

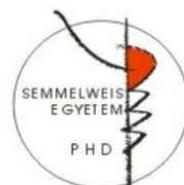
COMMUNITY PHARMACISTS' USE IN PRESENT CANCER CARE –
LITERATURE ANALYSIS AND QUESTIONNAIRE EVALUATION IN HUNGARY
AND GERMANY

PhD thesis

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1. List of Abbreviations

ADE	Adverse drug event
BH	Dr. Balázs Hankó, Ph.D.
DNA	Desoxyribonucleic acid
JT	Johannes Thoma
MTM	Medication therapy management
PICOS	Tool to specify study characteristics. Abbreviation for patients, interventions, comparison, outcomes and studies
PMC	PubMed Central
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL	Quality of life
RZ	Dr. Romána Zelkó, M. Sc., Ph. D., D.Sc.
SD	Standard deviation

Inpatient care	Inpatient care refers to all the services provided by pharmacists in a hospital.
Medium care	Medium care describes various types of cancer care that occur within specific institutions and healthcare facilities, which constitute neither hospitals nor community pharmacies.
Outpatient care	Outpatient care comprises pharmacists' services neither in hospital nor other settings of health facility but only in community pharmacies or home care services.
Community pharmacy	Public pharmacies; no restriction to town or countrified pharmacies
Town pharmacy	Pharmacy in a town with > 20000 inhabitants
Village pharmacy	Pharmacy in a village with < 20000 inhabitants

2. Introduction

The past years cancer has become a globally snowballing problem, expands to the most common cause of premature death and disability and is expected to escalate simply due to the growth and aging of population (World health organization, 2017; American cancer society, 2017; World health organization 2012).

The description cancer is derived from the phenotype of the animal shellfish which runs rampant with its fishing jars just as the blood vessel ramifications and metastases of the disease cancer. The disease cancer is characterized by a deficient coordination of somatic cells between growth, division and apoptosis. Additionally the repairing mechanisms are debilitated or not existent. Hence the replication of somatic cells is out of balance with the consequence of uncontrolled and unbroken cell division. Furthermore, many abnormal cancer cells are similar to healthy somatic cells. Therefore, our immune system is in many cases not able to identify and attack these cells in an efficient way. The tumour cells create new blood vessels by themselves which expand to the surrounding tissues and advance the proliferation.

Down to the present date the oncology time bomb predicted in 1999 by an American Cancer Society task force has exploded (Fasola et al., 2008). There is no longer doubt about increasing incidence and prevalence of cancer. The disease cancer presents national healthcare systems around the world a dramatic challenge. Despite of scientific progress the disease cancer is still fatal for many patients In developed countries there is a high probability that death will occur either with warning as a result of chronic disease or malignancy (Sullivan et al., 2011). Coming from a nature death and looking around in relatedness or the circle of friends there are almost only two reasons for natural death – cancer or cardiovascular diseases such as cardiac infarction or insult. The number of deaths caused by cancer increases every year. Every year 3.2 million Europeans are diagnosed with cancer, a figure that is expected to rise (Sullivan et al., 2011).

The discussion about possible reasons could fill out several separate dissertations. Public health initiatives and scientific advancements have us living longer and living and dying differently than in centuries past (Cortis et al., 2013). Patients receive more

treatments than ever before due to the increasing number of available agents (Mancini et al., 2012). The demographic development consequently leads to the absorption of greater amounts of noxious substances. Environmental and also nutritional conditions are changing none too in a positive way. It is a natural procedure that our cells revolve permanently and it is just as common that cells sometimes convert to abnormal cells. Therefore, the human being owns natural repairing machineries. But the higher the amount of poisons and the longer the absorbing time period there is a growing risk to overstrain this system with the consequence of falling ill with cancer occurring in many cases with spreading metastases and finally ending in the death. A substantial proportion of the worldwide burden of cancer could be prevented through the application of existing cancer control knowledge and by implementing programs for tobacco control, vaccination (for liver and cervical cancers), early detection and treatment, as well as public health campaigns promoting physical activity and a healthier dietary intake (Jemal et al., 2011).

Economic aspects will become an important parameter in future oncology care. (Fasola et al., 2008; Chastek et al., 2012; Schickedanz, 2010). The disease cancer is becoming a major economic expenditure and pushes national health systems to their personal and financial limits (Sullivan et al., 2011). Cost containment strategies are required to suppose the challenge of rising cancer diagnoses and oncology drug expenditure (Fasola et al., 2008). By now health care systems worldwide are faced with an ascending financial burden and a significant shortage of qualified oncology and hematology health care professionals by 2020 (Session et al., 2010; Hall et al., 2015). The diagnosis cancer often means little time left in the remaining life time of affected patients. It will take some time yet until certain types of cancer are no longer obligatory fatal. Therefore, the consensus from all groups concerned is that policy makers, politicians, patients, and health care professionals need to address the issue now (Thoma et al., 2016). Besides scientific progress, footraces to better and better drugs and promising therapeutic approaches one has to develop further ideas to limit this rapid emerging problem.

The idea of this PhD thesis was triggered in my pharmacy by the daily contact with cancer patients appearing with prescriptions of highly effective drugs and in the same

manner insufficient knowledge about intake, effects and consequences. Patients felt unsafe with the handling and there was a great demand for consultancy. Therefore, in my mind from day to day the suggestion matured that usage of pharmaceutical expert knowledge is urgently needed in oncology care.

Hoppe – Tichy investigated that demand for pharmacy cancer services is expected to at least double over the next decade (Hoppe – Tichy et al., 2010). There is need for affordable and good follow-up care especially for patients without any cancer treatment due to irreversible progression of tumour (Slanska et al., 2013). Patients with cancer require special pharmaceutical care in terms of medication selection, dose calculation, and pharmacokinetic and pharmacodynamic considerations (cf. Tuffaha et al., 2012). Systemic therapies are part of most therapeutic algorithms and for some malignancies they even seem to be the only option (Liekweg et al., 2004). Therapeutic strategies for cancer patients are highly individualized and include a variety of drugs with different pharmacological mechanisms and targets (Liekweg et al., 2012).

With their knowledge about drugs, pharmacists may be able to contribute in different ways to improve cancer care and complement the multidisciplinary cancer care team. Professionals could share the burden of care, and cross-border collaboration of expertise could be a major step toward increasing the survival and quality of life of cancer patients (Liekweg et al., 2004; Barth et al., 2009).

Much effort and research have been presented over the past years about the future of practice of oncology (Session et al., 2010). Only few studies discussed the beneficial role of community pharmacists' support in cancer care, such as provision of safe outpatient chemotherapy, assistance for home care patients or their positive influence on cancer patients' quality of life (Takagi et al., 2011; Satoh et al., 2014; Katori et al., 2007; Kawaguchi et al., 2012).

3. Objectives

In my PhD thesis I analysed the use of community pharmacists' in present cancer care of Hungary and Germany. My target was to focus on the analysis of the following questions:

What is quantity and utility of outpatient models of pharmaceutical cancer care compared to existing interventions of pharmacists in hospital or ambulatory oncology settings?

Is there need for community pharmacists in the daily reality of cancer patients in Hungary and Germany?

What is the opinion of health experts regarding the use of community pharmacists in cancer care?

4. Methods

4.1 Literature research

I performed broad literature research to get an overview of existing models of pharmaceutical care in oncology. I focused on outpatient models of pharmacists' interventions and compared them with models in hospitals or ambulatory settings. Thereby I received a picture of quantity and utility of community pharmacists' interventions in literature. I summarized my findings in a systematic review.

To perform PubMed database research I developed key questions, which seemed highly appropriate to the topic - quantity and quality of community pharmacists' interventions in oncology care.

The following 4 key questions were posed according to the "PICO" tool: What models of pharmacists' interventions exist in oncology care?

1. What beneficial outcomes of existing pharmacists' interventions in oncology care are reported?
2. Are there trials that consider the efficacy of pharmacists' interventions in oncology care?
3. Is there a disparity in quantity of scientific research between outpatient approaches of pharmacists' interventions and existing models in inpatient and medium oncology care?

4.1.1 Search

On basis of mentioned key questions I built 4 groups of key words. With the objective to hit all relevant contents preferably efficient database research was performed with several combinations of these key words, which produced studies containing information pertinent to these questions.

I used the following key words:

- cancer – carcinoma – oncology
- service – intervention – model – program – approach – setting – management – role
- pharmacist – patient – hospital – community – inpatient – outpatient – clinic – team – support – care – assistance
- cost – mental health – quality of life – efficiency – adverse drug reactions – drug interactions – complementary therapy – nutrition – palliative – symptom – pain – home

I combined two to four key words using the “and” connector to limit the number of irrelevant papers. To increase the likelihood of relevant hits I used diverse forms of single key words, such as pharmacist, pharmacy, and pharmaceutical. The combinations of search terms were determined by consensus of the investigators Johannes Thoma (JT), Romána Zelkó (RZ) and Balázs Hankó (BH). To reach diverse subject areas, I also used the “or” connector with many of the combined terms. I used the PubMed Central (PMC) advanced search builder and restricted searches on titles and abstracts to avoid accumulating nonessential papers. An example search strategy is included in the review protocol in chapter 6.1.7.

Information sources

The first electronic database search was performed on 26 November, 2013, in PubMed Central (PMC) to identify relevant information for addressing the main question. On 12 July, 2015, I specified concise search terms and performed an updated search to refresh our data pool. To identify studies that were missed by the electronic literature searches, I also manually searched journals. Additionally, the reference lists of all the identified studies were checked for related articles. Original authors were not contacted for further information. To ensure a comprehensive inclusion of relevant papers, I used the University of Illinois research guide to conduct an additional search.

Study selection

Screening and eligibility assessment was performed independently by the investigators. I reviewed the titles and abstracts to judge which ones included potentially relevant information. BH checked the titles and abstracts independently and RZ double-checked them. Any disagreement was resolved by consensus.

Data collection process

For data extraction I followed this same procedure to screen the full-text manuscripts, thereby applying the inclusion criteria to assess the validity of eligible trials. Through this process I determined which papers should be included in the systematic review. To keep track of the information pool it was necessary to structure the pool of information. Therefore, I allocated the received data to three clusters of care: inpatient, medium and outpatient. Admittedly a certain degree of subjectivity is not avoidable, but allocation was performed in all conscience and in consensus with all team members.

On basis of the first three key questions I received information, what models and what outcomes of pharmacists' intervention exist down to the present date and how effective pharmacists' interventions contributed to oncology care. With these structured data it was possible to illustrate and to compare quantity and utility of pharmacists' interventions in inpatient, medium and outpatient care. Thereby I was able to assess the fourth key question regarding the disparity between outpatient approaches of pharmacists' interventions compared to inpatient and medium care.

4.1.2 Eligibility criteria

Inclusion and exclusion criteria were specified using the PICO tool in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. I defined selection criteria in terms of participants, types of intervention, comparisons to appeared results without pharmacists' interventions and outcome measures.

4.1.3 Type of participants/problem

Participants with any type of malignant disease were included in the study. Malignant disease is defined as any malignant growth or tumour caused by abnormal and uncontrolled cell division, which may spread to other parts of the body through the lymphatic system or the blood stream. There were no restrictions imposed based on age, race or sex.

4.1.4 Type of intervention/comparison

Studies discussing existing models of pharmaceutical interventions in inpatient, medium, and outpatient oncology care, that compared their results to those of standard care were included. That is, the outcomes of pharmacists' interventions were compared with outcomes that occurred without pharmaceutical interventions. The terms "inpatient", "medium", and "outpatient" care are specified in chapter 3 - Data Items.

4.1.5 Type of outcome measure

I included studies reporting beneficial outcomes of pharmacists' interventions in oncology care, such as cost reduction, improvement of social-mental health, and enhancement of a patient's quality of life. Studies concerning reduction of adverse drug reactions and drug interactions, improved adherence to cancer therapies, and benefits of complementary therapies and nutritional support were also included. Finally, I included studies discussing the efficacy of pharmacists' interventions in oncology medical practices.

4.1.6 Type of studies

I included only peer-reviewed studies reporting existing models of pharmaceutical interventions in inpatient, medium, and outpatient oncology care that were published between 26 November, 2003 and 26 November, 2013, and conducted a subsequent search on 12 July, 2015, to bring our available data up to date. I did not impose limits

based on type of article, length of follow up or text availability; if an abstract or full text was missing or deficient I performed a hand search to retrieve the desired data. Finally, no language restrictions were imposed — foreign language texts were translated. Choosing only those studies that met the inclusion criteria, and without restricting the type of article I built a comprehensive analysis.

4.1.7 Review Protocol

The above mentioned methods of the literature analysis were documented in the following review protocol.

My Background was the occurrence of cancer patients in my own pharmacy with insufficient knowledge about intake and effects of anticancer drugs. Therefore, I posed the review question as follows: Is it necessary to further investigate quantity and utility of community pharmacists' interventions in oncology outpatient assistance?

Subsequently I created 4 key questions with the objective of comparing community pharmacists' approaches in outpatient care and interventions in inpatient and ambulatory care.

- What models exist in literature?
- What outcomes exist in literature?
- Are pharmacists' interventions efficient?
- Is there a disparity in quantity of scientific research regarding outpatient models of pharmacists' interventions and models in inpatient or medium care?

I defined inclusion criteria according to the PICOS tool. There was no restriction regarding the language of the analysed literature. If necessary, translation was performed. I only included peer reviewed studies. To maintain comprehensiveness there was no restriction referring to the article type.

Precondition for the inclusion of studies was the reporting on cancer patients. I only included studies discussing pharmacists' interventions in cancer care however formed. Subsequently I used studies comparing the results of pharmacists' intervention with standard care. This means the results of pharmacists' intervention was compared with the result occurred without pharmaceutical intervention. Referring to the outcome measure of the studies I focused on items such as drug interactions, cancer patients' quality of life, nutritional support, pain management, social – mental health or cost reduction.

Literature search was based on the information sources PubMed and University of Illinois research guide. With the objective of maximizing the data pool and receiving comprehensive results it was important for me to use two databases for my research. PubMed database was used for the main research. Afterwards the University of Illinois research guide was used for checking the PubMed database search terms for coherency and completeness. declared key words based on PICOS oriented key questions and classified them in 4 groups. Then I combined key words from each group to receive data preferably pertinent to the key questions.

Study selection was performed by reviewing titles and abstracts and then full text screening with application of inclusion criteria. The study selection was checked by three team members, independently from each other. The same procedure was exercised to extract the study data. The detailed process of study selection and data extraction is illustrated in 6.1.1.

With the objective of ensuring quality I appraised the quality of each individual study, took care of publication bias and selective outcome bias as illustrated in 6.1.8.

Data synthesis was performed by the allocation of received data to inpatient, medium and outpatient care. Subsequently I compared and estimated the results of scientific research concerning quantity and utility of community pharmacists' interventions.

Finally, I published the review in the International Journal of Clinical Pharmacy. I distributed a questionnaire in Hungary and Germany and analysed a potential

correlation of community pharmacists' interventions in literature and patients' needs in cancer reality.

On 12 July, 2015 I performed an update research and modified my original results. Almost 2 years after the first research my objective was to refresh the data pool and to avoid missing studies. Therefore, I performed the same research procedure and additionally tried to bring the search terms into a sharper focus. Thereby I was able to include studies published in the meantime since the first research. With the knowledge of the original data pool it was possible to search the received titles and abstracts systematic for missing content. As in the first research process the procedure was performed for the PubMed database and the Illinois research guide as well.

Synthesis of results:

PubMed Central

▼ literature search

2470 papers

Study selection:

▼ review of titles and manuscript,
double check

220 papers

▼ full text analysis,
application of inclusion criteria

68 papers

Data collection:

▼ inclusion in systematic review

Models, outcomes and efficacy of pharmacists' interventions

▼ allocation

Outpatient care

Inpatient care

Medium care

Comparison of outpatient approaches and inpatient and medium approaches

Response of 4 th key question

▼

Main questions response

Example search strategy:

cancer and review and service and pharmacist
or
cancer and intervention and pharmacist and pain
or
cancer and intervention and pharmacy and pain
or
oncology and service and community and pharmacist
or
oncology and pharmacist and service and outpatient
or
oncology and pharmacist and service and hospital
or
oncology and pharmacist and quality of life

4.1.8 Assessment of risks of bias

Validity of each individual study was confirmed by assessing the risks of bias on study and outcome level of all trials elected for review inclusion. Therefore, I appraised randomization and adequacy of allocation concealment as well as methods used to receive outcomes of individual studies. BH checked my findings. Besides bias in each individual study I also considered risks of bias across studies. I cannot obviate that there may be appropriate but missing studies. With the very broad and systemic search procedure I tried to reduce this risk of publication bias to the smallest possible level. In addition I tried to decrease the possibility of a one sided outcome reporting bias with a three person containing data collection process to a preferably small degree. Nevertheless, one has to be aware of these different scopes of occurring bias when interpreting the investigated results.

4.2 Questionnaire analysis

A self developed questionnaire was distributed to cancer patients in hospitals and pharmacies of Hungary and Germany to analyse cancer patients' attributes and their preferences regarding community pharmacists and cancer linked topics. Statistical evaluation of returned questionnaires provided an image of cancer patients' reality needs

The questionnaire consisted of 22 closed - ended questions and one open question in the end. I considered, which information seemed to be important to analyze current status quo in cancer care of both countries and how to explore patients' preferences and expectations from community pharmacists. Based on these thoughts questions with the target of receiving preferably comprehensive information were contrived.

I performed a tripartite validation procedure. The prepared questionnaire firstly was checked by BH, secondly by RZ and thirdly by five physicians. My objective was to avoid inappropriate questions or ambiguity and maintain validity, suitability and comprehensibility. It was a conscious decision to choose five health experts and not the target group for the questionnaire validation. I accurately deliberated whether it was constructive to ask health experts or the targeted patient group. Both groups show benefits and disadvantages. Physicians certainly can assume the questionnaire from the medical and technical perspective. But in comparison to cancer patients' physicians probably aren't able to put themselves into patients' physical and emotional atmosphere. The targeted patient group certainly is able to examine the comprehensiveness from the perspective of an ordinary person in a better way than physicians.

Both groups include the hazard of false positive results. On the one hand physicians could imagine that the task is clear anyway - no need for occupation with the questionnaire in an intense way. On the other hand the targeted patient group could be ashamed of admitting that they do not understand parts of the questionnaire. The main factor deciding against the targeted patient group was the knowledge of a sensitive

patient pool in exceptional circumstances with extraordinary physical and psychical strains.

With the knowledge of the benefits and disadvantages of both groups finally the ethical conscience predominated and I decided to ask the physicians for questionnaire validation to avoid unnecessary stress for the targeted patient group.

The validation of a questionnaire distributed in two countries also requires comparable questionnaire versions in both countries. I consciously developed the questionnaire together with BH in English language. I translated the English version to German and BH to Hungarian. I assumed that the translation of the well established English language to the particular native languages is less fault-prone than the direct translation from German to Hungarian. Both developers of the questionnaire also were the translators to their particular native language. Therefore, there is little likelihood of differences regarding the comparability of both versions and hence the obtained data. The level of comparability of both versions and the content identity of obtained data is comprehensible at anytime.

The questionnaire was distributed in 26 community pharmacies and 4 hospitals in Hungary and Germany from August 2013 to October 2014. Pharmacy selection was performed by reflecting on proper questionnaire randomization. I primarily classified the questionnaire distribution places into hospitals and community pharmacies. Then the community pharmacies were classified in town- (inhabitants > 20000) and village pharmacies (inhabitants < 20000).

The following distribution places were selected in Germany:

“Pharmacy in Westpark” Ingolstadt	(town pharmacy)
“Pharmacy in Hollis center” Ingolstadt	(town pharmacy)
“Pharmacy Riem Arcaden” Munich	(town pharmacy)
“Staren Pharmacy” Kelheim	(village pharmacy)
„Adler Pharmacy“ Mitterfels	(village pharmacy)
„Burg Pharmacy“ Kallmünz	(village pharmacy)

“Heilig-Kreuz Pharmacy Kelheim	(village pharmacy)
„St. Georg Pharmacy“ Mitterfels	(village pharmacy)
“Holzner Pharmacy” Bogen	(village pharmacy)
“Sonnen Pharmacy” Burglengenfeld	(village pharmacy)
„Barbara Pharmacy“ Maxhütte Haidhof	(village pharmacy)
„St. Anna Pharmacy“ Riedenburg	(village pharmacy)
“Hubertus Pharmacy” Bogen	(village pharmacy)
St.Johsef hospital” Regensburg	(hospital)
“University hospital” Regensburg	(hospital)

The following distribution places were selected in Hungary:

Mikszáth Pharmacy, Budapest	(town pharmacy)
Kútvölgyi Pharmacy, Budapest	(town pharmacy)
Szent Rókus Pharmacy, Miskolc	(town pharmacy)
Mária Pharmacy, Miskolc	(town pharmacy)
Patika Libra Pharmacy, Dunaújváros	(town pharmacy)
Patika 52 Pharmacy, Rácalmás	(village pharmacy)
Tölgyfa Pharmacy, Kerepes	(village pharmacy)
Szilasliget Pharmacy, Szilasliget	(village pharmacy)
Oroszlán Pharmacy, Szerencs	(village pharmacy)
Szent Miklós Pharmacy, Kunszentmiklós	(village pharmacy)
Magyar Korona Pharmacy, Kunszentmiklós	(village pharmacy)
Szent György Pharmacy, Kecel	(village pharmacy)
Kossuth Lajos Pharmacy, Apostag	(village pharmacy)

Semmelweis Egyetem , 1st Department of Internal Medicine (hospital)

Semmelweis Egyetem, 3rd Department of Internal Medicine (hospital)

On the one hand, I tried to manage the distribution in a way that approximately equal numbers of valid questionnaires could be received in community pharmacies and hospitals. On the other hand the intention was to receive approximately equal numbers of questionnaires in town and village pharmacies. Therefore, I assumed the characteristic patient flow of town and village pharmacies according to rational consideration. Accurate numbers of patient flow are difficult to receive, apply to the company secret and only few pharmacy owners would be willing to relinquish these sensitive data. In both countries there is a general trend that young people move to major towns and their parents and grandparents remain in the villages accompanying a lower average age in towns.

Major towns offer a magnitude of important factors for young people. There may be universities allowing academic studies or broader possibilities to enjoy the off time. Accordingly, in towns there often is a higher amount of active working population and consecutively superior spending power. Against this background the expectation was to deal in town pharmacies with an increased patient flow and consecutively with increased rates of questionnaire return compared to village pharmacies. Hence approximately triply village pharmacies were provided with questionnaires compared to the number of town pharmacies. Targeting valid and representative results there was a statistical calculation before questionnaire distribution referring to the required number of questionnaires. Presuming a confidence interval of 95% and a maximal tolerable sample error of 10%, the intention was to receive at least 100 questionnaires for evaluation. It was calculated with a basic population of 1,000,000 patients.

Due to the sensitive patient pool 25 % rate of response was calculated; Response rate was calculated by searching for a preferably comparable reference point and applying individual criteria of questionnaire composition, distribution proportions and target group attributes. Iversen et al. received in 2012 a questionnaire response rate of 52 % (Iversen et al., 2012). At the time of questionnaire distribution this reference was quite recent and exhibited similar setting conditions such as a paper based survey, questionnaire development based on the findings of a literature review, cancer patients' assessment of hospital care, cancer patients suffering from all kinds of cancer and

questionnaire distribution in inpatient and outpatient clinics. Our questionnaire comprised 9 pages and addressed a sensitive target group in extraordinary circumstances. It is known that the response rate decreases with increasing page number and sensitivity of the target group. The questionnaire was not mailed but distributed at the local distribution places. Therefore the target group did not receive the questionnaire directly. In each case of distribution there was either pharmacy or hospital staff between author and target group.

The success of questionnaire distribution on the one hand largely depends on addressing the target group. Hence the level of staff motivation is essential. There were no monetary or other incentives either for the patients or for the staff. The questionnaires were handed out to one crew member. Hence there is the obstacle of information transfer to the residual crew members. Just in bigger hospitals or pharmacies there is the risk of confusion and questionnaire loss. Additionally there is the fact of crew changes. In the worst case the crew member the questionnaires handed out to had left the pharmacy two weeks later accompanying the loss of all distribution information. Furthermore the long list of agents with oncology indication as inclusion criteria exhibits the drug names. In many cases prescriptions only contain the trade names of the product. The mental transfer to pull trade name and inclusion criteria together and subsequently to address the target patient is a further obstacle restricting the response rate.

All above mentioned issues the author wasn't able to influence. Finally the entire comparison of Iversen et al.'s reference and my distributed questionnaire is difficult. Considering above mentioned points and the authors' intention to calculate the response rate carefully a response rate of 25 % was assessed suitable.

Hence 400 questionnaires were intended for distribution. To avoid bias and to achieve proper randomization, the distribution points of questionnaires were elected in all cardinal directions in the surroundings of Budapest in Hungary and Regensburg in Germany and deliberately excluded pharmacies within a radius of 5 km to oncologists. Without this condition there could have been for example 100 questionnaires from one

pharmacy next to an oncologist due to the convenient clientele visiting this pharmacy frequently. Subsequently this condition was necessary to ensure the objective of equal numbers of questionnaires in town and village pharmacies.

If the pharmacy or hospital agreed we left 10 - 15 questionnaires at each distribution place. The questionnaires were delivered face to face at the particular distribution places. The procedure was continued up to the distribution of 400 questionnaires. 234 questionnaires were distributed in Germany and 180 in Hungary making a total of 414. Finally, 73 questionnaires were received in hospitals, 40 questionnaires in town pharmacies and 35 questionnaires in village pharmacies, making a total of 148.

Patients were screened by hospital and pharmacy staff by application of inclusion and exclusion criteria and were informed about the aim of the study. Pharmacy and hospital staff was not allowed to help the patients if any question came up. The questionnaire was voluntary and anonymous. Participants could decide if they wanted to answer directly in the pharmacy, hospital or at home. The involvement of the patients was diverging and mostly dependent on the physical constitution of the particular patients. End stage cancer patients were rarely in the mood for answering the questionnaire. Questionnaires answered at home then returned to the particular distribution place. After a few months all filled questionnaires were collected personally from the particular distribution places. Data handling occurred in accordance with the law of Hungary and Germany.

4.2.1 Inclusion criteria

Voluntary patients were only asked to answer the questionnaire, if they were treated with an anticancer drug, which was mentioned in a defined list. I developed this list and submitted it to BH and RZ for checking. The list included all prescription drugs in German market containing an oncology indication up to the time of distribution in August 2013 and is attached in Appendix in the end of the original questionnaire. Interview partners were elected if they verified their professional license and agreed to answer the questions.

Exclusion criteria

If patients were not able to answer the questionnaire due to physical or psychological restrictions, they were excluded from the study. Patients who were reluctant to answer were also excluded.

4.2.2 Evaluation/ Statistical methods

Statistical evaluation was performed by descriptive analysis. The statistical software and expert knowledge was provided by Andrea Meskó – Semmelweis University Budapest. If patients provided a rating on a scale analysis was performed by means of measure of central tendency and determination of standard deviation. The significance of differences among groups was evaluated with Bonferroni test. The level of significance was defined a priori at 5 %. Chi square test was used for categorical variables, Fischer exact test for border values. The one-sample Kolmogorov–Smirnov test method was used to identify the kind of distribution in two groups. The Mann–Whitney and Wilcoxon W-test methods were used to analyze group differences in the mean of an examined parameter.

4.2.3 Survey

The first part of questionnaire was aimed at investigating quite general questions, such as gender, age, the level of education, type of cancer or location, where the questionnaire has been received. The second part was targeted at evaluating patients' life style conditions such as smoking and collecting a picture of patients' attitude to cancer linked topics, such as information points, adverse drug reactions, reception of food supplements or mental support and assessment of pain or QoL. In the end patients had the possibility to state their wishes and expectations from community pharmacists to lift cancer patients QoL in future oncology care. The original questionnaire is attached in Appendix.

Our research is in compliance with the 1964 Helsinki declaration and its latter amendments or comparable ethical standards. There is no ethics committee approval because this study is based on a questionnaire survey with anonymous and voluntary participation. Due to the anonymous questionnaire survey there is no signing of informed consent. Instead the aim of the study was written at the top of the questionnaire and the purpose of this study was explained accurately to all volunteers orally.

4.3 Interview of professional health experts

I completed my image of pharmacists' contributions in oncology care by asking health experts about possible supportive interventions, main obstacles and solution approaches to cross these obstacles in future.

To amplify the information pool for assessment of community pharmacists' use in present cancer care the process of opinion making was finalized by asking five practicing oncologists and five community pharmacists to give their opinion to four self developed questions. I called oncologists and pharmacists in the surroundings of Regensburg and explained my project in detail. In case of agreement I made an appointment and visited the interview partners at their workplace in Germany. After exhibiting the job license I conducted the interviews in a relaxed face to face atmosphere. I tried to create questions, which permitted reception of preferably comprehensive answers to achieve a diversified picture of community pharmacists' support in cancer care. These questions were likewise checked by BH and RZ. A provident check for validity was performed in the same manner as aforementioned.

Professional health experts were asked to consider possible supportive interventions of pharmacists in oncology care, advantages for patients, main obstacles and solution approaches to cross these obstacles in future. Professional health experts were accepted as interview partners if they were able to exhibit their job license. Analysis was performed by comparison of content and quality of mentioned answers.

After literature research and the evaluation of cancer patients' questionnaire these expert assessments were the last brick of three information sources to complete comprehensive opinion formation for the assessment of community pharmacists' use in present cancer care of Hungary and Germany. Interviews were performed on the basis of the template attached in Appendix.

5. Results

5.1 Results of literature analysis – Models and outcomes of pharmacists' interventions in cancer care

The primary outcome measure was to estimate the quantity and utility of pharmacists' interventions in outpatient oncology care compared to inpatient and medium care. Literature searches identified 2470 papers. A review of those titles and abstracts retained 220 manuscripts for detailed analysis, on which full-text analysis was performed. After subsequent application of inclusion criteria, 68 papers remained, which were included in systematic review.

5.1.1 Inpatient care: Models, outcomes and efficiency of pharmacists' interventions

Several studies have investigated the importance of pharmacists providing direct patient care and patient education in oncology care including medication therapy management (MTM) (Schickedanz 2010; Ise et al., 2014; Avery et al., 2015); Döhler et al., 2011; Yeoh et al., 2013). For example, on a given clinic visit, the pharmacist enters the room with the primary nurse and goes through the medication containers the patient has brought in [Cortis et al., 2013; Voll et al., 2010]. This is in keeping with Swedish pharmacists, who work as members of the health care team and participate in medical rounds in the mornings together with physicians, nurses, and assistant nurses (Bremberg et al., 2006). Several studies discussed that patients seem to benefit from pharmaceutical care, as indicated by patients' self-reported outcomes such as reduced emetic episodes, improved quality of life, and satisfaction following implementation (Liekweg et al., 2012; Kawaguchi et al., 2012; McKee et al., 2011; Ibrahim et al., 2013; Silpakit et al., 2006).

Indeed, the significant role of clinical pharmacists with their understanding of medical practises in oncology settings has been published in reports, who claim that this team work benefits both oncologists and pharmacists and allows oncologists to focus on disease eradication as shown by Bremberg et al. (Bremberg et al., 2006). There are many studies of clinical pharmacy services showing that pharmacists contribute to safer

medication use, to the prevention and reduction of adverse drug reactions and interactions, to enhanced medication adherence, and to a continuum of oncology care (Liekweg et al., 2004; Ibrahim et al., 2013; Touchette et al., 2014; Leveque et al., 2014; Delpeuch et al., 2015; Khanal et al., 2010; Walter et al., 2014; Felton et al., 2014; Coutsouvelis et al., 2010; Katayama et al., 2006; Tuffaha et al., 2006; Inoue et al., 2004; Chan et al., 2009).

The importance of pharmacists that own a variety of clinical services in mental health care is also starting to be recognised around the world (Arunachalam et al., 2011; Richardson et al., 2014). Richardson et al., for example, indicated that implementing clinical pharmacy services in inpatient mental health has significant potential for improving economic, clinical, and humanistic outcomes for patients and for the mental health system (Richardson et al., 2014).

Pharmacists can also contribute to cost-reduction and a good cost-benefit ratio in palliative care settings (Bremberg et al., 2006; Norrström et al., 2010). Interestingly, other clinical fields have already demonstrated the benefits for patients receiving nutritional support or complementary therapy options (Tuffaha et al., 2012; Mousavi et al., 2013). Mousavi et al., for example, found that a clinical pharmacist-based nutrition support service significantly improved the nutritional status and clinical outcomes of bone marrow transplant patients (cf. Mousavi et al., 2013). Moreover, patients report significantly increased satisfaction after receiving MTM (Yeoh et al., 2013). The inclusion of pharmacists in the pain and symptom control clinic is favoured by patients and health care professionals, and provides increased efficiency to the clinic (Ryan et al., 2012).

5.1.2 Medium care: Models, outcomes and efficiency of pharmacists' interventions

There are several approaches that reflect an expanding role of pharmacists in the care of cancer patients in specialised settings (Shah et al., 2006; Valgus et al., 2011; Ruder et al., 2011; Chew et al., 2015; Van den Broucke et al., 2014; Ishimoto et al., 2004; Koshita et al., 2007). Supportive care in outpatient chemotherapy clinical centres, and

specialised cytostatic compounding pharmacies are just a few examples. Another example can be found in Japan, where the shortage of drugs available to physicians in hospitals has stimulated the creation of teams by medical institutions, to meet the needs of an increasing number of cancer patients (cf. Iihara et al., 2012). Moreover, there are an ascending number of models following the paradigm shift from a disease-focused towards a patient-focused, safe, effective and convenient approach [cf. Tuffaha et al., 2012; Liekweg et al., 2004).

Furthermore, pharmacists in the British Columbia Cancer Agency are often called on to advise patients on the use of complementary therapy such as herbs and dietary supplements (cf. Paul et al., 2013; Lemos et al., 2005). Pharmacy counselling services in an outpatient chemotherapy clinic are vital to a patient's understanding of their chemotherapy and supportive medication (cf. Ibrahim et al., 2013). First experiences show that patients fully agree with these pharmaceutical offers and may be willing to pay for pharmacy counselling services (cf. Ibrahim et al., 2013). Provision of drug therapy management, identification and reduction of drug-related problems, and prevention of drug interactions were reported as beneficial outcomes of pharmacists' interventions as shown by Tuffaha et al. (Tuffaha et al., 2012; Smith et al., 2014; Edwards et al., 2014; Lopez-Martin et al., 2014). Clinical pharmacists' contributions to palliative care, moreover, include patient benefits such as improved symptom control, satisfaction of patients and families and finally possibly longer survival with improved quality of life (Tuffaha et al., 2012; Atayee et al., 2008; Shamie et al., 2013; Gagnon et al., 2012). Similarly, Iihara et al. showed how pharmacists contributed to the increased efficacy of medical practises by reducing physicians' workloads (Iihara et al., 2012).

5.1.3 Outpatient care: Models, outcomes and efficiency of pharmacists' interventions

Patient-centred home care is a new model of assistance. It is based on patients' needs rather than on prognoses and takes into account the emotional and psychosocial aspects of the disease (cf. Tralongo et al., 2011). It is significant that several studies — especially in the field of outpatient palliative care — that have investigated the educational needs of pharmacists, have suggested that home palliative care offers ways

to integrate pharmacists into cancer pain management (Tralongo et al., 2011; Tait et al., 2013; O'Connor et al., 2013; Kato et al., 2011; Hussainy et al., 2006; Akai et al., 2009; Hussainy et al., 2010; Savage et al., 2013; O'Connor et al., 2011). However, few studies discuss collaboration approaches between community pharmacists and hospitals (Takagi et al., 2011; Satoh et al., 2014; Katori et al., 2007). There are studies — mainly in Japan — concentrating on pharmacists' assessments of outpatients (Suzuki et al., 2010). According to Needham et al., pharmacists visit patients at home to help them learn how to properly take their medications and to measure correct dosages.

In view of this, community pharmacists have begun sharing information about their patients through care conferences attended by doctors from clinics and nurses from visiting nursing stations (cf. Needham et al., 2002). The authors also describe how pharmacists provide information about prescribed drugs to the wives and daughters of patients who were in the end stages of cancer (Needham et al., 2002). Two Japanese studies suggested that the participation of a community pharmacist in palliative care is essential for patients and medical team members managing the extensive requirements associated with cancer pain (Kato et al., 2011; Akai et al., 2009). Additionally, Tralongo and colleagues found in an Irish context that home care reduced costs for patients by two-thirds compared with hospital care (Tralongo et al., 2011). Researchers describe the efficacy of pharmacists' interventions in cancer pain therapy, evidenced in improved efficiency of opioid treatment based on the recommendations of a community pharmacists' palliative care team (Needham et al., 2002). Finally, the results of literature research are illustrated in Table 1.

Table 1 Outcome of pharmacists' intervention in inpatient, medium and outpatient oncology care (Thoma et al., 2016). Pharmacists' interventions were beneficial and have proofed efficacy in all three fields of pharmaceutical care.

type of care	outcome of interventions	significance	references
inpatient care	Improved quality of life		18, 32-34
	improved nutritional status	yes	49
	patient satisfaction after receiving MTM	yes	29
	safe medication use,		
	enhanced medication adherence		17, 33, 35-45
	cost reduction for health care systems		31, 48
	oncologists can focus on disease eradication		34
medium care	reduction of physicians workload		58
	Improved understanding,		
	patients agree with counseling services		33
	improved drug therapy management		16, 61-63
	improved symptom control in palliative care,		
enhanced QoL		16, 64-66	
outpatient care	home care reduced costs of national health care systems		67
	essential support of medical team members in pain therapy		70, 72
	home education leads to better Understanding and correct intake		80

5.2 Results of questionnaire analysis

From the 180 in Hungary and 234 in Germany distributed questionnaires, 62 Hungarian and 86 German questionnaires returned. Hence in total 148 questionnaires were evaluable.

5.2.1 General results referring to basic attributes of the examined patient group

53 (35.8 %) of the 148 patients were men and 95 (64.2 %) women. The predominating age of cancer patients (41.9 %) was between 61 and 75 years as shown in Figure 1. 10.1 % of the patients were older than 75 years.

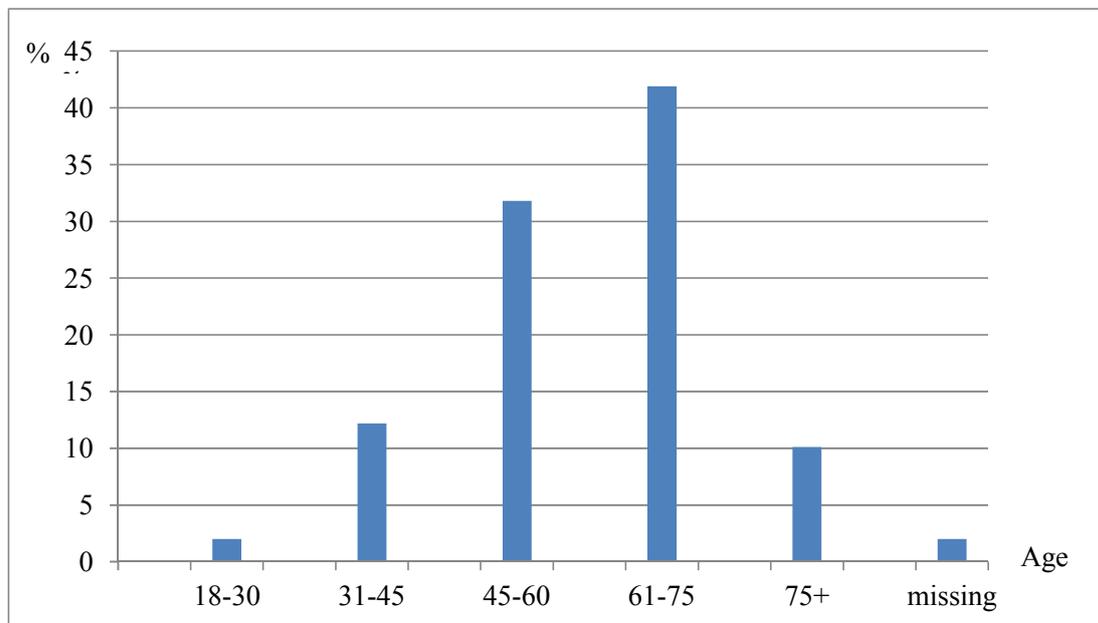


Figure 1 Age distribution of the examined cancer patient population (Thoma et al., 2018). The predominating age of cancer patients is between 61 and 75 years.

There was significant difference in age ($p=0.009$) of Hungarian and German participants. In Hungary 39.3 % of the asked patients were between 61 and 75 years old and in Germany 42.5 %. In Germany there was excess of patients older than 75 (11.0 %) compared to Hungarian patients (3.3 %). The results are illustrated in Figure 2.

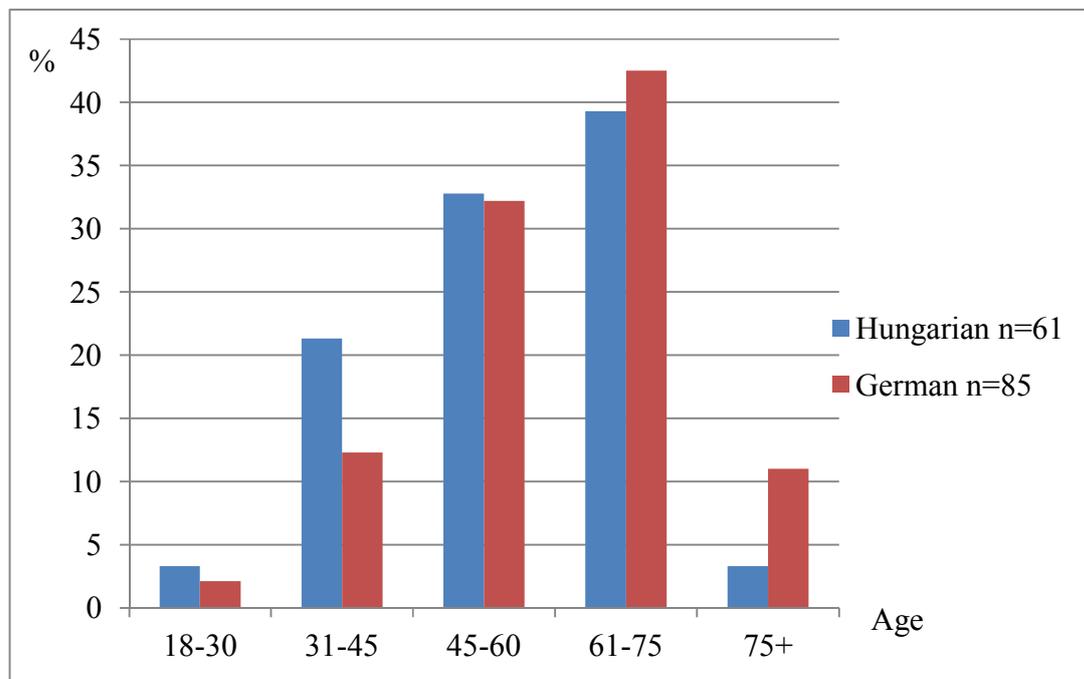


Figure 2 Age distribution of examined Hungarian and German cancer patients (Thoma et al., 2018). In Germany there was an excess of patients older than 75 compared to Hungarian patients.

The findings also showed significant difference regarding gender ($p=0.002$) between Hungarian and German cancer patients as illustrated in Figure 3. In Germany women (74.4 %) predominated, in Hungary quantity of male and female participants was equal (50.0 %). This result has to be assessed under special consideration of chapter 7.4 - clause 2.

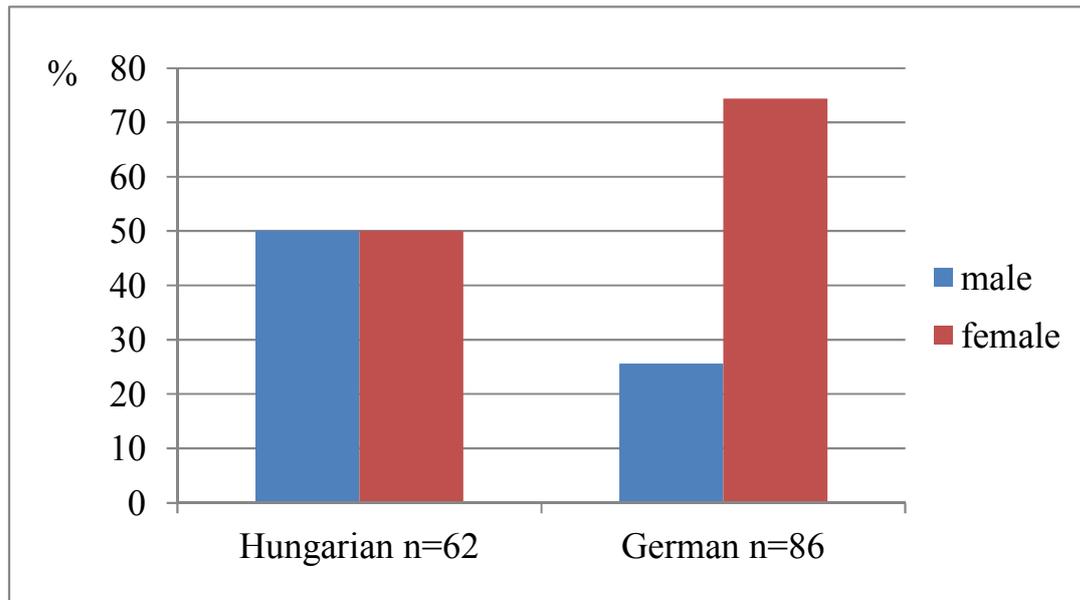


Figure 3 Gender distribution of examined Hungarian and German cancer patients. (Thoma et al., 2018). In Hungary ratio of male and female patients was equal, in Germany female cancer patients predominated.

According to the questionnaire breast (32.4 %) and bowel cancer (23.0 %) were the most common cancer types, which is illustrated in Figure 4. This result has to be assessed under special consideration of chapter 7.4 - clause 2.

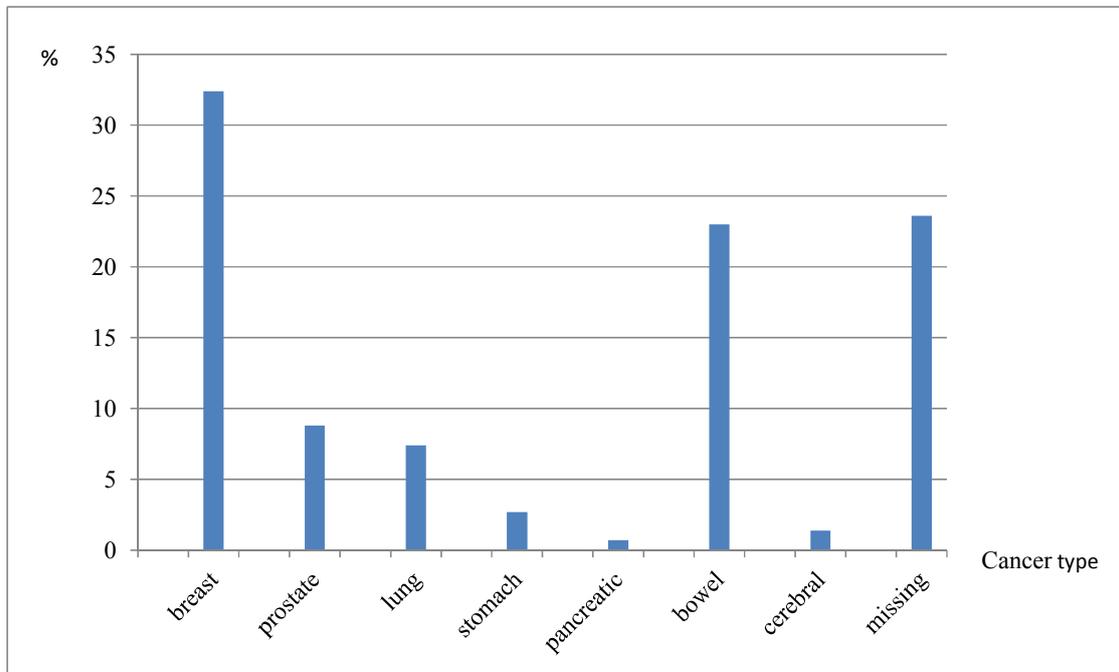


Figure 4 Partition of cancer types in the patient population (Thoma et al., 2018). The predominating cancer types were breast- and bowel cancer.

The results also indicated significant difference ($p < 0.001$) between Hungary and Germany in most common cancer type. In Hungary bowel cancer (51.6 %) occurred most frequently, whereas in Germany breast cancer (46.5 %) and prostate cancer (12.8 %) were the most common types as illustrated in Figure 5. This result has to be assessed under special consideration of chapter 7.4 - clause 2, too.

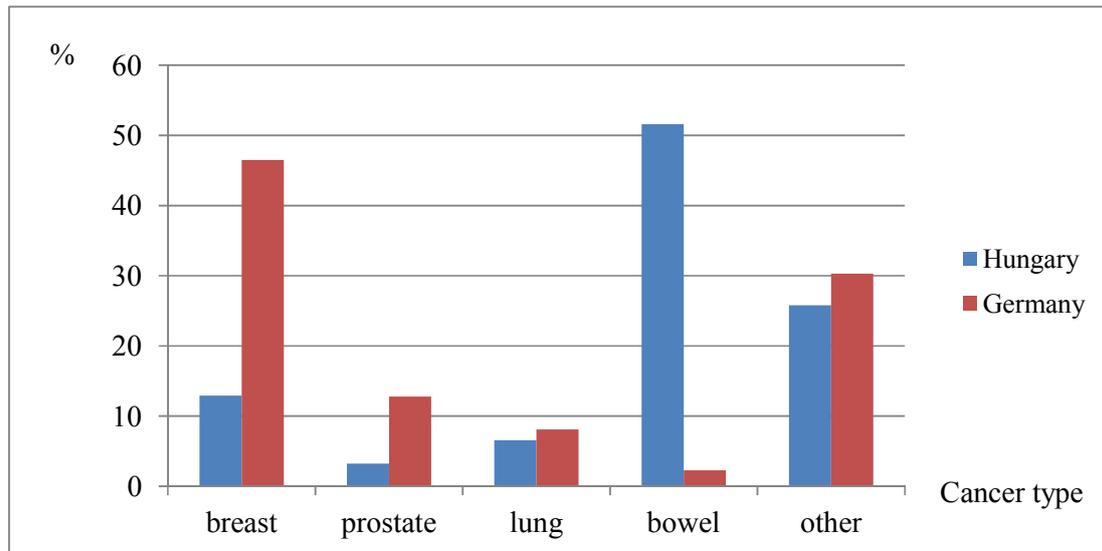


Figure 5 Partition of cancer types in Hungary and Germany (Thoma et al., 2018). In Hungary bowel cancer predominated, in Germany there was an excess of breast cancer patients.

Figure 6 illustrates that 64.2 % of the patients were diagnosed with cancer not longer than 3 years before.

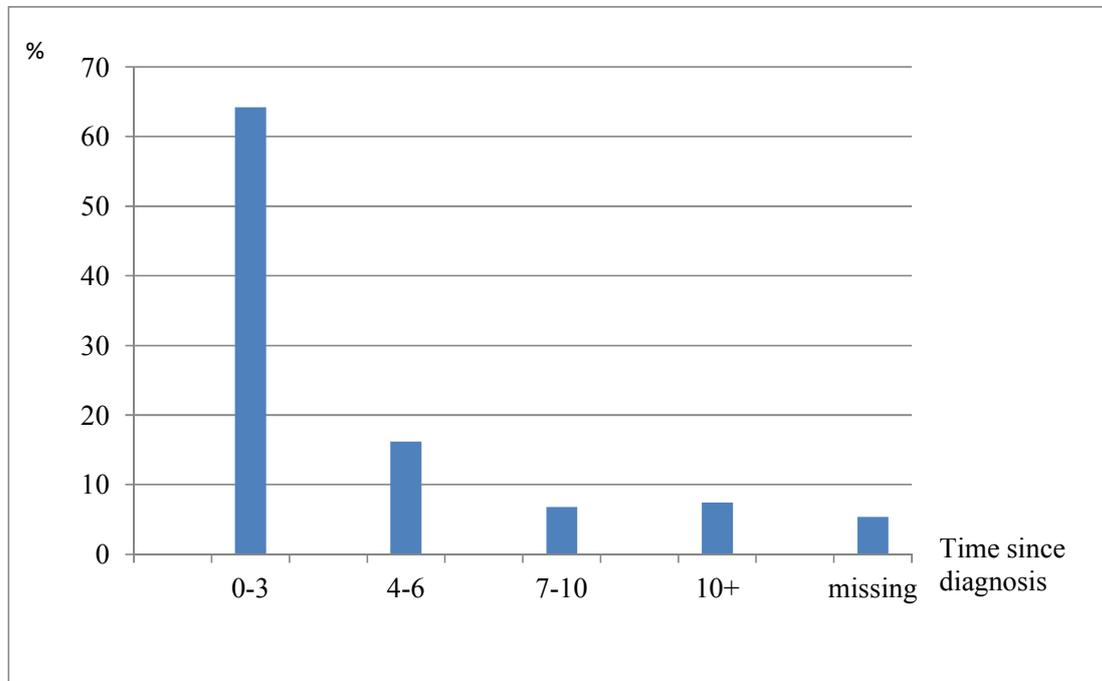


Figure 6 Time period since patients in examined patient population were diagnosed with cancer the first time (Thoma et al., 2018). An Excess of cancer patients was diagnosed with cancer not longer than 3 years before.

From the 62 Hungarian questionnaires 44 (71.0 %) were received in hospital, 11 (17.7 %) in town pharmacies and 7 (11.3 %) in village pharmacies. From the 86 German questionnaires 29 (33.7 %) questionnaires were received in hospitals, 29 (33.7 %) in town pharmacies and 28 (32.6 %) from village pharmacies. Above mentioned issues are illustrated in Table 2.

Table 2 Questionnaire distribution place (Thoma et al., 2018). In Hungary there was an excess of questionnaires received from hospital. In Germany reception of questionnaires was shared consistent.

	n = 148	hospital	town pharmacy	village pharmacy
Hungary	62	44 (71.0 %)	11 (17.7 %)	7 (11.3 %)
Germany	86	29 (33.7 %)	29 (33.7 %)	28 (32.6 %)

Table 3 indicates that one third of cancer patients were smokers (33.8 %) and two third non - smokers (64.9 %).

Table 3 Ratio of smokers and non - smokers in the patient population (Thoma et al., 2018). Two third of cancer patients were non-smoker.

frequency	smoker	non - smoker	don't want to answer	missing
N = 148	50 (33.8 %)	96 (64.9 %)	1 (0.7 %)	1 (0.7 %)

5.2.2 Results referring cancer patients attitude to community pharmacists and cancer linked topics

On a non percentage scale from 1 to 5 patients, who wanted information about cancer, chose significantly more often pharmacists (4.11 ± 1.11) and similar practitioners (4.33 ± 0.8) than website information (3.24 ± 1.68), social communication (3.06 ± 1.46) or television services (2.8 ± 1.45) as first information point. These findings are illustrated in Figure 7.

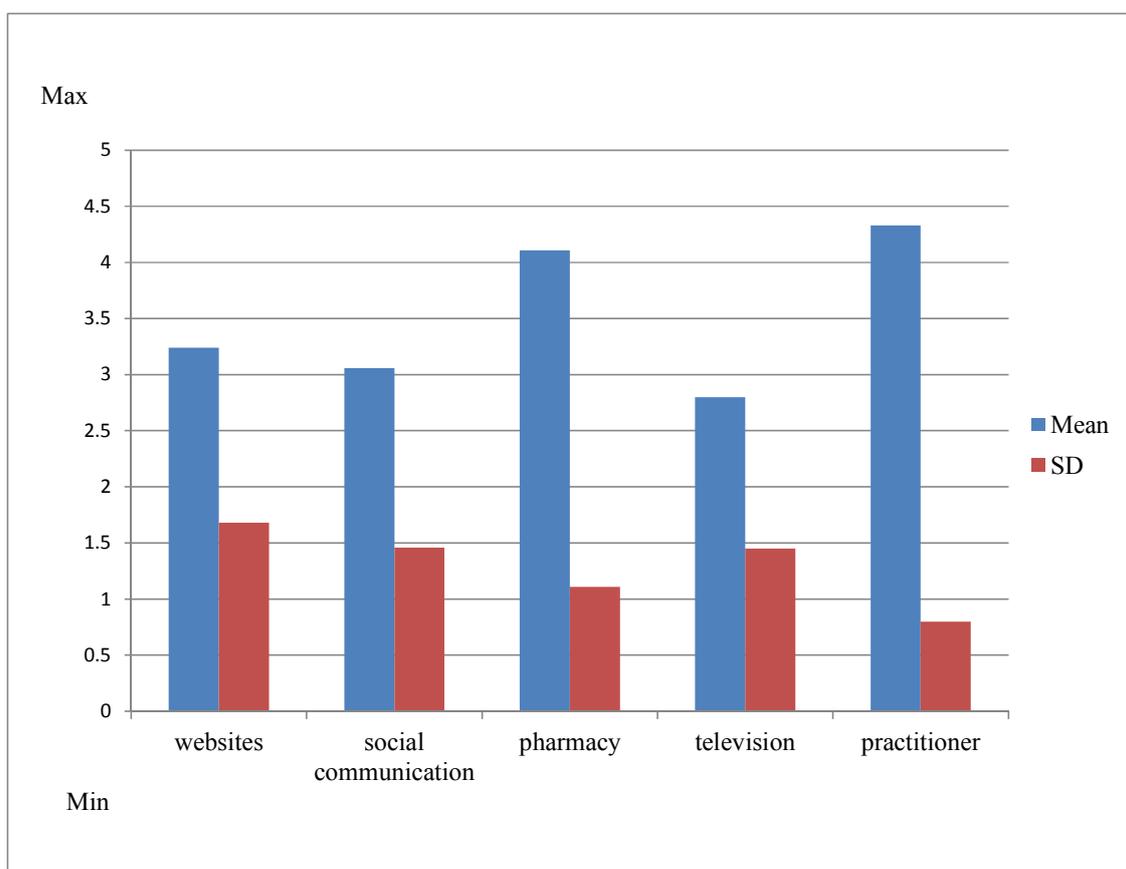


Figure 7 Cancer patients' expectations to get general information about cancer. Mean and standard deviation are illustrated (Thoma et al., 2018). On a non - percentage scale from 1 to 5 cancer patients excessively expected to get general information from pharmacy and practitioner.

Table 4 shows the significant difference ($p < 0.001$) in seriousness assessment of internet information (4.38 ± 2.32) and information in community pharmacies (8.23 ± 1.81).

Table 4 Seriousness assessment of cancer patients referring internet and pharmacy information (Thoma et al., 2018). On a non - percentage scale from 1 to 10 cancer patients assessed pharmacists' information by far more serious than internet information.

location	seriousness assessment	confidence interval	significance	p value ^{c,d}
	information valid Mean \pm SD	95% CI	yes	<0.001
pharmacies n =114	8.23 ± 1.81	7.88 - 8.55		
internet n =120	4.38 ± 2.32	3.99 - 4.81		
^c Statistical evaluation by means of "measures of central tendency" and determination of SD				
^d Nonparametric bootstrap procedure used to obtain 95% CIs.				

Figure 8 illustrates that on a non percentage scale cancer patients assessed the validity of the information points pharmacist (8.23 ± 1.81), practitioner (8.44 ± 1.54) and oncologist (9.5 ± 0.83) more valid compared to information from the family (5.03 ± 2.11), internet information (4.38 ± 2.32) and information in the neighborhood (3.28 ± 1.64). Television information (3.82 ± 1.63) and information from friends (4.28 ± 1.64) was also assessed less valid compared to professional health experts.

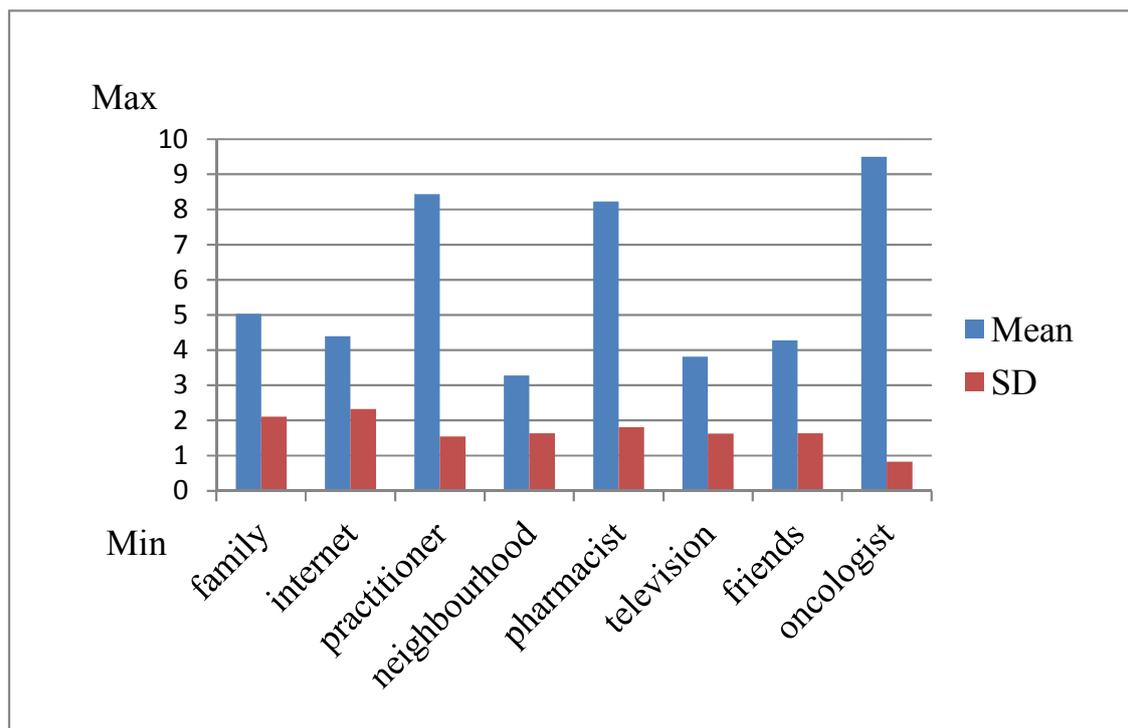


Figure 8 Assessment of cancer patients referring the validity of information points. Mean and standard deviation are illustrated (Thoma et al., 2018). On a non - percentage scale from 1 to 10 cancer patients assessed pharmacists' almost equal valid compared to practitioners.

48.6 % of the asked population took pain killers and 39.2 % stated to have difficulties with the right dosage of their pain killers, as shown in Figure 9.

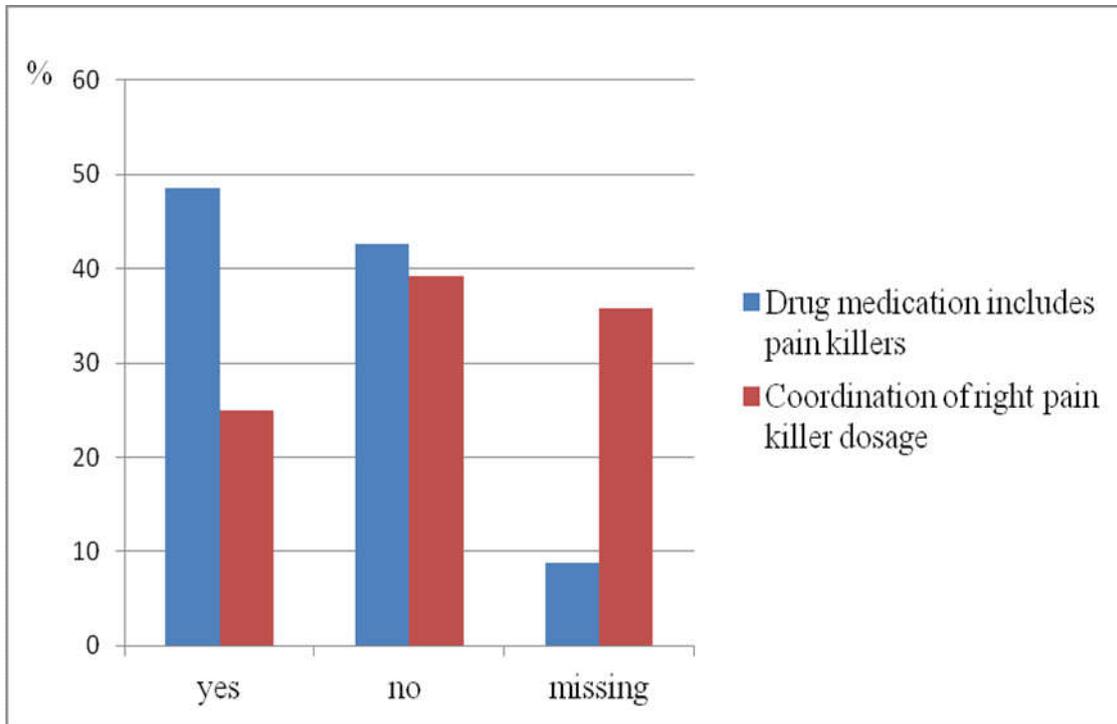


Figure 9 Cancer patients' assessment regarding pain killer use and the coordination of right pain killer dosage (Thoma et al., 2018). About half of the cancer patients took pain killer and almost half of the patients was not able to coordinate pain level and pain killer dosage.

There was significant difference ($p=0.012$) in coordination of pain level and adequate intake of pain killers between hospitalized patients and patients in community pharmacies. Table 5 shows that pain management in hospital was better. In hospitals 52.3 % of the patients were able to coordinate pain level and adequate intake of pain killers. In town pharmacies 20.0 % were able to do so, in village pharmacies 43.8 %.

Table 5 Coordination of current pain level and adequate intake of pain killers in the examined patient population (Thoma et al., 2018). Hospitalized patients had better coordination of pain level and pain killer intake compared to cancer patients in community pharmacies.

location	coordination		significance	p value ^{a,b}
	yes	no		
hospital n=44	23 (52.3%)	21 (47.7%)	yes	0.012
town pharmacy n=35	7 (20.0%)	28 (80.0%)		
village pharmacy n=16	7 (43.8%)	9 (56.2%)		
^a Evaluation with Bonferroni test method. Chi square test was used for categorical variables.				
Fischer exact test was used for border values.				
^b P value <0.05.				

48.6 % of the patients were able to assess their pain level, whereas 79.1 % of cancer patients were able to estimate their level of QoL, These findings are illustrated in Figure 10.

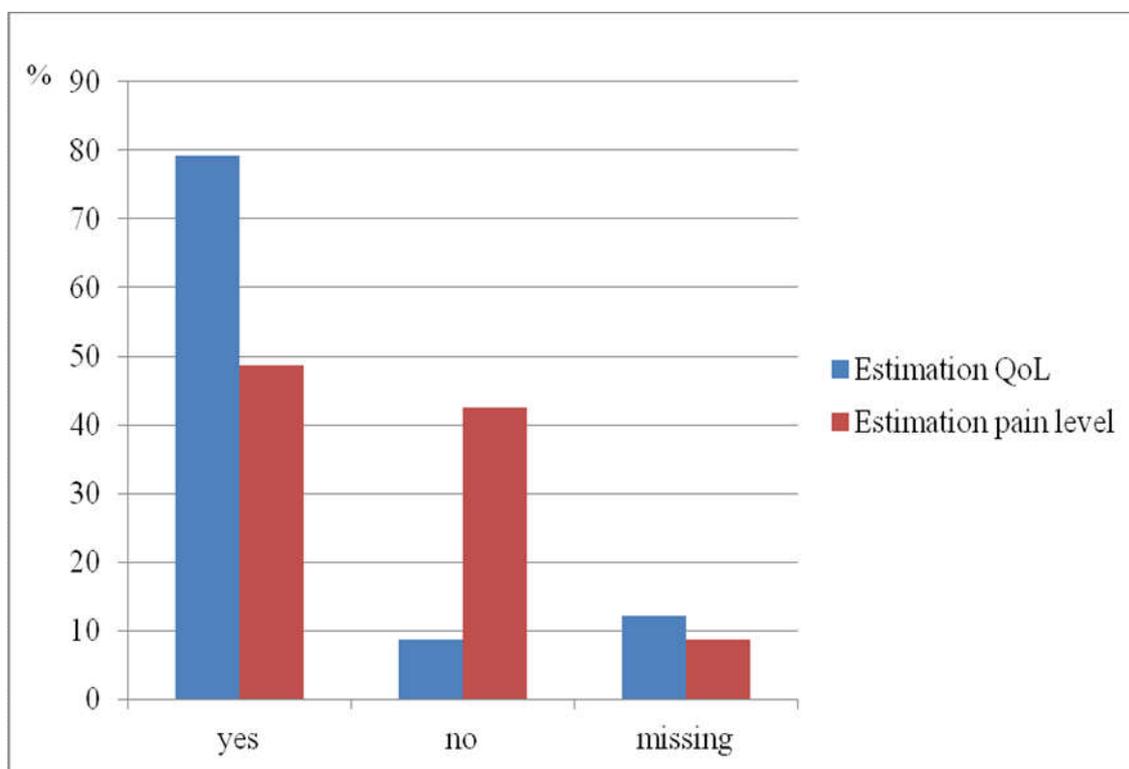


Figure 10 Ability of cancer patients to estimate their pain level and level of quality of life (Thoma et al., 2018). On a scale from 1 to 100 about three-fourths of cancer patients were able to estimate the level of quality of life. About half of the patients was able to estimate the pain level.

On a scale of 1 to 100, cancer patients' estimated level of QoL was 65.92 ± 19.25 in Hungary and 57.35 ± 23.45 in Germany. The evaluated median of estimated QoL differed in Hungary (70) and Germany (60). German data distribution was normally ($p = 0.62$). Hungarian data were not normally distributed ($p = 0.046$). The interquartile ranges (IQR) of both compared groups were 30. Above mentioned results are illustrated in Tables 6 and 7 and published in *Acta Poloniae Pharmaceutica – Drug Research* (Thoma et al., 2018).

Table 6 Estimated level of quality of life of Hungarian cancer patients (Thoma et al., 2018). On a non - percentage scale from 1 to 100 Hungarian cancer patients' level of quality of life was at 65.92 ± 19.25 .

statistic		bootstrap ^b				
			bias	std. error	95% confidence interval	
					lower	upper
n	valid	49		6	38	60
	missing	0	0	0	0	0
mean		65.9184	-0.0215	2.7222	60	71.0701
median		70	-0.26	3.0971	60	80
mode		70,00 ^a				
SD		19.2482	-0.18589	1.98193	15.24921	23.06492
percentiles	25	50	1.615	4.4468	45	60
	50	70	-0.26	3.0971	60	80
	75	80	-0.245	2.0449	70	80
^a Multiple modes exist. The smallest value is shown.						
^b Unless otherwise noted bootstrap results are based on 1000 bootstrap samples.						

Table 7 Estimated level of quality of life of German cancer patients (Thoma et al., 2018). On a non - percentage scale from 1 to 100 German cancer patients' level of quality of life was at 57.35 ± 23.45 .

statistic		bootstrap ^b				
		bias	std. error	95% confidence interval		
				lower	upper	
n	valid	79		6	68	89
	missing	0	0	0	0	0
mean		57.3544	0.148	2.6455	52.1291	62.5
median		60	1.28	4.3509	50	70
mode		70				
SD		23.44609	-0.34246	1.48849	20.14988	25.97786
percentiles	25	40	0.04	7.608	30	50
	50	60	1.28	4.3509	50	70
	75	70	3.5625	4.677	70	80

^b Unless otherwise noted, bootstrap results are based on 1000 bootstrap samples.

68.2 % of the asked patients had experiences with adverse drug reactions over the time period of treatment. 8.8 % of the participants stated, they have never been informed about possible occurring adverse drug reactions, which is illustrated in Figure 11.

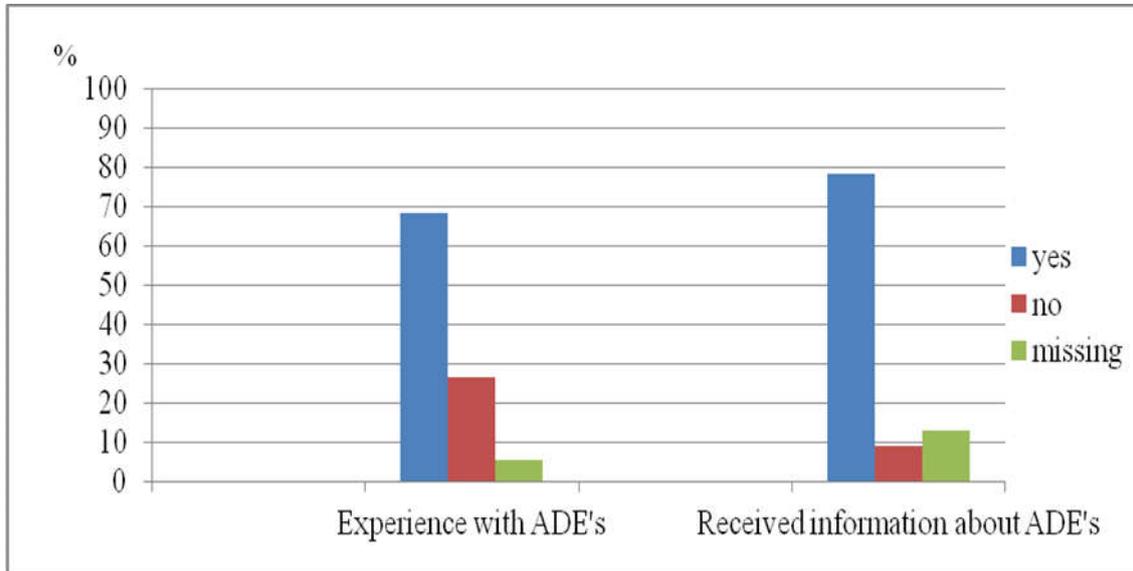


Figure 11 Experience of cancer patients with adverse drug events and with received information about adverse drug events (Thoma et al., 2018). About two third of cancer patients had experiences with adverse drug events. About three-fourths of cancer patients received information about adverse drug events.

Table 8 illustrates that 46.6 % of the patients indicated to expect more information about nausea as possible adverse drug reaction. Mucosa inflammation (11.5 %), enteritis (8.8 %) and immunodeficiency (8.8 %) were further interesting fields of adverse drug reaction for patients- Anorexia (0.7 %) and diarrhea (1.4 %) were relevant only for a very small part of asked population.

Table 8 Interest of cancer patients in fields of adverse drug reactions (Thoma et al., 2018). For cancer patients the most interesting field of adverse drug events was nausea.

frequency	nausea	Mucositis	enteritis	Immuno deficiency	anorexia	diarrhea	missing
n = 148	69	17	13	13	1	2	33
	46.6 %	11.5 %	8,8 %	8.8 %	0.7 %	1.4 %	22.3 %

Only 57.4% of cancer patients were satisfied with the information pool about cancer, which is illustrated in Table 9.

Table 9 Satisfaction of cancer patients with the information pool about cancer (Thoma et al., 2018). About one third of cancer patients was not satisfied with the information pool about cancer.

Frequency	yes	no	don't want to answer	missing
n = 148	85 (57.4 %)	43 (29.1 %)	15 (10.1 %)	5 (3.4 %)

54.1 % of the participants did not use food supplements for therapy completion. 49.3 % of the patients declared there has never been an offer regarding food supplements for therapy completion, which is illustrated in Figure 12.

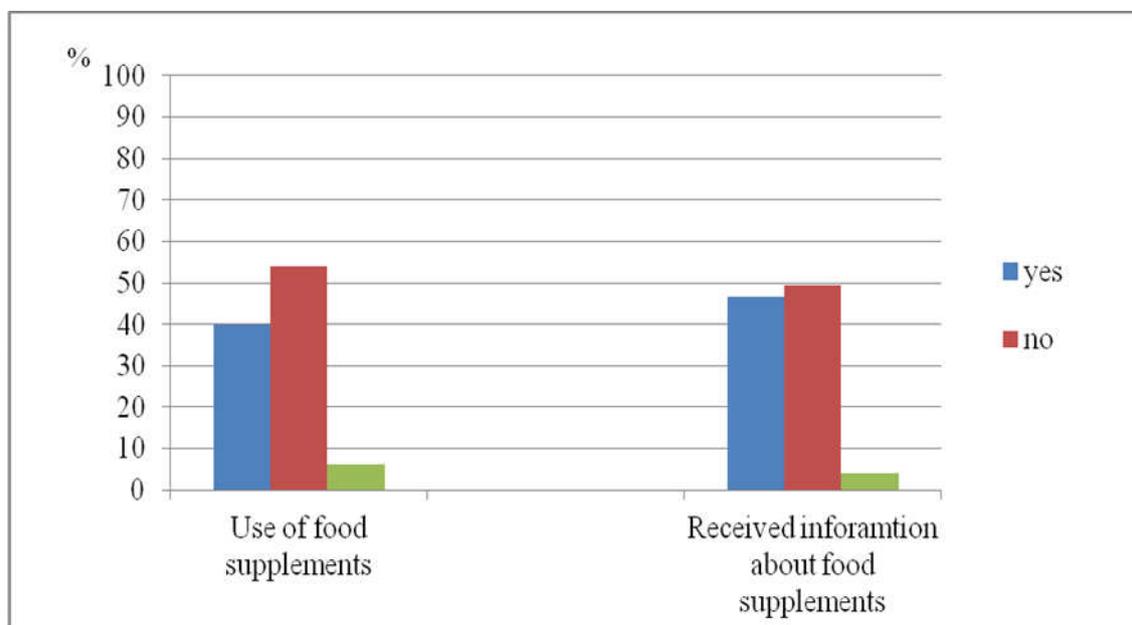


Figure 12 Assessment of cancer patients regarding the use of food supplements and received information about food supplements (Thoma et al., 2018). About half of cancer patients did not use food supplements and did not receive information about food supplements.

58.8 % of asked population answered to have never received an offer regarding therapy linked mental support but almost two third of the patients (60.8 %) thought that mental support would be helpful. Likewise, 50.7 % of the asked patients preferred professional mental support. 19.6 % of the patients preferred self help groups. These findings are illustrated in Figure 13 and Table 10.

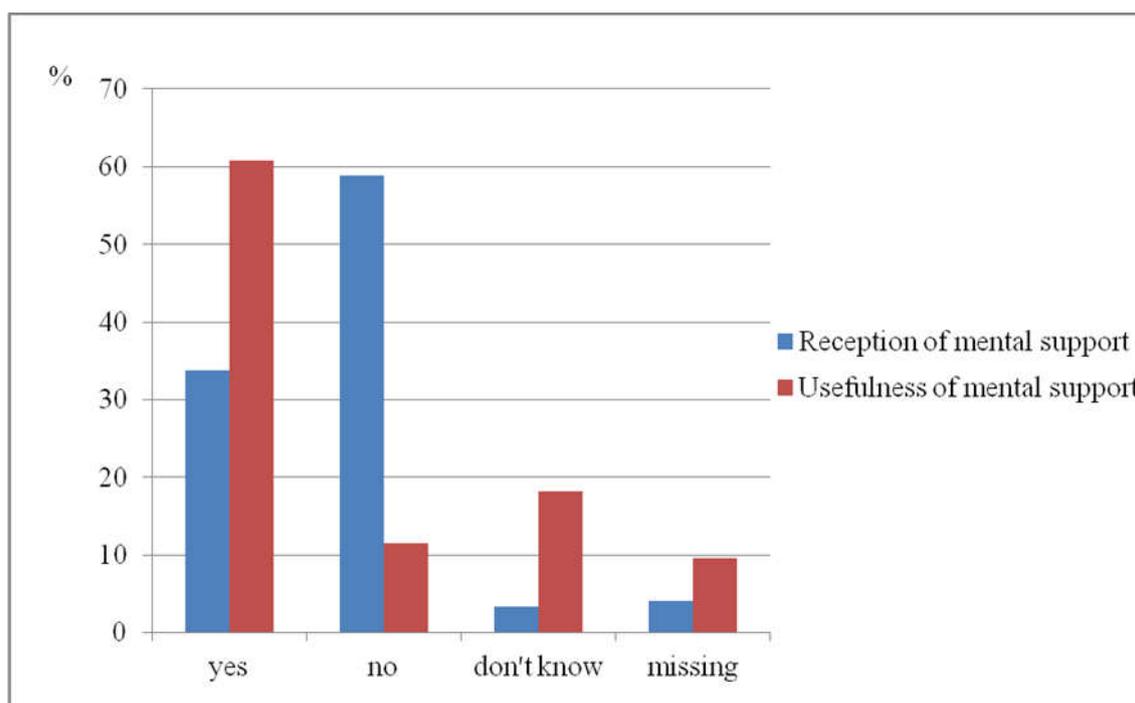


Figure 13 Estimation of cancer patients regarding reception and usefulness of mental support (Thoma et al., 2018). More than half of cancer patients did not receive mental support but assessed mental support useful.

Table 10 Cancer patients' estimation regarding their preferred kind of mental support (Thoma et al., 2018). Cancer patients preferred professional support compare to self help groups.

n	professional support	self help group	missing
148	75 (50.7 %)	29 (19.6 %)	44 (29.7 %)

The findings indicated no significant difference between patients in pharmacy or hospital in getting mental support ($p=0.600$). 31.1 % of the patients in pharmacy received mental support. In hospital the ratio was 39.7 %. But in the question "would it be helpful" there was significant difference. The pharmacy patients were more positive toward mental support ($p=0.002$). The results are illustrated in Figure 14 and Table 11.

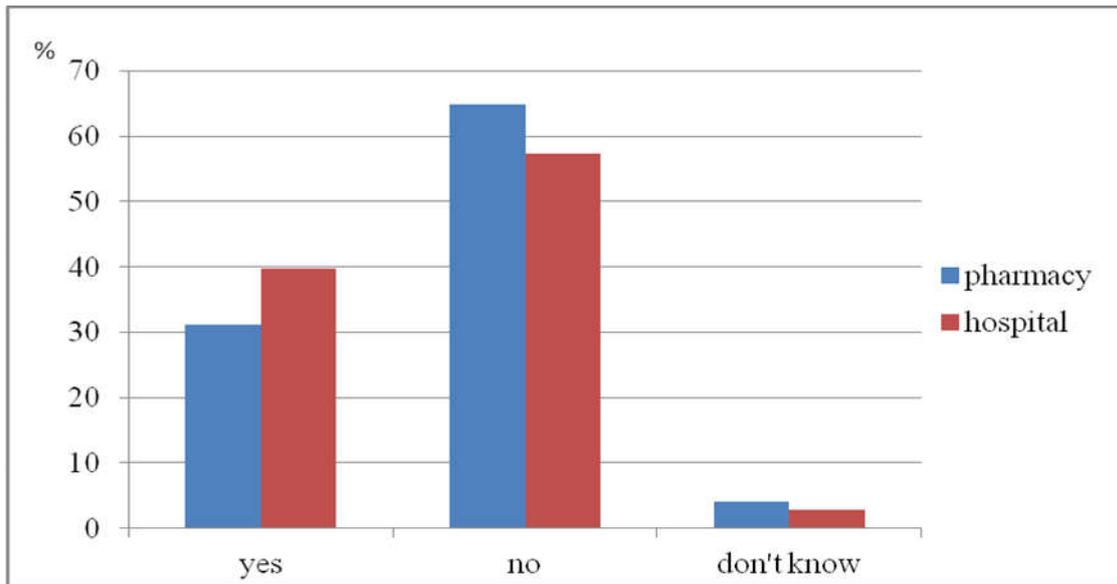


Figure 14 Ratio of received mental supply at hospitalized cancer patients and patients in public pharmacies (Thoma et al., 2018). Hospitalized cancer patients received more mental supply compared to patients in community pharmacies.

Table 11 Assessment of helpfulness of mental support at hospitalized cancer patients and patients in public pharmacies (Thoma et al., 2018). Compared to hospitalized patients cancer patients in community pharmacies assessed mental support more helpful.

location	mental support helpful			significance	p value ^{a,b}
	yes	no	don't know		
hospital n=65	35 (53.8%)	14 (21.5%)	16 (24.6%)	yes	0.002
public pharmacy n=69	55 (79.7%)	3 (4.3%)	11 (15.9%)		
^a Evaluation with Bonferroni test method. Chi square test was used for categorical variables.					
Fischer exact test was used for border values.					
^b P value <0.05.					

There was significant difference in occurred reception of food supplement advice between hospitalized patients and patients in public pharmacies (p=0.004). In hospitals 56.1 % of the patients received food supplement advice. In Town pharmacies the ratio of patients which had received food supplement advice was 24.4 %, in village pharmacies the ratio was 39.3 %. The results are illustrated in Table 12.

Table 12 Ratio of received food supplement advice at hospitalized cancer patients and patients in community pharmacies (Thoma et al., 2018). There was better food supplement advice in hospital compared to pharmacies.

location	food supplement advice		significance	p value ^{a,b}
	yes	no		
			yes	0.004
hospital n=66	37 (56.1%)	29 (43.9%)		
town pharmacy n=45	11 (24.4%)	34 (75.6%)		
village pharmacy n=28	11 (39.3%)	17 (60.7%)		
^a Evaluation with Bonferroni test method. Chi square test was used for categorical variables.				
Fischer exact test for border values.				
^b P value <0.05.				

5.3 Interview of physicians and pharmacists

(cf. Thoma et al., 2018)

Pharmacists' considered interventions to enhance medication adherence and reduce drug interactions. Flemings' research regarding non adherence to prescription medication as key factor driving costs in health care systems was already published in 2008 in the *Journal of Managed Care & Specialty Pharmacy* (Fleming et al., 2008). Home visitation offers especially in countrified areas resulting in ensured supply for immobile patients and better pain management were mentioned as well. In eyes of pharmacists the use of food supplements gives patients hope and the feeling to additionally contribute to their therapy.

Oncologists mentioned the check of sequences or stabilities of cytological treatments as interventions to reduce physicians' workload. Patient admission and residence in hospital could have been reduced with a precautionary medication check - up, which could have limited costs of national health systems. Oncologists especially emphasized expert knowledge. In eyes of physicians this knowledge was in some cases lacking and too complex for pharmacists. Physicians considered a main contact person in pharmacies as important and necessary to maintain a quick order and delivery process. Finally, pharmacists' interventions regarding pain care were estimated in a positive way. In physicians eyes a daily approachable contact person was meaningful for the diverse grades of different pain levels in the course of the disease cancer.

5.4 Limitations of the results

Consideration of the manuscript in context of several limitations is necessary. The subjective definition of inpatient, medium and outpatient care as well as the subjective allocation of received results to three groups and the possibility of publication bias, outcome reporting bias and bias within included individual studies have to be mentioned as weaknesses of my study regarding the results of my literature analysis.

Considering the questionnaire analysis special attention has to be paid to the risk of sampling bias. Concerning my unusual results regarding cancer type and gender equality in Hungary and Germany one has to consider missing representativeness. These data do not define the true national distribution situation and could be provoked by one sided selection of distribution places. The excess of bowel cancer could be not randomly influenced by the fact that 71.0 % of Hungarian questionnaires were received from hospital. The excess of breast cancer and female cancer patients in Germany could be not randomly influenced by a one sided questionnaire distribution in the clinic to a department specialised on female cancer diseases.

Moreover the list of agents with an oncology indication in German market contained a very broad spectrum of drugs. Therefore, patients with very different states of health were included, which resulted in a reduced comparability of patients groups.

Town pharmacies were not categorized precisely. According to our classification a town pharmacy could have represented a town with 20,001 inhabitants or a metropolis with 2 million inhabitants. This could have led to an obtained sample, which was not representative of the population intended to be analyzed.

The results were limited to a comparatively small population. The recovery of patients was difficult because cancer patients often missed mood or physical constitution to answer a questionnaire. Selection bias could have occurred in hospitals or pharmacies.

The result of this study is limited to the additional use of drugs which could have influenced the evaluated QoL results. Furthermore, the study is limited to the type of cancer itself affecting the results. The dependence on QoL and cancer type should be approached as one of the next steps in the future investigation of cancer patients QoL.

It's in the nature of things that staff motivation to distribute questionnaires may have differed in diverse departments with the result that there could have been reduced achievement of proper randomization. Executing staff was asked to address the patients and to document successful approaches and failed approaches as well. Since the executing staff in pharmacies and hospitals worked only partly in accordance with this guideline, the evaluation of the rate of response was not possible.

Even if pharmacy and hospital staff was schooled to elect only patients treated with a drug mentioned on the defined list we couldn't control all the operation modes of pharmacy and hospital staff.

Due to the dependence on the voluntary benevolence of the pharmacy owners and even more important on the collaboration with pharmaceutical staff in community pharmacies and hospitals this study is limited to the number of selected pharmacies and hospitals.

Then patients were allowed to take the questionnaire home. There was no possibility to control if they received help from family members. It was not possible to force patients answering to the questionnaire directly in pharmacy or hospital.

Patients who directly answered in their weekly visited pharmacy could have assessed pharmacists in a too positive way, because they would have been uncomfortable with a negative assessment.

Just as other studies this research was limited to under reporting of null results and over reporting of significant and positive outcomes. Finally, disappeared questionnaires,

confounding in hospitals or pharmacies or mistakes during the statistical evaluation procedure are further points my research is limited to.

6. Discussion

6.1 Explanation and critical evaluation of results

6.1.1 Results of literature research

Literature research was performed with the objective of analyzing quantity and utility of outpatient models of pharmaceutical cancer care compared to existing interventions of pharmacists in hospital or ambulatory oncology settings. In summary existing pharmacists' interventions are of highest quality and have proofed efficacy in all three fields of care. I compared the amount of research conducted on pharmacists' intervention approaches in inpatient and medium settings with that in outpatient settings; our results show that inpatient and medium models predominate in the literature. Nevertheless, a few studies also exist in outpatient fields. Unsurprisingly, there are more reported beneficial outcomes associated with inpatient and medium care compared with the results of pharmacists' interventions reportedly associated with outpatient oncology care. Altogether the majority of approaches focus on pharmacists' intervention in inpatient and medium care and the section of community pharmacists' interventions in outpatient care remains in big parts unexplored.

This is the first approach who evaluated a little ratio of existing community pharmacists' contributions in outpatient oncology care compared to an excess of approaches of pharmacists' interventions in inpatient and medium oncology care (Thoma et al. 2016).

6.1.2 Results of questionnaire research

The questionnaire research was conducted with the objective of analysing need for community pharmacists in the daily reality of cancer patients in Hungary and Germany.

Following investigated results underline need for community pharmacists' interventions in cancer care:

As human beings grow older and 41.9 % of people fall ill with cancer around the age of retirement between 61 and 75 years - shown in Figure 1 - there is need for specialised staff. 64.2 % of the patients were diagnosed with cancer not longer than 3 years before as shown in Figure 6. Considering the chronic and fatal property of the disease cancer there is the necessity of addressing this topic quickest possible with all available resources including community pharmacists.

My findings illustrate just if the severe topic is cancer the confidence of patients in specialized staff and experts is still high. Regarding the severe topic cancer patients want to receive qualified advice. Although internet information could be received faster physicians and pharmacists still enjoy a good reputation in the population and therefore patients accept waiting times due to their confidence in professionals' qualified services. Table 4 illustrates significant difference $p < 0.001$ in seriousness assessment of internet (4.38 ± 2.32) and pharmacists' information (8.23 ± 1.81).

Validity of pharmacists' information (8.23 ± 1.81) was assessed almost equal compared to practitioners' information (8.44 ± 1.54) as shown in Figure 8. Probably a purity representing white work coat prohibited doubts referring seriousness of a person. The digital evolution allowing everyone in the whole world to upload potentially unserious information to the internet could have been a further factor for this result (cf. BBC 2018). Especially cancer patients over 60 preferred information in pharmacies and similar at practitioner and oncologist. 35 of 78 patients older than 60 gave the pharmacy as preferred information point. These results illustrate demand for eye to eye advice and personal relationship between patients and professionals. A many years practiced habit could have been casual, too. The acceptance of pharmacists hypothesizes need for community pharmacists' interventions in daily cancer care.

Only 48.6 % of the targeted patient group was able to assess their pain level as shown in Figure 9. Probably it is difficult for patients to distinguish between unsustainable pain and lighter shapes of pain which impedes right intake of pain killer medications. The fact that 39.2 % stated to have difficulties with the right pain killer dosage shows the insecurity of patients in this point illustrated in Figure 9. In many cases cancer patients receive pain killer treatment in hospital and are discharged with a general medication

plan. At home standing on their own it is difficult for many patients to adapt pain killer dosage to their temporary requirement. In other cases patients visit several physicians and receive several pain killer prescriptions without the knowledge of one physician about the prescription of his colleague. This compulsory leads to confusion and subsequently a worse adjusted pain level of cancer patients. It is one of community pharmacists' ordinary tasks to help patients reducing their pain level by giving professional advice referring adequate drug intake. Additionally, it is not enforceable to meet oncologists or physicians weekly and not to mention daily. Therefore, community pharmacists' skills appear as promising alternative to help patients adjusting their pain killer dosage.

Due to the fact that almost half of cancer patients used pain killers and pain is a factor with high influence on patients' level of quality of life this topic is important for cancer patients which deserve to live as good as possible their remaining life time. Nevertheless, one has to take the statement of the WHO into account that cancer patients' perception of QoL depends not only on disease- and treatment-related factors but also on social relationships and individual value systems in relation to individual expectations and standards (World health organization, 2017; Singer et al., 2013). In the end of the questionnaire patients had the possibility to answer to an open question and state their wishes and expectations. The most important point for patients was to have persons they can talk to – medically and primarily from human perspective. Community pharmacists own this social potential and could give patients the feeling of importance and consequently an increased level of life quality in their remaining life time.

On a scale from 1 to 100 the investigated level of quality of life was in Hungary 65.91 ± 19.24 and in Germany 57.35 ± 23.44 as illustrated in Tables 6 and 7. Considering these results and above mentioned patients' expectations increase of patients' level of quality of life in case of intensified use of community pharmacists in cancer care could be hypothesized. The relevance of the topic quality of life for the assessment of community pharmacists' use in cancer care has to be assessed under consideration that this hypothesis has not proofed final evidence.

8.8 % of patients treated with anticancer therapies were not informed about possible occurring adverse drug reactions as shown in Figure 11. Only 57.4 % of asked patients were satisfied with the received information about adverse drug reactions as illustrated in Table 9. Referring the fields of adverse drug reactions patients were mostly interested in nausea (46.6 %) and mucosa inflammation (11.5 %) as shown in Table 8. The result hypothesize in most cases there is no need for exotic advice but rather for basic counselling services of professional staff like community pharmacists. I can confirm by first hand experience in my pharmacy the benefit and gratefulness of patients receiving detailed instructions regarding their drug intake.

49.3 % of the asked patients declared there had never been an offer regarding food supplement advice as shown in Figure 12. According to my opinion every patient has the right to be informed about existing possibilities of additional therapy approaches. Therefore, not only the enhancement of adverse drug reactions clearing up but also the break of prospective approaches regarding food supplement advice to patients are possible achievements of community pharmacists in cancer care.

58.8 % of the patients never received therapy linked mental support but 60.8 % thought it would be helpful as illustrated in Figure 13. More than two third preferred professionals compared to self help groups as shown in Table 10. Figure 14 and Table 11 illustrate that pharmacy patients were more positive toward mental support compared to hospitalized patients ($p=0.002$). In hospital in many cases patients were in a position of end stage. Perhaps they even wanted to think about mental support and had little hope left. The often long lasting personal relationship between patients and their community pharmacist could have led to a stronger confidence of patients in community pharmacists. The fact that patients have stronger confidence in professionals than in self help groups underlines the necessity of professional experts. In many cases patients are lonesome at home and pharmacists are the first contact person for patients' problems – including mental issues. Community pharmacists' position implicating the meeting of patients almost daily emerged as an important characteristic to assess patients' emotional state, which allows pharmacists to act as kind of mediator between patients and professionals in mental support.

Compared to town pharmacies (24.4 %) and village pharmacies (39.3 %) in hospital (56.1 %) there was more reception of food supplement advice as illustrated in Table 12. Additionally, in hospital (52.3 %) there was better coordination of pain killer intake compared to town pharmacies (20.0 %) and village pharmacies (43.8 %) as shown in Table 5. For adequate pain management continuance and a certain time period of contact with the patient is advantageous. In this point the capabilities for comprehensive supply are better in hospital. In hospital there was assistance round the clock. Clinical pharmacists held expert knowledge and patients were able to ask for food supplement advice or pain killer adjustments whenever they wanted. The beneficial roles of clinical pharmacists regarding individual nutrition counselling services were already reported (Tuffaha et al., 2012; Mousavi et al., 2013). In contrast outpatient cancer patients often are alone at home, the walk to the pharmacy is in many cases burdensome and therefore many emerging questions disappear. For those patients intensified interventions of community pharmacists and innovative approaches for home care services are of exceptional value.

In the introduction part I described that the incentive of this PhD thesis was the meeting of cancer patients in my pharmacy with insufficient knowledge about their medication. The considerations of this chapter highlight the need for community pharmacists in the daily reality of cancer patients. Providing integration and collaboration with community pharmacists as basic condition, pharmaceutical care can have an important share in future cancer care.

6.1.3 Results of health experts interviews

Interviews were conducted with the objective of receiving the opinion of health experts to community pharmacists' use in cancer care.

Both pharmacists and oncologists thought that in many cases patients could take profit from better coordination between health experts but there is a communication problem between pharmacists and physicians. Pharmacists mentioned home visitation offers and food supplement advice as important approaches. Oncologists emphasized the check of

cytotoxic treatments. Both expert groups considered detailed schooling of pharmacists in special fields of oncology as the most important point to maintain expert knowledge. Nevertheless, physicians still want to avoid limitations of their own skills and their therapeutic freedom. In contrast pharmacists battle the fame of the small brother besides physicians to be accepted as equated professional in health care.

Finally, considering community pharmacists' support in oncology care I am the first who matched a comprehensive research of existing pharmacists' interventions in literature, a patient reported questionnaire analysis in Hungary and Germany and a professional directed health experts' interview (Thoma et al., 2018)

6.2 Vision

6.2.1 Cancer care in the digital age

The term Digital Health will play a major role in future cancer care. The digital progress becomes quicker and quicker and a conflation between information technique and medicine is observable for several years. The advanced digital revolution since the turn of the millennium offers new possibilities of networking which allow the documented and clustered contribution of several experts to the therapy strategy of one patient. The digital revolution is at the same pitch as inventions like antibiotics or x-rays. 100 years ago nobody was able to imagine cardiac pacemakers. Now this is part of the standard operations in almost each bigger hospital. High technology not only enhances the way of documenting and transporting information but also influences cancer treatments in a direct way. High laser technique enables precise radiation of tumour cells without damaging surrounding tissues.

The new way of data transfer e.g. with electronic health cards allows the transmission of already imposed patient data without the loss of knowledge on the way from one expert to another. The electronic health card will be the next step in the German health system to consolidate the whole current patient medication received by physicians' prescription and at the recommendation of pharmacies. Thereby it could be easier for future studies to identify cancer patients' total medication. Sooner or later also electronic prescriptions

will replace the classical prescriptions on paper which promises faster processing and protection against forgery.

Today in medical practices in many cases lab data are still existent disordered and in hardcopy form. Often physicians view only the patient in front of them and act from the basis of their own experience. Considering the global burden of cancer adduction of clinical data of millions of cancer patients has to be intensified for diagnosis and therapy forms. Therefore, not only acquisition of data but also digital documentation and better classification in homogenous databases has to be intensified. Unburdened access from all areas of the world to those databases has to be forced. The connection of huge data pools is challenging but convertible with existing and further developing possibilities of digital information techniques. Besides taking care of patients and giving advice it will become a physicians' main task to create and document health knowledge which can be used by everyone in the whole world. If physicians daily contacted with patients intensify the documentation of their daily experiences and perceptions the huge pool of health information would not only be limited to theoretical scientific research but would also be extended with practical information. The combination of these two issues could render health knowledge of the human race more powerful.

There also are approaches of telemedicine offering patients video counselling services of physicians. According to my opinion one should try to use the beneficial digital possibilities but one should avoid the constrained overturn of the well established relationship of patients and professionals. There is no digital possibility which is able to substitute physical eye to eye advice permitting empathic interpretation of patients' physical and psychical conditions. Professionals still have to be able to touch patients for comprehensive perception of their needs.

Despite of above mentioned advantages the digital period is limited and exhibits disadvantages, too. The incidents in May 2017 in Great Britain show the vulnerability of the connected global world. Nobody considered a hacker attack possible which blocked the supply of total departments of hospitals and tried to press money. In case of

such a global blackout supply of millions of patients could be deficient with unpredictable consequences.

New approaches referring diagnosis and therapy in cancer care

A footrace between human advancements and adaptation processes of cancer cells is presumably. Similarly to bacterial cells it will become important who of the counterparts is a step ahead. Therefore, not only innovative therapy strategies but also new approaches of cancer diagnosis will be essential to identify reasons for the specific genesis of cancer.

Even if the tumour cells quickly expand malignant cells consistently die and emit DNA fragments into the blood stream. This fact is known for quite some time but the methods of reliable verification procedures have become better and better the past years. There are promising approaches especially regarding lung cancer to identify such DNA fragments in the blood stream of patients. Using such methods health experts could be able to diagnose cancer by taking blood samples instead of biopsies (Zhao et al., 2018; Han et al., 2017).

Thereby the amount of early detected cancer diseases could rise in future because of the simple and gentle method. Even now day to day millions of blood samples are routinely taken in the global world. It remains the secret of the future if cancer diseases can be detected some day by standardized blood tests. Analyzing the amounts of DNA fragments in the blood stream could be a step to limit the expansion of the disease cancer at the earliest possible stage.

Similarly to the so called metabolic syndrome at cardiovascular diseases it will be essential to recognize cancer risk factors. It is known that high blood pressure, diabetes, obesity and disruptions of the lipid metabolism are considered as main risk factors for falling ill with cardiovascular diseases. Detailed identification of cancer risk factors will be essential to be able to preclude cancer with preventive activities.

Using the experience values of above mentioned databases development of more efficient personalized therapy forms could be enabled. Down to the present date cancer patients' therapy response is still a big problem. Even if cancer type, cancer stadium and

patient characteristics are very similar there are big differences regarding the response to equal therapies. Referring to personalized therapy forms immunotherapy is a promising approach and has to be refined in future. Investigators try to analyse specific targets on tumour cells of the individual cancer patients and then try to activate the immune system of the patients to attack this target (American cancer society, 2018). Of course this technology is still in its infancy but besides the hoped better response of cancer patients to the treatment this kind of technology could provide cost efficiency.

From financial perspective one can imagine that it is more expensive to try three or four different cytotoxic therapy strategies and then has to assert that the patient has responded to none of those than treating patients with personalized high effective therapy forms (cf. Ventola et al., 2017). Considering such future approaches perhaps it could be no exceptional case if a human being becomes 100 years old. It remains to be seen and an ethical question if this is required generally.

6.2.2 Increasing cancer rates and personal shortage

The amount of cancer rise with increased age and the demographic development proceeds. This combination constitutes a vicious circle which is difficult to burst. Progressing financial and especially personal shortage will contribute to the strained situation in cancer care. Not only the general increase of cancer patients, but also the rising shortage of physicians poses a very difficult context. There are too many physicians aged 60+ and too little renewable young physicians.

Additionally, life is getting fast moving more and more, the human being suffers from a lack of time and therefore patients will decreasingly accept waiting times for medical specialists of one month or longer. Especially in countrified areas the distances between patient and the next physician will become larger.

For young human beings the job physician is no longer the dream job par excellence which is also visible in hospitals. Not only emergency services in countrified areas linked with particularly required accessibility round the clock, but also emergency

services in hospitals are associated with often understaffed working hours and bad payment. Especially prospective physicians in education arriving after university in hospital are confronted with adverse conditions. The graduation to a medical specialist often takes time with the consequence that finished medical specialists are often aged 35 to 45. Hence from the financial perspective even with the earnings of medical specialists it is difficult to counterbalance in the remaining man years the lead of persons which have begun working at the age of 15.

Then the past years a change of young people mindset is cognizable. The so called Work Life Balance becomes more and more important for young human beings. Many well educated and promising high school graduates consciously abstain from financial and career interests but gain a working life with little time pressure and free times from Friday midday to Monday.

All above mentioned issues contribute to the overload and a shortage of physicians in cancer care. Finally, especially in cancer care the enhancement of therapy strategies have led to life extension of patients (Lucke et al., 2010). Formerly patients would have simply died earlier, which also constitutes additional workload for physicians.

Therefore, in Germany politics even subsidises physicians in countrified areas with high amounts of money if they transfer their point of retirement from the age of 60 to the age of 70. Additionally, there are approaches, which facilitate access to the academic studies of medicine for high school graduates which achieved worse grade point averages but obligate themselves to at least 10 year lasting employments as physician in countrified areas. A greater extent of such approaches will be necessary to maintain specialised staff, comprehensive supply of patients and finally the limitation of cancer spreading.

6.2.3 The role of pharmaceutical care in future oncology care

Cancer care will be a central topic for pharmacists in the next decade. Considering the personal shortage it will be important to provide specific, research-based direction for implementing community pharmacists with their skills as health care professionals in

oncology care. For that purpose the standardized integration of pharmacists in medical teams will be essential to reduce the burden of physicians and oncologists workload.

This can only work if both pharmacists and physicians are able to talk on eye level and respect each other as equal members in the common fight against cancer. Considering the possibilities of the digital age the integration of several health experts in the medical team is much easier than in the past and presents no longer a problem. Since March 2017 in Germany the legal access to cannabis is facilitated. Cannabis is expected to help some of the cancer patients tolerating pain symptoms better than usual pain killers. Cannabis preparations are available as oily drops which alleviate accurate dose adaptation. In Germany the ultimate fabrication of these oily drops is task of community pharmacies. Hence a first step of community pharmacists' integration in oncology care has already happened.

Considering the chronic and ruthless properties of the disease cancer all experts conform that preserving of QoL is the minimum to do for cancer patients. It is the responsibility of all involved parties including pharmacists to arrange the everyday life of cancer patients as normal as possible and to consequently preserve cancer patients' level of QoL. For many cancer patients the main parameter deciding the level of QoL is pain. Since all cancer types can be longer fatal it will be of importance to develop strategies which attenuate cancer patients' pain to a tolerable level.

Patients' wishes regarding eye to eye advice and a personal relationship between patients and professionals will have to be emphasized. Time for this desire is lacking at physicians and especially in oncology care. Community pharmacists' skills are capable of shortening this lack – qualified and with an adequate time schedule. Therefore, community pharmacists will be required to execute precautionary medication check ups, and to counsel cancer patients regarding food supplements and coordination of pain level and adequate pain killer intake. Additionally, community pharmacists' will have to focus their social potential, which could avoid patients' loss of social integration in the community and give patients the feeling of importance and subsequently an increased level of quality of life in their remaining life time. Furthermore, community pharmacies

will have to develop new fields of actions such as home visitations. Those services provide local community pharmacies the opportunity of an additional source of income to stand up to the online pharmacies crowding in the market with dumping prices. Compared to online pharmacies only the local community pharmacists are able to execute contemporary home visitations. In times of financial shortage of national health systems there is less hope that health insurances will pay this service. It remains to be seen if patients are able and willing to pay such services privately.

Besides the efforts regarding community pharmacists' contribution to oncology care a continuous enhancement of already existing and beneficial approaches of pharmacists' intervention in inpatient and medium care may not be neglected. Presuming further education referring to expert knowledge in oncology care pharmacists can improve the efficacy of inpatient care in several ways. Patient directed counselling services guided by a main pharmacist are time intensive but hypothesize enhanced medication adherence and subsequently lower amounts of ADE's. Not only in community pharmacies but also in inpatient and medium care main contact persons will be essential to organize and collocate the diverse working procedures. As member of the medical teams pharmacists will be able to directly prevent ADE's in the framework of a medication check up and indirectly reduce physicians' workload.

In medium care patient focused approaches will emerge similarly to above mentioned services of pharmacists in inpatient care. It could become a task of pharmacists to alleviate patients the transition from hospital home or from home to hospital. Due to the physical and psychical constitution of cancer patients the involvement of family members will play a major role. On the one hand, patients confide in family members and on the other hand those people are cancer patients first contact persons at home. Pharmacists are able to retrace the medical history with their expert knowledge from the professional perspective. It should become pharmacists' task to convey this information in a comprehensible way to cancer patients' family members. Hospital admissions often very quickly after the last hospital release could be prevented with such clearing up procedures of family members.

The driving force of my project was the hope that my findings give a base for the discovery of future approaches, which limit the escalating problem cancer and allow positive influence on the supply of next generation cancer patients. To stay in reality by reason of the diverse, quick changing and different proceeding types of cancer the big breakthrough which erases the disease cancer is unlikely. Nevertheless, I feel confident that contributions of pharmacists to cancer patients' supply could be a little brick to get a grip on the expanding problem cancer in future.

Finally, the results of the dissertation have to be examined under consideration of the following issues.

Finally, the author of the dissertation is pharmacist which may have biased the unconscious interpretation of the answers.

There were a comparably small number of questionnaire participants. Therefore, further research should be conducted addressing a larger target population.

The setting of the distributed' questionnaire and the questions used for professional health experts' interview includes an unexpressed but sensible preconception that there is a need for pharmacists' intervention, which could bias the later questionnaire answers. Therefore future research should be conducted using modified questionnaires, divided in two arms for participants confirming need for pharmacists' interventions and for participants thinking there is no need for pharmacists' intervention in oncology care.

7. Conclusions

To contain the expansion of cancer it will be necessary to focus all disposable human and technical forces of the human race. My findings proofed great demand and usefulness of pharmacists' interventions in cancer reality and highlighted still room for intensified research engagement into community pharmacists' unspent skills in literature. My study gives an overall view of existing literature regarding quantity and utility of pharmacists' interventions in all fields of oncology care and compares the received results with patients and professionals needs in cancer reality of two European countries.

In literature analysis I investigated many approaches in inpatient, medium, and —
By means of the cross-national questionnaire analysis I collected comprehensive information from substantial participants of cancer care in two European countries to estimate community pharmacists' use in present cancer care. The questionnaire analysis and the interview of professional health experts helped me determine the extent to which interventions reported in the literature correlate with patients' and experts needs in cancer reality. Considering performed questionnaire analysis and conducted interviews with professionals the big majority of outcomes showed demand and usefulness of community pharmacists' support in cancer reality.

Both patients and professionals are open minded to further approaches of community pharmacists' interventions, such as home care services, medication Check-ups or assistance regarding mental supply. The control of adverse drug reactions and drug interactions has to be one of pharmacists' main tasks to avoid hospital admissions and subsequently reduce costs for health care system.

There is need for pharmacist guided pain management models for better symptom control in palliative care. A certain contact person in each pharmacy is important to ensure better communication and discussions on eye level with general practitioners and physicians in hospital. Based on my findings I believe that further investigation into

quantity and utility of community pharmacists' interventions is essential in present cancer care.

To give powerful guidance for the future equal communication between physicians and pharmacists on eye level, integration of community pharmacists in oncology outpatient assistance and of capital importance schooling of community pharmacists in special fields of oncology care have to be mentioned as only three possibilities to maintain expert knowledge, reduce physicians' workload, limit costs of national health systems and in conclusion enhance cancer patients supply.

This PhD thesis could be the basis for further approaches. It remains to be seen if and to what extent community pharmacists' contribution will find a way into oncology care.

7.1 Novelty of the thesis

- Considering community pharmacists' support in oncology care I am the first who matched a comprehensive research of existing pharmacists' interventions in literature, a patient reported questionnaire analysis in Hungary and Germany and a professional directed health experts' interview.
- This is the first approach who evaluated the little ratio of existing community pharmacists' contributions in outpatient oncology care compared to an excess of approaches of pharmacists' interventions in inpatient and medium oncology care.
- There is no other approach in this modality which discovered a reverse correlation of a shortage of investigation efforts into community pharmacists' interventions in literature and rising demand and usefulness of community pharmacists' interventions in cancer patients' reality.

7.2 Practical relevance of the thesis

- To limit cancer the quickest spreading disease down to the present date it is mandatory to develop new approaches and exhaust all available human and technical resources.
- Considering personal and financial shortages national health systems may not exclude the qualified and little used resource community pharmacists.
- It is important to develop new strategies regarding cancer patients QoL because cancer is a disease which rapidly leads to death and often many cancer patients have little time left in their remaining life time.
- On a variety of grounds community pharmacists' integration in oncology care is useful for cancer patients QoL.
 - Evaluation of cancer patients' QoL showed still room for improvement of cancer patients' QoL.
 - The most important point for cancer patients was to have persons they can talk to – medically, from human perspective and with an adequate time schedule.
 - The social and pharmaceutical potential of community pharmacists is able to cope with those needs.
 - Physicians and patients are open towards community pharmacists' interventions in cancer care.
- The almost weekly visit of cancer patients in the pharmacy could be used for essential adjustments of pain killer dosages.

- About 50 % of the examined patient population are not able to assess their pain level.
- Only one fourth of the examined patient population stated to be able to coordinate pain level and right pain killer dosage.
- By first - hand experience I can confirm cancer patients' demand for specialized pharmaceutical care.
 - In my pharmacy cancer patients appear daily with insufficient knowledge about intake, effects and consequences of highly effective drugs.
 - Two third of the examined patient population had experiences with ADE's.
 - Less than 60 % of the examined patient population was satisfied with the current information pool regarding ADE's.
- Intensified clearing up about risks of smoking is necessary.
- There are accumulated needs in community pharmacies regarding food supplement advice.
 - About the half of the examined patient population was not informed about food supplements for therapy completion.
 - Food supplement advice in hospital was better compared to community pharmacies.
- There is need for intensified mental support for cancer patients, because only one third of the examined patient population received mental support, but two third stated that mental support would be useful.

- The weekly visited community pharmacists can operate as mediator between cancer patients and professional experts in mental support. Patients, who received the questionnaire in public pharmacies were more positive towards mental support than hospitalized patients.
 - Professional experts in mental support were preferred by the examined patient population compared to self - help groups.
- As opposed to internet information the examined patient population had confidence in the validity of pharmacies as first information points in always the same manner than in practitioner information.
- All above mentioned results indicate great demand and usefulness of community pharmacists in cancer reality.
- Integration of community pharmacists' in oncology care has to be encouraged.
- Increased schooling of community pharmacists in special fields of oncology care and talking on eye level between physicians and pharmacists provide a basis to integrate pharmacists as coequal team members in cancer care.

8. Summary

Cancer is on the fast lane and could replace cardiovascular diseases as the most common cause of human death in future. In face of this expanding problem national health systems struggle with less human and financial resources. There is a growing risk that these contrary points will gape apart onwards in future. I tried to explore if pharmacists can contribute to the containment of this escalating problem. I analysed incident and extent of scientific research regarding pharmaceutical contributions in oncology care. Thereby I was able to classify existing approaches in literature and got an overview of current supply of cancer patients. Additionally, I explored community pharmacists' use in present cancer care with a self - developed closed ended questionnaire distributed to cancer patients in hospitals, town pharmacies and village pharmacies of Hungary and Germany and interviewed professionals of health care. Thereby I analysed cancer patients' situation and needs and received a picture of essential requirements from pharmacists in the daily reality of cancer patients and professionals. My findings show great demand and usefulness of community pharmacists in oncology care. In summary I performed a broad literature research and collected comprehensive information from substantial participants of cancer care in two European countries to estimate community pharmacists' use in present cancer care. Within the framework of my PhD thesis I was the first who matched literature research and reality analysis of community pharmacists' contributions to oncology care in Hungary and Germany. The comparison of these two projects resulted in the discovery of a reverse correlation between an untended issue in scientific literature and great requirements for pharmaceutical support in oncology reality. The results of my PhD thesis should be the basis for further investigations and a better use of unspent resources in national health systems.

9. Összefoglalás

A rosszindulatú daganatos megbetegedések a jövőben várhatóan a leggyakoribb halálozási okot jelentik, megelőzve a kardiovaszkuláris kórképek okozta halálozást. A nemzeti egészségügyi rendszereknek az egyre növekvő problémával szemben egyre kevesebb emberi és pénzügyi erőforrással kell megküzdeniük. Fokozottan fennáll annak a kockázata, hogy ezek az egymás ellenében ható tendenciák a jövőben még kifejezettebbek lesznek. Doktori munkám során célul tűztem ki annak a feltárását, hogy a gyógyszerészek hozzájárulhatnak-e ennek a növekvő problémának a mérsékléséhez. Szisztematikus irodalomelemzést végeztem, hogy képet kapjak az onkológiai ellátással kapcsolatos gyógyszerészi szerepvállalás módjairól és azok mértékéről¹. Így a szakirodalomban fellelhető módszereket osztályoztam, és áttekintettem a daganatos betegek jelenlegi ellátását. Emellett kórházakban, magyar és németországi városi és kistéleplési gyógyszerárakban egy saját fejlesztésű, zárt kérdésekből álló kérdőíves felmérést végeztem onkológiai betegek körében, hogy a közforgalmú gyógyszerészek jelenlegi szerepét vizsgáljam az onkológiai betegek ellátásában, valamint a témában interjút készítettem egészségügyi szakemberekkel². Elemeztem az onkológiai betegek helyzetét és szükségleteit, és képet kaptam a gyógyszerészekkel szemben támasztott elvárásokról. Eredményeim megerősítik, hogy a közforgalmú gyógyszerészi gondozás iránt jelentős igény van az onkológiai ellátás területén is. Összefoglalva, széleskörű szakirodalmi kutatást végeztem és átfogó információt gyűjtöttem az onkológiai betegek ellátásának résztvevőiről két Európai Unió országban, azzal a céllal, hogy felmérjem a közforgalmú gyógyszerészek alkalmazását a jelenlegi onkológiai ellátás gyakorlatában. Doktori értekezésem keretében elsőként hasonlítottam össze az irodalmi adatokat a magyar és német közforgalmú gyógyszerészek onkológiai ellátásban betöltött valós szerepével. A két projekt összehasonlításának eredményeként fordított összefüggést találtam a tudományos szakirodalomban elhanyagolt gyógyszerészi szerep és az onkológiai betegek gyógyszerészi gondozásának igénye között³. Doktori értekezésem eredményei további vizsgálatok alapját, valamint a nemzeti egészségügyi rendszerek forrásainak jobb felhasználását eredményezhetik.

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11. Bibliography of own publications

All publications are related to the thesis

1. Thoma J, Hankó B, Zelkó R. (2016) The need for community pharmacists in oncology outpatient care: a systematic review. *Int J Clin Pharm*, 38: 855-862.
2. Thoma J, Zelkó R, Hankó B. (2018) Community pharmacists' use in cancer care of Hungary and Germany – a comprehensive evaluation of a patient intended questionnaire complemented with estimations of professional health experts. *Acta Pol Pharm – Drug Research*, 75: 229-240.
3. Thoma J, Zelkó R, Hankó B. (2019) Comparison of cancer patients' quality of life in Hungary and Germany – a cross national questionnaire analysis. *Acta Pol Pharm – Drug Research*, 76: 159-165.

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13. Appendix

Questionnaire

Dear patient, my name is Johannes Thoma and I am pharmacist. I want to make contribution to enhancement of cross national pharmaceutical support of cancer therapy in Europe. Therefore, the following questionnaire was designed. It would be nice if you could find a few minutes two respond to these questions for enabling better pharmaceutical support during cancer treatment in future.

Study cover: Patient desire for more pharmaceutical support during process of cancer therapy.

Goal: Improvement of cancer treatment especially according to patients' life quality conditions

Inclusion conditions:

- Patients will be asked to answer these questionnaire, if they get any agent mentioned in annexed list
- Pharmacists are not allowed to help patients, if there arise any questions according to answering to these questions

General conditions:

- The questionnaire will be distributed in Germany and Hungary. In each case two hospitals as well as 10 village and 3 town pharmacies will be chosen for distribution.
- Pharmacists have to note down number of tries and success, when asking patients to answer to these questions
- Pharmacists respectively clinical staff should work towards filling out questionnaire in pharmacy respectively hospital in order to raise up quantity of returned questionnaires

Declaration of confidentiality: The questionnaire is anonymous. All received data will not be passed down to third persons.

The questionnaire was designed in cooperation with Semmelweis University Budapest



Please select only one predetermined answer of each question. Otherwise this question is invalid and cannot be evaluated.

1. Which gender do you have?

male:

female:

2. How old are you?

18-30

31-45

46-60

61-75

75+

Where did you receive this questionnaire?

town pharmacy

village pharmacy

hospital centre

3. Which type of cancer do you have?

breast cancer

prostate cancer

lung cancer

stomach cancer

pancreatic cancer

bowel cancer

cerebral cancer

If your type of cancer is not mentioned above, please name

.....

4. How long is the period of time since diagnosis?

1-3 years

4-6 years

7-10 years

more 10 years

5. Which education level do you have?

basic school secondary school grammar school
university degree don't want to answer

6. Do or did you smoke?

Yes No don't want to answer

If yes, how long is the period of time since starting smoking, please name

.....

7. Smoking can be a starting point for falling ill with cancer! Please estimate how much you agree with this statement?

(1 = don't agree, 10 = fully agree)

1-----2-----3-----4-----5-----6-----7-----8-----9-----10

8. If you want to get information about cancer in general, what is your first information point?

family internet general practitioner

neighbourhood pharmacist television

friends oncologist

10. Are you satisfied with your pool of information?

Yes

No

don't know

If not, what would you expect to get the situation improved?

There are a few statements below, please assess, how much you would agree?

(1 = don't agree, 5 = fully agree)

detailed websites for cancer patients 1-----2-----3-----4-----5

better communication within social environment 1-----2-----3-----4-----5

special consultation offers in pharmacies 1-----2-----3-----4-----5

special broadcast program on television 1-----2-----3-----4-----5

consultation during practitioner visitation 1-----2-----3-----4-----5

Have you ever had side effects during cancer treatment?

Yes

No

If yes, before you had side effects, did anyone inform you about typical possible adverse reactions?

Yes

No

11. In which fields of typical adverse drug reactions would you expect to get more information before treatment? (You can make more than one mark)

nausea

mucositis

enteritis

immunodeficiency

anorexia

diarrhoea

any other

12. Did you ever be informed about food supplements for cancer therapy completion especially according to reduce side effects and interdependencies in your drug medication?

Yes

No

If yes, what was your information resource?

pharmacist

magazines

practitioner

internet

social environment

television

13. Are you satisfied with your pool of information?

Yes

No

don't know

If not, what would you expect to get better information?

There are a few statements below, please assess, how much you would agree?

(1 = don't agree, 5 = fully agree)

detailed websites for food supplement information 1-----2-----3-----4-----5

better communication within social environment 1-----2-----3-----4-----5

special consultation offers in pharmacies 1-----2-----3-----4-----5

special broadcast program on television 1-----2-----3-----4-----5

consultation during practitioner visitation 1-----2-----3-----4-----5

14. Do you already use food supplements for therapy completion?

Yes

No

If yes, what kind of supplement(s) do you use? Please name them!

.....

15. Have you ever got any mental support according to handle the psychic situation during cancer treatment?

Yes

No

don't know

16. Would it be helpful to get any mediation for mental support?

Yes

No

don't know

If yes, which kind of support would you prefer?

professional mental support

self help group

any other

17. Have you ever had pain due to your cancer?

Yes

No

If yes, do you think, you can estimate your level of pain?

Yes

No

If, yes, please categorise your pain level on a scale from 1 to 10?

(1 = no pain, 10 = maximum pain)

1-----2-----3-----4-----5-----6-----7-----8-----9-----10

18. Does your drug medication include pain killers?

Yes

No

If yes, please name them!

.....

Do you think you can coordinate current pain level and right dosage of pain killers?

Yes

No

19. Have you ever had any analysis about your quality of life conditions?

Yes

No

20. Do you think you can estimate your current quality of life?

Yes

No

If yes, please estimate your current level of quality of life on a scale from 1% - 100%!
(1 = no life quality, 10= = maximum life quality)

1-----20-----30-----40-----50-----60-----70-----80-----90-----100

What would you expect from pharmacists to raise up your quality of life conditions? Please note your desires!

.....

.....

.....

Thank you very much for taking time to answer these questions!

Yours sincerely,



Johannes Thoma

Questions for oncology physicians and pharmacists

General Information:

This survey is anonymous. There will be no transmission of information to third persons.

1. Gender:
2. Age:
3. Years of practice:
4. Type of exercise

Is there according to our opinion need for pharmacists' intervention in oncology care?

If yes please specify from your position why and please specify the intervention:

If no please specify why not:

Please try to get into patients' mind. Which advantages/ disadvantages of pharmacists' interventions are reasonable?

Do you think pharmacists are ready to do so?

Which main obstacles do you imagine?

How would you climb this cliff? Which solutions are reasonable?

List of agents with an oncology indication in Germany in August 2013

Agent	ATC Code	Agent	ATC Code	Agent	ATC Code
Doxorubicin	L01DB01	Azathioprin	L04AX01	Glatirameracetat	L03AX13
Tacrolimus	L04AD02	BCG - Vaccine	L03AX03	Daunorubicin	L01DB02
Cytarabin	L01BC01	Interferon beta 1b	L03AB08	Triptorelin	L02AE04
Pemetrexed	L01BA04	Bicalutamid	L02BB03	Gemcitabin	L01BC05
Anastrozol	L02BG03	Temozolamid	L01AX03	Methotrexat	L01BA01
Nilutamid	L02BB02	Bleomycin	L01DC01	INF alpha natur	L03AB01
Leflunomid	L04AA13	Carboplatin	L01XA02	Leuprorelin	L02AE02
Exemestan	L02BG06	Docetaxel	L01CD02	Oxaliplatin	L01XA03
Nelarabin	L01BB07	Irinotecan	L01XX19	Etanercept	L04AB01
Bevacizumab	L01XC07	Mycophenol acid	L04AA06	Epirubicin	L01DB03
Interferon beta 1a	L03AB07	Everolimus	L04AA18	Cetixumab	L01XC06
Bortezomib	L01XX32	Certolizumab pegol	L04AB05	Estramustin	L01XX11
Vinblastin	L01CA01	Cisplatin	L01XA01	Etoposid	L01CB01
Vincristin	L01CA02	Verteporfin	L01XD02	Capecitabin	L01BC06
Filgrastim	L03AA02	Aldesleukin	L03AC01	Golimumab	L04AB06
Abatacept	L04AA24	Sirolimus	L04AA10	Basiliximab	L04AC02
Paclitaxel	L01CD01	Infliximab	L04AB02	Goserelin	L02AE03
Peginterferon alpha 2a	L03AB11	Tocilizumab	L04AC07	Ciclosporin	L04AD01
Peginterferon alpha 2b	L03AB10	Interferon alpha 2a	L03AB04	Natalizumab	L04AA23
Panitumumab	L01XC08	Temsirolimus	L01XE09	Idarubicin	L01DB06
Letrozol	L02BG04	Topotecan	L01XX17	Dasatinib	L01XE06
Cefarabin	L01BG06	Interferon alpha 2b	L03AB05	Ustekinumab	L04AC05
Interferon beta 1b	L03AB08	Gefitinib	L01XE02	Buserelin	L02AE01
Toremifen	L02BA02	Carbamid- OH	L01XX05	Sunitinib	L01XE04

Fulvestrant	L02BA03	Mitotan	L01XX23	Lepatinib	L01XE07
Degarelix	L02BX03	Alemtuzumab	L01XC04	Tamoxifen	L02BA01
Fludarabin	L01BB05	Rituximab	L01XZ02	Erlotinib	L01XE03
Fluoruracil	L01BC02	Megestrol	L02AB01	Nilotinib	L01XE08
Flutamid	L02BB01	Plerixafor	L03AX17	Tegafur, combinations	L01BC53
Tegafur	L01BC03	Fotemustin	L01AD05	Anagrelid	L01XX55
Imatinib	L01XE01	Vinorelbin	L01CA04	Ralitrexed	L01BA03
Trastuzumab	L01XC03	Pegfilgrastim	L03AA13	Adalimumab	L04AB04
Sorafenib	L01XE05				