Age distribution patterns of patients with conventional ductal adenocarcinoma of the pancreas. A single-institution study of 580 cases re-evaluated using current histopathological diagnostic criteria

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There are a few studies concerning epidemiology of pancreatic ductal adenocarcinoma (PDAC) in the Polish population. Analysis of age distribution patterns of patients with different types of cancer may be useful for studying their specific biology.
In the present study we aimed to describe age distribution patterns of 580 patients with PDAC diagnosed in one centre during a 25-year period. All the histopathological diagnoses were re-reviewed using current histopathological diagnostic criteria. Age distributions of selected subpopulations of patients (defined based on gender, potential tumour resectability and type of the surgery) were compared using mean values, medians, age frequency density plots and logarithmic plots of age-specific frequencies.
The mean and median values of patients' age were 60.8 y and 61.0 y, respectively. Females were approximately 2 y older than males at the time of PDAC diagnosis. Females with non-resectable PDAC were approximately 2 y older than females with resectable tumours. Mean age values of males with non-resectable and resectable PDAC were similar. Patients treated with pancreaticoduodenectomy were approximately 2 y older than patients undergoing other types of resections. Age distribution density plots showed that some subgroups of patients studied were somewhat heterogeneous and might include several yet poorly recognized clinico-pathological entities. Logarithmic plots of age-specific frequencies showed that PDAC epidemiology is in concordance with a multistage theory of carcinogenesis.
PDAC is an age-dependent cancer. Single-institutional pathology-oriented cancer epidemiological databases may add some information to population-based cancer registries.

Key words: pancreatic neoplasms, pancreatic cancer, pancreatic ductal carcinoma, age, vital statistics, incidence.

Introduction

In 1954, [1] Drs. Armitage and Doll in their landmark paper described that age-oriented epidemiological data may be successfully used for generation of hypotheses concerning carcinogenic pathways.

It is now clear that analytical studies on age distribution patterns (ADPs) may be useful for exploring:

- process of carcinogenesis,
- dynamics of incidence rates,
- cohort and period effects,

- cancer risk factors,
- biology of both sporadic and inherited neoplasms, etc. [2-6].

However, the usefulness of such approach has been appreciated in pathology community only recently [7-10]. Therefore, a scant number of papers focused on application of epidemiologic tools for exploration of pathology-oriented databases are available.

Population-based data concerning cancer incidence and mortality rates make an excellent baseline to generate and/or test hypotheses on age-related phenomena in cancer epidemiology. However, they frequently do not contain appropriate histopathological variables. A significant proportion of cancer diagnoses abstracted in these data files may be stated based on clinical/radiological grounds only, without histopathological and/or cytological verification. Microscopic diagnoses, even if available, may be biased since they are made by many pathologists who may use not strictly the same diagnostic criteria [7, 8].

Therefore, studies based on single-institutional experience may be also valuable for description of epidemiologic-pathologic data despite their well-recognized limitations. The strength of that approach results from the application of strict diagnostic criteria to the studied clinico-pathological entity by a limited group of pathologists.

Conventional pancreatic ductal adenocarcinoma (PDAC) is one of the most frequent and most deadly abdominal cancers throughout the world [11-13]. In 2007, 1575 males and 1607 females were diagnosed with pancreatic malignancy in Poland [14].

Some population-based studies concerning the epidemiology of pancreatic malignancies in Poland are available [15, 16]. However, histopathological data were not included in those studies.

Among pancreatic malignancies newly diagnosed in Poland in 2007, only 49% of these diagnoses in males and 44% in females were verified microscopically [14]. This indicates that studies on epidemiological analysis of pathological data may provide an additional, independent view concerning PDAC epidemiology.

The aim of the present study was to describe age-related characteristics of a large group of patients with PDAC treated and diagnosed in a single reference centre for pancreatic diseases during a 25-year period.

Material and methods

Data acquisition

Data on all cases of pancreatic resections and surgical biopsies evaluated in our Department between 1985 and 2009 were selected from paper and computerized databases of pancreatic specimens. Additionally, autopsy database was searched for cases of newly diagnosed pancreatic neoplasms. All these cases were checked for microscopic slides availability. The available slides were retrieved from departmental archives. If slides were not available (mainly because they were sent for second opinion on patient's or clinician's request) archives of paraffin tissue blocks were searched – if blocks were available, new sets of slides were prepared and stained with haematoxylin and eosin in a routine manner.

Histopathological diagnoses

Only cases with available slides or paraffin blocks were included in the present study. These cases were examined microscopically by two of the authors (L.L. and J.P.) and new histopathological diagnoses were established. The primary (signed-out) diagnoses were not taken into consideration. The diagnostic criteria were based on the recent US Armed Forces Institute of Pathology Fascicle on pancreatic neoplasms [17]. Based on these criteria, cases of conventional, usual-type PDAC were selected.

The cases of PDAC variants (adenosquamous carcinoma, colloid carcinoma, medullary carcinoma, and others), cases of invasive carcinomas associated with intraductal papillary neoplasms and mucinous cystic neoplasms, non-ductal tumours (endocrine neoplasms, solid-pseudopapillary neoplasms, and others), secondary tumours and non-malignant or non-invasive lesions were carefully excluded.

Evaluation of pancreatic cytopathology samples should always be done with substantial support of clinical and radiological data [18]. Unfortunately, clinical data on many patients (particularly those diagnosed before 2000) diagnosed with cytology in our Department could not have been obtained for re-review. Therefore, cases with only cytological material available were not examined and hence excluded from the present study.

All strictly diagnosed PDAC cases were checked for patients' gender and age, year of diagnosis, and type of surgery. In all the analyses, values of age at first diagnosis were taken into account.

Histopathological diagnosis of PDAC was made in the resection specimens obtained by two types of surgical procedures:

- pancreatic resections (in patients with potentially resectable or 'borderline' resectable cancers treated with pancreaticoduodenectomy, middle segment pancreatectomy, distal pancreatectomy, or total pancreatectomy), and
- palliative surgical procedures for non-resectable cancers. Tumours were classified as non-resectable considering locoregional invasion (particularly invasion of mesenteric vessels) and/or metastatic

deposits, mainly in liver and peritoneum. In these patients, primary tumour and/or metastases were surgically biopsied ('open biopsy'). Moreover, many of these patients were treated with by-pass procedures.

Cases with non-resectable pancreatic tumours which were suggestive of PDAC diagnosis based on radiological and/or clinical examination or surgically examined during laparotomy were included in the study only when the surgical biopsy of primary tumour and/or metastatic deposits confirmed the diagnosis of PDAC and/or metastatic adenocarcinoma.

All autopsy cases were advanced and therefore included into 'non-resectable cancers' group.

Statistical analysis

A selected panel of methods was used in the statistical analysis of ADP of patients with PDAC.

Firstly, mean and median age values, as well as standard deviations (SDs) and interquartile ranges (IQRs) were calculated, both in the entire study population and in the selected subpopulations defined based on the patients gender and type of surgery.

Secondly, age frequency density plots (AFDP) [7, 8] were drawn.

As showed by Drs. Armitage and Doll [1], plotting of incidence rates against age on logarithmic scales is a useful epidemiologic method for theoretical modelling of multistage carcinogenic pathways. Linear slope of that association is in full concordance with classic hypotheses of cancer development assuming a gradual accumulation of molecular and/or microenvironmental events leading to malignancy [1, 6-10]. Since no true incidence rates of PDAC in the studied population were available for the analysis (numbers of individuals at risk of developing PDAC were unknown), logarithmic (log-log) plots of incidence rates against age [1, 5, 7, 10] could not be sketched. Therefore, in the third step, age-specific frequencies (instead of age-specific incidence rates) were plotted against age on log-log scales.

The graphs (AFDPs and log-log plots) were prepared based on 5-y age intervals (20-24, 25-29, 30-34, …, 85+), similarly to PDAC reports of cases abstracted in the US Surveillance Epidemiology and End Results (SEER) database [7, 11] and database of the Polish National Cancer Registry (NCR) [14].

All the calculations were based on strictly defined study population and any null or alternative hypotheses were formally tested. For the same reasons, confidence intervals were not calculated.

A database of PDAC cases was established using the Microsoft Excel programme.

Results

Five hundred and eighty cases of conventional PDAC were included in the study. Basic characteristics of the study population were described in Table I. There was slight predominance of males in the studied population. Two-thirds of the PDAC cases were treated with potentially curable pancreatic surgery. Pancreaticoduodenectomy was the most frequent type of pancreatic resection. A minority of cases were diagnosed in autopsy. Although the age range was wide, the mean and median values were very similar, suggestive of potentially normal ADP.

To address this issue in more detail, a histogram, AFDPs and age-specific frequency log-log plots were sketched. In the histogram of age distribution across the entire study population (Fig. 1) one can notice that PDAC was very infrequent in patients under 40 years old. Above this value PDAC frequency quickly increased and peaked at the age of 60 y. PDAC was frequent in patients up to 75 y, however it was a rare diagnosis above this age. These observations were confirmed in AFDP (Fig. 2). The median age value was around 60 y. However, the plot was not symmetrical since a slight increase in PDAC frequency in patients between 50 and 55 years could be noticed. As presented on a log-log plot (Fig. 3), an increase in PDAC frequency between ages of 30 and 60 years was well approximated with a straight line. This fact was in agreement with the observations of Drs. Armitage and Doll [1] concerning other cancer types and suggestive of multi-step carcinogenic pathway of PDAC development. Interestingly, the frequency of PDAC rapidly decreased in older patients, particularly in patients aged 75 or older. A configuration of log-log plot (Fig. 3) may suggest a slight increase in the PDAC frequency in patients younger than 25 y. However, this information was of no practical value because of extreme rarity of true PDAC in this age group.

Table I. Basic clinico-pathological data of the study population

STUDY POPULATION	580
Gender:	
males	303/580 (52.25%)
females	277/580 (47.75%)
Potentially resectable PDAC:	376/580 (64.83%)
pancreaticoduodenectomies	333/580 (57.41%)
middle segment pancreatectomies	2/580 (0.34%)
distal pancreatectomies	35/580 (6.03%)
total pancreatectomies	6/580 (1.03%)
Non-resectable PDAC:	204/580 (35.17%)
surgical biopsies*	171/580 (29.48%)
autopsies	33/580 (5.69%)
Age:	
mean (standard deviation)	60.8 (10.0)
median (interquartile range)	61.0 (54.0-68.0)
range	23-87

**many of these patients were treated with palliative by-pass procedures*

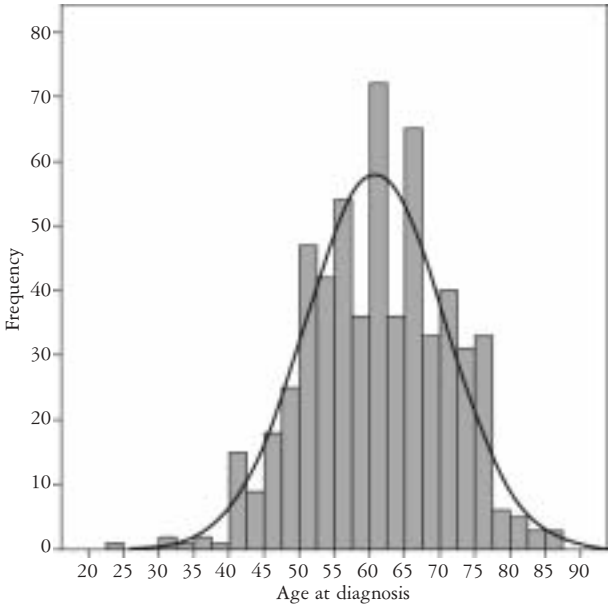

Fig. 1. Histogram of age of the entire study population

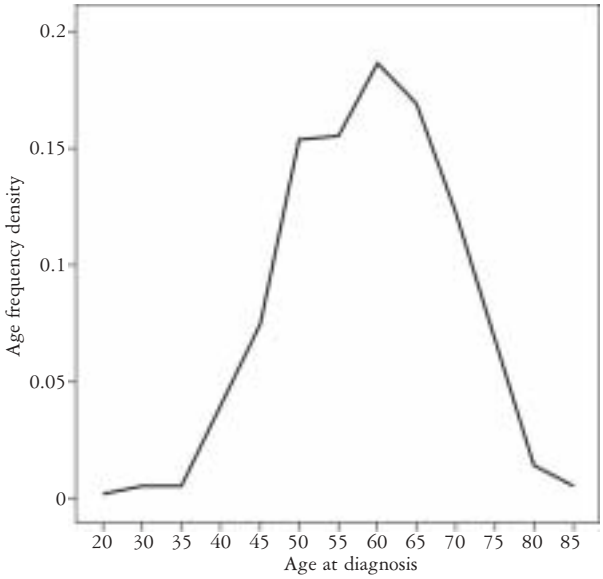

Fig. 2. Age frequency density plot of the entire study population

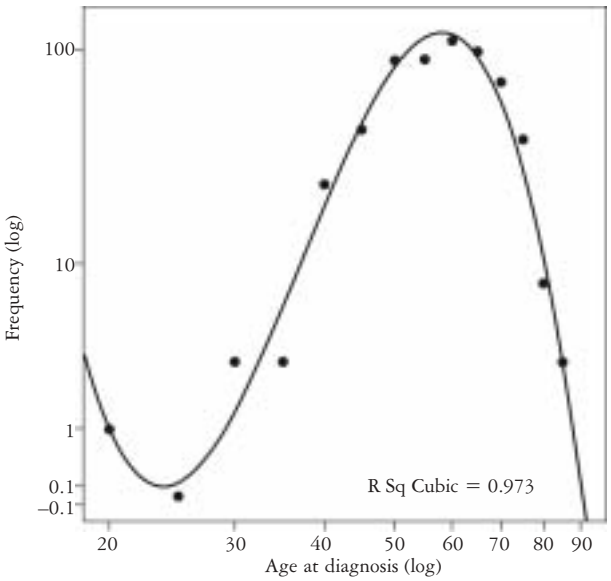

Fig. 3. Log-log plot of age-specific cancer frequency in the entire study population

In the next step, ADPs in males, females and in patients with potentially resectable and non-resectable cancers were compared. Mean (and SD) age of males and females with PDAC were 60.0 (9.3) and 61.9 (10.6), respectively. Medians (and IQRs) were 61.0 (53-67) and 62.0 (54-70), respectively. It was clear that females were approximately 2 years older than males at the time of PDAC diagnosis. AFDP (Fig. 4A) revealed that ADPs in males and females differed. Age distribution in males was unimodal and almost bell-shaped. In contrast, age distribution in females was wider and plateaued at the age of 50 years to 65 years. There was also slight overrepresentation of females among PDAC patients aged over 70 years. Frequency patterns for both genders in log-log plot (Fig. 4B) were similar in shape but not identical. Both showed a near linear increase between ages 30 y and 60 y and a rapid decrease up to the age of 85 years. However, the slopes for males and females were not parallel, what suggested at least minimally different exponential rates of increase in PDAC age-specific incidence [7]. This could indicate that the PDAC carcinogenic pathways are very similar in both genders but other factors, like susceptibility of epithelium to formation and progression of neoplasia may differ between them. Alternatively, the levels of prevalence of risk factors might influence the ADPs in both genders. However, this issue could not be clearly explained based on the studied data and remained speculative.

It is worth mentioning that observation concerning different ADPs in males and females could not be made based solely on comparison of mean/median age values – AFDP and log-log plot were necessary to address specifically this issue. As seen in Fig. 4B and additionally showed in Fig. 4C, the male-to-female rate decreased with age of PDAC diagnosis, what confirmed the overrepresentation of females among patients with PDAC at the age of 70 and older.

Mean and median values of age in patients with potentially resectable and non-resectable PDAC are presented in tables 2 and 3. Patients with potentially resectable tumours were approximately 1 year

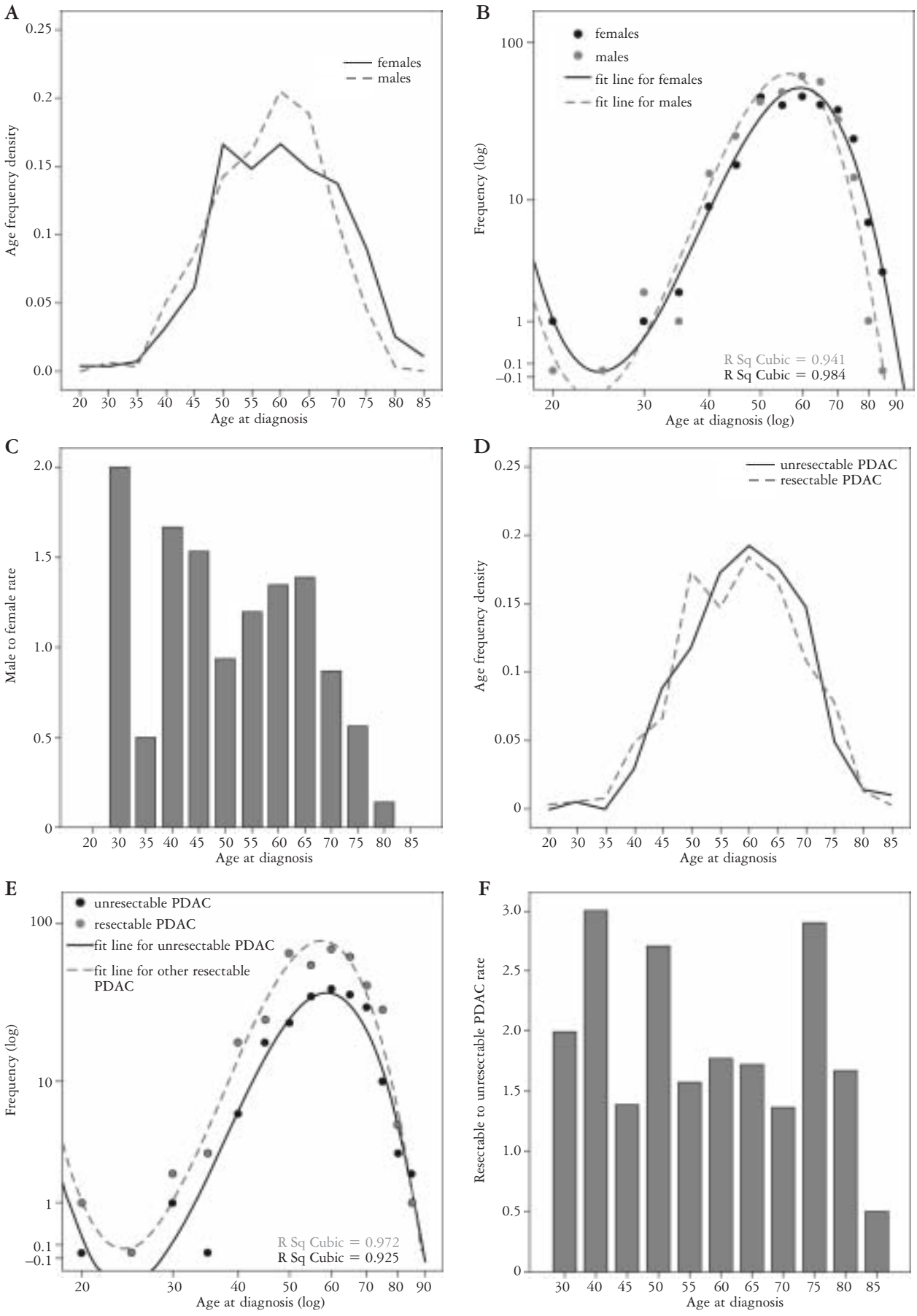

Fig. 4. Age frequency density plots (A, D, G, J), log-log plots of age-specific cancer frequencies (B, E, H, K) and rates (C, F, J, L) in the selected subpopulations defined based on patients' gender, potential respectability, and types of surgery (*continued on next page*)

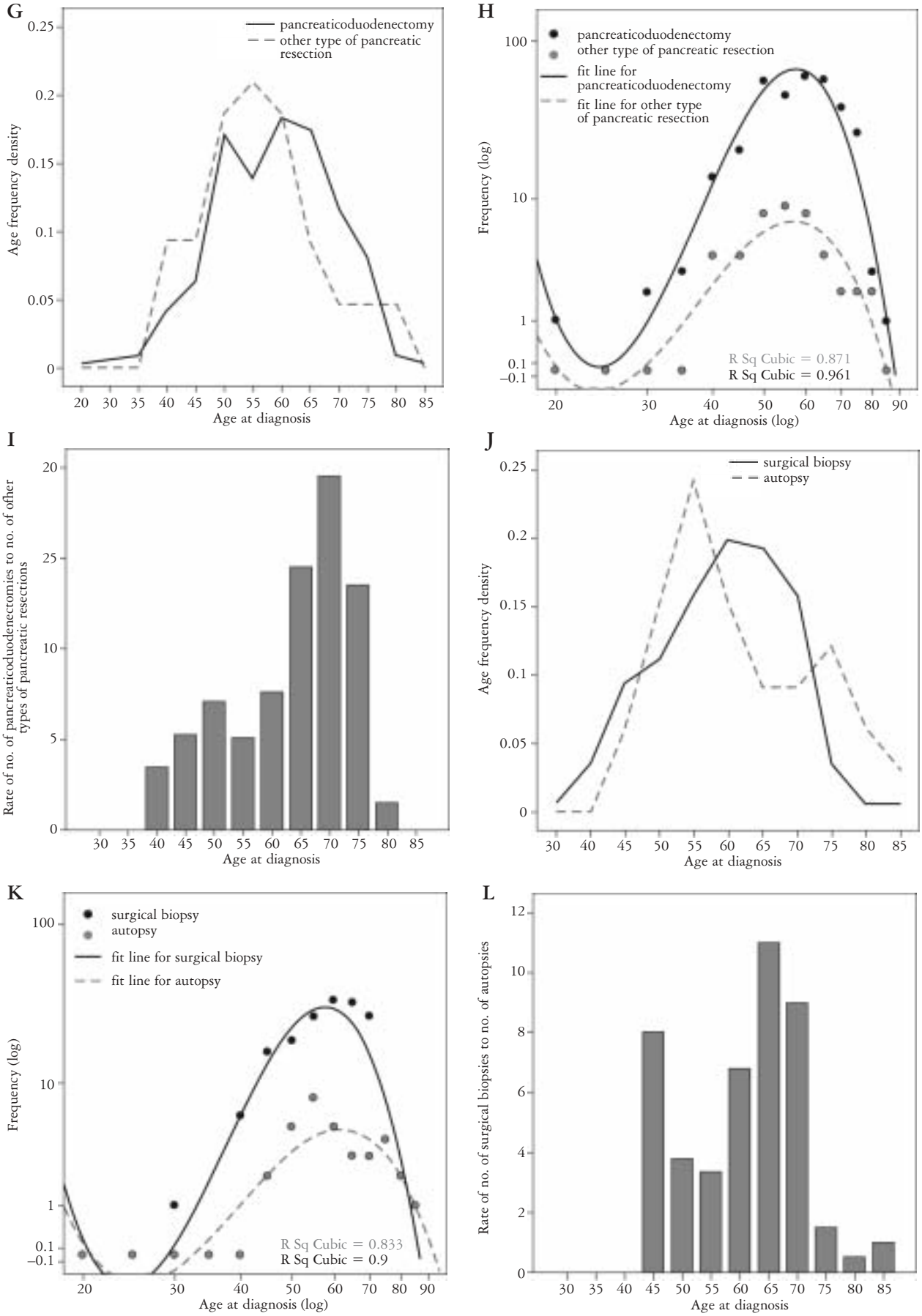

Fig. 4. Age frequency density plots (A, D, G, J), log-log plots of age-specific cancer frequencies (B, E, H, K) and rates (C, F, J, L) in the selected subpopulations defined based on patients' gender, potential respectability, and types of surgery

younger than patients with non-resectable tumours (Table II). However, when studied in more detail (Table III) that observation remained true for females but not males. There were no differences in mean age of males with potentially resectable and non-resectable PDAC. ADP of patients with non-resectable PDAC (Fig. 4D) was unimodal and symmetrical with peak at the age of approximately 60 years. In contrast, bimodality of age distribution of patients with resectable PDAC could be noticed. Many patients with resectable PDAC were at a similar age as patients with non-resectable tumours, however a subgroup of younger patients with resectable tumours could be distinguished. Their age distribution peaked at the age of 50 year, i.e. about 10 years younger than the rest of patients with resectable cancers. The shape and localization of log-log frequency plots (Fig. 4E) to x-axis in patients with potentially resectable and non-resectable cancers were parallel, indicating that age cannot be considered as a significant risk factor for non-resectable tumour for an individual patient. Bimodal ADP of patients with potentially resectable PDAC indicated that this subpopulation was somewhat heterogeneous. It is to be proven whether there are any biological and clinical aspects of tumours in these 2 groups of patients which could have resulted in such an observation. As showed in figure 4F, there were no specific trends of the rate of potentially resectable to non-resectable PDAC cases according to the age of patients.

Interestingly, some heterogeneity in ADPs of patients treated with different types of potentially curative surgery could be distinguished. Patients treated with pancreaticoduodenectomy were approximately 2 y older than patients who had other types of pancreatic resections (Table II). Mean age of patients treated with pancreaticoduodenectomy was comparable to patients who were treated with palliative procedures and diagnosed in surgical biopsy. The ADP of patients who underwent pancreaticoduodenectomy resembled that previously described for all patients treated with pancreatic resections (Fig. 4G). Importantly, the log-log plots of PDAC frequencies against age of patients treated with pancreaticoduodenectomy versus other types of pancreatic resections (mainly distal pancreatectomies, as described in table I) were not parallel, suggesting at least partially different clinico-pathological characteristics and/or tumour biology of PDAC of pancreatic head and tail. The rate of the number of pancreaticoduodenectomies to the number of other types of pancreatic resections increased between the ages of 40 y up to 70 y (Fig. 4I), indicating overrepresenta-

Table II. Mean and median age values of patients with potentially resectable and non-resectable cancers – types of surgical procedures

Age	Resectable PDAC			Non-resectable PDAC		
	PPD	Other	Total	Surgical biopsy	Autopsy	Total
Mean (SD)	60.7 (10.1)	58.4 (10.5)	60.5 (10.2)	61.1 (9.3)	63.4 (11.0)	61.5 (9.6)
Median (IQR)	61 (53-68)	57 (52-64)	61 (53-68)	62 (55-68)	61 (55-73)	62 (55-68)

Table III. Mean and median age values of patients with potentially resectable and non-resectable cancers – genders

	Resectable PDAC			Non-resectable PDAC		
Variable	Males	Females	Both genders	Males	Females	Both genders
Age						
Mean (SD)	59.9 (9.5)	61.1 (10.9)	60.5 (10.2)	60.2 (9.1)	62.9 (10.0)	61.5 (9.6)
Median (IQR)	61 (53-67)	61 (53-70)	61 (53-68)	60.5 (54-66.5)	62.5 (56-70.5)	62 (55-68)
Procedures						
Pancreaticoduodenectomy	178	155	333	–	–	–
Middle segment pancreatectomy	2	0	2	–	–	–
Distal pancreatectomy	18	17	35	–	–	–
Total pancreatectomy	1	5	6	–	–	–
Surgical biopsy	–	–	–	89	82	171
Autopsy	–	–	–	15	18	33
Total	199	177	376	104	100	204

PPD – pancreaticoduodenectomy

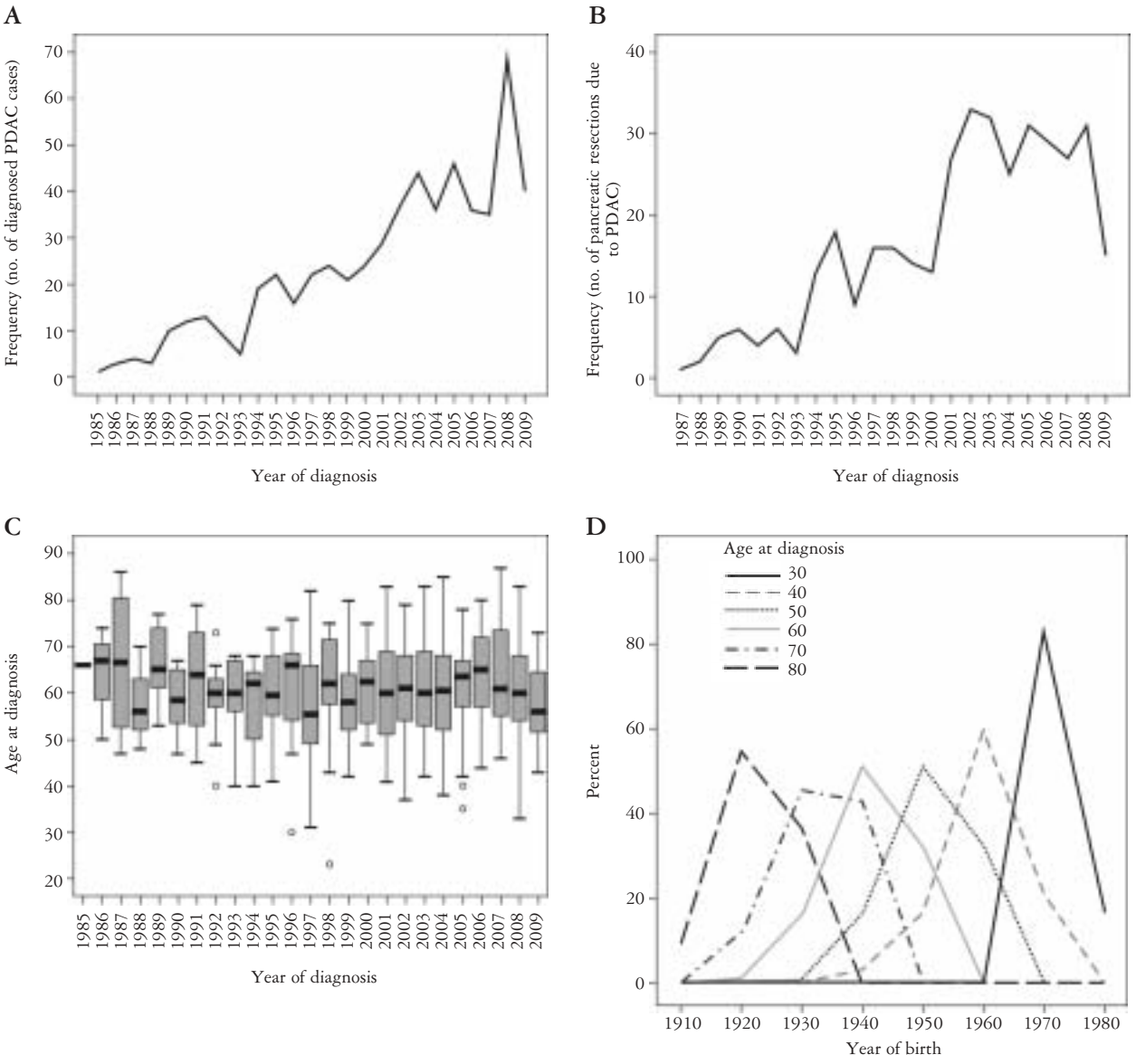

Fig. 5. Frequencies of cases of pancreatic ductal adenocarcinoma diagnosed during the study period in all patients (A) and in patients treated with pancreatic resection (B). Box and whisker diagram of patients' age in the study period (C – thick black bars indicate medians, red boxes – interquartile ranges, whiskers and dots – range and outliers). D – frequencies of cases in selected age groups against year of patients' birth

tion of PDAC in pancreatic head to PDAC in other pancreatic segments in older patients.

ADP of patients with non-resectable PDAC diagnosed in surgical biopsy was unimodal (Fig. 4J). Many patients with PDAC under the age of 45 could not be treated with curative intent and therefore they were treated with palliative procedures (manuscript concerning this issue in preparation). Autopsied patients with PDAC represented the oldest subpopulation within the study group (mean age 63.4 y, Table II). Two peaks in age distribution of patients diagnosed with PDAC during autopsy were noted (Fig. 4J) at the age of approximately 55 and 75 y. The reasons for that remained unclear. As showed in Figury 4K, log-log plots of age distribution in patients with PDAC diagnosed on biopsy and during autopsy were not parallel. The analysis of rate of the number of surgical biopsies and surgical autopsies (Fig. 4L) did not show any specific relationship of this rate with patient's age.

It is known that two significant effects may influence both the age distribution and incidence rates of cancers – period effects and birth cohort effects [5, 11]. The data from the present study could not be used for studying the period effect, since the frequencies of diagnosed PDAC cases (Fig. 5A) and

PDAC cases treated with pancreatic resections (Fig. 5B) during the study period was influenced mainly by increasing interest of the centre in pancreatic diseases and/or certain economic reasons rather than true trends of incidence rates. The median age of all patients at the time of PDAC diagnosis in our centre (Fig. 5C) and those treated with pancreatic resection (specific data not shown) have not changed since the 1980s. As showed in Fig. 5D, no specific differences in distribution of PDAC cases diagnosed in different age groups compared to the patients' year of birth could be distinguished. This indicated that birth cohort effect was not seen.

Discussion

In patients older than 10 y the incidence of major types of cancer increases exponentially with age [19]. The reason for that remains unclear. Older patients usually have a longer history of exposure to potential cancer risk factors. In these patients internal mechanisms of eliminating primary malignant cells may be not so effective as in younger ones. Moreover, it may take many years to accumulate genetic alterations (e.g. DNA hypomethylation, DNA damages by endogenous oxygen and/or inadequate DNA repair, telomeres instability) in tissues until malignancy will develop [4, 6]. Some researchers stated that ageing was not an *a priori* cancer risk factor and duration of exposure to carcinogens but not biological age explains an increase in cancer incidence in older patients [20].

The biology of most frequent PDAC precursor lesions (pancreatic intraepithelial neoplasias) is well documented [21, 22]. However, at present no specific screening test for the early detection of PDAC or its precursor lesions in general population is available [23]. In high risk patients (particularly those with PDAC in their families or those with hereditary cancer syndromes) endoscopic ultrasound screening may be useful [23].

In the USA, pancreatic cancer is the fourth most common cause of death in cancer patients irrespective of gender [21, 24]. The pancreatic cancer incidence rates in Poland in males and females are relatively high comparing to other European countries [13]. About 10% of PDAC cases develop based on an inherited predisposition [13]. Cigarette smoking is the major risk factor for PDAC and contributes to development of up to 40% of PDAC cases [11, 13, 15].

The incidence of exocrine pancreatic cancers remained stable in the USA from 1970s to 2000s (assessed based on SEER database) [7, 24, 25], or slightly decreased [26], what might have resulted from a decreased prevalence of cigarette smoking [26]. However, there were probably no specific changes in primary prevention, cancer detection rate, screening approaches or susceptibility of the tissue to cancer development in the USA during that period [7]. The age-standardized incidence rate of pancreatic cancer in males in Poland decreased from 1999 to 2007 (rates: 7.0/100 000 and 6.0/100 000, respectively). The age-standardized incidence rate in females remained relatively constant (rates: 4.2/100 000 and 4.1/100 000, respectively) [14]. Similarly, age-standardized mortality rates of pancreatic cancer in Poland decreased slightly from 1992 to 2002 in males but not in females [16].

Five-year survival rates of PDAC are very poor and range from less than 2% (metastatic disease) up to 30% (patients with localized disease treated with curative surgery [21, 24]. The 3-year survival rates of males and females with PDAC of pancreatic head are almost the same (5.3%). In contrast, a 3-year survival rate in females with PDAC of pancreatic body or tail (2.4%) is lower comparing to males (4.5%) [24]. In more than half of the patients, potentially curative resection cannot be performed at the time when the disease is diagnosed. Despite this, the overall survival of patients with PDAC increased from the 1970s to the 2000s in the USA [25] as well as in Poland [27], including patients with localized and metastatic disease.

According to a study based on 58,526 PDAC cases gathered in the SEER database between 1988 and 2002, mean age of patients diagnosed with PDAC in the USA is 70.2 ±12.5 y [28]. The proportion of females in that population was 51.6%. Localized, regional, distant, and unstaged disease concerned 8.4%, 27.1%, 46.4%, and 18.2% of patients, respectively [28]. Only 11% of PDAC cases were primarily resected. Among patients who had pancreatic resections, the percentage of localized, regional, distant, and unstaged disease was 17.1%, 70.8%, 9.9%, and 2.2% of cases, respectively. Approximately three-fourth of cases (76.8%) were localized in the pancreatic head [28]. Interestingly, the mean age of patients with PDAC treated with pancreatic resection (as reported in the SEER database between 1998 and 2003) was lower (65.0 y) in comparison to all PDAC patients [29]. The percentage of females among pancreatectomized PDAC patients was 50.6% [29]. In the US population, about 4% of PDAC cases are diagnosed in autopsy or at the time of their death certificate (SEER 1988-2002) [30].

As mentioned previously, we are not aware of population-based studies on pure conventional PDAC in the Polish population, which were based on strict PDAC diagnostic criteria. However, many epidemiologic aspects concerning patients with pancreatic malignancy in Poland may be retrieved from freely available NCR database [14]. Based on these data we calculated that the median age of males and females with pancreatic malignancy diagnosed in

Poland between 1999 and 2007 were in age groups of 65-69 years and 70-74 years, respectively. Female proportion was 48.7%. Unfortunately, no data concerning the stage of the disease and long-term survival were available.

A study on "pancreatic duct cell cancer" by Professor Popiela and associates provided superb data concerning epidemiology of pancreatic cancer based on a group of 947 patients treated in a single regional referral centre between 1972 and 2003 [27]. The mean age of patients with pancreatic cancer was 62 y, the males constituted 58% of patients. Two-thirds of the cases were localized in the pancreatic head. 91.1% of cases were at stage IV (distant metastatic disease). The authors of that study showed that overall survival of patients with pancreatic cancer (statistically) increased from the 1970s to the 2000s both in patients treated with pancreatic resections and those who were not candidates for potentially curative surgery [27].

The mean and median age of patients with PDAC described in the present study were 60.8 years and 61.0 y, respectively. The values were about 10 y lower than those reported in Polish [14] and American [28] population-based registries, but comparable to the values reported in the single-institutional Polish study mentioned earlier [27]. In the USA, patients having pancreatic resections are approximately 5 years younger than all the patients with pancreatic cancer [29]. Dr Baxter and colleagues showed that younger (less than 50 years old) patients with PDAC in the USA were more likely to have pancreatic resections than older ones [30]. A similar observation wad made by Dr. Sharp and colleagues in Ireland [31]. All these facts may indicate that many of older patients with suspected pancreatic cancer in Poland are not considered as candidates for pancreatic resection. It is not clear whether this results from a more advanced stage of the disease in old patients or existent co-morbidities in those patients.

Nowadays it is clear that not only molecular data but also selected epidemiologic studies may contribute to a better understanding of the biology of neoplasia [7, 8, 10]. Large population-based as well as institutional databases of patients with cancer may be used for an analysis of age distribution patterns of specific clinical and pathological diagnostic entities. Not only basic parameters (such as mean and median values, SDs, or IQRs) but also more sophisticated methods (AFDPs and logarithmic plots of age-specific incidence rates) [7, 8] may be useful for in-depth studies of cancer epidemiologic data [8, 9]. The incidence of many types of cancer was studied using a log-log plot approach [1, 7-10]. The epidemiologic age-specific characteristics of majority of these entities were in full agreement with classic carcinogenic pathways, i.e. log-transformed incidence rates increased with log-transformed age with a linear slope. In 2009, Dr. Henson and colleagues confirmed this observation for PDAC in the US population (assessed using the SEER database, 1973-2005) [7], which was in agreement with observations of Drs. Armitage and Doll [1]. Interestingly, the ADPs of cases of gallbladder, extrahepatic biliary tract and ampulla of Vater were very similar in distribution (i.e. parallel on log-log plots), despite significant differences in raw frequencies of these tumour types in the population. This was suggestive of similar mechanisms of development of (exocrine) carcinomas in these locations, which may be also attributed to common embryogenesis, similar histology and differentiation. Moreover, the epithelium in these localizations may share a certain level of susceptibility to specific risk factor/carcinogens what may lead to tumour development (field effect). In comparison, Dr. Henson and associates showed that ADP of pancreatic endocrine carcinomas was not parallel to previously listed exocrine neoplasms and therefore suggestive of completely different epidemiology and biology [7].

In the present study we showed that relative frequency of PDAC decreased above the age of 70 years. In contrast to the data presented in the present study, Dr. Henson and colleagues did not observe any decrease in the incidence rates in older (above 70 years) patients when they plotted it against age on log-log display based on results from SEER database [7]. Instead, the incidence rate increased gradually from the age of 30 y up to 80 y. To address this issue further, we compared AFDPs of males (Fig. 6A) and females (Fig. 6B) diagnosed with PDAC in our centre between 1999 and 2007 and those with pancreatic malignancy reported in the NCR database (1999-2007) [14]. We found significant differences in the configuration of AFDPs in both genders between these two studied populations. There was significant overrepresentation of males over 70 y in the population-based database comparing to our one. The number of cases diagnosed in males over 75 years rapidly decreased in both populations, but as described in the NCR database [14], the incidence rate of pancreatic malignancy in males over 75 y was higher than in younger ones (this apparent inadequacy results from absolute decrease of number of persons at risk over 75 years). The comparison of AFDPs of females in our database and in population-based database [14] showed that majority of females diagnosed with pancreatic cancer in Poland are over 60 years old, i.e. they are older than majority of women diagnosed in our centre. These observations confirmed what was earlier mentioned, that Polish patients over 65 years with suspected pancreatic cancer are rarely treated and diagnosed in surgical centres. Older patients are also

rarely treated with by-pass procedures in Poland, since the median age of patients with non-resectable PDAC diagnosed in our centre (62 years, many of these were treated with by-pass procedures) was lower than median age of all patients listed in population-based database [14]. Interestingly, despite significant differences between AFDPs of males and females with PDAC described in the present study and those with pancreatic malignancy abstracted in the NCR database, the log-log plots of both these two populations (Fig. 4B and 6C) showed a linear slope between the ages of 30 years and 60 years. Another related issue is a phenomenon of cancer suppression at old age, recently studied by Dr. Harding and colleagues [32].

The majority of patients with resectable PDAC in our centre were treated with pancreaticoduodenectomy (88.6%). It is not surprising since PDAC in pancreatic head usually become symptomatic at the earlier stage (in comparison to cancers of pancreatic body or tail) when the potentially curative resection may be still performed [24, 31]. The similar observations were made by Dr. Lau and colleagues [24]. They showed that 77.5% of PDAC cases in the USA

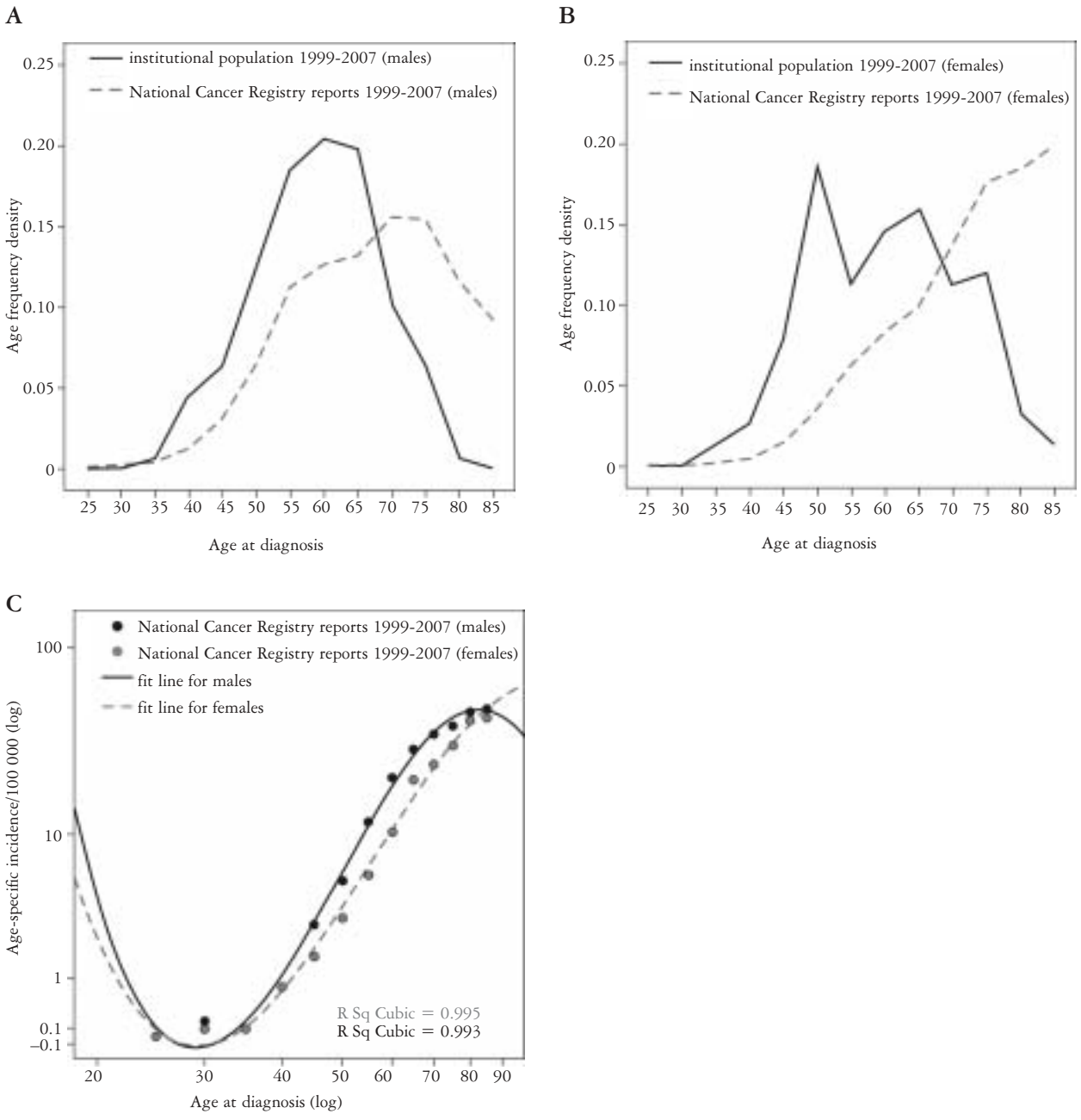

Fig. 6. Age frequency density plots of males (A) and females (B) abstracted in the database in our institution (1999-2007) and in the Polish National Cancer Registry (1999-2007). C – log-log plots of age-specific cancer frequencies of pancreatic cancer in males and females (based on data of the Polish National Cancer Registry 1999-2007)

are in the pancreatic head (SEER 1973-2002), whereas 22.5% in body or tail [24]. Those in body/tail were more frequently diagnosed in the advanced (i.e. distant metastases) stage (72.7%) comparing to PDAC of the head (39.2%). Interestingly, locally invasive body or tail PDAC are associated with better 3-year survival rate (20%) comparing to locally invasive head PDAC (9%) [24].

As described in the NCR database [14], less than 50% of pancreatic malignancies in Poland was verified microscopically. This result was comparable to those reported in Ireland (41.7%) [31], but lower to those reported in Denmark (73%) [33] and in the USA (approximately 75%, SEER database (1977-2005) [25, 26]. Interestingly, the proportion of PDAC diagnosed microscopically in the USA has not increased since the 1970s [25, 26].

In the present study we showed that male to female rate of patients with PDAC decreased with age. This observation was in agreement with previous reports based on the U.S. SEER registry [34] and may be caused by both environmental (particularly cigarette smoking) and genetic factors [34].

Similarly to the present study, significant birth cohort effect among US PDAC patients did not exist [5].

Recently, it was postulated that clonal models rather than multistage carcinogenic pathways may better explain epidemiological cancer data. Moreover, several additional issues, such as cancer risk factors, individual genetic susceptibility and age-specific cancer acceleration should be taken into consideration where new carcinogenetic models based on epidemiologic data are created [10]. However, a classic log-log model of cancer incidence can be still used in adequate context due to its simplicity and surprisingly good, but not perfect fit to the observational data.

Our study has several limitations. Firstly, true incidence rates were not available, since numbers of patients at risk of developing PDAC were not known. They could not be even estimated since many patients treated and diagnosed in our centre lived in other parts of the country. Therefore, results of the study do not represent regional status of the PDAC epidemiology. For this reason, any specific time trends (including period effects) could not be tested. Secondly, it is possible that some patients were treated with palliative by-pass procedures due to clinical diagnosis of pancreatic malignancy but the surgical biopsy was not performed. Since our study is based on strict histopathological inclusion criteria, we could not include these patients in our calculations irrespective of their prevalence during the study period. Thirdly, cases diagnosed with cytology without histopathological confirmation were not included in the present study. As mentioned previously, we do not believe that these samples may be re-evaluated and re-diagnosed retrospectively if the highest standards of clinico-pathological correlation are to be met. Fourthly, the data of the NCR registry cited in the present study were based on cases of diagnosis of pancreatic malignancy instead of diagnosis of pancreatic cancer. Considering our experience with non-ductal neoplasms of the pancreas, we believe that a great majority of patients with pancreatic malignancy under the age of 40-45 years listed in the NCR database suffered from neuroendocrine or solid-pseudopapillary (mainly females) neoplasms, but not from pure PDAC. However, in our discussion we focused rather on the problem of PDAC epidemiology in older patients rather than younger ones. The significant discrepancies in epidemiology of old patients with pancreatic malignancies between our database and the NCR database rather did not result from inclusion of cases of neuroendocrine neoplasms in the category of pancreatic malignancies in the NCR database. "Neuroendocrine carcinomas" constitute less than 2% cases of all pancreatic malignancies (SEER 1973-2002) [35] and their incidence rate in patients in the age of 60 y or older is 14-28 times lower than the incidence rate of "exocrine cancers" [26].

Conclusions

In the present study we have showed that pure pancreatic ductal adenocarcinoma is an age-dependent cancer. Females were approximately 2 years older than males at the time of PDAC diagnosis. Females with non-resectable PDAC were approximately 2 years older than females with resectable tumours. Mean age of males with non-resectable and resectable PDAC was similar. Patients treated with pancreaticoduodenectomy were approximately 2 years older than patients undergoing other types of pancreatic resections. Age distribution density plots showed that some studied subgroups of patients were somewhat heterogeneous and might include several yet poorly recognized clinico-pathological entities. Logarithmic plots of age-specific frequencies showed that PDAC epidemiology is in concordance with multistage theory of carcinogenesis.

Single-institutional pathology-oriented cancer epidemiologic data may add some information to population-based cancer registries.

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