Research protocol
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Early Diagnosis of Abdominal cancer in General Practice

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1. Relevance

Cancer is a leading cause of death. The number of new cases is increasing every year. The reasons for this are complex and in part due to an ageing population, but cancer affects all age groups. The general practitioner (GP) participates actively in the diagnosis of cancer (1;2) and is directly involved in the initial diagnosis of more than 80% of all cancer cases with some variation for different forms of cancer (3). GPs must confront the professional challenge that among many patients with possible cancer symptoms, only a handful actually has cancer. Published studies show that cancer is an area where the GP needs all his or her clinical competence (4;5). Early diagnosis is generally considered decisive for a good prognosis. Research is needed to clarify how the GP can work more efficiently towards early clinical diagnosis of cancer (6).

The relationship between abdominal symptoms and cancer needs to be clarified and will be studied in the present cohort study. Our research takes place in general practice surgeries and is based on real patients, with six months prospective recording of new cases of cancer and data related to these patients. Such research could contribute to improving cancer diagnostic work in general practice (7). Our research for the first time will try to benefit from collaboration in the CA-PRI network (The Cancer and Primary Care Research International Network) (http://www.ca-pri.com/) created in 2008, that aims to promote international research collaboration about cancer in primary care. The project leader is member of the Executive group of CA-PRI and was invited key-note speaker when the network was established.

2. Aspects relating to the research project

The main objectives (also described in the *grant application form)* are:

Primary objective:
To investigate the importance and impact of symptoms, findings, supplementary investigation, co-morbidity and the GP's degree of suspicion of cancer in abdominal cancer diagnosis in primary care.
Secondary objectives are to establish:
-Validity figures (sensitivity, specificity and likelihood ratio) of recorded symptoms and of combined focal and general symptoms in relation to abdominal cancer generally, and in relation to major forms of abdominal cancer, like colorectal cancer and ovarial cancer.
-Predictive value of symptoms in the total patient population and in national patient populations.
-Correlations between symptoms on the one hand and supplementary tests, imaging, referral and follow-up in the GP's own surgery on the other
-Symptom differences between the sexes in forms of cancer affecting both sexes, and between age groups
-Good diagnostic strategies for the GP towards the recognition of different forms of abdominal cancer

2.1. Background and status of knowledge

2.1.1. Clinical studies about cancer are mostly performed in hospitals. Many studies are relevant for general practice, but clinical realities differ between general practice and hospitals, and research based diagnostic strategies also need data from patients consulting in general practice.

Our research project builds on experience from previous studies on early diagnosis of cancer (8;8;8;9) and is part of an ongoing greater "umbrella" project about cancer care in general practice (10;11). In this greater project, data about possible cancer symptoms for all sorts of cancer, collected in general practice, and questionnaire and interview data about how the GP is involved in diagnosis and treatment of cancer, are about to be analysed. One PhD student recently submitted a first article. From the data already collected we have seen that more detailed data are needed about the important group of cancer forms located in the abdomen, and about abdominal symptoms and cancer in general.

Interesting studies about the relationship between symptoms and cancer have been performed in primary care with different methodologic approaches; cohort study (4), qualitative (12) or case control (13) design. Some studies have made systematic reviews of published studies of symptoms like haematuria (14) or of diagnostic delay (15). Reducing unnecessary delay is both of psychological and prognostic importance in many cases (5;16). A strategy like "fast track" referrals for suspected cancer has not yet improved outcomes in the UK (17) but is receiving attention in Denmark (18). "Alarm symptoms" increase the risk of cancer, but the diagnosis is still rare (19).

Among abdominal cancers, colorectal cancer is the most common form, while ovarian cancer has received attention because of its reputation as a "silent killer" (20) . For colorectal cancer, a British study has investigated pathways to the diagnosis (21) and prospective risk after rectal bleeding (22). Most alarm features have poor sensitivity and specificity for colorectal cancer (23), but maximizing sensitivity of tests may improve diagnostic strategies in primary care (24;25). A potential for cutting mortality through improved practice in primary care seems to exist (26). For ovarian cancer, studies with varied methodology (27;27-29) have shown that this cancer may be less "silent" than was previously thought. However, identifying potential patients in primary care remains difficult (30;31) because predictive value of single symptoms will remain low in a large primary care patient population. This is also so for urological cancer becoming manifest through haematuria (32) (14) . Prostate cancer in locally advanced stage have clinical features similar to benign prostate hypertrophy. The clinical challenges of this has been studied by Hamilton et al (33;34), but wise primary care diagnostic strategies are not clear. For other and more rare forms of abdominal cancer data from primary care are scarce, and even studies from hospitals and epidemiological cancer registers will often be based on case-control design of certain but limited value. Studies in primary care require multi-practice collaboration, and symptoms in actual patients will often be the natural starting point rather than the disease.

2.2. Approaches, hypotheses and choice of method
2.2.1. Method and material
We want to do a cohort study including approximately 110-120 000 consecutively consulting patients in general practice. Through international collaboration around 600 GPs will be recruited to register all patients consulting during ten workdays within a period of one month. Earlier studies have shown some symptoms to be valid but unspecific in relation to different forms of cancer.

Our primary care collaborative study is expected to give rather detailed information and expand current knowledge about how GPs can deal with symptoms in consultations with individual patients. Such knowledge is an important prerequisite for GP work toward earlier diagnoses of cancer. For example, while single "alarm" symptoms have been studied to some extent (but hardly enough) in primary care, studies focusing on general symptoms or the combination of symptoms are rare (35) . Also, the focus on symptoms presented is a realistic clinical starting point in general practice and may give information not covered by epidemiological or hospital based research. Our design permits analysis both from starting

point "symptom" and also from starting point "specific cancer disease". We hypothesize that the study can identify combinations of symptoms that have higher predictive value than single symptoms, and that we may find differences between the sexes in symptom presentations of the same kind of cancer.

We choose a patient-near design that is not possible in the many studies based on patient registers. The prospective cohort and patient-near design is rare in clinical studies in primary care. The cohort design combines prospective follow-up with retrospective analysis and is less sensitive to recall bias than the more common case-control studies. For practical procedures, see 3.2.1

2.2.2. Power calculations

Cancer incidence in Norway 2008 was 0,55%, and for abdominal forms of cancer approximately 0,27% (36). Sick persons consult more than the average population, and in our previous study the number of cancers recorded were higher than expected from incidence figures. In this yet unpublished study we found 350 new cases of cancer in 65 000 patients, or 0,54% over the 10 day period, collected by 330 GPs, i.e. slightly more than one cancer case per GP. This corresponds to each GP diagnosing 15-20 cases of cancer every year, considering that some working days are spent outside the surgery in mother and child clinics, old people's homes, etc..The number is higher that the commonly quoted figure of six to ten new cases of cancer yearly in a GP's surgery, and it is possible that we should expect the number of cancer cases in our study to be lower then one case per GP. In Norway, 49.3% or approximately half of cancer cases are abdominal forms of cancer. Colorectal cancers make up 13,0% of all cancers, and ovarial cancers 1,7% (36)

Like Hamilton et al. (37) we base our power calculations on the symptom of abdominal pain. In Norwegian general practice, 1,8% of consulting patients in the year 2000 had an ICPC diagnosis of abdominal pain. The true percentage must be a little higher, because abdominal pain may not have been recorded as the main diagnosis. In a British study (38) , 10% of the adult consulting population had abdominal pain. We choose an expected frequency of abdominal pain to be between these two figures; i.e. 5%, for use in calculations.

In the British study (38) 42,4% of colorectal cancer patients presented abdominal pain. We expect 40% of patients with any kind of abdominal cancer to present abdominal pain before diagnosis. This is compared with 5% of patients without abdominal cancer. We then get two proportions: P1=0,0222 (number of patients with abdominal cancer and abdominal pain divided with the number of all patients with abdominal pain) and P2=0,0018 (number of patients with abdominal cancer and without abdominal pain divided with the number of all patients with abdominal pain). We choose a statistical significance level of 0.05 and power of 0.9. Based on power calculations for compared proportions (two-sided Z test with unpooled variance) we then need to include 10 960 patients to show whether abdominal pain is a valid, discriminating symptom in relation to abdominal cancer.

We also made a calculation based on a scenario with less difference in the frequency of abdominal pain in patients with and without abdominal cancer. The highest incidence of abdominal pain we found registered in consulting patients in general practice was 10% (38). In a case-control study of ovarian cancer abdominal pain occurred in 55% of the patients but in only 18 % of stage I patients, and "pain in side of trunk and flank" occurred in only 19% (39). Using these "worst case scenario" proportions of 10% and 19% (P1=0,0053 and P2=0,0025) we need to include 72 760 patients.

Each GP will record a maximum of 20 patients for 10 days or 200 patients. With international collaboration we this time want to have around 600 GPs record data about their patients, thereby expecting data about approximately 110-120 000 patients. With one new case of abdominal cancer for every second GP this will include data about 300 abdominal

cancer patients and a similar number of patients with other forms of cancer, or perhaps 250 cases of abdominal cancer if we get less than one cancer case per GP. With this size of the cohort, the expected number of patients with and without cancer could be high enough to calculate validity data for some less frequent single symptoms and for combinations of symptoms both for abdominal cancers in general and for some individual cancers located in the abdomen.

2.2.3. Outcome.

Analysis of sensitivity, specificity and likelihood ratio of recorded symptoms and combination of symptoms. It will be interesting to combine focal and general symptoms and see which combinations seem to have greatest importance for a diagnostic strategy. Predictive value of symptoms in the total GP population and in national GP populations can be calculated. The value of a GP hunch for cancer will be suggested, as well as the value of supplementary examinations and referrals. Data will also show which of the listed symptoms are correlated to GPs' ordering of supplementary tests or referrals, or follow-up consultations in the GP's own practice. We want to analyze differences between males and females to look for effects similar to what has been shown for coronary disease (40), that symptoms may differ between the sexes. A similar analysis may compare older and younger patients.

2.2.4. Pilot study

A pilot study has been performed by the principal investigator and should be performed by national coordinators in each country before start. The time zero form is simple to complete. If completed after each patient, it normally takes less than one minute per patient. It is also possible to complete one form at the end of each working day. The form used six months later will be completed by each GP for only one or two patients in most cases and is also relatively short and simple to complete. It is a modified and shortened version of a form used in previous studies of cancer patients in primary care (2)

2.3. The project plan, project management, organisation and cooperation

The project period and project plan encompassing the project's main activities and milestones are provided in the *grant application form.*

2.3.1. Project plan

At time zero

A simple and well-known audit form, developed especially for registrations in general practice, is used (Appendix 1). In this form, anonymous registration of symptoms and other variables in consecutively consulting patients in general practice will be done. For 10 working days within a period of one month each GP should complete one form per day with space for recording a maximum of 20 patients each day. All patients (however max 20) consulting during one of the ten days, with and without abdominal symptoms and regardless of the purpose of their visit, should be recorded, as a minimum with sex and date of birth. For patients presenting abdominal symptoms, additional data should be recorded. This has been tested and will take about one minute per symptomatic patient.

      The variables deal with symptom(s), duration of symptoms, whether the consultation is a first or a subsequent visit to the GP for the presented problem, findings from different organ systems, supplementary blood tests, imaging, referrals, follow-up in general practice,, , the GP's degree of cancer suspicion at the end of the consultation, and prior cancer diagnosis.

After six months
Anonymized data about patients diagnosed with a cancer during the period between the initial registration and six months later will be asked for from each participating GP. These individual patient data are recorded on a 5-page simple questionnaire (Appendix 2). The GP must find this information in electronic patient records from the days of initial recording. Records for all (ideally 20 patients x 10 days = 200) patients must be reviewed regardless of whether they presented symptoms or not. This will take about one hour for each GP. The interval of six months has been chosen because a cancer present during the initial consultation will usually have become manifest and diagnosed six months later. For example, in an interview study with women with ovarian cancer, most women said their symptoms started about five months before their cancer was diagnosed (Mayor 2009 again). The interval is also short enough to increase the probability that a recorded symptom has something to do with the yet undiagnosed cancer. Each GP can be expected to find zero to two cancer patients stemming from the ten-day registration period, and half of these cancers will be abdominal forms of cancer. Completing one cancer patient form will take about fifteen minutes. Patients with non-abdominal cancers will also be recorded.

If a GP has more than 20 consulting patients in the surgery on one day and thus does not register the last consulting patients on that day, then it is not expected that such patients are reported on the six month form, even if cancer has been diagnosed. Such omissions are expected to be rare and haphazard and should not distort analysis. Telephone consultations and mere renewal of prescriptions should not be counted as consultations.

2.3.2. Organisation
The project base with the project leader, project partner, project coordinator, PhD student and project technician will be at the Institute of Community Medicine, University of Tromsø, Norway. The University of Tromsø also provides support through the permanent technical and administrative staff. Our Institute has an active teaching environment and offers PhD teaching courses. A number of PhD students work at the Institute.

The project leader is Professor Dr. Med. Knut Holtedahl whose main research interest is early diagnosis of cancer and who is head of the General Practice section of the Institute of Community Medicine.

Project partner is professor II at the University of Tromsø Anna Luise Kirkengen. She is an experienced researcher with broad theoretical orientation and long clinical practice.

The project group in Tromsø has prepared the protocol and the forms to be sent to the GPs at time zero and after 6 months. International collaboration is established. Informal contacts at the latest CA-PRI meeting in spring 2009 showed considerable interest in recruitment of GPs from other delegates and written expressions of collaboration interest has been collected from five countries (the Belgian/Dutch team is counted as one). Norwegian GPs will be recruited from the project base in Tromsø.

All forms and guidelines will be printed in Norway and distributed from The University of Tromsø to the international collaborators. We plan to furnish pre-packed and pre-addressed envelopes to GPs in the collaborating countries, and pre-addressed return envelopes. When completed, forms will be collected by the international collaborators and then sent to The University of Tromsø where data registration and analysis will be carried out and articles written for international publication.

International collaboration:
Through the international CA-PRI network we have invited selected researchers with experience in cancer research in primary care to be international partners. Researchers from several countries have been invited to be international partners and act as national

coordinators and co-researchers. At present, the following partners have returned signed expressions of interest:

1. Professor Eva Grunfeld, University of Toronto, Canada. Experienced researcher with follow-up of cancer patients in primary care as her main research interest.
2. Professor Jon Emery, University of Western Australia. Chair of the Cancer Australia Primary Care Collaborative Cancer Clinical Trials Group.
3. Professor Frank Buntinx, Leuven University, Belgium, together with Profesor Geert Jan Dinant, Maastricht University, the Netherlands, to form one Belgian-Dutch collaboration group. Prof. Buntinx has a major research interest in early diagnosis of urinary cancer in primary care, and prof. Dinant has broad primary care research interests, among them the question of "gut feeling" in early diagnosis. He already has another research cooperation with the Primary Care unit at the University of Tromsø.
4. Clinical lecturer Elizabeth Delaney, University of Aberdeen, Scotland. Research interests in early diagnosis of cancer, especially skin cancer and ovarian cancer. Professor David Weller, Edinburgh, who is co-founder of the CA-PRI network, has suggested that he will support Dr. Delaney's work with the study in Scotland.
5. Professor Lars Borgström, University of Linköping, Sweden. Head of Department of Family Medicine. Experienced researcher with broad interests within family medicine and health services research.

Their acceptances are enclosed in the grant application form.

In Mai 2010 in Toronto, Canada, there will be a CA-PRI meeting where our project will be presented. During the CA-PRI meeting the project leader and the project coordinator will meet with the international collaborators to discuss the project and get scientific input from the partners and to finalise and agree on the practical planning. The international partners are expected to contribute to the project with their scientific knowledge and experience. This already began when the draft of the project was presented on the 2009 CA-PRI meeting. The international partners will be offered co-authorship according to the Vancouver editorial rules, where it is expected that they also participate with comments and ideas during the writing of articles. After international publication, international partners will be free to analyse and publish separately their national data.

Furthermore they are expected to:
- Help translate the forms, letters and guidelines to the GPs into the language they use in their country, if it is not English or Norwegian.
- Address GP colleagues that could be recruited as collaborators and try to obtain their consent.
- Act as a local coordinator and be prepared to serve as a contact person and answer questions from participating GPs on mail. The project staff in The University of Tromsø will be happy to assist if difficult questions are asked.
-Collect pre-addressed, pre-stamped return envelopes with completed forms from each GP. Once or twice a month the coordinator should forward the envelopes to The University of Tromsø.

Concerning plans for an overseas fellowship, the Danish research centre for cancer diagnosis in primary care is located at the Research Unit for General Practice at Aarhus University, where there is an active research environment and where a number of PhD degrees have been produced in later years.

2.3.3. Data handling
A program for electronic reading of the forms has been made and has been used in a previous study. The completed forms should be returned to the national coordinator in each country in a pre-addressed and pre-stamped envelope, and the forms will be forwarded to the University

of Tromsø for electronic treatment with manual surveillance. Only the individual GP will know the identity of any single patient.

Quantitative data will be recorded and analyzed in SPSS.

2.3.4 Time plan
The project period and progress plan encompassing the project's main activities and milestones are also provided in the *grant application form*.

2010: Discussions and meeting with international collaborators. Protocol completed. Questionnaires finalized and made ready for distribution..
2011: Data collection. Plans for an overseas research stay at the recently established Danish research centre for cancer diagnosis in primary care in Aarhus, Denmark
2012 : Analysis and beginning of article writing. Three clinical epidemiological articles about the relationship between collected variables and cancer are planned.
2013: Presentations at international and national congresses. Article writing continues.
2014: Concluding work.

2.4. Budget
Budget information is included in the *grant application form.*

3. Perspectives and compliance with strategic documents
3.1. Compliance with strategic documents
The project repesents patient-near research, which complies with the goal that the Norwegian Research Council has set for the announced grant. Cancer research in primary care could comply with ideals about better coordination of health services, expressed in the Health Ministry's recent Coordination reform document from 2009. The Research strategy document from the Health Department for 2006-11 defines "Practice-near" research in primary care as very important. The project is also in concordance with a research strategic document from the General Practice Association (within the Norwegian Medical Asociation) from 2005. Finally, the Institute of Community Medicine at the University of Tromsø has got research in general practice as one of its three main research strategic interests.

3.2. Relevance to society
Mortality from cancer has declined in later years. Contributing to further decline is considered one of the main goals of public health in all countries.

3.3. Environmental perspectives
Not relevant in this project

3.4. Ethical aspects
The already completed cancer project with similar design had clearing from the Regional Medical Ethics Committee and permission from the Data Surveillance Authority in Norway. All necessary permissions will be applied for in the present project. The researchers will not know other personal patient data than sex and date of birth, and where the patient's GP works.

3.5. Gender equality and gender perspectives
The recruitment of consecutively consulting patients in general practice will assure participation of both genders in the study. Cancer affects both sexes, and we will look for sex differences in symptomatology , cfr 2.2.3..

4. Communication with users and utilisation of results

4.1 Communication with users

National coordinators will communicate by mail, on telephone and through yearly meetings at the CA-PRI conferences. Each national project coordinator is expected to have close communication with participating GPs and be available on the phone around the time of registrations. Publications and a certificate of participation will be sent to all participating GPs who want this (a question about this has been included in the six months form).

4.2. Dissemination plan

Publication in international medical journals, presentations in international and national conferences.

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