity ($I^2 = 22.2\%$). The pooled prevalence in familial atypical multi-mole melanoma syndrome (FAMMM) was 5% (95% CI 3%–9%), in hereditary pancreatitis (HP) was 4% (CI 1%–14%), in hereditary breast-ovarian cancer syndrome (HBOC) or *BRCA1/BRCA2* or *PALB2* mutation carriers was 6.3% (95% CI 3%–14%), and in Peutz-Jeghers syndrome (PJS) it was 12.2% (95% CI 4%–32%). Notably, in all these genetic syndromes but HP, there was no heterogeneity ($I^2 = 0\%$).

at the baseline examination in each subgroup. These data were available for all studies but one.[21] The pooled rate of solid lesions at baseline resulted respectively in: 1.6% (95% CI 1%–3%; $I^2 = 0\%$) in FPC, 5.8% (95% CI 2%–14%; $I^2 = 0.8\%$) in HBOC or *BRCA1/2* mutation carriers, 4.6% (95% CI 2%–12%; $I^2 = 35\%$) in FAMM, 12% (95% CI 4%–32%; $I^2 = 0\%$) in PJS, and 7.2% (95% CI 1%–30%; $I^2 = 0.8\%$) in HP. The number of pancreatic cancer cases and the relative proportion of unresectable/metastatic cases were respectively 12 (25% metastatic) in FPC, 15 (20% metastatic) in FAMMM, four (25% metastatic) in HBOC, and one (0% metastatic) in HP. No PDAC cases were diagnosed in PJS patients.

Discussion

As data on the prevalence of lesions diagnosed during surveillance programs in individuals at high risk of PDAC are scanty and heterogeneous, we conducted a meta-analysis to estimate the pooled prevalence of solid and/or cystic lesions, and more important, whether detected lesions could be considered a successful target of surveillance. We also calculated the pooled estimated rate of detected lesions during the course of subsequent surveillance rounds, the prevalence of lesions diagnosed by either EUS or MRI, and the differential prevalence of lesions among the various HRI subgroups.

Data from 1588 enrolled HRIs were included. The pooled prevalence of solid and cystic lesions in these individuals was 5.8% and 20.2%, respectively (Figure 2). The pooled prevalence of lesions considered a successful target of surveillance according to the CAPS definition was 3.3% (Figure 3), while the actual pooled prevalence of "preneoplastic" target lesions (advanced IPMNs and PanIN3 lesions) was 1.6% (see Supplementary Figure 1). The pooled estimated rate of lesions considered a successful target of surveillance during follow-up amounted to five cases per 1000 pyrs, equal to an annual risk of 0.5% (Figure 4).

EUS seemed able to diagnose more solid lesions and MRI more cystic ones (Figure 5). Moreover, the rate of lesions considered a successful target of surveillance was much lower in FPC compared to HRI with specific syndromes (Figure 6). This is not surprising as in FPC the causal mutation is unknown despite a clear autosomal dominant inheritance pattern. Therefore, half of FPC individuals undergo surveillance without carrying the causal mutation.

Of the 1588 screened HRIs, 6.8% underwent surgery, with histologically confirmed lesions considered a successful target of surveillance in 3.3%. To date,

there is little consensus about which lesions detected by surveillance represent an indication for surgery,[4] considering the morbidity of pancreatic surgery.[27] It is unknown whether for example in the case of BD-IPMNs the same criteria for resection apply in HRIs compared to sporadic cases.[28] A recent study showed that cystic lesions diagnosed in HRIs with a known mutation are more prone to progress compared to those discovered in FPC individuals, although this latter group had a significantly higher prevalence of cystic lesions.[29] There is also evidence of a high rate of lymph node involvement and poor prognosis in HRIs with PDAC even with very small lesions.[9,18] This might justify a more aggressive attitude toward resecting precursor lesions in this setting.

A proportion of patients diagnosed with PDAC ($n = 9$, pooled prevalence 1%) were identified at an advanced/metastatic stage. Two of them were prevalent cases diagnosed at baseline. The other patients who underwent surgical resection with positive resection margins, or who were diagnosed with an unresectable interval cancer during subsequent follow-up, however, should be considered a failure of surveillance. The proportion of unresectable PDAC was similar in people with FPC, FAMMM, and HBOC. This raises concerns about the validity of currently performed surveillance programs.

In four cases the resected lesions were pNENs, only one[2] with diameter >1.5 cm. The European Neuroendocrine Tumours Society guidelines[30] would not recommend surgery for incidentally detected pNENs <2 cm.

Few studies compared the diagnostic yield of EUS and MRI/magnetic resonance cholangiopancreatography. A high concordance between the two methods was described by Canto et al.,[6] while only a 55% agreement was shown by Harinck et al.[7] for the detection of clinically relevant lesions. In the present study, the pooled prevalence of solid lesions detected by EUS was higher compared to MRI (5.2% vs 4.1%), while MRI had a higher yield for cystic lesions (22.4% vs 16.6%). The pooled prevalence of lesions considered a successful target of surveillance was similar for EUS and MRI. A limitation of this analysis is the high heterogeneity between studies in terms of MRI protocols, and the use of radial EUS in some studies, while linear EUS is able to detect more pancreatic lesions in HRIs.[31] The two methods might be considered complementary rather than interchangeable in surveillance programs,[7] and their use should be tailored considering local expertise.

The yield of surveillance programs in different HRI subgroups is another interesting subject. The pooled prevalence of lesions considered a successful target of surveillance in the present meta-analysis was 3% in FPC individuals, representing the majority of people screened, 4% in HP, 5% in FAMMM, 6.3% in HBOC, *BRCA1/2,* or *PALB2* mutations carriers, and 12.2% in PJS. Notably, while the results obtained in FPC showed a certain heterogeneity, this was not the case in patients with genetic syndromes. It would be attractive to tailor surveillance in terms of age at which to start, modality, and follow-up intervals based on the frequency and growth characteristics of the lesions diagnosed in each HRI subgroup.

Vasen et al.[15] recently reported that IPMNs with high-grade dysplasia and multifocal PanINs3 were more frequent in FPC compared to FAMMM patients, while the rate of diagnosed PDAC was higher in this latter group. Further studies into the differential risk and growth characteristics of the various subgroups of HRIs are needed.

This is the first study to systematically appraise the available literature evidence from surveillance studies in HRIs for developing PDAC. Although we developed a priori hypotheses for sensitivity analyses considering likely sources of heterogeneity, the observed heterogeneity between studies reflecting differences in surveillance tests, intervals, type of reported lesions, and kind of HRIs enrolled is a potential limitation. The lack of individual patient data limited the possibility of performing any analysis other than that of aggregate data, and the influence of factors such as the age of the individuals enrolled in the surveillance programs, and the relevance of risk factors such as smoking, could not be appropriately considered.

In conclusion, the pooled prevalence rate of resected lesions that can be considered a successful target of surveillance during PDAC surveillance programs in HRIs is 3.3% with an annual risk of 0.5%. The pooled prevalence rate of successful "premalignant" target lesions is, however, lower and equal to only 1.6%. A higher prevalence rate was observed in HRI carriers with a specific DNA mutation compared to HRIs with FPC in whom the mutation is unknown.

Declaration of conflicting interests

None declared.

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Appendix 1

Search strategy

The following search strategy was employed: (Neoplasm, Pancreatic OR Pancreatic Neoplasm OR Neoplasms, Pancreas OR Pancreas Neoplasm OR Neoplasms, Pancreatic OR Cancer of Pancreas OR Pancreas Cancers OR Pancreas Cancer OR Cancer, Pancreas OR Cancers, Pancreas OR Pancreatic Cancer OR Cancer, Pancreatic OR Cancers, Pancreatic OR Pancreatic Cancers OR Cancer of the Pancreas) AND (Cancer Early Detection OR Cancer Screening OR Screening, Cancer OR Cancer Screening Tests OR Cancer Screening Test OR Screening Test, Cancer OR Screening Tests, Cancer OR Test, Cancer Screening OR Tests, Cancer Screening OR Early Diagnosis of Cancer OR Cancer Early Diagnosis) AND (High Risk OR High-Risk individuals OR High-Risk patients OR High-Risk cohort OR High-Risk population OR FPC OR familial pancreatic cancer OR inherited pancreatic cancer OR HBOC OR hereditary breast and ovarian cancer syndrome OR BRCA OR FAMMM OR familial atypical multiple mole melanoma OR PJS OR Peutz-Jeghers syndrome OR HNPCC OR hereditary nonpolyposis colorectal cancer OR PALB OR mismatch repair gene mutation OR Genetic Susceptibility OR Genetic Susceptibilities OR Susceptibilities, Genetic OR Susceptibility, Genetic OR Genetic Predisposition OR Genetic Predispositions OR Predispositions, Genetic OR Predisposition, Genetic).

Results of First-round of Surveillance in Individuals at High-risk of Pancreatic Cancer from the AISP (Italian Association for the Study of the Pancreas) Registry

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INTRODUCTION: **Surveillance programs on high-risk individuals (HRIs) can detect pre-malignant lesions or early pancreatic cancer (PC). We report the results of the first screening round of the Italian multicenter program supported by the Italian Association for the study of the Pancreas (AISP).**

METHODS: **The multicenter surveillance program included asymptomatic HRIs with familial (FPC) or genetic frailty (GS: *BRCA1/2*, p16/*CDKN2A*, *STK11/LKB1*or *PRSS1*, mutated genes) predisposition to PC. The surveillance program included at least an annual magnetic resonance cholangio pancreatography (MRCP). Endoscopic ultrasound (EUS) was proposed to patients who refused or could not be submitted to MRCP.**

RESULTS: **One-hundreds eighty-seven HRIs underwent a first-round screening examination with MRCP (174; 93.1%) or EUS (13; 6.9%) from September 2015 to March 2018.The mean age was 51 years (range 21–80).One-hundreds sixty-five (88.2%) FPC and 22 (11.8%) GF HRIs were included. MRCP detected 28 (14.9%) presumed branch-duct intraductal papillary mucinous neoplasms (IPMN), 1 invasive carcinoma/IPMN and one low-grade mixed-type IPMN, respectively. EUS detected 4 PC (2.1%): 1 was resected, 1 was found locally advanced intraoperatively, and 2 were metastatic. Age > 50 (OR 3.3, 95%CI 1.4–8), smoking habit (OR 2.8, 95%CI 1.1–7.5), and having > 2 relatives with PC (OR 2.7, 95%CI 1.1–6.4) were independently associated with detection of pre-malignant and malignant lesions. The diagnostic yield for MRCP/EUS was 24% for cystic lesions. The overall rate of surgery was 2.6% with nil mortality.**

DISCUSSION: **The rate of malignancies found in this cohort was high (2.6%). According to the International Cancer of the Pancreas Screening Consortium the screening goal achievement was high (1%).**

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PC) is one of the deadliest solid tumors. It is predicted to become the second cause of tumor-related death by 2030 [1]. Surgical resection is the only potential cure and it is possible in less than 20% of patients at the time of diagnosis [2]. PC is usually asymptomatic until the disease has spread outside the gland, causing jaundice or abdominal and back pain. However, similarly to other solid tumors, even PC has precursor lesions, namely pancreatic intraepithelial neoplasia (PanIN), and intraductal papillary mucinous neoplasms (IPMN) [3, 4].

Considering the wide window of opportunity to detect PC at its earlier stages [5] and the low incidence of this tumor (6.3–7.3 per 100,000 people in Europe) [6], it might seem

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reasonable and advantageous to focus diagnostic efforts to identify precursor lesions or early PC on a selected population of high-risk individuals (HRIs). Population screening is not recommended.

In 2013, the International Cancer of the Pancreas Screening (CAPS) Consortium established that PC screening should be recommended only for HRIs with a lifetime risk of PC greater than 5% or a fivefold increased relative risk, as this would eventually lead to a better prognosis [7].

Guidelines for screening define two groups of HRIs: (a) individuals with a defined genetic syndrome (GS) (e.g., Hereditary breast and ovarian cancer syndrome, familial atypical multiple mole melanoma (FAMMM) syndrome, Peutz-Jeghers Syndrome, *PRSS1*-related hereditary pancreatitis, and Lynch syndrome) or genetic mutations (*PALB2* gene mutations); (b) individuals without a diagnosed syndrome but with familiar pancreatic cancer (FPC) [8]. According to the CAPS Consortium, the goal of a PC surveillance program should be the identification of early (pT1N0M0R0) PC, or advanced precursor lesions such as PanIN3 or high-grade IPMN [7]. However, an internationally standardized protocol for PC surveillance is not available yet, as the current evidence is based on single- or multi-centric experiences with heterogeneous policies in terms of inclusion criteria, diagnostic methods, and frequency of screening being adopted [9, 10]. Three recent meta-analyses reported that the probability of reaching the screening goal is satisfactory [9–11], thus reinforcing the rationale in the pursuit of the early diagnosis of PC.

In 2010, the Italian Association for the Study of the Pancreas (AISP) developed a position paper for the surveillance at high-risk of PC, including both HRI with familial and genetic predisposition [12]. In 2015, an official registry of asymptomatic HRI was created following these guidelines. This manuscript reports the results of the first-round of screening.

METHODS

Definition of individuals at high risk and surveillance protocol

In 2015, six Italian high-volume centers started the enrollment of HRIs according to the Italian Guidelines [12]. Criteria for entry into the registry as an HRI include being defined as FPC if having: ≥ 3 relatives affected by PC until the third degree of kinship (TDR) or 2 relatives affected if at least one being a first-degree relative (FDR); having a known genetic mutation of *BRCA1*, *BRCA2*, or p16/*CDKN2A* genes with at least a FDR or a second degree relative (SDR) affected by PC; a previous diagnosis of *PRSS1*-related hereditary pancreatitis or Peutz-Jeghers Syndrome (PJS). Whenever possible, the diagnosis of pancreatic cancer in affected relatives had to be verified through medical records evaluation. Demographic, clinical, and anamnestic data were prospectively collected by each center involved. HRIs aged > 18 could enter the surveillance registry after having signed a proper informed consent.

Each enrolled subject received an outpatient visit and was offered a baseline MRI with 1.5 T to 3.0 T Cholangio-Wirsung-MRI (MRCP). MRI with MRCP was chosen as a baseline diagnostic method because of no radiation risks, low complication rates, and high sensitivity [13–15]. In case of a normal MRCP the subjects were planned to receive annual MRI for 5 years. Identified lesions were classified as solid or cystic with or without connection to pancreatic ducts. Patients who refused or could not be investigated by means of MRCP were offered endoscopic ultrasound (EUS) as first screening tool. EUS was also proposed to patients with alterations at baseline MRI, according to the local practice at each center. Any indication for surgery was center-based after a multidisciplinary board meeting. Each center received the local ethics committee approval and enrolled subjects signed a proper informed consent. The registry is currently promoted through word of mouth, social networks, YouTube channels, the websites of the individual Institutions, as well as the website of the AISP (http://www.aisponline.it). The potential HRIs contact the involved centers spontaneously or they are referred by the general practitioner or other medical doctors. A genetic testing is not part of the protocol, but can be advised at each Centre based on clinical judgment.

Recorded Variables

The surveillance registry data include age, gender, category of risk (FPC or defined GS), total number of relatives with PC and degree of kinship, age of the youngest relative with PC, smoking and alcohol history, personal medical and oncological history, presence of diabetes, and time of its diagnosis.

Statistical Analysis

The chi-squared test was performed to test for differences of categorical parameters between subgroups, and *t*-test for continuous variables. A multivariate logistic regression analysis was performed to identify any risk factor associated with MRCP/EUS detection of pre-malignant or malignant lesion.

RESULTS

Population Characteristics

Between September 2015 and March 2018, 245 eligible subjects were offered to enter the registry and accepted, and through March 2018, 187 subjects (76.3%) completed the first round of screening and represent the study population described in the present manuscript. According to the risk categories, FPC and GS cases were 165 (88.2%) and 22 (11.8%), respectively. Table **1** shows the composition of the risk categories, as well as their demographics. The population of HRIs included 100 women and 87 men. Mean age was 52 ± 12. The mean number of affected relatives was 2 (range 1–5). Fifty-two (27.8%) HRIs had ≥ 2 FDR affected and the mean age of the youngest affected relative was 61 (range 28–79). Twenty-five HRIs (13.3%) reported a personal history of previous neoplasms, mostly gynecological cancers. MRCP and EUS were used as initial screening methods in 174 (93.1%) and 13 (6.9%) HRIs. Nine HRIs (4.8%) received EUS as supplementary investigation after MRCP. Of note, the reliability of reported family history of pancreatic cancer was verified in 120 out of 187 HRIs (64.1%) through evaluation of charts or other original documents of affected family members.

Table 1 Detail and demographics of HRIs enrolled

Characteristics of asymptomatic HRI who were enrolled in the registry	*n*
FPC	165 (88.2)
HBOC (*BRCA1*)	5 (2.7)
HBOC (*BRCA2*)	5 (2.7)
FAMMM (p16/*CDKN2A*)	3 (2.7)
Peutz-Jegher syndrome (*STK11/LKB1*)	5 (1.6)
Hereditary pancreatitis (*PRSS1*)	4 (2.1)

Variable	All patients (*n* = 187)	FPC (*n* = 165)	GS (*n* = 22)	*p* Value
Age, mean (SD)	51 ± 12	51 ± 12	47 ± 11	n.s.
Female, gender	100 (53.4)	67 (54.5)	33 (51.5)	n.s.
Ever smokers/ current smokers[a]	28 (15)	24 (14.5)	4 (18.1)	n.s.
Any regular alcohol intake	16 (8.5)	12 (7.2)	4 (18.1)	n.s.
AYR with PC, median (IQR)	61 ± 10	60 ± 11	66 ± 8	n.s.
Personal history of malignancies, n (%)	25 (13.3)	19 (11.5)	6 (24)	n.s.
HRI with 1 FDR affected	120 (64.2)	110 (66.7)	11 (50)	n.s. < 0.05
HRI with ≥ 2 FDR affected	53 (28.3)	53 (32.1)	—	n.s
HRI with family history of malignancies	118 (63.1)	101 (61.1)	17 (77.3)	
Number of relatives affected, median	1	1	1	

Data are expressed as number (%) or as mean (± SD)
HRI high-risk individual, *FPC* familial pancreatic cancer, *HBOC* hereditary breast–ovarian cancer syndrome, *FAMMM* familial atypical multiple mole melanoma, *GS* genetic syndrome, *AYR* age of the youngest relative, *FDR* first-degree relative
[a]Ever smoker is a person who has smoked 100 cigarettes or more in his/her lifetime.

MRCP Findings and Risk Categories

Figure 1 depicts the flow-chart of screening results. Overall, 44 (25.3%) HRIs had an abnormal finding at MRCP, with pancreatic cystic lesions being the most frequently diagnosed abnormality ($n = 42$). At MRCP the presumed radiological diagnosis of these cysts was mostly branch-duct IPMN (BD-IPMN) ($n = 28$, 64.2% of the cysts detected, 14 (51.9%) were multifocal. The mean diameter was 9 mm (range 3–25). Two (1.3%) HRI received a diagnosis of a suspected solid pancreatic mass, which was not further confirmed at EUS. One subject received a diagnosis of mixed-type (M)-IPMN, that was found to be a BD-IPMN at EUS. One subject with PJS received a diagnosis of malignant main-duct (MD)-IPMN, which was confirmed by EUS with fine-needle aspiration (FNA), and one FPC subject was diagnosed with a M-IPMN, further confirmed by EUS. Surgery revealed an invasive carcinoma/IPMN and a low-grade M-IPMN, respectively, in these two cases. No complications related to MRCP were reported. The diagnosis rate of MRCP for pre-malignant (IPMNs) or malignant lesions was 17.2 and 0.6%, respectively. BD-IPMNs and undefined cysts are currently enrolled in institution-specific follow-up programs for pancreatic cystic neoplasms. The diagnosis rate of MRCP for cystic lesion was 24.1%.

EUS Findings

The flow-chart of Fig. 1 reports EUS findings. Thirteen (6.9%) HRIs received EUS as first-line investigation. EUS detected 4 PC (30.8%) (all confirmed by FNA), 1 (7.7%) undefined cyst, 2 (15.4%) EUS features of chronic pancreatitis and one solid pseudopapillary tumor (7.7%). The examination was normal in 5 cases (38.5%). Two tumors were deemed amenable to surgery, the remaining two being metastatic cases that were treated with chemotherapy. In 9 further cases EUS was performed as supplementary diagnostic tool after MRCP, due to suspicious findings. In such cases, EUS confirmed 6 MRCP findings and deemed insignificant 2 suspected solid lesions and 1 suspected M-IPMN found at MRCP, that revealed to be fibrotic areas and a BD-IPMN, respectively. No complications related to EUS were reported. The 2 undefined cysts are currently enrolled in Institution-specific follow-up programs for cystic pancreatic neoplasms.

Risk Categories and MRCP/EUS Findings

Table 2 reports the MRCP/EUS findings of the cohort, comparing the results obtained in the groups of FPC and GS cases. When comparing the FPC and GS HRIs, there was no difference either in the rate of abnormalities and malignancies detected (27.9 vs 27.3% and 2.2 vs 4.5%, Fisher's exact $p = 1$ and $p = 0.469$, respectively). No malignant lesions were diagnosed in the *BRCA1/2* HRIs subgroup.

Surgery and Pathology

After multidisciplinary consultation, surgery was offered to 5 subjects (2.6%). Two total pancreatectomies and 2 distal pancreatectomies with splenectomy were performed. One further PC case deemed resectable was found locally advanced intraoperatively and a bypass surgery was performed. Pathology revealed an invasive carcinoma/IPMN, 1 PC (T1N0M0R0), a pseudopapillary tumor and a low-grade panglandular M-IPMN. No postoperative complications were reported. Considering the CAPS guidelines [7], the diagnostic yield of the present study for success of surveillance with diagnosis of target lesions was 1%. The 90-day postoperative mortality was nil.

Risk Factors Associated with Diagnosis of Pre-malignant or Malignant Lesion

A binary logistic regression analysis was performed with the diagnosis of pre-malignant or malignant lesion as dependent variable (yes/no), to ascertain the effects of age ($\leq > 50$ years), gender, alcohol and smoking habit, number of relatives affected

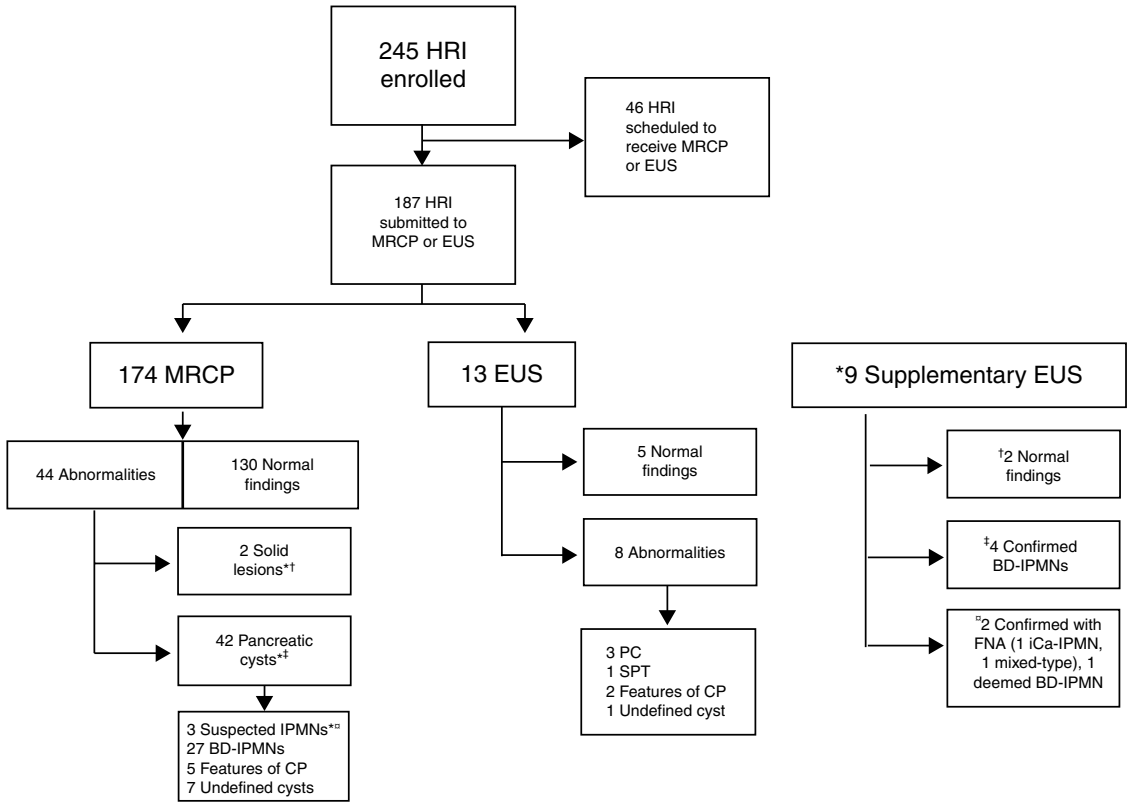

Fig. 1 Flow-chart of study results. HRI high-risk individuals, MRCP magnetic-cholangio pancreatography, EUS endoultrasonography, IPMN intraductal papillary mucinous neoplasm, BD-IPMN branch-duct intraductal papillary mucinous neoplasm, CP chronic pancreatitis, PC pancreatic cancer, SPT solid pseudopapillary tumor, FNA fine-needle aspiration, iCA-IPMN invasive intraductal papillary mucinous carcinoma. * = supplementary EUS

Table 2 MRCP/EUS findings per categories (p=n.s.)

Category of risk		
Screening results	**FPC (n=165)**	**GS (n=22)**
Abnormalities	46 (27.9)	6 (27.3)
PC	4 (2.2)	1 (4.5)
BD-IPMN	26 (15.7)	1 (4.5)
Undefined cystic lesions	7 (4.2)	1 (4.5)
Suspected solid lesions	2 (1.2)	—
Features of CP	5 (30.3)	2 (18.1)
M-IPMN	1 (0.6)	—
Degenerated IPMN	—	1 (4.5)

Data are expressed as number
FPC familial pancreatic cancer, *GS* genetic syndrome, *PC* Pancreatic ductal adenocarcinoma, *BD-IPMN* branch-duct intraductal papillary mucinous neoplasm, *CP* chronic pancreatitis, *M-IPMN* mixed-type intraductal papillary mucinous neoplasm

($\leq/>2$), number of FDR affected ($\leq/>1$), previous history of any malignancy (yes/no), medical certification of relatives suffering from PC (yes/no), and familial or genetic predisposition. At the multivariate analysis, age > 50 years (OR 3.3, 95%CI 1.4–8), smoking habit (OR 2.8, 95%CI 1.1–7.5), and having > 2 relatives with PC (OR 2.7, 95%CI 1.1–6.4) were independent factors associated with the diagnosis of pre-malignant and malignant lesions at MRCP/EUS (Table 3). Table 4 depicts the detailed individual features of HRIs who received a diagnosis of malignancy.

Follow-up

At the time this manuscript was written 2 out of 5 patients that received a malignant diagnosis were alive (mean follow-up 6.2 months, range 2–12). The two patients submitted to surgery were alive and free of recurrence after a median follow-up of 6.5 months. Of the remaining three patients who were diagnosed with an advanced disease, two died after a median follow-up of 7 months from the diagnosis; one patient died due to cardiovascular disease.

DISCUSSION

This is the first report of the Italian multicenter study on HRIs submitted to surveillance. After the first round of screening 28.3% (n=53) of subjects were diagnosed with a MRCP/EUS abnormality. Five malignant lesions were detected (2.6%); an unexpectedly high number of PC were identified by EUS (n=4, 2.1% overall), whereas MRCP identified only 1 invasive carcinoma/IPMN (0.6%). Of note, the category of HRIs that reported the

Table 3 Binary logistic regression analysis for risk factors associated with the diagnosis of a pre-malignant or malignant lesion at MRCP/EUS

Variable	Univariate Analysis (OR; 95% CI)	*p* Value	Multivariate Analysis (OR; 95% CI)	*p* Value
Male sex	(1; 0.4–1.1)	0.946		
Age > 50 years	(4.1; 1.7–9.6)	0.001*	OR 3.3, 1.4–8	0.008*
Ever smoking	(4.6; 1.9–11.1)	0.001*	OR 2.8, 1.1–7.5	0.032*
Alcohol drinker	(1; 0.2–3.8)	0.951		
Number of relatives affected > 2	(3.6; 1.6–8.1)	0.001*	OR 2.7, 1.1–6.4	0.026*
Number of FDR affected > 1	(1; 0.4–2.3)	0.967		
Previous history of any malignancy	(1; 0.8–1.2)	0.287		
Diagnosis of a defined GS	(0.4; 0.1–1.8)	0.253		
Verified certification of affected family members	(1; 0.4–2.3)	0.954		

FDR first-degree relative, *GS* genetic syndrome

greatest number of MRCP/EUS abnormalities was the one made of FPC subjects, however, the small sample size of the non-FPC subcohort does not allow us to make further speculations regarding this difference.

The diagnostic yield for MRCP/EUS was 24% for cystic lesions. The great majority of the detected cysts were BD-IPMN ($n = 28$, 62.2% of the cysts detected, 14.9% of the whole cohort). This finding is not surprising, as these lesions are frequent incidental findings in the general population, given the wide use of cross-sectional imaging, and it is debatable whether they should be considered a positive result of the screening process or not. This prevalence is in line with data already reported in a metanalysis by Signoretti et al. in 2018, where the pooled prevalence of cystic lesions in HRI enrolled in surveillance program was around 20% [9].

The rate of malignancies detected (2.6%) in our cohort is one of the highest reported so far [9–11, 16]. Notably, all but one malignancy was detected by EUS. As only 4.8% of probands was submitted to both MRCP and EUS, it is not possible to speculate about any possible difference in the detection rate of solid or cystic abnormalities with the two techniques. Current literature suggest that the two techniques are complementary with MRCP being able to detect more easily any cystic lesion, whereas EUS is likely more sensitive in the detection of solid ones [9, 17]. Two out of the five (40%) cancers diagnosed in the screening asymptomatic subjects were at a metastatic stage, and one was locally advanced. This rate is higher than in previous reports [9, 10], however this finding is consistent with a calculated pooled prevalence of 1% [9], and it cannot be considered a failure of a surveillance policy as the present results regard first-screening round only. On the other hand, in the two PC cases who received radical surgery, pathology revealed pT1 disease, thus potentially suggesting that surveillance led to early diagnosis with improved survival. Globally, there were no unnecessary surgical procedures being performed for benign lesions in this series, as the other resections were due to a M-IPMN and a solid pseudopapillary tumor, for whom surgery is the treatment of choice.

Personalization of the surveillance strategy is a key issue in screening protocols for pancreatic cancer. We therefore investigated factors that were associated with an increased risk of diagnosis of pancreatic abnormalities. HRIs aged > 50 years, ever smokers, and subjects with > 2 relatives with PC had a significantly increased risk of having a diagnosed pre-malignant or malignant lesion. Previous studies partially explored the association between such factors and the detection of a worrisome abnormality [18–20]. However, those studies were retrospective and more prone to bias or lack of information, and these three factors were not reported as independently associated with risk of significant abnormalities at a multivariate analysis before. Despite the design of this registry regarding each center discretion on the use of MRCP or EUS as a screening tool based also on patients' preference, it likely that in such a subgroup of HRIs the combined use of both MRCP and EUS, or their alternate use, possibly at shorter intervals, might be appropriate.

Some limitations, however, should be considered. First, although MRI with MRCP was the first-line examination in most cases, some subjects were investigated by EUS first, due to personal preferences. However, the results obtained by the two diagnostic tools are pooled in the present analysis to reflect the actual rate of significant findings in the whole cohort. Secondly, a quote of the diagnosed small pancreatic lesions considered BD-IPMN at MRCP might be other cystic lesions, despite experienced radiologists have been involved. The present protocol, indeed, did not include the need to perform EUS in all cases of cystic lesions, but this was done in some instances, similarly to what is considered common practice in sporadic cystic lesions. Finally, in our logistic regression analysis we considered as outcome variable the diagnosis of any malignant or pre-malignant pancreatic lesion, including BD-IPMN and not malignant lesions only. This was done due to the relatively low rate of malignant lesions which would not permit a meaningful analysis. Third, compared to current literature [9, 10], our registry differed on the age to initiate the surveillance and this might have been responsible for differences in the detection rate of pre-malignant or malignant lesions. However, the mean age of our cohort is in line with the one other studies [9, 10], giving more strength to the finding that HRI > 50 years are at higher risk to be diagnosed with a worrisome lesion.

Another limitation of this study regards the lack of a standardized genetic screening for pathogenic mutations associated with PC risk in individuals with FPC. Indeed, a significant group of subjects with FPC have been found to carry *CDKN2A* mutations, both in Italy [21] and in the Netherlands [22]. In addition, Vasen et al.

Table 4 Features of high-risk individuals who received a diagnosis of malignancy

Patient	Category of Risk	Location	Size (mm)	Pathology-Stage [25]	Treatment	F-up	F-up (mo)
1	PJS	Body	20	iCa/IPMN (pT1N0M0R0) Stage 1 A	DPS	Alive, FoR	11
2	FPC	Body	25	Stage IV	Chemotherapy	Deceased[a]	2
3	FPC	Head	40	cT4N1M0, Stage III	Bypass surgery	Deceased	2
4	FPC	Head	30	pT1N0M0R0, Stage 1 A	TP	Alive, FoR	4
5	FPC	Head-Body	70	Stage IV	Chemotherapy	Deceased	12

PJS Peutz-Jeghers syndrome, *iCa* invasive carcinoma, *DPS* distal pancreatectomy with splenectomy, *FoR* free of recurrence, *FPC* familial pancreatic cancer, *PC* pancreatic ductal adenocarcinoma, *LAPC* locally advanced pancreatic cancer, *TP* total pancreatectomy, *PD* pancreaticoduodenectomy.
[a]due to cardiovascular problems

found a higher diagnostic yield in GS subjects than in FPC ones [23]. Since we have not performed a genetic testing in all HRIs, we cannot exclude that some of this subjects may have been carriers of genetic mutations and that they have been deemed as belonging to the FPC group, due to familial aggregation only. This might have been generated an intrinsic bias on our results, when comparing the two groups. Recently, the possibility to investigate pancreatic cancer susceptibility genes with genetic testing at the time of diagnosis of all PC has been proposed [24]. Future studies, especially in the setting of HRIs, should therefore include genetic testing.

Some of the limitations reported might have been addressed by building a proper surveillance program, based on MRCP and EUS imaging, genetic testing, and shared among the Institutions involved. The form of the registry, with a high level of center discretion in the diagnostic pathway to follow, had been chosen since no dedicated funds were available and each center draws from personal resources and facilities.

In conclusion, the first-round screening results in Italy report a high rate of pancreatic malignancies ($n = 5$, 2.6%), mostly being advanced at baseline (60%). We identified factors associated with an increased risk of diagnosis of malignant or pre-malignant pancreatic lesions in HRIs (age > 50, smoking habit and > 2 relatives diagnosed with PC). Whether these data will also reflect an increased risk of developing de novo lesions or of progression of initial finding needs to be investigated during the following screening rounds that are planned for a duration of at least five years, with a planned end of enrollment in 2020.

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CONFLICTS OF INTEREST

Guarantor of the article: Salvatore Paiella

Specific author contributions: Study planning and conducting: SP, GC, GB, CB, MF, AZ, RP, SC; Data collection: SP, MS, RAZ, SC, IF, AG, LL, AL; Data interpreting: SP, GC, GMC, MF, RS, CB, AZ, MS, SC, RP; Drafting of the manuscript: SP, GC, AZ, GMC, MF, SC, MS, EI, RP, RS, AZ, LF; Manuscript review: CB, LF, MF, AZ, GB. All authors have approved the final draft submitted.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE?

- ✓ Pancreatic cancer surveillance programs may detect malignant and pre-malignant lesions in high-risk individuals.
- ✓ Two groups of HRIs can be identified, one with a familial predisposition and one with a known genetic frailty.

WHAT IS NEW HERE?

- ✓ After the first-round of screening of the Italian registry the rate of malignancies was 2.6%.
- ✓ Some risk factors for the detection of pre-malignant or malignant lesions were found.

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Systematic review and meta-analysis: Prevalence of incidentally detected pancreatic cystic lesions in asymptomatic individuals

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ABSTRACT

Background & aims: Pancreatic cystic lesions (PCLs) are frequent incidental findings. As most PCLs require costly diagnostic evaluation and active surveillance, it is important to clarify their prevalence in asymptomatic individuals. We therefore aimed at performing a systematic review and meta-analysis to determine it.

Methods: a systematic search was conducted and studies meeting inclusion criteria were included. The prevalence of PCLs was pooled across studies. A random effect model was used with assessment of heterogeneity.

Results: 17 studies, with 48,860 patients, were included. Only 3 were prospective; 5 studies were conducted in the US, 7 in Europe, 4 in Asia and 1 in Brazil. The pooled prevalence of PCLs was 8% (95% CI 4–14) with considerable heterogeneity ($I^2 = 99.5\%$). This prevalence was higher in studies of higher quality, examining older subjects, smaller cohorts, and employing MRCP (24.8% vs 2.7% with CT-scan). The pooled rate of PCLs was four times higher in studies conducted in the US than in Asia (12.6% vs 3.1%). 7 studies reported the prevalence of mucinous lesions, with a pooled rate of 4.3% (95% CI 2–10; $I^2 = 99.2\%$), but of 0.7% only for worrisome features or high risk stigmata.

Conclusion: The rate of incidentally detected PCLs is of 8%. Mucinous lesions are the most common incidentally detected PCLs, although they rarely present with potential indication for surgery. The observed different rates in the US and other geographic Areas suggest that different protocols might be necessary to help balancing costs and effectiveness of follow-up investigations in asymptomatic subjects.

Introduction

Pancreatic cystic lesions (PCLs) are frequent incidental findings diagnosed during abdominal ultrasonography or cross-sectional imaging. The increasingly widespread use and the improved detection accuracy of imaging tests have led to an epidemic of PCLs with prevalence rates reported as high as 40%, in a clinical scenario that might be considered that of a "technology-related disease" [1].

PCLs comprise different entities, each of them with peculiar biological behavior ranging from benign to premalignant or frankly malignant neoplasms [2]. Mucinous pancreatic cystic lesions are associated with a potential risk to develop malignancy and deserve either an active treatment or surveillance [3], while serous cysts are benign lesions [4]. Intraductal Papillary Mucinous Neoplasms (IPMNs) represent the most common PCL. According with current guidelines [5–8] they should be treated surgically in the presence of major symptoms, morphological changes often defined as high risk stigmata (HRS), or when malignancy is demonstrated by cytology. In the presence of an IPMN of the branch ducts (BD-IPMN) with size exceeding 30 mm or thickened and enhanced cystic wall or non-enhancing mural nodule or moderate main duct dilatation (5–9 mm) or in presence of abrupt change in pancreatic duct caliber with distal gland atrophy (characteristics usually named worrisome features –WF–), surgery might be considered and endoscopic ultrasound (EUS) with or without aspiration/biopsy is

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indicated to better analyze the morphology/cytology of the PCL, in order to stratify the risk of malignancy.

However, the vast majority of IPMNs are BD-IPMNs without any of the above mentioned signs and in patients who would be fit for surgery, these lesions require follow-up by means of Magnetic Resonance Imaging (MRI) with contrast medium and cholangiopancreatography (MRCP) or with EUS with specific time intervals.

In a recent meta-analysis [9] the risk of malignant transformation of these lesions has been calculated to be equal to 7/1000 per year, and despite the need to maintain surveillance in the long-term is debated [10], recent data suggest that it cannot be stopped after 5 years [11–13].

The surveillance of PCLs, and particularly of IPMNs, has become a challenge for health\insurance systems considering their substantial costs and resource burden. Moreover, the sustainability of a surveillance policy depends on the actual prevalence of PCLs in the general population. It is, therefore, important to clarify as accurately as possible the prevalence of PCLs, and particularly of mucinous cystic lesions, in subjects without a history of pancreatic disease. However, these data are sparse, heterogeneous, with a wide range of prevalence rates, but no systematic and comprehensive analyses examined this issue. The present systematic review and meta-analysis aimed at evaluating the prevalence of incidentally diagnosed PCLs, particularly mucinous lesions.

Materials and methods

Search strategy

A computerized literature search of the MEDLINE database did not identify any publication related to systematic review on the prevalence of incidentally diagnosed pancreatic cystic lesions in healthy subjects or in asymptomatic population. A MEDLINE search was therefore run until January 2018. Specific search terms were: *(pancreatic cyst OR pancreatic cysts OR pancreatic cystic lesions OR intraductal papillary mucinous neoplasia OR pseudocyst OR pancreatic mucinous cyst) AND (radiological technique OR magnetic resonance OR multi-detector OR radiological imaging OR EUS OR ecoendoscopic ultrasound OR tomography OR MRI OR cholangiopancreatography OR abdominal imaging OR US OR MDCT OR CT) AND (occasional OR incidental OR incidence OR prevalence OR accidentally OR asymptomatic)*. The methodology was developed from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [14].

The titles of all identified articles were screened to ascertain their relevance. Abstracts and/or full texts of selected potentially relevant papers were evaluated. Possible further articles were identified by hand-searching reference lists in order to identify potentially relevant studies, missed at our search. In the case of duplicate publications, the most recent or the most informative one in terms of number of cases or available data, was included.

Inclusion/exclusion criteria

Studies were considered if they met the following criteria: 1) written in English; 2) inclusion of patients without history of pancreatic disorders or symptoms suggestive for them; 3) all patients underwent second or third level imaging (CT-scan, MRI ± MRCP or EUS) not to investigate primarily the pancreatic gland; 4) data about prevalence and characteristics of cystic lesions were reported.

Studies were excluded if they were available as abstract only because the abstracts did not allow full data extraction. We also excluded: 1) case reports or small case series of <20 cases; 2) papers investigating the prevalence of pancreatic cystic lesions in specific subset of patient, such as liver/pancreas transplanted patients or cluster of patients with specific type of neoplastic disease.

Two independent reviewers (G.Z. and M.S.) carried out study identification and selection and resolved their disagreements by discussion or by consulting a third reviewer (G.C.). Excluded studies and the reasons for exclusion were recorded.

Data extraction and quality assessment

Two reviewers (G.Z. and M.S.) independently extracted the data from each study and resolved their disagreements by discussion or by consulting a third reviewer (G.C.).

From the studies that met the eligibility criteria, the following data were collected: 1) study: publication year, study design, study location; 2) patients: total number of asymptomatic patients evaluated, age, sex, risk factors for pancreatic disease; 3) imaging: type of imaging procedure, imaging review, indication for imaging; 4) cases: total number of patients incidentally diagnosed with PCLs, prevalence according with age; 3) cyst features: single cyst, mean/median cyst size, maximum cyst size, connection to the main duct, location, calcification, MD dilatation, worrisome features and/or high risk stigmata; 4) Cyst diagnosis: IPMN, pseudocysts, MCN, SCN; 5) extra-pancreatic cysts.

We then developed a summary table of the relevant studies listing the population characteristics and outcomes.

The quality of the studies was evaluated independently by two reviewers (GZ and MS) using the Newcastle-Ottawa Scale with a dedicated quality appraisal tool including 7 items. Studies with a score ≥7 were considered of high quality [15].

Statistical analysis

A meta-analysis of all eligible studies identified was planned using the software package Comprehensive Meta-Analysis (Biostat, Englewood, NJ, USA) using a random-effects model [16]. In addition to within-study variance, the random-effects model considers heterogeneity among studies. The corresponding 95% confidence intervals (CI) were calculated using exact methods and assuming a Poisson distribution. We present the random-effect model because we believe that the relevant variation in the risk is most likely a consequence of inter-study differences. The quantity of heterogeneity was assessed by means of the I^2 value [17]. The I^2 quantity describes the percentage of total variation across studies that is caused by heterogeneity and not by chance. We considered an I^2 value of 25% or lower as trivial heterogeneity, and an I^2 value of 75% or higher as considerable heterogeneity. Publication bias was assessed using the Begg and Mazumdar test. A p-value <0.05 was accepted as statistically significant. Before performing the analysis, we developed the following a priori hypotheses to examine whether these had any effect on the prevalence of PCLs in asymptomatic individuals and to explore reasons for any heterogeneity observed: (a) type of imaging employed to investigate the pancreas (MRCP vs MDTC or MRI); (b) sample size (<1000 or ≥ 1000 individuals); (c) mean age (≥55 or <55 years) of the analysed population; (d) area of origin (i.e. United States, European or Asian countries); (e) quality of the studies (quality score <7 or ≥7/10).

Results

Search result and study selection

The study selection process is summarized in Fig. 1. A total of 1070 references were identified by the MEDLINE search. After a primary screening of the titles, 1009 studies were excluded because they did not fit the area of interest.

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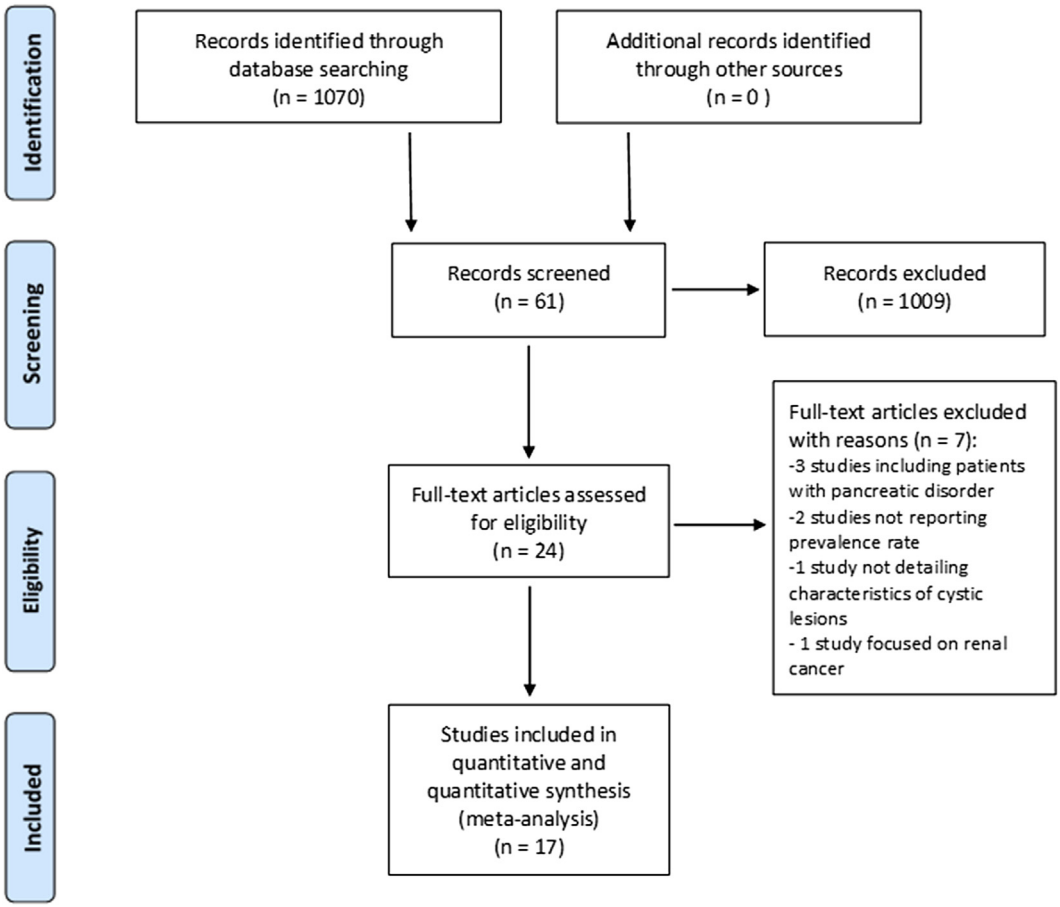

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of assessment of studies identified in the systematic review.

The remaining 61 records were screened in more detail and 24 were considered potentially appropriate for the analysis.

Of these, 7 studies were discarded with reason: 3 studies [18–20] also enrolled patients with an history or suspect of pancreatic disorders, 2 studies [21,22] did not provide sufficient data to calculate the prevalence rate because the denominator was not expressed, 1 study [23] did not describe the characteristics of the diagnosed cystic lesions and 1 study [24] analysed a specific patients' cluster (renal tumors).

Finally, 17 studies fulfilled all inclusion criteria, and were considered both for qualitative analysis and quantitative synthesis.

Study characteristics and quality assessment

The 17 included studies were published between 2008 and 2018 [1,25–40]. Five were conducted in the USA, 7 in Europe (4 in Italy and one respectively in The Netherlands, Germany and Turkey), 4 in Asian countries (two studies both in Korea and in Japan) and one in South America (Brazil). All papers were in English language.

Three studies [30,36,39] investigated the prevalence of incidental PCLs in a specific subgroup of patients compared with controls and we included in our analysis only data concerning the latter.

Overall, 48,860 asymptomatic patients without history or clinical suspect of pancreatic disorders were included.

The descriptive characteristics of the seventeen included studies are summarized in Table 1.

All studies were mono-institutional and the study design was cross-sectional for all of them, being retrospective in 14 and prospective in 3 [25,34,35], respectively. The number of enrolled patients ranged from 110 [36] to 21,745 [37], and the percentage of males ranged from 26% [31] to 65% [28].

The mean age of the enrolled subjects ranged from 47 [31] to 68 years [39], while these data were not available in two studies [32,33]. The performed diagnostic procedures varied considerably among the studies. However, all but one study [39] in which the 192 enrolled patients underwent different investigations (either CT scan or MRI ± MRCP), employed a single diagnostic tool.

Abdominal MRI with or without intravenous contrast was the most commonly employed diagnostic procedure (11 studies). MRCP was also performed in 6 of them [1,29,30,38–40] with a huge variability: in two studies [1,39] it was employed in a minority of patients (respectively 19% and 15%) and in another one [29] all patients underwent MRCP and only a little part of them (20%) was investigated also with MRI with intravenous contrast.

Five studies considered exclusively MDCT scans ± contrast medium [25,26,32,33,37] and only one study [34] employed EUS.

Few studies reported patients' exposition to well known risk factors for developing pancreatic disorders (such as cigarettes smoking, alcohol consumption, increased BMI and diabetes mellitus) [1,34,38,40] and first degree family history for pancreatic diseases [1,28,38].

While a "pancreatic indication" for the diagnostic procedure was an exclusion criterion for study inclusion, the study employing EUS [34] included 6% of cases with a previous acute pancreatitis episode. As it was clarified that the episode occurred at least 3 months before the study enrolment, with pain resolution 8 weeks before the EUS and no evidence of acute fluid collection or

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Table 1
General features of the 17 studies included in the quantitative analysis.

Author (year)	Country	Study Setting	Study design	Patients	Male (%)	Mean Age	Diagnostic procedure(s)	Imaging revision	Indication	Patients with PCLs (%)	Age of patients with PCLs	Patients with Mucinous lesions (%)
Kromery (2018) [40]	Germany	Single center	Retrospective	1077	521 (48.4)	55.8	WB-MRI (1.5T) +MRCP	Yes	Healthy population	494 (45.9)	60.5 (SD ± 11.6)	NR
Zerboni (2017) [39]	Italy	Single center	Retrospective	192	118 (61)	68	MDCT + c.e.; or MRI 1.5T ± c.e.; or MRCP	Yes	Not pancreas related	19 (10)	73 (95% CI 68.1–78.7)	14 (74)
Mizuno (2017) [38]	Japan	Single center	Retrospective	5296	3189 (60.2)	55.7	MRI + MRCP 3T, (thickness 3–5 mm)	Yes	No medical indication	724 (13.7)	62.6 (SD ± 10.7)	393 (54)
Chang (2016) [37]	South Korea	Single center	Retrospective	21,745	13,046 (60)	51.8	MDCT + c.e. (thickness 3 mm)	Yes	Not pancreas related	457 (2.1)	58 (SD ± 10)	383 (84)
Kim J.A. (2016) [36]	USA	Single center	Retrospective	110	49 (44.5)	47.5	MRI 1.5T (thickness 6–10 mm)	Yes	Not pancreas related	25 (22.7)	NR	NR
Ulus (2016) [35]	Turkey	Single center	Prospective	118	71 (60)	47.4	WB-MRI 1.5T	No	Healthy population	1 (0.8)	NR	1 (100)
Moris (2016) [1]	USA	Single center	Retrospective	500	252 (50)	60	MRI ± c.e. (1.5 or 3 T); MRCP 19%	Yes	Not pancreas related	208 (41.6)	63.8 (SD ± 11.2)	72 (35)
Sey (2015) [34]	USA	Single center	Prospective	341	154 (45)	59	EUS ± FNA	No	Not pancreas related	32 (9.4)	NR	NR
Ippolito (2015) [33]	Italy	Single center	Retrospective	6389	NR	NR	MDCT + c.e. (thickness 2–5 mm)	Yes	Not pancreas related	192 (3)	63 (SD ± 11)	NR
Zanini (2015) [32]	San Marino (Italy)	Single center	Retrospective	650	355 (55)	NR	16-MDCT ± c.e. (thickness 2.5 mm)	Yes	Not pancreas related	35 (5.4)	77 (53–93)	NR
de Oliveira (2015) [31]	Brazil	Single center	Retrospective	2583	672 (26)	47	MRI (3T) + c.e.	No	Not pancreas related	239 (9.3)	61 (SD ± 12.4)	NR
Matsubara (2012) [30]	Japan	Single center	Retrospective	1226	686 (56)	62	MRI (1.5 T, thickness 5 mm) and MRCP	Yes	Not pancreas related	123 (10)	69 (38–88)	NR
Girometti (2011) [29]	Italy	Single center	Retrospective	152	87 (57)	57	MRCP (1.5 T); MRI + c.e. (20%)	Yes	Not pancreas related	68 (44.7)	NR	48 (71)
de Jong (2010) [28]	Holland	Single center	Retrospective	2803	1822 (65)	51	MRI + c.e. (1.5 T)	Yes	Without medical indication	66 (2.4)	60 (SD ± 10.9)	NR
Lee (2010) [27]	USA	Single center	Retrospective	616	259 (42)	54	MRI (1.5 T, thickness 4 mm)	Yes	Not pancreas related	83 (13.5)	69 (SD ± 13)	NR
Laffan (2008) [26]	USA	Single center	Retrospective	2832	1445 (51)	58.2	16-MDCT + c.e.	Yes	Not pancreas related	73 (2.6)	NR	NR
Kim Y.S. (2008) [25]	South Korea	Single center	Prospective	2230	1338 (60)	57.5	16-MDCT + c.e.	Yes	Asymptomatic patients, CRC screening with CTC	4 (0.2)	NR	4 (100)

PCL = pancreatic cystic lesion; NR = not reported; MDCT = multidetector computed tomography, MRI = magnetic resonance imaging, T = tesla; MRCP = magnetic resonance cholangio-pancreatography, WB-MRI = whole body magnetic resonance imaging, EUS = endoscopic ultrasound, FNA = fine needle aspiration; CTC = computed tomography colonoscopy; CRC = colorectal cancer; c.e. = contrast-enhanced.

pseudocyst at the previous abdominal imaging, this study was not excluded.

As far as regards the quality of the included studies, the Newcastle-Ottawa score ranges from 4/10 to 9/10. Only six studies were scored as “high quality” (>7/10) [1,28,31,34,38,40].

Pooled prevalence rate of pancreatic cystic lesions

The prevalence of incidentally diagnosed pancreatic cystic lesions ranges from 0.2% to 45.9%, with a pooled prevalence of 8% (95% CI 4–14), as detailed in Fig. 2. No publication bias was found (Begg and Mazudmar Kendall's tau = −0.07, p = 0.64). There was however a considerable heterogeneity between the studies ($I^2 = 99.5\%$).

In order to explore possible reasons for this substantial heterogeneity, we repeated the analysis based on our a priori hypothesis considering different covariates (see Fig. 3). Studies with mean age of the enrolled subjects ≥55 years old [1,25,26,29,30,34,38–40] had a pooled prevalence of 11.3%, while those with mean age <55 years [27,28,31,35–37] of only 5.7%. In both cases, however, the heterogeneity was very high (I^2 >99% for both).

When we analysed the results taking into consideration the performed diagnostic procedure, the pooled prevalence of PCLs resulted 2.7% (95% CI 2–4) in the studies employing MDCT ± c.e. [25,26,32,33,37,39], without a reduction of heterogeneity ($I^2 = 93.7\%$). In the four studies using MRCP [29,30,38,40] the prevalence of PCLs was instead as high as 24.8% (95% CI 10–48), with similar heterogeneity ($I^2 = 99.5\%$). When the sample size of the studies (<1000 or ≥1000) was considered, a higher pooled prevalence was seen in studies with <1000 enrolled subjects

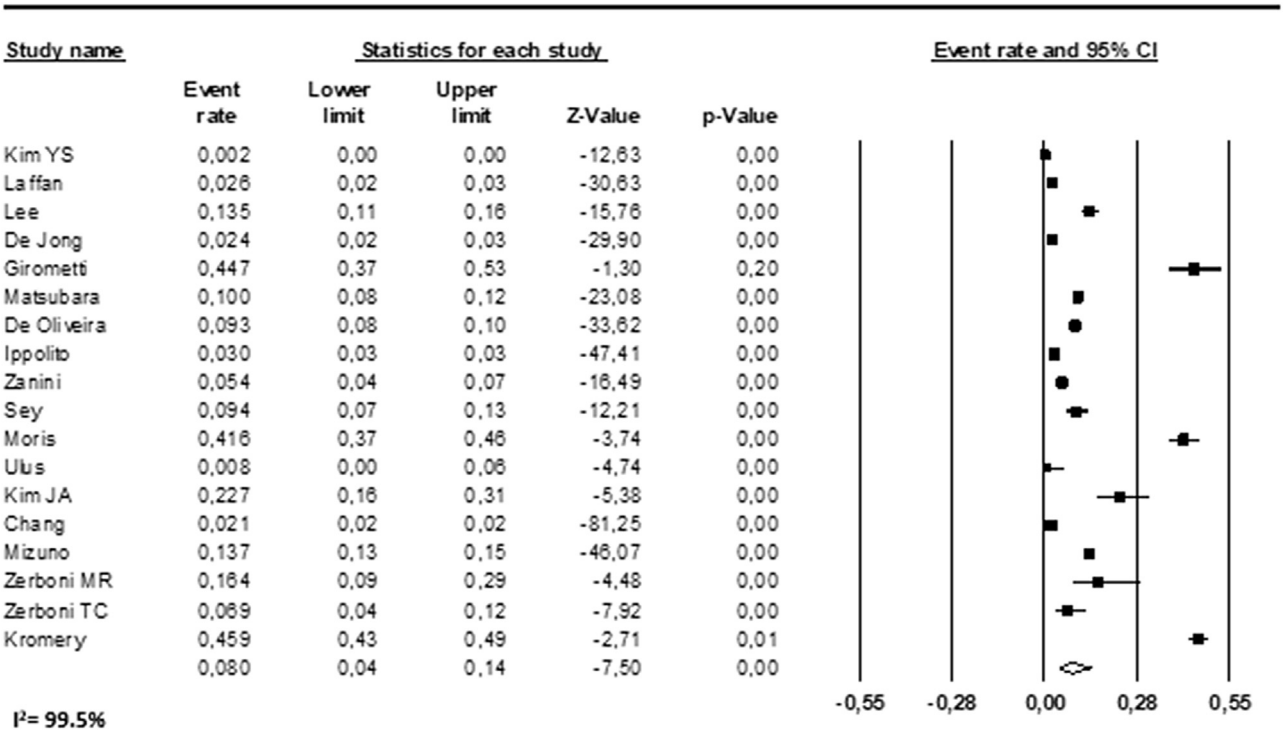

Fig. 2. Pooled prevalence of all pancreatic cystic lesions (PCLs) in the 17 examined studies. The pooled prevalence resulted of 8% (95% CI 4%–14%), with considerable heterogeneity ($I^2 = 99.5\%$).

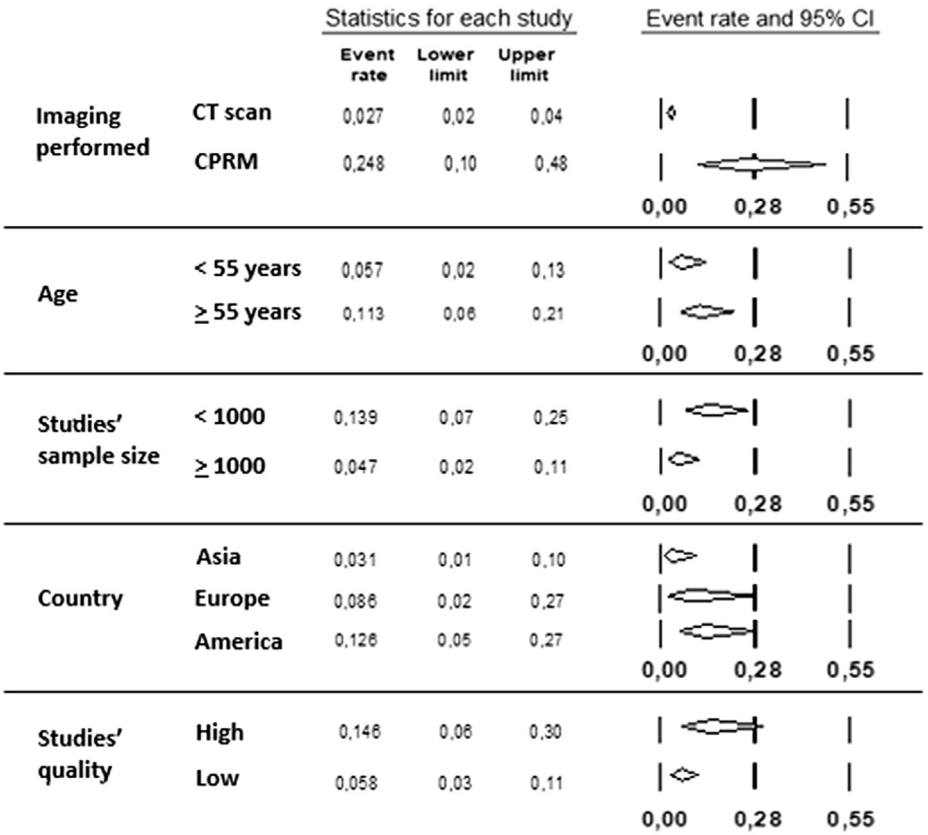

Fig. 3. Prevalence of PCLs according to variables considered a priori for sensitivity analysis: A) age (studies with mean/median population age ≥55 years compared with those with mean/median age <55 years); B) different diagnostic procedures [studies using CT scan ± medium contrast vs Magnetic Resonance Cholangio-Pancreatography (MRCP) with or without MRI]; C) sample size (<1000 vs ≥ 1000 cases); D) geographic area in which the studies were conducted (Asia, Americas and Europe); E) quality of the study (high vs low quality).

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[1,27,29,32,34–36,39] (13.9%, 95% CI 7–25; $I^2 = 97.4\%$) compared to those enrolling ≥1000 people [25,26,28,30,31,33,37,38,40] (4.7%, 95% CI 2–11; $I^2 = 99.7\%$).

When considering the country of origin, the pooled prevalence of PCLs resulted 3.1% (95% CI 1–10; $I^2 = 99.7\%$) in studies conducted in Asia [25,30,37,38], 12.6% (95% CI 5–27; $I^2 = 99\%$) for those carried out in the Americas (either US or South America) [1,26,27,31,34,36], and 8.6% (95% CI 2–27; $I^2 = 99.6\%$) for those conducted in Europe [28,29,32,33,35,39,40].

As far as regards the quality of the studies, the six studies of "high quality" [1,28,31,34,38,40] score had a higher pooled prevalence of PCLs of 14.6% (95% CI 6–30), with $I^2 = 99.5\%$, when compared to the 11 studies with a "lower quality" score [25–27,29,30,32,33,35–37,39], which showed a pooled estimate rate was of 5.8% (95% CI 3–12), with $I^2 = 98.8\%$.

Pooled prevalence rate of mucinous cystic lesions and of lesions harbouring clinically relevant features

Seven of the 17 studies reported data on the specific type of PCLs. In these studies, the pooled prevalence of all PCLs was 7% (95% CI 2–19), with substantial heterogeneity ($I^2 = 99.6\%$) and the pooled prevalence of lesions diagnosed as of likely "mucinous nature" was 4.3% (95% CI 2–10; $I^2 = 99.2\%$) (see Fig. 4). Most of these PCLs were considered IPMNs.

Of the included 17 studies, 5 did not provide details about the morphology of the PCLs [25,36–38,40]. Of the remaining studies, 4 did not report cases with morphological aspects suggestive of "worrisome features" or "high risk stigmata" [1,26,28,29], whereas in eight studies [27,30–35,39] these characteristics were mentioned. The rate of lesions with worrisome features (WF) or high risk stigmata (HRS) such as solid nodules, thickening of the wall and main duct calibre > 5 mm ranged from 0.1% to 3.6%. The pool prevalence of either WF and/or HRS at diagnosis resulted of 0.7% (95% CI 0–1) with considerable heterogeneity ($I^2 = 85.3\%$) (see Supplementary Fig. 1).

Most of the included studies did not provide information regarding the follow-up of the incidentally diagnosed PCLs, and when available, these data were limited to a small fraction of the examined cohort.

Discussion

To our knowledge, this is the first meta-analysis investigating the prevalence of incidentally diagnosed PCLs in individuals asymptomatic for pancreatic disorders. In the present study, data from seventeen publications were analysed, resulting in a pooled prevalence rate of 8%, with a wide range (0.2%–45.9%) and considerable heterogeneity.

Only seven of the included studies provide sufficient data to define the nature of the PCLs. In these studies, the pooled prevalence of PCLs was of 7% and that of mucinous lesions was 4.3%, representing 60% of all incidentally diagnosed PCLs. However, at the time of incidental diagnosis, a minority of these lesions (0.7%) harboured features that might pose the suspicious of malignancy and an indication for surgery, such as main pancreatic duct dilation, thickened wall and mural nodules. Unfortunately, the included studies were not focused on the follow-up of these lesions, so their clinical relevance in the long-term could not be examined.

The strengths of the present study include an exhaustive literature search, rigorous statistical methods, and pooling of data to allow synthesis of all the available evidence examining the possible yield\burden of testing for pancreatic cysts in asymptomatic individuals. Nevertheless, the most relevant weaknesses of the study, as concerns many systematic review and meta-analysis, arise from the limits of the available evidence.

Most of the studies eligible for the current analysis were retrospective and for five of them the past medical history was not available; however, they include patients that were asymptomatic at the time of examination, without known health co-morbidities.

Moreover, since the included studies evaluated the radiological results collected during a long time span (up to 10 year), imaging were obtained with different machines and protocols. The authors of the studies with a longer time of recruitment considered, however, the effect of the different distribution of radiological modalities on the PCLs' rate. Moris et al. [1] tried to objectify this correlation performing an adjusted multivariate-analysis, that showed a very strong relationship between PCLs detection and both the MRI hardware and the software versions. Therefore, they confirmed the direct relationship between the number of PCLs detected and the newer MRI version used. On the other hand, Kim J.A. and colleagues [36] matched cases and controls (respectively patients affected by autosomal dominant polycystic kidney disease -ADPKD- and patients who underwent abdominal MRI imaging without history or suspect of both ADPKD and pancreatic disorders) not only for demographic characteristics but also for the timing of abdominal procedures (within 1 year of each other), in order to reduce the "technology influence" on the results.

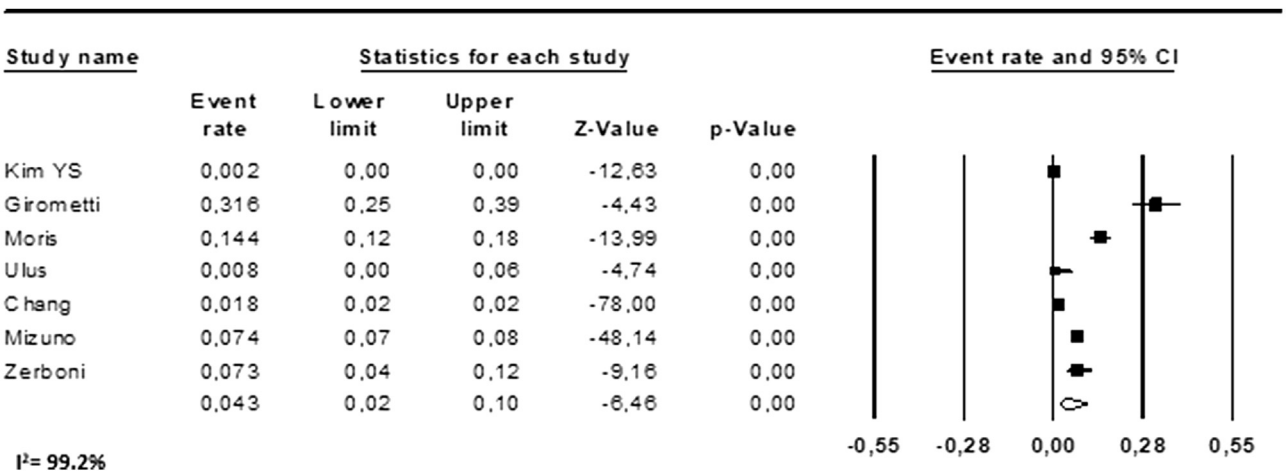

Fig. 4. Prevalence of pancreatic Mucinous Cystic Lesions in studies providing sufficient data to define the nature of the PCLs. The pooled prevalence resulted of 4.3% (95% CI 2%–10%) with considerable heterogeneity ($I^2 = 99.2\%$).

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The highest [40] and one of the lowest [35] rates of PCLs were surprisingly reported by two studies using the same radiological procedure, such as whole body MRI. Paramagnetic contrast was not administrated in both, but, probably, the complementary use of MRCP in one of them [40] could explain the increasing rate of pancreatic findings, although the difference remains huge.

As mentioned before, a considerable degree of heterogeneity was present in all the conducted analyses. A number of a priori hypotheses were made to explain heterogeneity, such as age, country of origin, number of enrolled subjects, different type of abdominal cross-sectional imaging and quality of the study. However, while some of these factors influence the rate of PCLs, they could not explain heterogeneity.

The pooled estimate rate of occasional PCLs was higher in older subjects. This result is in line with previous autopsy series [41] reporting a rate of incidental PCLs of about 25%, which increases with age. The pooled rate of incidental PCLs also increased in studies enrolling a lower number of patients, in those with a higher quality score and in patients undergoing MRCP. As far as concerns the country of origin, the pooled rate of PCLs was four times higher in studies conducted in the US than in those conducted in Asia (12.6% vs 3.1%), with roughly intermediate results in Europe (see Fig. 3). This pooled data was in contrast with Laffan's et al. results [26], according to which Asians had an increased odds ratio of 3.57 (CI 95% 1.05–12.13) of having a pancreatic cyst compared with other racial groups.

A possible explanation for this difference might be that half of the studies with a better quality score were performed in the US. Also, risk factors associated with an increased risk of pancreatic cancer and of PCLs, such as diabetes and obesity [1,38,40,42] might be more common in the US. The possible role of geographical/racial differences might deserve further investigation also in view of “patients’ tailored work-up” during the management of PCLs.

Despite the limitations listed above, notably the results of the meta-analysis are similar in terms of incidence of PCLs to those of the only prospective study performed with EUS (respectively pooled rates of 8% and 9.4%), strengthening the reliability of the present data. Indeed, EUS performed after TC or MRI increases the rate of pancreatic cystic lesions undiagnosed by initial cross-sectional imaging [43]. A more recent study on this topic and employing EUS was published after our search [44]. In this study the rate of PCLs in asymptomatic subjects was as high as 24%, in line with the data from autopsy series mentioned above [41], confirming the high sensitivity of EUS in diagnosing PCLs.

In conclusion, the findings of this meta-analysis highlight the considerable high prevalence of PCLs in asymptomatic and/or apparently healthy individuals. Furthermore, taking into account both the higher prevalence of PCLs in older and asymptomatic subjects and the presence of comorbidities and the low rate of potential malignant features, radiological follow-up in this group of patients is expected not to be always cost-effective [45]. These data reinforce the need to redefine the surveillance strategy proposed by international consensus guidelines, according with a new scale of clinical risk based on individual subjects’ characteristics.

Authors’ potential competing interests

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2018.11.014.

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