NEW RESEARCH TRENDS IN GASTROENTEROLOGY:

PANCREATITIS IS IN DANGER

Ph.D. Thesis

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Publications related to the subject of the thesis:

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LIST OF ABBREVIATIONS

AP	acute pancreatitis
CP	chronic pancreatitis
C-P	clinical pancreatitis
C-PC	clinical pancreatic cancer
CRF	clinical research form
CRO	clinical research organization
eCRF	electronic clinical research form
E-P	experimental pancreatitis
E-PC	experimental pancreatic cancer
GDP	gross domestic product
GERD	gross domestic expenditure on R&D
GI	gastrointestinal
GTI	Global Talent Index
HPSG	Hungarian Pancreatic Study Group
IBD	inflammatory bowel disease
IBS	irritable bowel disease
IRI	Industrial Research Institute
NDA	new drug application
NIH	National Institute of Health
NME	new molecular entity
OECD	Organization for Economic Cooperation and Development
PC	pancreatic cancer
PPP	purchasing power parity
RCT	randomized controlled trials
R&D	research and development
WHO	World Health Organization

Introduction

By definition research and development (R&D) is a process of creating new products, processes and technologies that can be used and marketed for mankind's benefit in the future.

Factors influencing R&D activity

1. R&D expenditure

The R&D growth is driven by the country's economic strength and growth which is measured by the gross domestic product (GDP). In the last decade there was a serious global decrease in funding due to several reasons including the global financial crisis from 2008 through 2010 affecting seriously both central and industrial funding of research.

The latest global evaluation and forecast done by the Industrial Research Institute (IRI) is positive about future R&D spending increase, rising attitude towards partnerships and improving overall health of global economy [1]. The growth in global R&D investments is based on growing spending in Asian countries, especially in China. Asian R&D spending has a 41% share in global spending and increasing while North America and Europe has a 28% and 21%, respectively and declining, but globally the USA is still the largest single country in R&D spending. China's total R&D expenditure is expected to exceed that of the USA's by 2019. Concerning Europe, Germany, France and the UK are in the forefront of R&D spending [2].

The total global R&D expenditure was $1,805 billion in 2014, the United States having a 26.9% share with $485 billion, while Europe's share and spending was 21.5% and $388 biilion.

Health related R&D is 10 to 20% of total R&D expenditure in the majority of the countries. There are some exceptions though, the most extreme is Switzerland with 40.6% and Russia with its 3.2% (Table 1).

2012 (in billion PPP dollars)	Total R&D	Health related R&D	As % of total R&D
USA	453.54	105.82	**23.3%**
China	257.00		
Japan	151.02	21.96	14.5%
Germany	96.46	13.46	14.0%
UK	38.39	9.83	**25.6%**
France	54.26	8.43	15.5%
South Korea	64.05	7.62	11.9%
India	40.24	5.82	14.5%
Canada	25.05	5.48	**21.9%**
Switzerland	13.04	5.30	**40.6%**
Italy	26.67	4.12	15.4%
Spain	19.17	3.77	19.7%
Australia	21.23	3.76	17.7%
Sweden	13.37	2.52	18.9%
Netherlands	14.60	2.37	16.2%
Turkey	12.40	2.03	16.4%
Denmark	7.24	1.97	**27.2%**
Russia	37.85	1.23	**3.2%**
Poland	7.74	1.02	13.1%
Norway	5.06	0.93	18.3%
Hungary	2.85	0.74	**25.9%**
Finland	7.38	0.69	9.3%
Czech Republic	5.33	0.44	8.3%
Romania	1.74	0.17	9.8%
Croatia	0.66	0.17	**25.8%**
Ukrain*	2.80	0.14	5.0%
Slovakia	1.13	0.11	10.0%
Serbia*	0.66	0.08	12.6%
Estonia	0.70	0.06	7.9%
Latvia	0.41	0.04	10.8%
Belorussia	1.08	0.04	3.6%
Lithuania	0.19	0.02	12.3%

Table 1. **Total R&D and health related R&D Expenditures.**
Data source: World Health Organization (WHO), Global Observatory, Health R&D, http://gohrd.azurewebsites.net/Country

The largest investor into and key player in health related R&D is the USA. However, the business investment have strongly declined in the last decade and governmental investment, trying to compensate is limited. There are also uncertainty in the future of healthcare companies with the changing political environment. Still, the investment is expected to grow.

The second largest investor into R&D is China. Concerning China's health related R&D spending, there is no data available in WHO Global Observatory, but definitely there is a strong will in China to become a key leader in health related R&D and innovation in the future. This effort manifested in 1) spending 1.17 billion USD for promoting life and

medical sciences in 2012, 2) the state investing 1.1 billion USD in new drug development between 2011-2015, 3) growing number of researchers return from overseas with training in biomedical sciences, 4) more than three hundred clinical research organizations (CRO) providing preclinical and clinical research services to pharmaceuticals, presenting a pharmaceutical R&D innovation potential, 5) lifting price controls on hundreds of western medications by the government in 2015 or 6) fighting with corruption in the drug registration process [3]. Despite all these efforts, there are still ways to improve the education system repressing creativity, to shorten the new drug registration process, which is extremely long, to solve product safety issues and improve the intellectual property regulations. Still, forecasts expect China to become the number one player in health related R&D in the near future, however different forecasts expect it to happen within different time frames [1, 2].

In Europe, Germany, France, UK, Switzerland and Spain are the largest health related R&D spenders. Northern European countries are emerging from smaller countries thanks to their more intense investments in research and education. Remarkably, Central and Eastern European countries have little sources for health-related R&D.

2. Human Resources

Beyond financial resources, investing in human capital is key to innovation and economic development. The USA has an education system traditionally supporting creativity and innovation. As it is mentioned earlier, this is not the case in China. Also, in Europe, especially in Central-Eastern Europe there is a lot to do to improve the education. The European Union regards the human resource development in R&D as priority and started several initiatives like the European Research Area (ERA), the Framework programs, the Innovative Union or the Scientific Advice Mechanism (SAM) to support the European research system. Research and Development Statistics (based on the data reported to OECD and Eurostat in the framework of the joint OECD/Eurostat international data collection on resources devoted to R&D) show that Israel, Korea, Japan, Sweden, Finland and Denmark had the highest R&D intensity (gross domestic expenditure on R&D in percentage of the GDP) and the highest number of researchers per 1000 employments in 2014, while China had almost the lowest number of researchers per 1000 employments. This is an area where China

could improve substantially and it is expected to do so. Central Eastern European Countries are in the last third of the countries in both parameters [2].

The Global Talent Index is representing a countries potential to develop, attract and retain talent, measured by demographic trends, educational infrastructure, quality of the labor force and the ability of a country's economy to foster competitive and internationally-oriented environment [4].

The US is ranking first in Global Talent Index (GTI) thanks to its excellent universities and the high overall quality of its workforce. We can find also the Nordic countries (Denmark, Finland, Sweden, Norway) and the developed Asia Pacific countries (Australia and Singapore) in the top ten, this result derives from the substantial investment in education or openness to foreign investments. China is 31st but the pace of improvement between 2011 and 2015 is the highest among the sixty countries in the index. The Czech Republic, Poland, Slovakia and Hungary are between the 25th - 30th places in this order.

3. Other important factors influencing R&D activity

Because of the limited space in this work, I decided to summarize the other, also important factors influencing R&D activity. The political environment defines the actual priorities for the nation and the general attitude towards research. Action plans, stakeholder associations, patient organizations may influence political and economic decisions by collecting and disseminating information, effectively representing a society with the same interest and publishing white papers to draw the attention to important research or other healthcare areas to be supported.

The regulatory framework may support or impede improvement. The length and transparency of China's new drug registration process or the under regulated intellectual property protection were mentioned earlier as negative examples.

The underdeveloped infrastructure could be a limiting factor in innovation as well.

The health related R&D needs should be defined also by the global disease burden providing more funds to low and middle income countries to struggle with diseases relevant to them [5].

Concluding, the environment influencing health related R&D is very complex and multifactorial, thus there are several possibilities to improve the situation.

Aims

I. To understand the research trends in the field of gastroenterology and highlight the most endangered areas based on the gastrointestinal research publications in the last 50 years.

II. To identify possibilities of developing a better environment for pancreatic research and improvement of patient care within the framework of the Hungarian Pancreatic Study Group.

- Patient registries – building registries and biobanks in acute pancreatitis (AP), chronic pancreatitis (CP) and pancreatic cancer (PC) – prospectively collecting clinical data to understand the development of the diseases, to monitor current diagnostic and therapy practices. Biobanks – collecting biological samples to explore the genetic background of the diseases.
    - Developing the protocol, questionnaires, other documents for the patient registries and biobanks.
    - Developing the webpage and electronic data administration system for the patient registries.
    - Enrolling healthcare centers to become multicentre.
    - Elaborating the way of data quality control and data curation.
    - Providing a platform for research ideas in pancreatology. Developing research collaborations.
    - Becoming multinational, multicentre
- EBM guidelines
    - Adaptation of existing international guidelines
    - Organizing a consensus meeting
- Education of doctors and students
    - Publishing guidelines
    - Presentation of guidelines

I. Understanding the research trends in gastroenterology

Background

As the USA is the largest single country in R&D spending, we started the evaluation of the R&D expenditure structure there. Four major players are sponsoring biomedical research in the USA (and in most of the countries with minor alterations): federal government (through NIH), state and local governments, private non-profit organizations (including foundations) and industry. Global biomedical research funding has started decreasing in the 21st century. The budget for the NIH, which is the largest contributor to biomedical research, has increased by an annual growth rate of 7.8% for 1994-2003, followed by an annual growth rate of 3.4% for 2003-2007, then started to decrease by 2.0% in 2008 [6-8]. The American Recovery and Reinvestment Act pumped $10 billion into the NIH in 2009-2010 compensating for the losses due to the financial crisis, but traditional federal funding was declining further through 2014 [1]. Moreover, data on corporate investment trends published by the Biotechnology Industry Organization in February 2015 showed a general decrease (from $21 billion (2004–2008) to $17 billion (2009–2013)) in research investment in novel drug R&D and drug improvement R&D [9]. However, investment trends in the different disease categories have been highly variable. The top funded disease area was oncology with its 24% of venture funding share in the last 10 years, followed by Neurology and Infectious Diseases with 12.1% and 10.9%, respectively. On the contrary, financing for Psychiatry, Gastrointestinal and Respiratory Diseases altogether made up less than 10% of the total spending. Shockingly, the biggest drop was in the area of gastroenterology disease (62% from $828 million to $311 million), a wake-up call to academic researchers to boost research activity in the field. Since academic research usually provides the basis for industrial R&D, our aim was to understand the research trends in the field of gastroenterology and highlight the most endangered areas.

Evaluating scientific activity

Sciences use tools and resources like scientists, money and time to produce scientific knowledge with outcome oriented goals like benefitting health, preventing disease and return on investment (Figure 1).

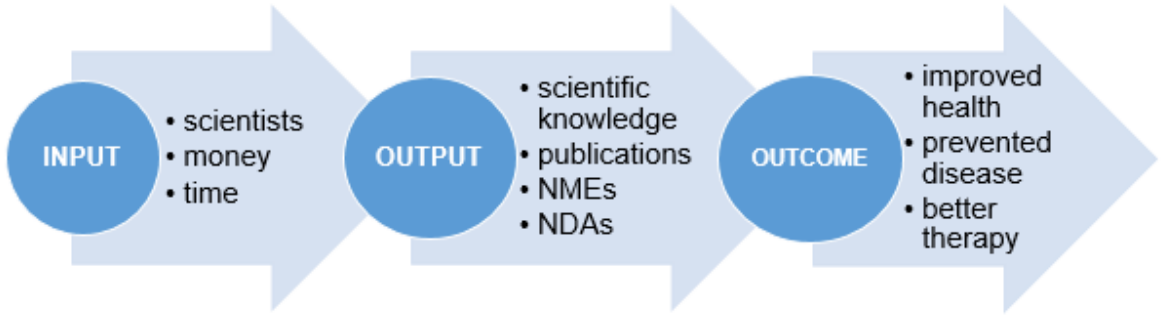


Figure 1. Scientific production process

Though, it has its limitations described later, scientific knowledge can be represented by publications in the scientific literature.

Based on a PubMed count of biomedical publications, general trends of biomedical scientific literature show that both publication number and author number have risen exponentially between 1965 and 2014. Moreover, the average number of authors per publication has more than doubled, the number of scientific journals has tripled since 1965 [6]. In this growing environment we tried to flashlight the basic facts and shares within gastroenterology and pancreatology.

Methods

1. Analyzing scientific activity in the different areas of gastroenterology

In the first part of the study, we searched PubMed hits between 1965 and 2015 for pancreatic diseases (diabetes, pancreatitis and pancreatic cancer); benign gastrointestinal (GI) diseases, such as upper GI tract disorders (reflux, oesophagitis, Barrett's syndrome and gastritis), lower GI tract diseases (inflammatory bowel diseases and irritable bowel syndrome) and hepatitis; and malignant GI diseases, such as gastric, oesophageal, colon, liver and pancreatic cancers. Altogether, 1,554,325 articles were analyzed.

2. Detailed analyses of basic and clinical studies on pancreatitis and pancreatic cancer

Since the biggest drop in research activity was in pancreatology, in the second part of the study we aimed to search PubMed for ‘experimental pancreatitis’ (E-P; 3,767 articles were found), ‘experimental pancreatic cancer’ (E-PC; 3,697 articles), ‘pancreatitis AND clinical trial’ (C-P; 2,470), ‘pancreatic cancer AND clinical trial’ (C-PC; 4,321). Altogether, 14,255 articles were analyzed. All the available abstracts were checked. The final analyses were only performed on articles which contained original data in pancreatic research (6,628) in the categories described above. After the exclusions, we conducted a detailed analysis of 1,871 articles in E-P, 1,726 in E-PC, 1,079 in C-P and 1,952 in C-PC. The following parameters were collected from the articles: (1) number of countries and (2) countries, (3) number of centres involved in the research, (4) the journal’s impact factor (IF; based on the last available IF for the journal) and (5) whether the trial was registered in an official trial registry (only for clinical trials). An article was defined as ‘multinational’ if more than five countries were involved in the study and ‘multicentre’ if more than five centres took part. Analyses were performed for individual countries. An analysis of the individual parameters was conducted on the group of articles where the given parameter was available.

All PubMed searches took place on 23 December 2015.

Limitations

Counting publication and citation numbers and impact are designed to measure scientific efficiency and productivity but recent studies raised concerns about the quality of biomedical literature claiming that irreproducibility and lack of transparency are the main problems [6]. Also, without thoroughly studying of outcomes, it is impossible to evaluate the efficiency of scientific activity, but estimating the output may provide a crude picture of scientific activity in the field.

The search was performed in PubMed, which provides a substantial selection of scientific literature, but of course it does not provide full coverage of all scientific activity.

Another limitation was the lack of information on specific parameters in some of the individual abstracts. These abstracts were excluded from the analysis of that particular parameter.

Finally, due to the extremely high number of articles, the impact factors (IF) of the articles were not calculated for the year of publication, but based on the journal's IF for the most recent year (2014).

3. Statistical analysis

To investigate differences in research activity, we compared the confidence intervals (CI) of the proportions. We used the equation for large samples,

$p^* \pm z \times \sqrt{\frac{p^* \times (1-p^*)}{n}}$, where $p^* = \frac{m}{n}$, m=number of articles/disease and n=number of all articles.

To analyze the changes of research activity, we compared the slopes of the regression with an estimation of CI. One-way ANOVA was used with Dunnett's post hoc test (unequal variances were assumed) to compare the IF between countries and centres. Chi-square tests were employed for relationship analysis. Statistical analyses were done by IBM SPSS Statistics v 20.0 (IBM Corporation, Armonk, NY, USA).

Values are expressed as means ± standard error (S.E.M.) if not stated otherwise. A *P* value <0.05 was considered statistically significant.

Results

1. Research activity on pancreatitis has decreased compared to other gastrointestinal diseases

In the first part of the study, we characterized research activity on different parts of the GI tract. In 1965, among the major benign GI disorders, 51.9% (CI 49.58–54.22) of the research was performed on hepatitis, 25.7% (CI 23.63–27.75) on pancreatitis, 21.7% (CI 19.76–23.30) on upper GI diseases and only 0.7% (CI 0.34–1.13) on the lower GI disorders. Half a century later, in 2015, twelve times more research was being carried out on benign GI disorders. However, while research on the lower GI tract had increased 383 times, that on hepatitis eleven times and that on the upper GI tract ten times, the number of studies on pancreatitis had risen only five times. These nonparallel changes led to a situation in which only 10.7% (CI 10.27–11.11) of the research activity in 2015 was being performed on pancreatitis from among the benign GI disorders (Figure 2). Since research on the upper GI tract and hepatitis rose parallel

to the average increase of the research on the GI diseases, we can assume that the great loss of interest in pancreatology was accompanied by a great upturn in research in the lower GI disorders, namely, inflammatory bowel disease (IBD) and irritable bowel disease (IBS).

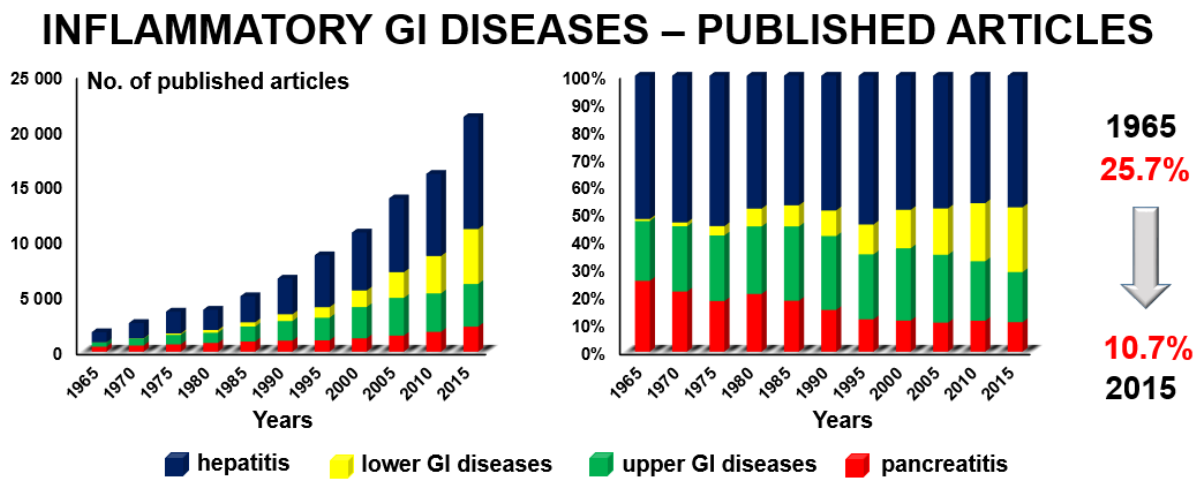


Figure 2. Inflammatory GI diseases. From 1965 to 2015, the great loss of interest in pancreatology was accompanied by a major increase of research in the lower GI disorders, namely, IBD and IBS.

2. Research activity on pancreatic cancer has risen slightly compared to other GI cancers

In 1965, among the major malignant GI disorders, research was conducted on the different forms of cancer as follows: cancer of the liver: 33.9% (CI 31.89–35.93); the stomach: 29.1% (CI 27.18–31.04); the colon: 14.6% (CI 13.05–16.05); the pancreas: 11.9% (CI 10.55–13.29); and the oesophagus: 10.5% (CI 9.20–11.80). Fifty years later, in 2015, twelve times more research was being performed on malignant GI disorders, an increase of exactly the same level as that of the studies on the benign GI disorders. While the relative research activity on liver and oesophageal cancer did not change, a clear decrease was observed in studies on gastric cancer (from 29.1% to 20.2%), with the biggest rise found in the research on pancreatic cancer (1.5 times) (Figure 3).

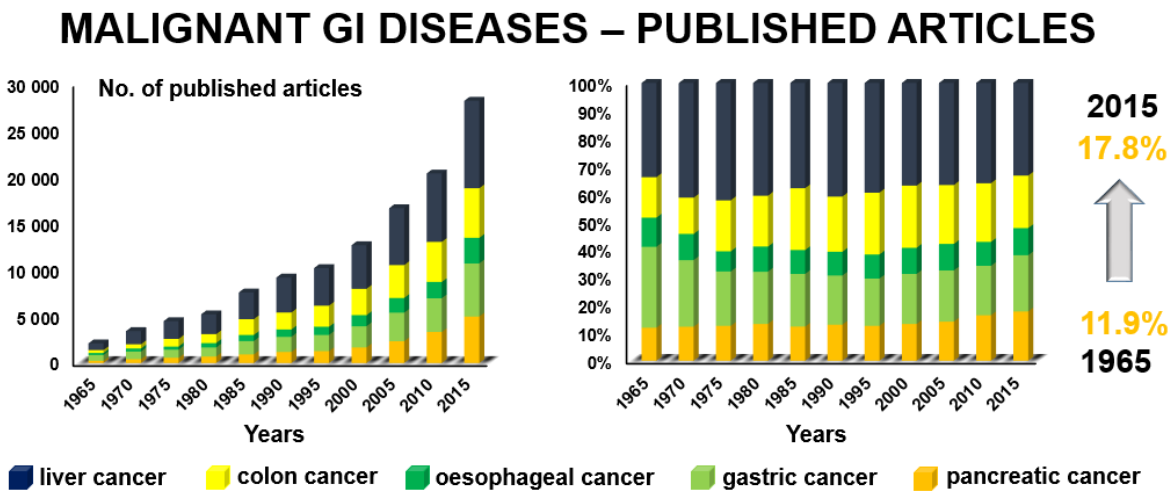


Figure 3. Malignant GI diseases. The biggest increase was found in research activity on pancreatic cancer.

3. Research on pancreatitis has decreased compared to that on other major pancreatic disorders.

Since the biggest drop in GI research interest was in the area of pancreatitis, we continued our study by analyzing the trends in pancreatic diseases. Here we compared the changes of research activity in diabetes, pancreatitis and pancreatic cancer. In 1965, 71.8% (CI 69.99–73.51) of the research was performed on diabetes, 18.1% (CI 16.63–19.65) on pancreatitis and 10.1% (CI 8.93–11.29) on pancreatic cancer. Although 18 times more studies were being conducted on the pancreas 50 years later, the relative interest in pancreatitis had dropped to 5% (CI 4.88–5.28). The relative activity did not change very much in pancreatic cancer (from 10.1 to 11.2%); however, research interest in the endocrine pancreas rose by 11.9% (Figure 4).

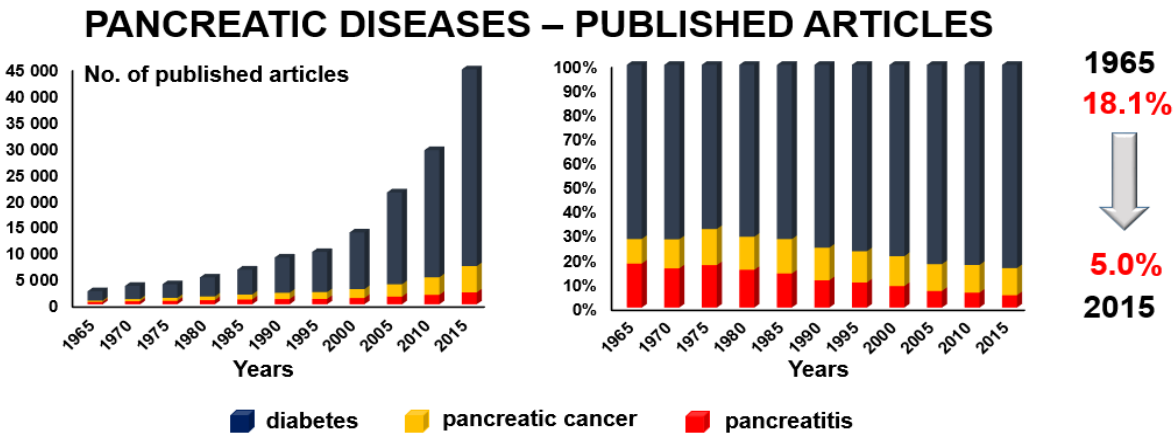


Figure 4. Pancreatic diseases. The relative interest in pancreatitis dropped from 18.1% to 5%.

Analyzing the dynamic of the changes, we can assume that the biggest rise in pancreatic research activity in the last five years was in experimental pancreatic cancer. However, the number of clinical trials – especially on pancreatitis – started to decrease (Figure 5).

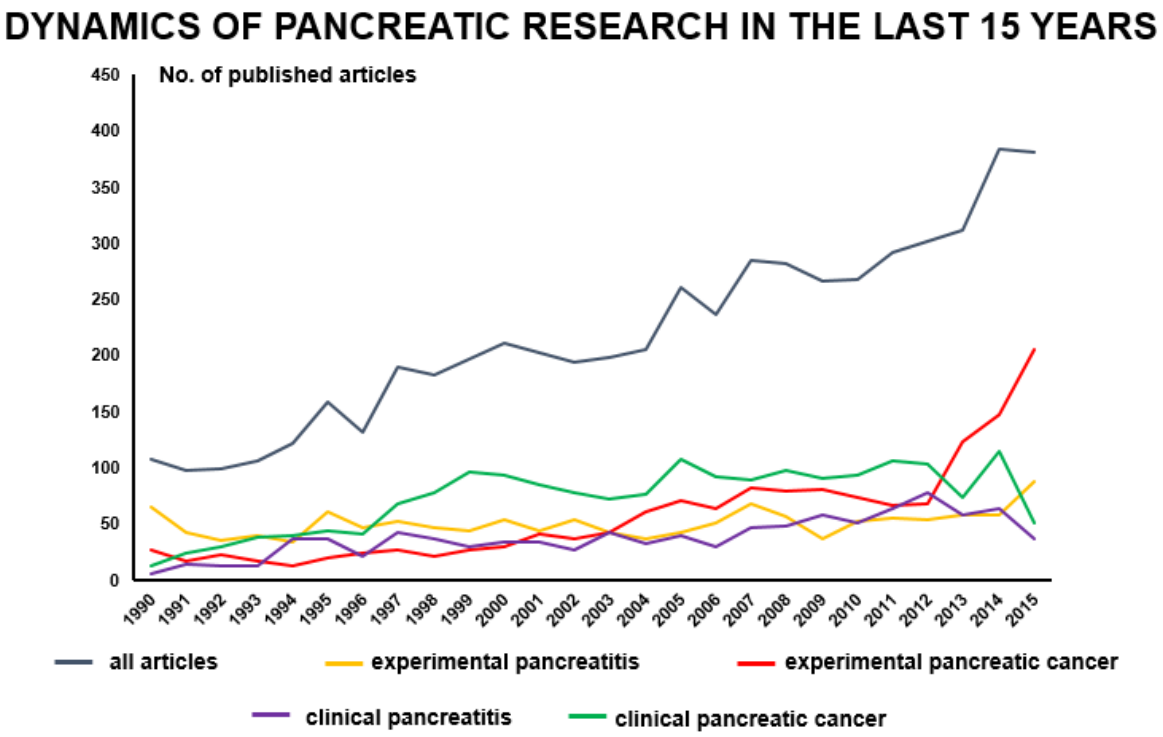


Figure 5. Dynamic of pancreatic research. The biggest rise of pancreatic research activity in the last five years was in experimental pancreatic cancer. However, the number of clinical trials – especially on pancreatitis – started to decrease.

4. The USA, Germany and Japan published the highest number of articles in pancreatology.

As stated above, 6,628 articles contained original research on basic or clinical pancreatology (involving 7,927 countries). Regarding the continents, 47.8% of all participation involved Europe, 28.8% North America, 20.4% Asia and the Middle East, 1.2% Australia and Oceania, 1.2% South America and 0.5% Africa (Figure 6).

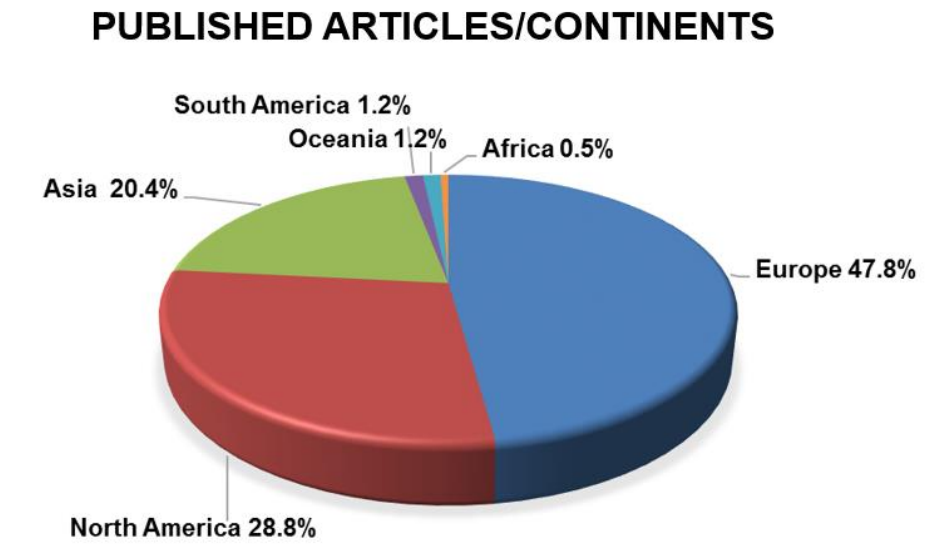


Figure 6. Published articles per continent. 47.8% of all the articles came from Europe and 28.8% from North America.

In terms of the four subgroups (E-P, E-PC, C-P and C-PC), while Europe has the leading role in E-P, C-P and C-PC studies, North America has the highest share in E-PC research. Among the subgroups, C-P has the lowest proportion of all articles on all the continents (Table 2).

THE SHARE OF THE CONTINENTS

A EXPERIMENTAL PANCREATITIS

Continent	E-P	Share
Europe	1179	53.8%
Asia	463	21.1%
North America	461	21.0%
South America	55	2.5%
Oceania	22	1.0%
Africa	12	0.5%
Total	2192	100.0%

B EXPERIMENTAL PANCREATIC CANCER

Continent	E-PC	Share
North America	909	41.1%
Europe	835	37.8%
Asia	409	18.5%
Oceania	30	1.4%
South America	17	0.8%
Africa	11	0.5%
Total	2211	100.0%

C CLINICAL TRIAL - PANCREATITIS

Continent	C-P	Share
Europe	653	56.0%
Asia	289	24.8%
North America	188	16.1%
South America	14	1.2%
Oceania	13	1.1%
Africa	9	0.8%
Total	1166	100.0%

D CLINICAL TRIAL - PANCREATIC CANCER

Continent	C-PC	Share
Europe	1124	47.7%
North America	726	30.8%
Asia	456	19.3%
Oceania	29	1.2%
South America	13	0.6%
Africa	10	0.4%
Total	2358	100.0%

Table 2. **Published articles. The share of the continents in the four research subgroups.** Europe has the leading role in E-P, C-P and C-PC, while in the E-PC research North America has the highest share. Among the subgroups C-P has the lowest share of all articles in all continents.

Regarding the location of research, not surprisingly, countries with the largest population had an advantage: the USA was involved in the largest number of research articles (26.8%), followed by Germany (10.4%), Japan (10.2%) and China (6.4%) (Figure 7 and Figure 8). Altogether, these four countries participated in more than 50% of the research on pancreatology.

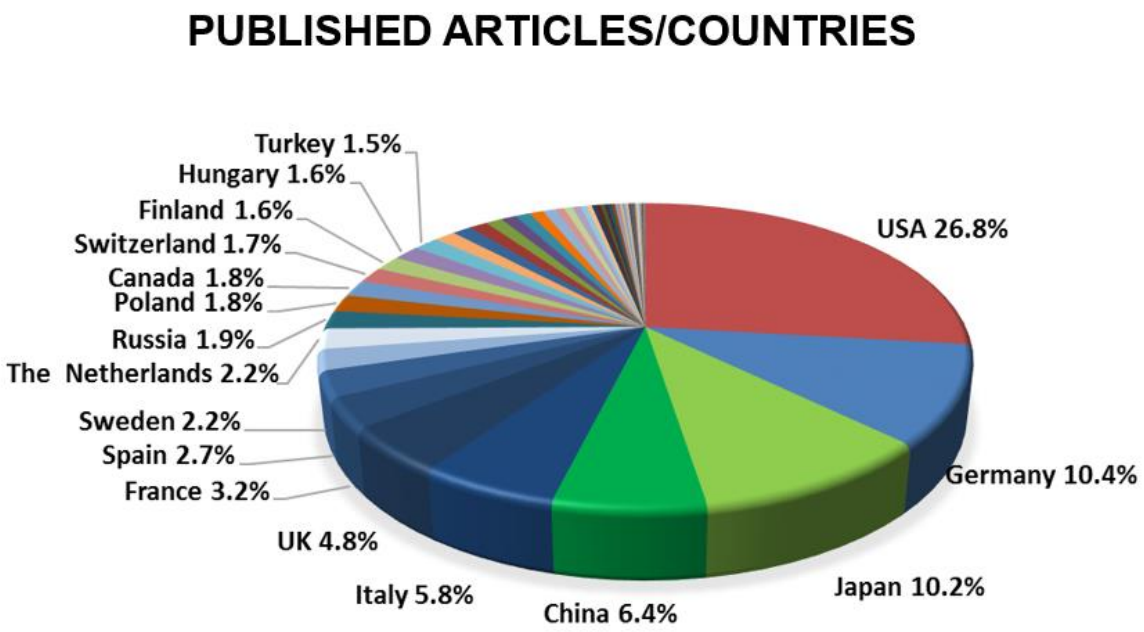
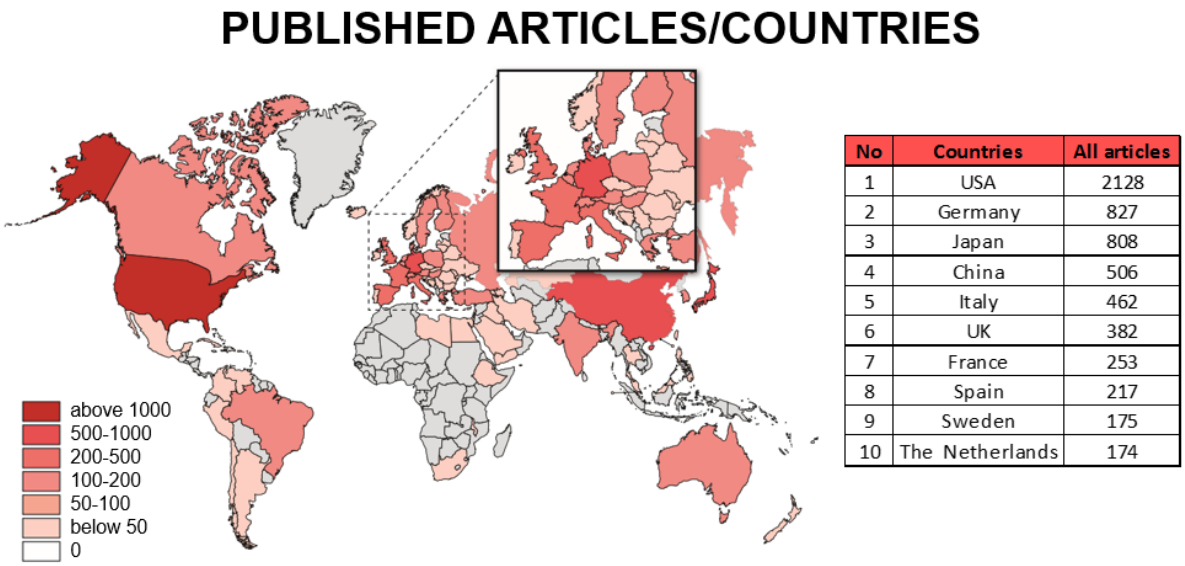


Figure 7. Published articles per country. The USA, Germany, Japan and China together account for more than 50% of all published articles in pancreatology.



No	Countries	All articles
1	USA	2128
2	Germany	827
3	Japan	808
4	China	506
5	Italy	462
6	UK	382
7	France	253
8	Spain	217
9	Sweden	175
10	The Netherlands	174

Figure 8. Map of published articles. The USA was involved in the largest number of research articles, followed by Germany, Japan and China.

Detailed analyses of the four subgroups revealed that the USA led all four subgroups. The countries that ranked second in the subgroups were Germany in the experimental research groups (E-P and E-PC), China in C-P and Japan in C-PC (Table 3).

THE SHARE OF THE COUNTRIES IN THE 4 SUBGROUPS

A EXPERIMENTAL PANCREATITIS

Countries	E-P	Share
USA	437	19.9%
Germany	281	12.8%
Japan	237	10.8%
China	162	7.4%
UK	92	4.2%
Russia	91	4.2%
Turkey	90	4.1%
Finland	78	3.6%
Poland	74	3.4%
Spain	68	3.1%
Sweden	68	3.1%
Italy	65	3.0%
Hungary	51	2.3%
France	45	2.1%
Brasil	41	1.9%
Switzerland	33	1.5%
The Netherlands	28	1.3%
Canada	24	1.1%
Austria	22	1.0%
India	21	1.0%

B EXPERIMENTAL PANCREATIC CANCER

Countries	E-PC	Share
USA	852	38.5%
Germany	225	10.2%
Japan	207	9.4%
China	142	6.4%
Italy	114	5.2%
UK	113	5.1%
France	53	2.4%
Canada	52	2.4%
Spain	47	2.1%
Switzerland	44	2.0%
The Netherlands	42	1.9%
Sweden	37	1.7%
Australia	29	1.3%
Hungary	25	1.1%
Belgium	20	0.9%
Poland	19	0.9%
Korea	15	0.7%
Greece	13	0.6%
Austria	13	0.6%
Denmark	12	0.5%

C CLINICAL TRIAL - PANCREATITIS

Countries	C-P	Share
USA	170	14.6%
China	134	11.5%
Germany	105	9.0%
Japan	79	6.8%
Italy	68	5.8%
UK	61	5.2%
Spain	53	4.5%
The Netherlands	50	4.3%
Russia	45	3.9%
France	32	2.7%
India	31	2.7%
Hungary	29	2.5%
Denmark	28	2.4%
Finland	27	2.3%
Poland	27	2.3%
Korea	23	2.0%
Sweden	20	1.7%
Greece	20	1.7%
Switzerland	14	1.2%
Turkey	13	1.1%

D CLINICAL TRIAL - PANCREATIC CANCER

Countries	C-PC	Share
USA	669	28.4%
Japan	285	12.1%
Germany	216	9.2%
Italy	215	9.1%
France	123	5.2%
UK	116	4.9%
China	68	2.9%
Canada	56	2.4%
The Netherlands	54	2.3%
Sweden	50	2.1%
Korea	50	2.1%
Spain	49	2.1%
Greece	46	2.0%
Switzerland	41	1.7%
Belgium	40	1.7%
Austria	33	1.4%
Australia	27	1.1%
Poland	25	1.1%
Hungary	21	0.9%
Taiwan	20	0.8%

Table 3. Published articles. The share of the countries in the four research subgroups. The USA led all of the four research subgroups, however, the second was Germany in the experimental research groups (E-P, E-PC), whereas China had the second place in the C-P while Japan in the C-PC group.

5. The density of active pancreatic researchers is highest in the Scandinavian countries.

Comparing the data per population of 10 million, small countries came to the fore. Scandinavian countries are clearly the most active in pancreatic research per capita. None of the big countries were in the top five (Figure 9).

PUBLISHED ARTICLES/10m/COUNTRIES

No	Countries	Articles per 10 million
1	Finland	233
2	Sweden	181
3	Switzerland	160
4	Denmark	127
5	Hungary	127
6	The Netherlands	103
7	Germany	100
8	Austria	82
9	Belgium	80
10	Greece	77

Figure 9. Map of published articles per population. The Scandinavian countries are clearly the most active in pancreatic research per capita.

Detailed analysis has also revealed interesting differences between the countries (Table 4). E-P research is led by Finland, E-PC by Switzerland, C-P by Denmark and C-PC by Sweden.

PUBLISHED ARTICLES/10M IN THE 4 SUBGROUPS

A EXPERIMENTAL PANCREATITIS

Countries	E-P/10M
Finland	143
Sweden	70
Hungary	51
Switzerland	40
Germany	34
Denmark	30
Austria	26
Norway	21
Poland	19
Ireland	19
Japan	19
New Zealand	17
Belgium	17
The Netherlands	17
Israel	15
UK	14
Spain	14
USA	13
Turkey	12
Italy	11

B EXPERIMENTAL PANCREATIC CANCER

Countries	E-PC/10M
Switzerland	53
Sweden	38
Iceland	30
Germany	27
USA	26
Hungary	25
The Netherlands	25
Denmark	21
Italy	19
Luxembourg	18
Belgium	18
UK	18
Japan	16
Austria	15
Ireland	15
Canada	14
Lithuania	13
Israel	13
Australia	12
Greece	12

C CLINICAL TRIAL - PANCREATITIS

Countries	C-P/10M
Denmark	49
Finland	49
The Netherlands	30
Hungary	29
Sweden	21
Latvia	20
Greece	18
Switzerland	17
Germany	13
Spain	11
Italy	11
Belgium	10
UK	10
New Zealand	9
Norway	8
Poland	7
Lithuania	7
Czech Republic	6
Israel	6
Japan	6

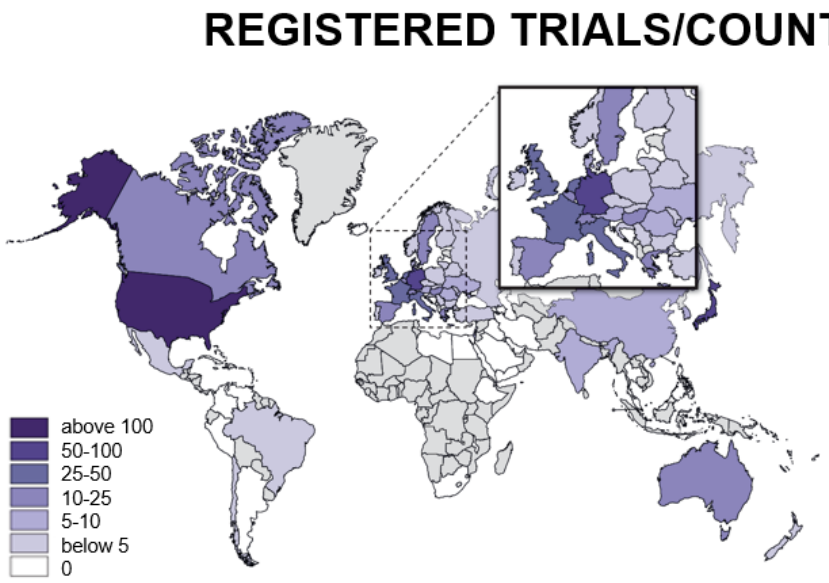
D CLINICAL TRIAL - PANCREATIC CANCER

Countries	C-PC/10M
Sweden	52
Switzerland	50
Greece	41
Austria	39
Norway	37
Belgium	36
Italy	35
The Netherlands	32
Finland	29
Denmark	26
Germany	26
Japan	22
Hungary	21
USA	21
France	19
UK	18
Israel	16
Canada	16
Australia	11
Spain	10

Table 4. Published articles per 10 million population in the four research subgroups. When we normalize the number of published articles to 10 M population, E-P research is led by Finland, E-PC by Switzerland, C-P by Denmark and C-PC by Sweden.

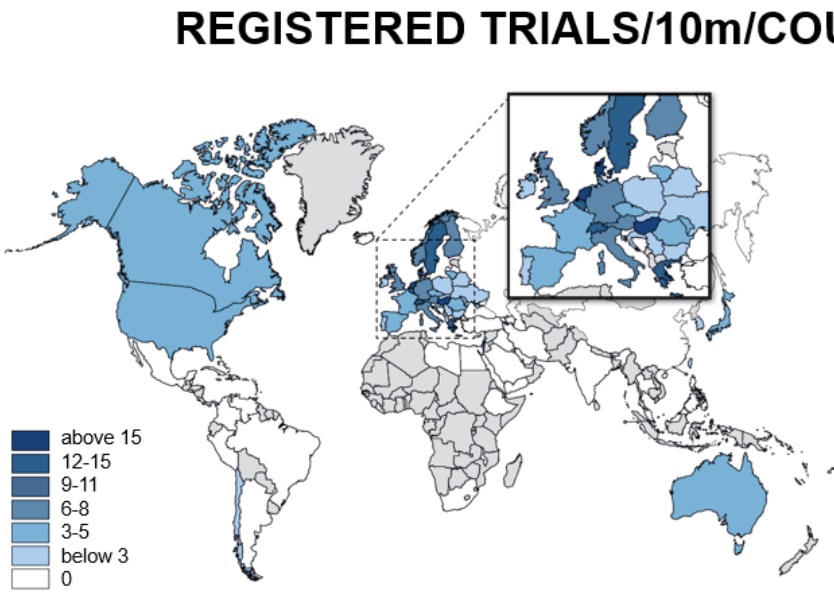
6. The USA and the Netherlands are in the forefront in registered clinical trials.

The highest level of evidence is obtained from registered clinical trials. Unfortunately, only 13.4% of all trials were registered in our analysis of the period between 1965 and 2015. With regard to the absolute numbers of registered clinical trials in pancreatology, the big countries register the highest number of trials (Figure 10). Comparing registered clinical trials per person, Dutch researchers have been the most active, followed by Hungary, Denmark and Sweden (Figure 11). The above results are based on publication numbers between 1965 and 2015, but three out of these four countries, Denmark, Sweden and The Netherlands accompanied by Estonia and Finland had the largest number of actively recruiting registered trials per person in August 2012.



No	Countries	All registered trials
1	USA	122
2	Germany	69
3	Japan	53
4	Italy	48
5	UK	36
6	The Netherlands	32
7	France	29
8	Canada	18
9	Hungary	16
10	Belgium	15

Figure 10. Map of registered trials. The big countries hold clear leading positions.



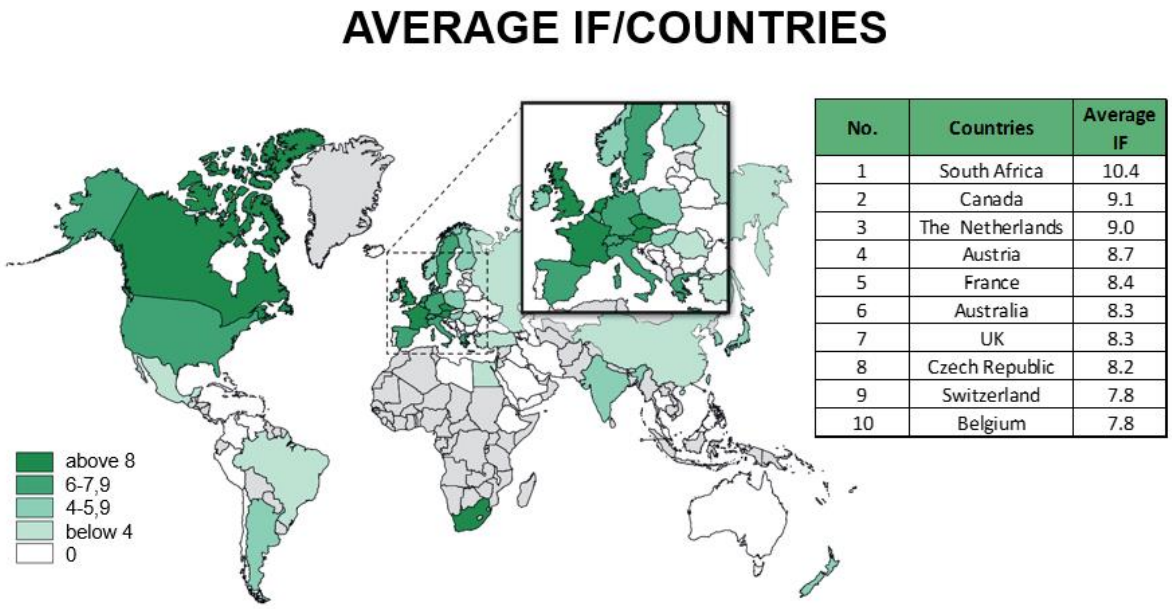
No	Countries	Registered trials per 10 million
1	The Netherlands	19
2	Hungary	16
3	Denmark	16
4	Sweden	14
5	Belgium	13
6	Greece	13
7	Switzerland	12
8	Germany	8
9	Austria	8
10	Italy	8

Figure 11. Map of registered trials per population. Comparing the registered clinical trials per population of 10 million, Dutch researchers are the most active.

7. Multinational and multicentre studies provide the most valuable research in pancreatology.

Detailed analyses showed that there are no big differences between the average impact factors (IF) of countries. Countries with a low number of articles, such as South Africa and Canada, have the highest average IF. Over 30 countries produced an average IF higher than 5 (Figure 12 and 13). Therefore, practically speaking, the quality of research is not country-dependent. However, detailed analysis of the articles

revealed that there is a strong correlation between the number of countries per study and the quality of the article. In a single-nation article, the average IF is 4.652 (± 0.10), when only a single centre is involved. However, the involvement of more than 6 centres in a single nation increased the average IF of articles to 7.094 (± 0.37). Notably, multicentre and multinational studies achieved the highest average impact 19.278 (± 2.55) (Figure 14 and 15).



No.	Countries	Average IF
1	South Africa	10.4
2	Canada	9.1
3	The Netherlands	9.0
4	Austria	8.7
5	France	8.4
6	Australia	8.3
7	UK	8.3
8	Czech Republic	8.2
9	Switzerland	7.8
10	Belgium	7.8

Figure 12. Map of average impact factor/country. There are no big differences between the average IF/country.

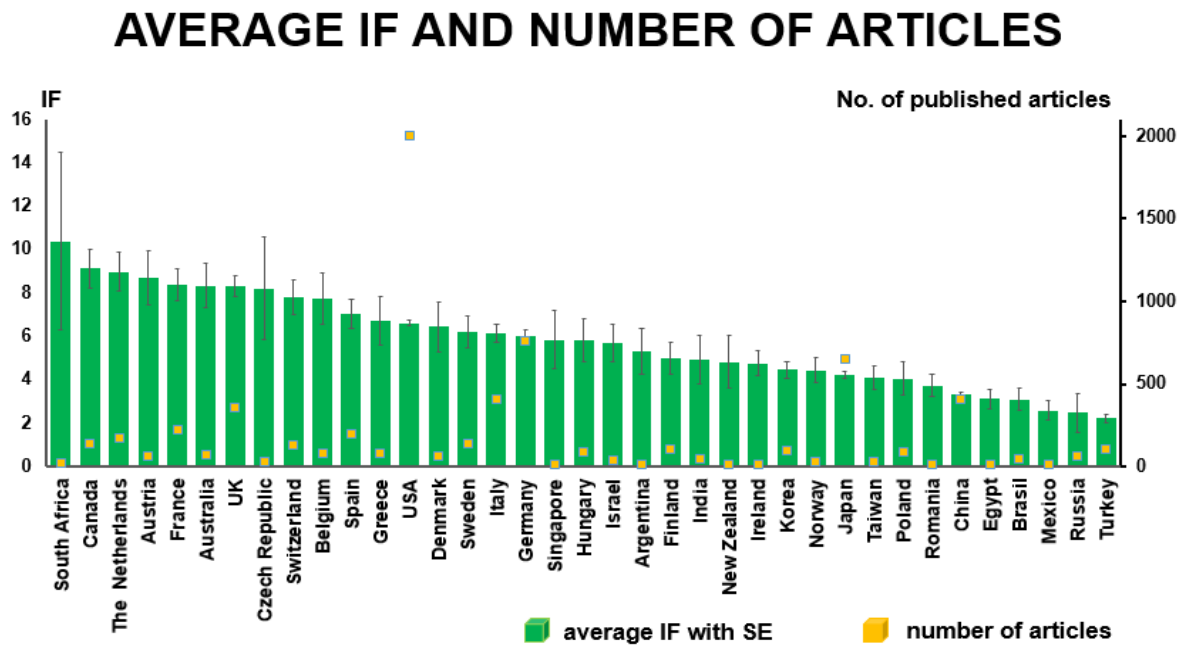
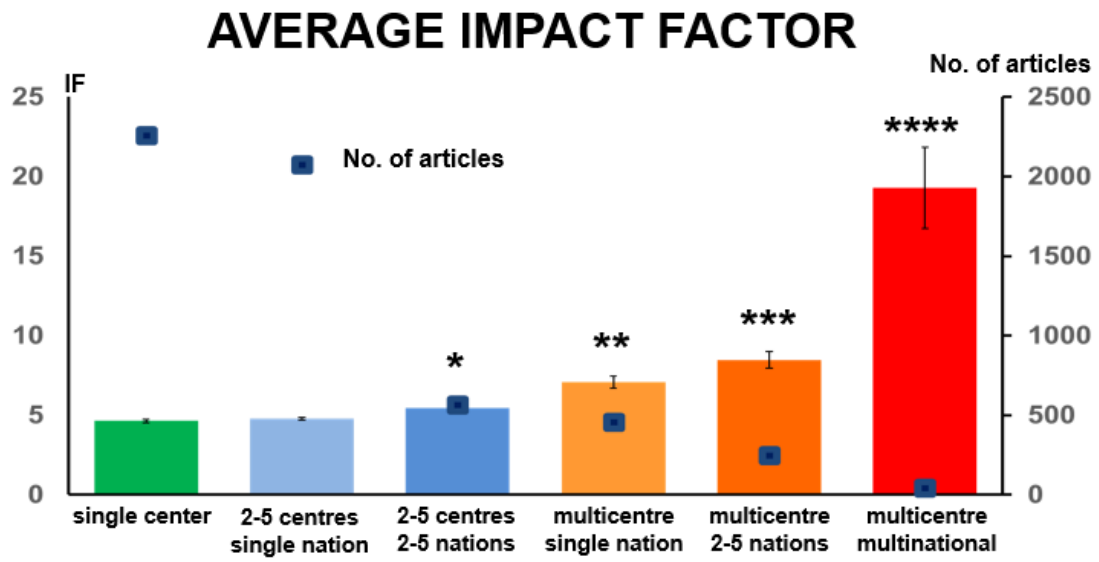
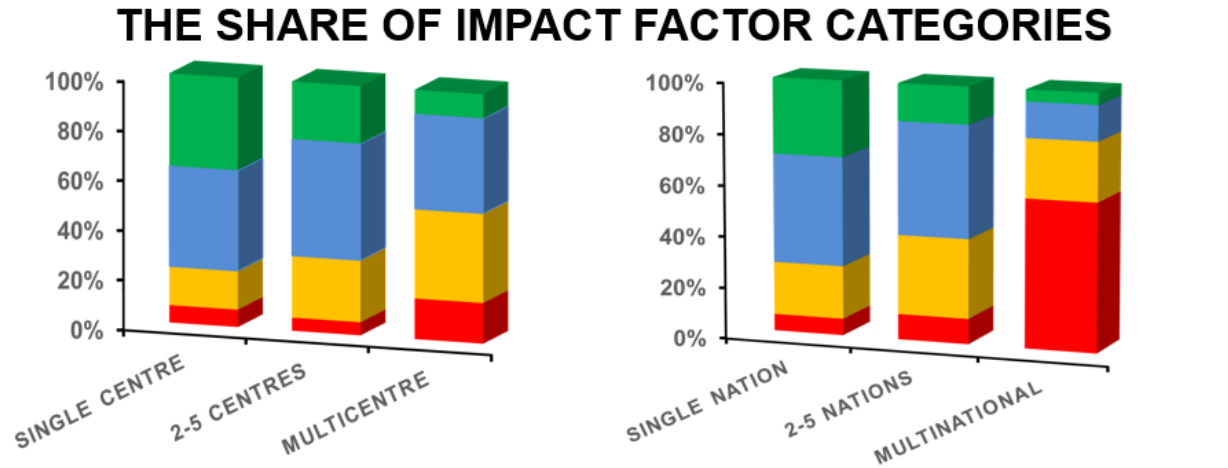


Figure 13. Average impact factor per country. Over 30 countries achieved an average IF higher than 5. Values are expressed as means ± standard error (S.E.M.).



		number of articles	average IF	SE
single centre	single nation	2257	4.652	0.107
2-5 small number of centres	single nation	2077	4.786	0.098
	2-5 small number of nations	566	5.451	0.206
multicentre	single nation	458	7.094	0.377
	2-5 small number of nations	248	8.465	0.525
	multinational	42	19.278	2.552

Figure 14. Average impact factor by number of centres and nations. Both multicentre and multinational approaches increase the impact of the papers. *: p=0.009 vs. single centre single nation; **: p<0.001 vs single centre/single nation; ***: p<0.001 vs 2-5 centres/2–5 nations and vs multicentre/single nation; ****: p<0.001 vs all groups. Values are expressed as means ± standard error (S.E.M.)



	NUMBER OF ARTICLES		
IF category	single centre	2-5 centres	multicentre
above 10	197	155	126
between 5-10	441	734	278
between 2-5	1138	1378	294
under 2	1055	686	76

	NUMBER OF ARTICLES		
IF category	single nation	2-5 nations	multinational
above 10	366	87	25
between 5-10	1170	273	10
between 2-5	2415	389	6
under 2	1686	129	2

Figure 15. The share of average impact factor categories. There is a strong correlation between the number of countries per study and the quality of the article.

Discussion

With regard to gastrointestinal diseases, there is significant morbidity, mortality and, of course, spending within national health budgets [10-14]. In the USA, not only are 60–70 million people affected by such diseases each year, but they also cause around a quarter million deaths annually and generate an estimated cost of $150 billion per year [12]. There is no specific therapy for many of these diseases, including pancreatitis and pancreatic cancer [15-17]. Of course, first, the pathomechanisms of the disease should be understood, which might reveal new therapeutic targets and consequently might attract the biomedical industry [18-21].

The levels of research activity in academia and the biomedical industry are remarkably interdependent [22-26]. Gastroenterology is no longer attractive for investment by biomedical firms or medical grant agencies [13]. Therefore, here we aimed to hold a mirror up to the researchers and funding agencies to better understand the research activity in the field. Of course, the hospitalization dynamics and requirements for different diseases in the areas of gastroenterology differ. Since 2000, while some hospital admissions have decreased for certain diseases (e.g., cholelithiasis by 14%, gastro-oesophageal reflux by 32% and alcoholic liver diseases by 5%) and others have risen (acute pancreatitis by 30%, *Clostridium difficile* infection by 237%), the highest number of admissions are due to acute pancreatitis (over 250,000/year), with the highest annual costs ($2.5 billion) in the USA [12]. A Scottish study revealed a ten-fold rise in the incidence of acute pancreatitis among men, and about half of that among women, from 1961 to 1985 [25]. After that, in the following ten years, it further increased by 65% [26]. Moreover, the incidence rate of chronic pancreatitis also rose. For example, the hospital admission rate for chronic pancreatitis doubled in the UK within ten years [27].

Therefore, needless to say, boosting research activity in the field of pancreatitis is not only important medically but also economically. However, despite its great importance, pancreatic research suffered the biggest loss of interest in gastroenterology, a trend which could be either due to the lower activity in academic research and/or the lack of specific therapy (i.e., no income for the companies) for most of the diseases affecting either the endocrine or the exocrine pancreas.

What did we find and what can we do?

Strengths: It is clear from our analysis that both large and small countries are contributing to pancreatic research. The literature on pancreatology is dominated by the United States, Germany, China, Japan, Italy and the UK, just like in other scientific fields, such as ‘pain’ [28] and ‘oncology’ [29]. The same countries have the highest R&D funds, whereas the density of pancreatic research is the highest in the Netherlands, Finland, Sweden, Denmark and Hungary. We have observed a positive trend in the publication of pancreatic cancer research, although the reason is definitely the highest corporate funding share in oncology and multifactorial action plans, such as those in the USA and Europe (www.pancan.org, www.eupancreas.com), which increase awareness and may influence decision makers and promote grant funding [30].

Weaknesses: There are 50 countries in Europe, but only 23 are actively publishing in the field (with more than ten published articles each in 50 years). The majority (84.8%) of the articles under analysis represent a single nation, and 39.9% are single-nation and single-centre studies with no cooperation with others. Not surprisingly, without cooperation, the possibilities for data collection were limited; therefore, only a few high-quality multinational and multicentre observational clinical trials or RCTs were performed [31-36]. It is important to highlight that the Central and Eastern European, African, South American and Asian countries are facing the biggest difficulties as their sometimes poor infrastructure and lack of resources make them an undesirable research partner. Moreover, grant proposals submitted from these countries are usually rejected. More than 50% of the European countries (representing more than 200 million people!) are only slightly involved in pancreatic research, a situation which is a huge mistake and luxury in the field. In addition, patient care is also diminished since evidence-based guidelines are only published in a few countries in Eastern and Central Europe [37-42].

Opportunities: This analysis provides clear evidence that multicentre, multinational cooperation can achieve better-quality trials and higher impact in the field. International

patient registries and biobanks should be created to stimulate quality multicentre observational trials, RCTs and translational research [43-49]. Importantly, following the success of pancreatic cancer action plans that probably contributed to the four-fold rise of E-PC research activity in the last few years, the same action should be initiated for pancreatitis.

Threats: If research on pancreatitis is to decrease further, journal editors may consider pancreatology an even lower priority, thus resulting in fewer publications in top journals. Perhaps it almost goes without saying that this will be followed by fewer grants and less activity in the field, thus continuing the vicious circle seen in the last 50 years, which has resulted in no specific treatment for acute pancreatitis.

Conclusion

Countries that have the largest biomedical R&D investments, like the USA, Japan, and Germany, publish the highest number of scientific papers. Smaller countries with much less sources, like Sweden, Finland, Denmark or Hungary, may increase their impact by more intense financial and human resource R&D investments and also by international co-operations.

Substantially more academic and other clinical research should be performed in gastroenterology providing higher evidence for more therapeutic solutions. Activity in pancreatitis research has been rapidly decreasing. These data strongly suggest to governments, industry and non-profit organizations that they should consider pancreatitis an endangered field of research and sponsor far more international networks and academic R&D activities.

II. DEVELOPING A BETTER ENVIRONMENT FOR PANCREATIC RESEARCH

Introduction

There is still no specific therapy for many of the pancreatic diseases, including acute pancreatitis and pancreatic cancer [15-17]. Establishing the diagnosis, preventing the progression and treating clinical symptoms are still challenging in chronic pancreatitis [50-51]. Pancreatology is a small area within gastroenterology and it is hard to individually organize studies, obtain grants, which result in a small amount of studies, and those studies are mainly single centre retrospective trials.

As our previous analysis showed, industrial investments into gastroenterology research has been decreasing in the last decade just like the activity in pancreatology research, especially concerning pancreatitis. This analysis has also confirmed the well-known fact that multinational-multicentre trials are of higher quality, providing higher evidence and impact, but the share of the multinational-multicentre studies are very low. Consequently, there is still much space for improving both the quantity and quality of research activity in the field of pancreatology. In this chapter I would like to evaluate the possibilities of changing this poor situation and sum up of steps the Hungarian Pancreatic Study Group has made as a start for improvement.

Background

There are different ways of acquiring information on healthcare performance, disease development or treatment details. These methods provide different data quality, and evidence levels resulting in different quality of research and publications having different impact. The more requirements are set for data quality, the less limitations will accompany the research. (Figure 16).

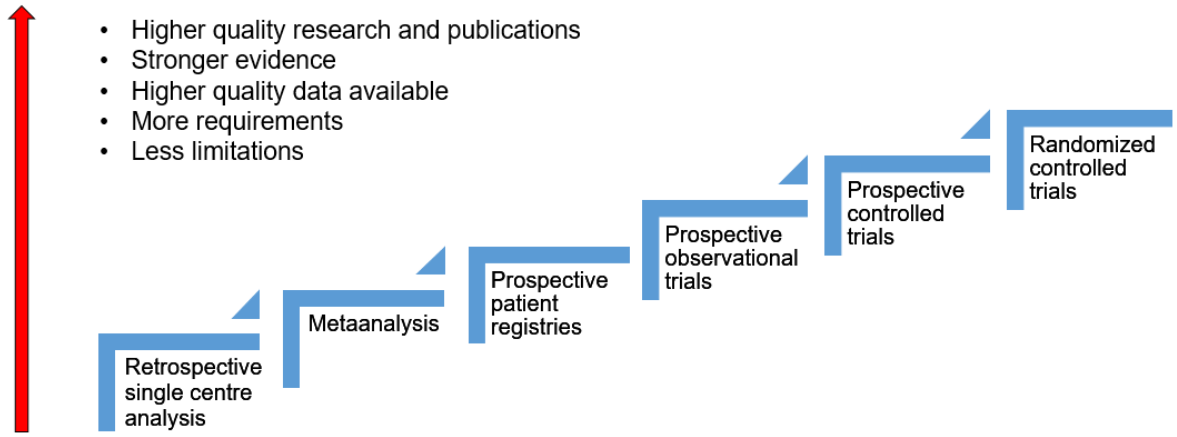


Figure 16. The association between the method and quality of research.

The easiest way is to **retrospectively analyze** data from a single center database, national medical information system or hospital discharge data [52-53] or sending out questionnaires to institutions [54] or patients [55]. However, retrospective data are limited and often insufficient in quantity or quality.

The other way is collecting all cohorts and studies and conduct a **meta-analysis**. In this way we can identify areas where data are missing or insufficient. A recent meta-analysis [56] used 35 population representative pancreatic cancer cohorts for incidence and mortality analysis. These cohorts represented Europe, North-America and Asia quite well, but cohorts from Africa, Australia & Oceania and South-America were missing from the evaluation.
Concerning acute pancreatitis, only 10 cohorts were analyzed from 5 countries, the USA, the UK, Sweden, Denmark and Taiwan, 6 of the cohorts coming from Northern-Europe. In case of chronic pancreatitis the situation is even worse, the meta-analysis was done on only 3 cohorts collected from Sweden, Denmark and the USA. There were little data available both for acute and chronic pancreatitis.

Patient registries are the first step from retrospective research towards good quality, high evidence randomized controlled clinical trials. While enrolling patients, there is a possibility to include questions usually missing from general medical records. These registries are useful in 1) understanding the current practice, 2) comparing the practice with other institutions, countries, 3) following patients, 4) controlling guideline

compliance, 4) analyzing collected data, writing scientific papers, 5) educating young doctors and in consequence of these former actions, 6) improving healthcare. If a biobank is connected to the database, genetic analyses also can be performed.

There are several initiatives of multicenter pancreatic patient registries mainly in the USA, UK, Spain, the Netherlands: 1) APPRENTICE (Acute Pancreatitis Patient Registry to Examine New Therapies in Clinical Experiences), 32 centres, 12 countries have joined, only clinical data, http://caperpancreas.org/beta/index.php/apprentice 2) INSPPIRE (International Study Group of Pediatric Pancreatitis In Search for a cuRE), University of Iowa (Aliye Uc), NIH funded project, 14 centres, 4 countries, 250 children, clinical data and biological samples [57-58]. 3) EUROPAC (European Registry of Familial Pancreatic Cancer and Hereditary Pancreatitis), University of Liverpool (Bill Greenhalf), 249 families with chronic pancreatitis and 168 families with more than one case of pancreatic cancer [59]. 4) CARE (Dutch Chronic Pancreatitis Registry), 1218 patients, multicenter, single nation [60]. 5) PanGem-Fam (Spanish registry of hereditary pancreatic cancer), 42 families, follow-up, screening program [61]. These registries are very important initiatives, but most of them are concentrating on a small area of pancreatology or they do not collect biological samples.

We can conclude that more data are needed and there are no data (or very little) from Central and Eastern European countries. Also, there are no large biobanks for genetic studies, especially in AP and CP.

As it was confirmed by the previous analysis, **clinical trials**, especially **randomized controlled trials** provide the highest quality data and evidence level, but unfortunately there is a lack of registered clinical trials in pancreatology.

Aims

Our aims were to collect clinical data and biological samples prospectively for further studies in acute pancreatitis (AP), chronic pancreatitis (CP) and pancreatic cancer (PC), to recruit centres in order to increase the quality of the research, to provide a database and biobank for pancreatic research open for all participants and to make the results widely available, open access.

Building on the experiences, findings and joined centres of the patient registries, the further aim of the Hungarian Pancreatic Study Group was to plan and conduct

observational clinical trials and improve the management of pancreatic patients by adapting the international evidence-based guidelines and educating doctors and students.

Methods

Research plan: the research plan should include the research protocol, the research questionnaire, the patient information form, the patient informed consent form and the participation agreement of the joining centers.

Ethical approval: For developing a registry and a biobank, a research plan should be approved by the Secretary of Medical Research Council, Scientific and Research Ethics Committee.

Recruiting centres: the registry and biobank is open for every institution that is able to collect all necessary data. In case an institution intends to join the registry, a signed letter of intent and a webpage registration is needed. There must be at least one dedicated person in every institution to enroll patients and upload data into the registry.

Patient enrollment: the patient should be informed on the purpose of the research and blood sampling and the Patient Informed Consent Form should be signed before any enrollment.

Data collection: As data registration should be available at the different institutions, the HPSG has developed a web-page and a web-based electronic data administration system. All forms are available from the website and data upload can be accomplished online.

Collected clinical data: the collected information is different for every diagnosis and may include details from the patient's medical history (pancreatic diseases, other diseases, pancreatic disorders in the patient's family), risk factors (smoking and alcohol drinking habits), symptoms and clinical signs, details of physical examination, laboratory parameters, imaging examinations, other examinations (histology, cytology, functional tests) conservative, endoscopic, surgical, oncological and supportive therapy details, complication, etiology.

Collected samples: the collection, delivery and storing of blood samples and other biological samples are processed according to the protocol.

Data quality control: there is a four-step controlling of data in the registry. The person who uploads data will approve the forms as a first controller then the local professional

(doctor, who takes part in the trial) needs to check and approve forms, the third control is a central administrative control done by the central administrative team of the registry and finally the professional supervisor of the registry approves the forms.

Data and sample access: researchers actively contributing to the biobank and registry or collaborating researchers may access to data and samples after a formal application with the full scientific proposal, using the HPSG Biobank and Registry Project Application Form. The use of samples and data are free of charge and should serve research purposes only.

Publications: any results based on the data of the HPSG Registry for Pancreatic Patients, can only be published with the consent of the HPSG.

Results

1. Establishing the Registry for Pancreatic Patients

In 2001 the pancreatic research group in Szeged won a Welcome Trust Initiative Research Development Award which allowed to start high quality research in Szeged. Seven years hard work resulted in an international presence in basic science in pancreatology [62,63]. As a result of the evaluation of the clinical research status in Hungary in 2011, it was clear that (1) pancreatic clinical research lacks a national organization (study group), (2) a common voice, (3) international visibility, (4) national EBM guideline, (5) pancreatic biobank and (6) multicenter clinical trials. To find a solution for these problems, the Hungarian Pancreatic Study Group (HPSG) was founded in 2011 and started the process of developing a national, then an international multicenter network for pancreatic research.

The process included several steps for network development: the first step was the foundation of the National Pancreas Registry including data of acute and chronic pancreatitis and pancreatic cancer cases, also including a biobank with blood samples. The study data collection was approved by the Secretary of Medical Research Council, Scientific and Research Ethics Committee, approval number is 22254-1/2012/EKU (391/PI/2012) and in 2016 the permission was extended until 2021. The enrollment of patients started in September 2012. The patients are enrolled after written informed consent. To involve more and more Hungarian centers it was necessary to individually contact them and organize trainings on patient enrollment and data administration. A functional webpage and a data administration system was developed, that made

possible for the centers to provide data and directly upload them into the database. The registry started with one Hungarian center in Szeged, soon, the number of joined Hungarian centers and enrolled patients started to grew rapidly, reaching 26 centers and 1200 patients in 2014. After 2014 international centres are contributing also to the development of the registry. In 2016, 39 institutions from 4 countries are uploading data to the AP, CP and PC general registry, 33 institutions from 23 countries to the trial database but altogether 99 centres have joined or in the process of joining (Figure 17).

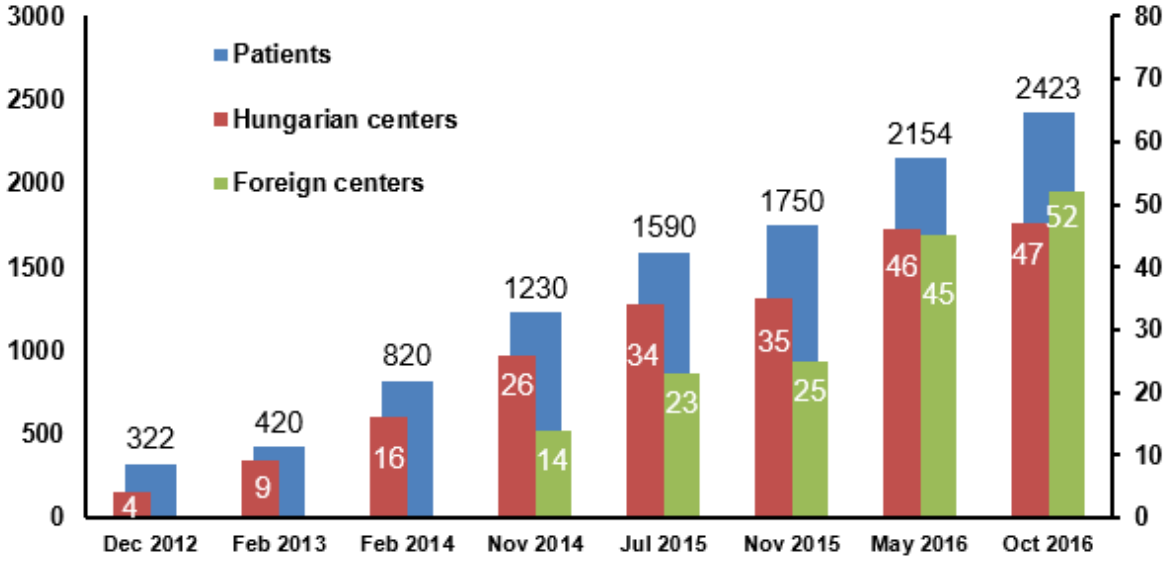


Figure 17. Registry for Pancreatic Patients. Joined centres and enrolled patients 2012-2016

The organization of the 1st and 2nd Conference of the Hungarian Pancreatic Study Group (held in Nov 2012 and Dec 2013 in Szeged, Hungary) made it possible to hear presentations on the clinical research practice and collaborations in other countries (Germany, The Netherlands) to involve professionals in pancreatology in HPSG activities, also to present the initiation and development of the National Pancreas Registry.

Going from the West to the East, it became clear, that most of the Eastern and Central European countries are in the same situation. Therefore, we strongly believe that our experience worth sharing with the others and we also aim to share our web facilities in pancreatology to stimulate more research in the field.

How to join?

Registries and prospective clinical trials are open for all centers that are able to provide quality data, comply with the protocols and have secured the compliance with the local institutional and national ethical requirements. Participation in researches and authorship policies in publications are regulated in the protocols that are available on the website of the Hungarian Pancreatic Study Group (www.pancreas.hu).

2. Analyses based on registry data and biological samples

Based on the HPSG Registry for Pancreatic Patients several genetic and three cohort studies have been completed and published.

1. Pancreatic cancer. Multicenter Prospective Data Collection and Analysis by the Hungarian Pancreatic Study Group [17]

There were 338.000 new cases of pancreatic cancer worldwide in 2012, this is 4% of all cancers diagnosed. Pancreatic cancer is the 7th among cancer deaths worldwide (GLOBOCAN 2012). In Hungary 2545 cases were registered in 2012 and it is the 5th in number of cancer deaths (Hungarian National Cancer Registry). The 5 year survival is less than 5%. There are limited data available on the management of pancreatic cancer, especially in Central and Eastern Europe.

Therefore we enrolled 354 patients with pancreatic cancer into our registry from 14 centres between September 2012 and March 2014. The mean age of the population was 65.2 years (SD 11.5, range: 23-88 years). 53.4% of the patients were male and 46.6% were female. Participating centres included gastroenterology, endoscopic, oncology and surgical departments. 80% of the patients were enrolled from six institutions situated in Szeged (2), Pécs (2), Székesfehérvár and Budapest. Collected data included demographics (age, gender), risk factors (alcohol consumption, smoking, body mass index, acute or chronic pancreatitis, diabetes mellitus, familial PC in the medical history, any pancreatic disease in family history), symptoms and clinical signs (fever, abdominal pain, diarrhea, jaundice, weight loss), cancer related data (date of diagnosis, location of the tumor, histological type, the method to obtain histological information, CA 19-9 level at the time of diagnosis, imaging results confirming diagnosis and staging), endoscopic, surgical, oncological and supportive therapy.

This Hungarian cohort provided useful information on demographics, the frequency of recurrent AP and CP in the medical history, histological type, details on endoscopic

management of obstructions and independent predictors for overall survival. The cohort also showed the areas to improve, namely, much more information is needed on interventional, oncological and supportive therapy.
The article was published in June 2016.

2. Prospective, Multicentre, Nationwide Clinical Data from 600 cases of Acute Pancreatitis [64]
Acute pancreatitis is a serious condition with high mortality and it is a leading cause of acute hospitalization for gastrointestinal diseases. There is still no specific therapy for the treatment and there were no large, nationwide, prospectively collected AP data on the diagnosis and the management of AP. Also, compliance to evidence based guidelines are proved to reduce mortality and severity, however this was not validated on a large nationwide cohort. The aim of this study was to analyze the management of AP on a large population in Hungary and validate the major recommendations of the IAP/APA evidence-based guidelines for the management of AP.
600 patients were enrolled prospectively between January 2013 and January 2015 from 17 Hungarian centres. In this cohort, 56% of the patients were male and 44% were female (Figure 18).

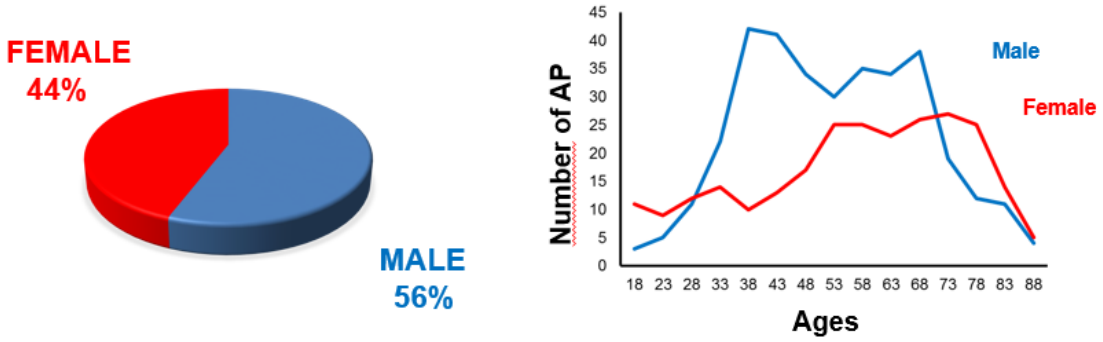


Figure 18. Gender and age distribution of the 600 acute pancreatitis cases in the Hungarian cohort.

Eighty six parameters were collected including diagnosis and management (physical examination, laboratory parameters, imaging), demographics, risk factors, endoscopic (ERCP, EUS), surgical and conservative therapy (fluid resuscitation, antibiotic therapy, pain management) and complications (pancreatic, organ failure, death).

The nationwide cohort of 600 cases of AP has showed the major determinants and associations of severity and mortality in AP and also emphasized the importance of the compliance to evidence-based guidelines.
The article was published in October 2016.

3. Chronic pancreatitis. Multicenter Prospective Data Collection and Analysis by the Hungarian Pancreatic Study Group [65].
Chronic pancreatitis is a progressive inflammatory disease causing irreversible structural and functional damage of the pancreas. CP may seriously affect the quality of life causing pain and maldigestion. The pathomechanism of CP is still poorly understood, and without the classical clinical symptoms, the diagnosis in early stages are challenging. There are limited number of prospective cohorts available on the management of CP and there was none from Hungary, therefore we aimed to collect data from CP patients in Hungary in a prospective manner.
229 patients were enrolled between 2012 and 2014 from 14 Hungarian centres. The mean age of the patients was 54.63 years. 73.8% of the enrolled patients were male and 26.2% were female. Data collection included demographics, etiology, risk factors, symptoms and clinical signs, laboratory parameters, imaging examinations, conservative and interventional therapy and complications.
The cohort concluded that the first nationwide prospective data collection provided important information for improving the treatment of the disease. However, quality of data collection on diagnosis details and on the progression of the chronic disease should be improved.
The article is submitted.

4. Genetic analysis CELA3A, CELA3B [66]
The Hungarian Pancreatic Study Group has organized the collection of biological samples together with clinical data for the Registry for Pancreatic Patients. The permission for the biobank was obtained in 2012. The biobank is located at the First Department of Medicine, University of Szeged.
Chronic pancreatitis is a progressive, relapsing inflammatory disease of the pancreas which often develops in the background of genetic susceptibility. In the study the hypothesis was tested that changes in complex formation between human proelastases and procarboxypeptidases might alter risk for CP.

This genetic study was completed on samples from 225 unrelated patients with CP (including 120 with alcoholic CP and 105 with idiopathic CP) and 300 controls with no pancreatic disease. Individuals were enrolled to the HPSG Registry for Pancreatic Patients from 11 Hungarian centers between 2012 and 2016.

The study demonstrated that variants affecting amino-acid position 241 in human CELA3A and CELA3B are not associated with CP, indicating that changes in complex formation between human proelastases and procarboxypeptidases do not influence the risk for CP. The observation that intronic variant c.643-7G>T in CELA3B was significantly underrepresented in alcoholic CP patients suggests this might be a protective variant.

The article was published in December 2016.

3. Becoming multinational

In November 2014, the 3rd Conference of the Hungarian Pancreatic Study Group was organized together with the 9th International Symposium on Alcoholic Liver and Pancreatic Diseases and Cirrhosis, making the event an excellent occasion to involve international participants and the Eastern and Central European Pancreatic Study Group was founded. Several Eastern and Central European centers delegated their professionals and HPSG had the opportunity to present the development of the National Pancreatic Registry, which has become international, just like the multicenter observational clinical trials initiated by the HPSG.

4. Planning and developing observational clinical studies

The HPSG initiated four multicenter, observational clinical trials, namely:1) EASY for establishing an easily obtainable, accurate clinical scoring system that can stratify patients according to the severity of acute pancreatitis in the first 6-12 hours after admission, 2) PINEAPPLE to establish a clinical scoring system to evaluate the necessity of pancreas enzyme test or imaging examination when a child appears at the emergency unit with abdominal pain, 3) APPLE for exploring the course of pediatric pancreatitis and specify the genetic background of the disease and 4) PREPAST to evaluate the role of preventive pancreatic stents at the early course of acute biliary pancreatitis evaluating complications and overall outcome compared to the standard ERCP techniques.

All of these trials were presented and discussed on an international meeting, received the necessary ethical approvals and registered in the ISRCTN trial registry accepted by the WHO. The Scientific Committee of the International Association of Pancreatology has accepted all four trials to promote them among the members. An electronic CRF was developed for all of the trials and all documents, including protocols, patient informed consent forms, questionnaires, ethical permissions, are available on the HPSG website, not only in Hungarian, English and Russian, but also in several other languages. Already 33 international centers have already actively contributing to the trials, from 23 different countries (Table 5) and additional 30 countries have expressed their intent to join, several of them are under the process of acquiring the local ethical permission.

Country	City	Institute	PINEAPPLE	APPLE	EASY
Austria	Salzburg	Universitätsklinik für Kinder- und Jugendheilkunde der Paracelsus Medizinischen Privatuniversität		√	
Belarus	Gomel	Gomel Regional Clinical Hospital			√
Czech Republic	Ostrava	Centrum péče o zažívací trakt, Vítkovická nemocnice a.s.			√
Finland	Helsinki	Helsinki University Central Hospital			√
Hungary	Balassagyarmat	Dr. Kenessey Albert Hospital	√	√	
Hungary	Budapest	Heim Pál Children's Hospital	√	√	
Hungary	Budapest	First Department of Pediatrics and Pediatric Health Center, Semmelweis University	√	√	
Hungary	Budapest	Second Department of Internal Medicine, Semmelweis University			√
Hungary	Debrecen	Second Department of Medicine, University of Debrecen			√
Hungary	Debrecen	Department of Pediatrics, University of Debrecen		√	
Hungary	Kiskunhalas	Department of Pediatrics, Kiskunhalas Semmelweis Hospital		√	
Hungary	Nyíregyháza	Jósa András University Teaching Hospital of County Szabolcs-Szatmár-Bereg	√	√	
Hungary	Pécs	Department of Pediatrics and Pediatric Health Center, University of Pécs		√	
Hungary	Pécs	First Department of Medicine, University of Pecs			√
Hungary	Szeged	Department of Pediatrics and Pediatric Health Center, University of Szeged	√	√	
Hungary	Szeged	First Department of Medicine, University of Szeged		√	√
Hungary	Szeged	Emergency Unit, University of Szeged		√	√
Hungary	Székesfehérvár	Department of Pediatrics, St. George University Teaching Hospital of County Fejér		√	
Hungary	Szekszárd	János Balassa County Hospital	√	√	
Hungary	Veszprém	Csolnoky Ferenc Regional Hospital			√
Hungary	Zalaegerszeg	Zala County Hospital		√	

Country	City	Institute	PINEAPPLE	APPLE	EASY
Italy	Padua	Department of Surgery, Oncology and Gastroenterology, University of Padua			√
Italy	Rome	S. Andrea Hospital University "Sapienza"			√
Japan	Tokyo	Keio University			√
Latvia	Riga	Pauls Stradins Clinical University Hospital			√
Lithuania	Vilnius	Vilnius University Hospital Santariskiu Klinikos (Santariškių Klinikos)			√
Romania	Targu Mures	Mures County Emergency Hospital			√
Romania	Timisoara	"Victor Babes" University of Medicine and Pharmacy		√	
Russia	Simferopol	Medical Academy named after SI Georgievsky			√
Russia	St. Petersburg	Saint Luke Clinical Hospital			√
Spain	Sant Pere de Ribes	Consorci Sanitari del Garrof			√
Ukraine	Kiev	Bogomolets National Medical University			√
USA	Cincinnati	Division of Gastroenterology, Hepatology and Nutrition, Cincinnati Children's Hospital Medical Center	√		

Table 5. Countries and institutions actively participating in the observational clinical trials of the Hungarian Pancreatic Study Group.

The HPSG in cooperation with the Institute of Genetics, University of Szeged, has organized the genetic consultation for those patients who (whose parents) would like to know the result of the genetic test done with research purpose in the scope of APPLE trial.

5. Adapting evidence based guidelines

In 2014 The Hungarian Pancreatic Study Group proposed to prepare Evidence Based Guidelines for the management of acute pancreatitis, chronic pancreatitis, autoimmune pancreatitis, pancreatic cancer and pediatric pancreatitis. The international guidelines were translated and completed or modified where it was necessary by the preparatory and consultant team appointed by the HPSG. The guidelines were presented, discussed and accepted on a consensus meeting held on 12th September 2014 [38-42]

6. Educating young doctors and students

The HPSG is committed to improve the lives of patients suffering from pancreatic diseases. To disseminate the EBM guideline for pancreatic diseases, the HPSG printed a hard copy of the published Hungarian guidelines. The book is available at the conferences and can be ordered directly from the study group. As the compliance to

the guidelines are crucial for a better management of the diseases [67-68], the HPSG is organizing training courses and presentations at conferences and at universities.

Ways to improve

1. Organizing more clinical trials, both observational trials and RCT's
2. Improving existing data collection by data quality control
3. Following patients in CP from the date of diagnosis
4. Organize cooperation between gastroenterology, surgery and oncology institutions and departments for a better quality data collection in PC
5. Recruiting more international centers

Conclusions

Current barriers in pancreatology should be eliminated by an international research network, cooperation between pancreatic communities in different countries that will result in more and higher quality prospective multicenter observational clinical trials and RCTs, EBM guidelines available in more countries, improvement of compliance through education, influence on national financing of pancreatology, ultimately in quality research. To reach this goal, transparency, trust, visibility and teamwork are absolutely essential. The Hungarian Pancreatic Study Group undertakes the task of coordination and administrative support and it is open for initiatives and ideas.
In the future the HPSG/ECEPSG plans to involve more international centers, organize multicenter observational clinical studies and randomized clinical trials.

New results

Analyzing the research trends in gastroenterology

1. From 1965 to 2015, the great loss of interest in pancreatology was accompanied by a major increase of research in the lower GI disorders, namely, IBD and IBS.
2. Among the malignant GI diseases the biggest increase was found in research activity on pancreatic cancer.
3. Concerning pancreatic diseases (pancreatitis, pancreatic cancer, diabetes), the relative interest in pancreatitis dropped from 18.1% to 5%.

4. The USA, Germany and Japan published the most scientific papers in pancreatology and this is parallel with the R&D investment shares except for China where the investment has increased substantially only in the last few years.
5. The Scandinavian countries are clearly the most active in pancreatic research per capita and this is most probably caused by the higher R&D intensity and human resource investments in these countries.
6. Multicentre and multinational clinical trials provide the highest impact in pancreatic research.

Developing a better environment for pancreatic research

1. Improving the Registry for Pancreatic Patients – data collection, documentation, electronic surface, centre enrollment, data analysis.
2. Participation in data analysis based on the Registry for Pancreatic Patients, resulting in published articles.

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