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DIAGNOSIS OF CANCER IN GENERAL PRACTICE

A Study of Delay Problems and Warning Signals of Cancer, with Implications for Public Cancer Information and for Cancer Diagnostic Strategies in General Practice.

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Knut Arne Holtedahl M.D.

To my mother, for her courage
and patience in her fight
against cancer

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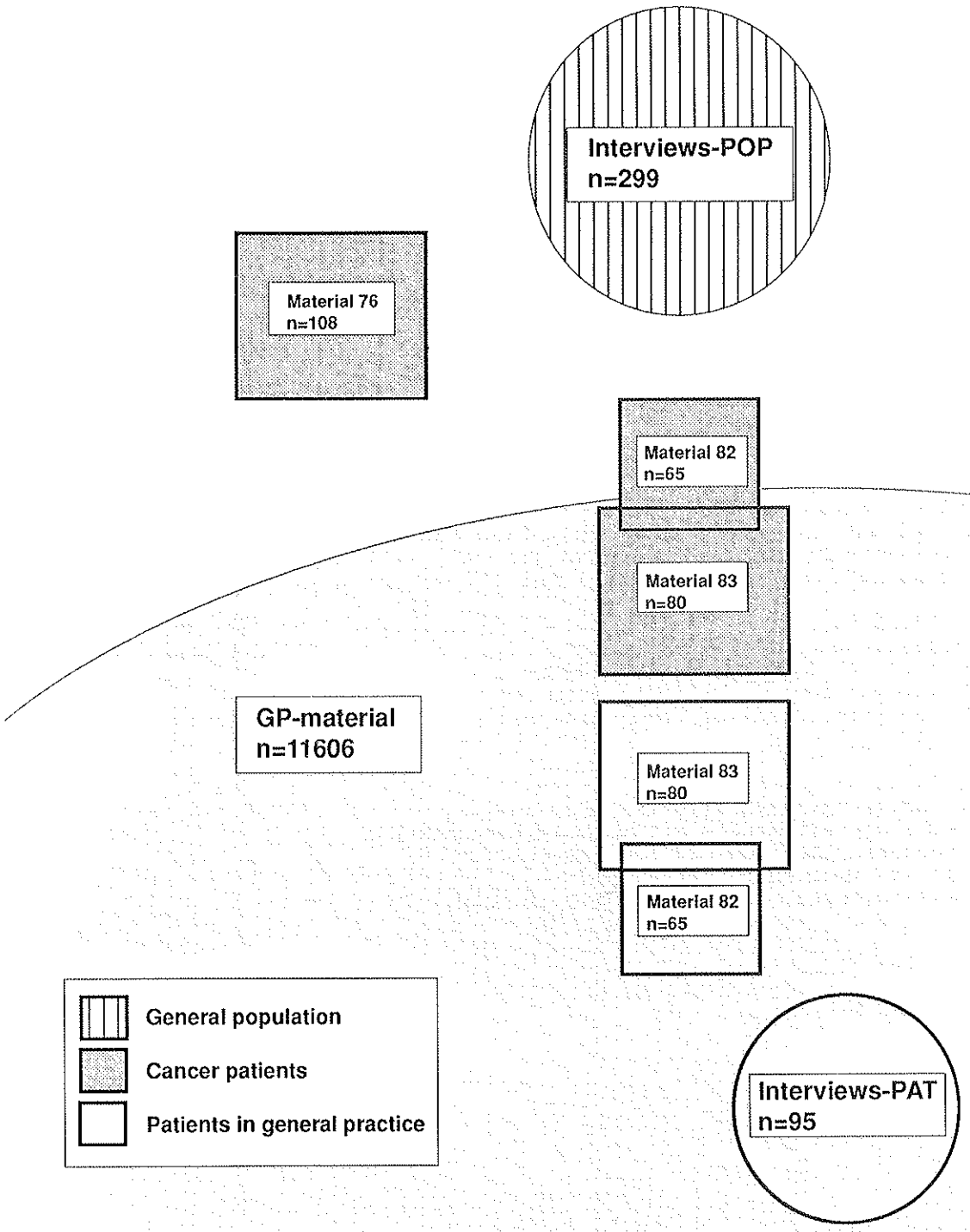
Fig.4

The six different materials:
Material 76, Interviews-POP, GP-material, Interviews-PAT, Material 82, Material 83



SUMMARY

Early diagnosis is beneficial to most cancer patients. The benefit vary, and the demonstration of prognostic improvement is complex. Cancer associations and medical personnel have worked for many years to encourage early consultation in case of possible cancer symptoms. The justification of such a goal is discussed in **chapter 1** on the basis of relevant literature. There seems to be many important reasons to continue this work.

General practitioners have a very important role in the work excluding or leading up to a cancer diagnosis. Many patients are afraid of having cancer. Considering the possibility of cancer in a patient is daily work. The general practitioner's challenge is to create a sound basis for decisions, whether it results in treatment based on a diagnosis, an appointment for further diagnostic follow-up, or referral to specialist services. However, two major problems often make decisions difficult: First, the prevalence of cancer in the general practice population is very low, and second, many of the symptoms of cancer are common symptoms in a variety of diseases and ailments. Many investigations have shown that the diagnosis of cancer is often delayed for a long time after the onset of symptoms.

The aims of the present investigations are presented in **chapter 2**. They were to answer the following questions:

1. What is the quantitative importance of cancer diagnostic delay in the municipality of Tromsø, Norway, and what are the reasons for any such delay?
2. People have been encouraged by cancer associations to consult for symptoms which may be caused by cancer, especially for the "Seven warning signals of cancer". How appropriate and how useful are these warning signals?
3. What are the cancer diagnostic strategies available to general practitioners?

In **chapter 3** the main part of Materials and methods is described. All the investigations were not planned from the start, and the process of thought leading up to the different investigations, is described. Experiences during daily work in general practice initiated this process.

The delay study in **chapter 4** has confirmed findings from other parts of the world, that patient delay as well as doctor's delay in cancer is a considerable problem. Almost half of the patients had delay from the onset of symptoms to the first consultation, and almost half had delay from the first consultation to diagnosis. The overlap was such that 74% of all the cancer patients in Tromsø in 1976 had some kind of diagnostic delay.

In **chapter 5** the frequent occurrence of warning signals has been amply demonstrated in various population groups. Twenty-five percent of a general population sample in Tromsø said they had experienced one or more warning signals during the preceding three months. About half had contacted a doctor for their warning signal. Especially for young people with low cancer incidence it can hardly be justified to encourage consultation in all cases of warning signals. Most people have a broader definition of warning signals than general practitioners. General practitioners recorded warning signals in 5.4% of 11 606 consultations (GP-material). In a sample of general practice patients interviewed immediately after a consultation, 28% said they had presented a warning signal.

Chapter 6 describes the study of warning signals from the medical records of the cancer patients from the delay study (Material 76), and in two other materials (Material 82, Material 83) of cancer patients with their age- and sex-matched control patients without clinical signs of cancer. The group of cancer patients in Material 83 as well as all the control patients in Material 82 and Material 83 had been in the cohort of patients who previously consulted a general practitioner. Each patient then had been classified in one of two groups, with or without warning signal(s).

Combining warning signals and subsequent cancer diagnoses confirm that there is an association between warning signals and cancer. The proportion of patients with warning signals was about five times higher in yet undiagnosed cancer patients than in patients without a cancer diagnosis during the next eighteen months. The calculated likelihood ratio of 4.8 is based on an estimated number of patients in the cohorts and is probably a little too low because of bias. Likelihood ratio calculated for

the age- and sex-matched patients only, was 1.5. This is because the rate of warning signals increases with age in ordinary patients, but not in cancer patients. It is the patient's age rather than the warning signal which makes cancer a realistic possibility. The positive predictive value of a warning signal was 3.7% in all the patients from general practice, but 8.3% in patients 60 years of age or more.

Odds ratio as an estimate of relative risk for cancer based on analysis of matched pairs was 1.9 (0.8-5.1) for a warning signal recorded at a single consultation less than eighteen months before diagnosis, and 7.8 (3.3-22.4) for a warning signal recorded from the medical records.

Altogether, the warning signals do not discriminate well between cancer and non-cancer. An additional problem is that some warning signals are less important in younger age groups. Also, one or two of every five cancer patients do not experience any warning signal before diagnosis and must find their way to a doctor through other symptoms or signs of bodily dysfunction, or in some cases through check-ups or screening. These patients are a heterogeneous group although some forms of cancer more often than other forms present without warning signals. No single symptom other than the warning signals seems important; the only possible candidate might be "Pain which does not move or disappear", but this was found to be even less specific for cancer than any "official" warning signal.

The reliability of warning signal recording from medical records has been tested in an inter-observer study. The validity of warning signal recording from medical records has been discussed extensively, especially the problems attached to variation in what different doctors write in their patients' records. It has been concluded that the findings concerning cancer-related warning signals in this study have high reliability and validity.

The diagnostic role of a low haemoglobin concentration or a high erythrocyte sedimentation rate has been examined. Again the diagnostic value is reduced by low specificity for cancer, but the general practitioner should always try to explain abnormal values.

In **chapter 7** the findings are discussed in relation to public cancer education. Publishing warning signals may have served a purpose at a time when it was unusual to contact a doctor for anything but very serious disease. Today it is hardly necessary to encourage higher consultation rates for these symptoms. People already consult readily for them, and most important, there is evidence from the present and from other studies that people with cancer are the people which are most difficult to convince that they should consult when they experience a warning signal. Fear and lack of knowledge about body function and cancer seem to combine to produce such an effect.

Cancer information should try to avoid a public image of advice from up above, defined by experts to be "good for you". Rather, the information should meet demands based on people's own experience. A person who sees cancer in a family member asks questions about cancer. A young person with a rising interest for the balance in nature may accept to see cancer in the light of a pollution problem. It is suggested that public information about cancer should be put in a modern context; ecology, anti-pollution, care for old people, democratic sharing of knowledge and social rights combined with individual resposibility. Messages should be adapted to the media and to the people who receive the message. There should be appropriate emphasis on prevention. The general practitioner's role in cancer information is important and has been discussed.

Reducing delay caused by general practitioners will reduce an important part of present-day delay between a cancer patient's first consultation and diagnosis. General practitioners, although very aware of their importance in this diagnostic work, today hardly follow any systematic cancer diagnostic strategy. **Chapter 8** introduces the concepts of "data clues", based on various personal characteristics and on previous, chronic or present illness, "symptom clues" partially inspired by the seven warning signals, and "traps" more or less specific to cancer diagnostics. Such notions should be part of conscious probability thinking, evaluating the risk of cancer in individual patients. Single symptoms like the warning signals almost never have high predictive value in general practice for important disease like cancer.

Single symptoms are a good starting point, but need to be combined with other evidence before decisions about diagnosis, treatment, referral to specialist, or follow-up in general practice can be taken.

A two-step strategy is outlined. Step one puts the patient into relevant risk groups and thereby reduces the number of false positives, or the number of patients suspected of having cancer who do not have such disease. Step two considers improvement of each general practitioner's cancer diagnostic routines and reasoning. Good organ based knowledge is advocated. Such knowledge has been published in a separate manual "Early Diagnosis of Cancer in General Practice" not included in the present presentation.

Chapter 9 sums up and concludes concerning the three major topics treated:

1. Cancer diagnostic delay
2. The importance of the Seven warning signals of cancer
3. Cancer diagnostic strategies in general practice

INTRODUCTION

Cancer is a group of diseases where the control of cell division and tissue growth is progressively disturbed over time (1). Untreated cancer usually invades adjacent and more distant tissue and becomes lethal. With modern treatment it was estimated in 1983 that 45% of all persons with serious cancers in the United States survive five years after start of treatment, compared to persons of the same age, sex, race, and time period from the general population (2). For patients who survive five years, the chances of surviving 20 years are 85% (2).

Treatment requires diagnosis. Diagnosis requires that the patient consults a doctor and that the doctor carries out a relevant diagnostic procedure. In most cases the first doctor consulted is a general practitioner. Behind my investigations is the idea or hypothesis that most patients with cancer will benefit therapeutically from having their cancer detected as early as possible. My studies try to explore how practical early diagnosis is, especially how public health education and general practitioners can contribute.

Before the aims of my investigations are specified any further I shall briefly consider the importance of ageing and environmental carcinogens for cancer incidence, and I shall look at some of the literature which has discussed whether early diagnosis of cancer is useful. Professional and lay attitudes to this question will also be considered briefly. The attitude of a physician has implications for diagnostic action (3) as well as for the attitude he[1] more or less consciously transmits to his patients.

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[1] The usual dilemma: physicians (and patients) are of course **he or she**

1. THE FOUNDATIONS OF CANCER DIAGNOSTIC WORK

1-1. Incidence, age and environmental carcinogens.

In countries where the average age of living exceeds seventy years, about one quarter of the population will be affected by cancer ([4]). With improving living conditions in other countries it is probable that more people will survive other diseases and thereby be more susceptible to cancer. AIDS-associated cancer may become important in younger persons ([5]).

Cancer incidence increases with age in industrialized countries, and this may be partly due to the ageing process itself ([6]). In human somatic cells the ageing process is correlated with genomic plasticity. Chromosomal alteration is related to malignancy. After somatic growth ceases in younger years, mitotic activity varies in different tissues. Frequent cell turnover implicates chromosomal activity. In most cells with continuous mitotic activity cancer is the predominant age-related disease. In Norway in 1986 68% of cancer in males and 60% of cancer in females were found among people aged 65 years or more ([7]).

With increasing age the time of exposure to life-style and other environmental carcinogens also increases ([8],[9]). Fibroblasts in vitro have been shown to have a critical limit of total cell divisions (6). Replicating cells in vivo are thought to have such an intrinsic limit and finally become senescent. Acceleration of cell turnover for any reason will hasten the advent of age-related diseases. Gastrointestinal and epidermal cells combine surface defense and continuous mitotic activity, making such cells vulnerable to the combined action of carcinogens and the ageing process. Such cells are the origin of some of the most common forms of cancer, with a marked rise in incidence with advancing age. Eighty to ninety per cent of cancers are carcinomas, most of them growing from cells in contact with the outside world: skin, stomach, colon, lung, cervix.

At present the most important carcinogens are associated with personal habits (8): Tobacco is by far the single most important factor contributing to cancer deaths. The role of diet may be important, but the findings in different studies are inconsistent

([10]). Alcohol consumption increases the incidence of some forms of cancer and particularly seems to increase the carcinogenic effects of tobacco ([11]). Geophysical factors cause a great proportion of skin cancers. Reproductive factors are important for cancer of the breast and genital organs ([12]). Occupational factors contributing to cancer are important, but far less so than tobacco (8,9). The rapidly increasing number and complexity of industrial chemicals might be expected to increase cancer incidence, but no such trend has yet been registered. Nuclear plant accidents with liberation of radioactive pollutants may contribute to local increases in cancer incidence in the future

1-2. Is early detection useful?

The definition of "early detection" is not clear. The term has been used in different ways by different authors and for different forms of cancer. Detection of apparently localized forms of cancer will usually be considered as early detection. Prognostic considerations as well as staging and grading criteria for individual neoplasms are often taken into account. In asymptomatic people "early detection" may refer to detection by a special examination or test earlier than the cancer would have been discovered without such tests, i.e. before the patient would have sought care spontaneously for signs and symptoms ([13]). This definition does not refer to the stage of the tumour ([14]). A short time period from the first symptom until treatment is started will usually be a criterion of early detection felt to be very important by a patient or a general practitioner, at least as long as there is no obvious distant spread of the tumour. What is considered a short time period may vary for different forms of cancer. Three weeks may seem to be much in breast cancer, three months would perhaps be considered acceptable by most doctors in the case of an epipharyngeal cancer. The prognostic implications may vary for individual tumours.

In discussions about usefulness prognostic considerations are necessary. Early detection should reduce the need for painful and mutilating treatment and it should contribute to less suffering and infirmity in survivors. But first of all it should save

lives. Whether this is the case is assessed in randomized controlled trials and in survival analyses.

a. Randomized controlled trials

Randomized controlled trials with mortality as an endpoint (RCTM) are most convincing (14,15). Periodic mammographic screening of asymptomatic women has been shown to reduce mortality from breast cancer, although recent results from the Malmö study (16) are less clear than the results from the American HIP study (17) and the Swedish two county trial (18). The Council on Scientific Affairs of the American Medical Association estimates that the epidemiological evidence for the effectiveness of mammography in women aged 50 years and older is strong, and that evidence for effectiveness of mammographic screening in women 40-49 years is growing (19). In Norway introduction of systematic mammography screening for women 40-74 years of age has been proposed (20), but a consensus conference in 1989 temporarily turned down the proposal. The efficacy of the method was not thought to outweigh inconveniences, especially the necessary follow-up of positive findings in women who did not have breast cancer (21).

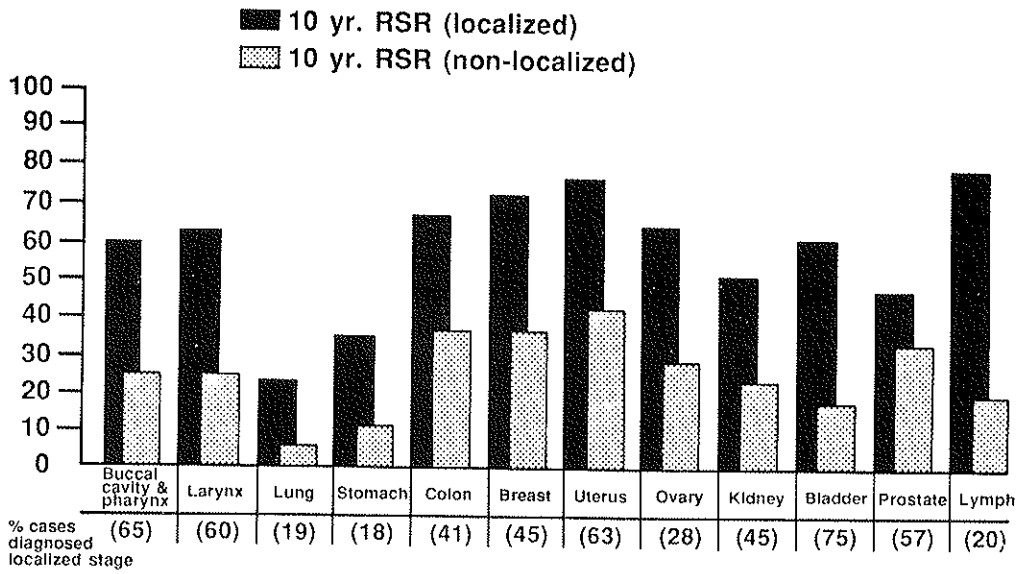
Lowered mortality has also been shown for colorectal cancer in a multiphasic health checkup study based on 20 cases of cancer in the study group and 25 cases in the control group (22)

b. Survival

Randomized controlled trials take much time and resources and usually require inclusion of many patients. For most types of cancer less persuasive evidence must do. Length of survival is the second best criterion of a good prognosis (14).

Miller (23) in 1976 compared ten-year survival rates for localized and non-localized disease. Except for cancer of the lung and stomach he found that ten-year relative survival rate was approximately 50% or more for the localized stage of each cancer considered. He thought that there was a useful form of early detection or prevention in twelve forms of cancer which together represented 80% of all cancers and 70% of all cancer mortality (fig 1). Miller (23) omitted from his list cancers of the oesophagus, pancreas, biliary tract, and also leukaemia. For these

Fig. 1. Comparison of long-term survival rates in patients with localized and non-localized cancer. From Miller (23).



diseases he did not think that a benefit of early diagnosis could be established.

In the United States in the 1930s, less than one of every five cancer patients was still alive five years after start of treatment. In the 1950s, this figure was one of every four, and in the 1970s one of every three cancer patients survived five years (4,24). It was noted in the introduction that relative survival rate (RSR), which is observed survival rate divided by expected survival rate (25) is approaching 50%. In Norway 1968-75 5-year relative survival rate varied from 2% for patients with pancreatic cancer to almost 100% for patients with cancer of the lip (25). More than half of the female patients and about one third of the male patients had a 5-year RSR of more than 50%. The differences were mainly due to a high 5-year RSR for cancer of the breast and cervix, and a low 5-year RSR for lung cancer, four times more frequent in males than in females at that time. The increase in 5-year RSR over time has been shown for several forms of cancer in Norway from 1953-1957 to 1972-1975 (25).

Even after distant spread rapid establishment of a diagnosis may be important: For lung and bone metastases from differentiated thyroid carcinoma survival has been shown to depend on how extensive the metastases were at the time of discovery (26).

c. Stage improvement

Stage at the time of diagnosis is important except for a few forms of cancer. For cancer of the pancreas and oesophagus prognosis is poor even with localized disease. For cancer of the thyroid and testis prognosis is generally good. Five-year RSR is high and regional metastases give only slightly lower rates than localized disease. In the case of cancer of the testis modern therapy has caused a spectacular improvement in prognosis. Cure has become the goal and may be expected for 90-95% of the patients with localized testicular disease. Still, stage is important since cure is expected for only about half of the patients with advanced disease (27). The TNM system (28), which is the most commonly used staging system for many forms of cancer, was introduced partly because of its prognostic value.

A change in stage toward relatively more cancers discovered in a localized stage may suggest improved prognosis. Such a stage improvement has been shown for several forms of cancer. Some time after the initiation of a screening program it is common to demonstrate such an effect. Cancer of the cervix has till now not been subject to centrally organized screening based on population registries in Norway, although such screening has been recommended based on experience from other countries (29). But for middle aged women unsystematic cytological test activity has been quite high for many years (30). Most of the tests have been performed by general practitioners. From the 1960s there has been a steady increase in incidence with an improvement in stage distribution, followed by a fall in incidence for middle aged women in the 1980s. During the whole period there was a steady increase in 5-year RSR for cervical cancer (31). For breast cancer incidence has increased and stage distribution has improved. Stage-specific survival did not improve much from 1955 to 1980 despite a better survival for localized (stage I) breast cancer than for more advanced breast cancer. Lund (31) interprets this as probable

improvement in early detection, based on public health education including the teaching of breast self-examination (BSE) and improved diagnostic work by physicians. Based on the experience with cancer of the cervix Lund thinks that a lowered mortality for breast cancer may be expected in the near future.

Stage improvement has also been shown for colorectal cancer after screening for occult blood in stool (32), while there are more contradictory results for BSE and breast cancer (33). In Queensland in Australia, where the incidence of melanoma is very high, advanced stages of melanoma are less frequent than in studies from other countries. This has been attributed to a sustained programme of public and professional education about skin cancer (34). For clinical Stage I melanoma it has been shown that prognosis is related to the depth of penetration of the primary lesion into the dermis (35,36).

d. Bias in the interpretation of cancer registrations

The problem with survival figures and demonstration of stage improvement is the possibility of bias, i.e. a systematic departure of results from the correct value as a consequence of errors in design or investigational technique (37). Improved prognosis is at best only part of what we are measuring. Tumours discovered early in their natural course leave more life-time to their hosts than the same kind of tumours discovered at a later stage. Lead-time bias is then possible: a longer life is not necessarily improved survival because of early treatment. Another bias is due to the variation in growth rate of the tumour. Slow-growing tumours are detectable longer than fast-growing tumours. That means that tumours detected in early symptomatic stages of the disease or at screening generally are slower-growing and have a better prognosis than tumours which are faster-growing and more aggressive. Such length-time bias will add to the longer survival rates of patients with localized tumours (38).

Trasti & Hoel (39) in Norway have argued that intensified diagnostic effort and a more available and modern health service system detect many more slow-growing cases of cancer than before, and that this is the main reason for apparent improvement of prognosis in all stages. Langmark & Magnus (40) answered that

analysis of combined incidence rates and case fatality rates for several forms of cancer show real prognostic improvement. Incidence rate is the number of new cases of cancer in the population at risk over a period of time, usually per 100 000 persons per year. Case fatality rate is the number of deaths from cancer in per cent of the number of clinical cases ([41]). Mortality rate is the product of incidence rate and case fatality rate (40). Increased incidence apparently has many other causes in addition to an improved diagnostic service. Adjusted for the increasing population of old people there is in almost all white populations with available data a real increase in the incidence of malignant melanoma believed to be caused by increased exposure to the sun ([42]). There is a consistent increase in colorectal cancer in most of the Western world, probably due to dietary factors (11). For both these diseases a reduced case fatality rate has been shown from the period 1960-69 to the period 1970-79 in Norway, and this is much more important for prognostic considerations than an increased mortality rate resulting from increased incidence (40). A reduced case fatality rate also has been shown for stomach cancer, where the incidence in western countries is steadily decreasing, presumably because of dietary factors (11) which affect incidence much more than any improved detection. The mortality rate for stomach cancer is decreasing sharply, but again it is the more moderate decrease in case fatality rate which is the best indicator of improved prognosis. There is a slight increase in mortality rate over time for all forms of cancer, but the increase is less than what might be expected from the increase in incidence. Langmark & Magnus think this is due to a combination of earlier diagnosis and better treatment (40).

Feinstein & al ([43]) say that patients with the same anatomic stage of a cancer may have markedly different prognoses, and that omission of analysis of the preceding clinical manifestations is responsible for many problems in statistics. For lung cancer and rectal cancer a staging system considering both clinical and anatomical groups has been shown to predict prognosis better than a staging system based on anatomical groups alone ([44]). Prediction of 5-year survival for Hodgkin's disease through classification of symptoms has been shown to be as efficient as prediction based on anatomic staging ([45]).

Even in randomized trials with large groups of patients and international cooperation there are difficulties such as inter-observer variation among pathologists ([46]), grading difficulties based on varying cell patterns within one tumour ([47]), and inconsistent relationship between morphologic pattern and biologic behaviour. For prostate cancer nuclear DNA has been shown to correlate better than morphologic grading to prognosis ([48]). Progress in these fields is quite recent for many forms of cancer.

Cancer registries try to reduce bias by taking into account staging and histologic grading criteria of individual tumours, Analysis of birth cohorts may control confounding factors; i.e factors which distort the outcome because they vary in frequency in the groups which are compared ([49],37). In cancer such factors may change incidence and mortality of cancer although they have nothing to do with improved prognosis through early detection and improved treatment. Examples of such confounding factors are different living conditions and different parity for different generations. Sex and age of the patient evidently is very important. Cancer registries usually publish age-specific incidence rates for each sex. In addition incidence rates usually are age-adjusted in relation to a defined standard population like that of the whole world ([50]).

e. Other considerations

Iatrogenic complications are possible during investigations or treatment. Early diagnosis then indirectly may shorten the life-span or reduce the quality of life for some patients. On the other hand it is quite evident that treatment for localized disease in many cases must be milder and give less side effects and complications than treatment of advanced cases. Early treatment also may be cheaper, but the complex questions of cost-benefit will not be discussed here.

1-3. Early detection through screening

Eddy (14) discusses the use of diagnostic tests for cancer in asymptomatic persons. He thinks the evidence provided by observing a shift in the stages of cancers detected by special tests lies somewhere between that provided by flipping a coin and that

provided by a single randomized controlled trial: it is highly suggestive of reduced mortality, but not definitive. Recommendations about the use of any such test should ideally be based on not only one but several randomized controlled trials for each form of cancer. The problem is that there are very few such studies, and that for most cancers the frequencies are so low that randomized controlled trials would require tens or even hundreds of thousands of people. Eddy says that there are no absolute criteria for determining the effect of early detection on cancer mortality. Evidence from many sources must be examined. Figures 2 and 3 sum up Eddy's personal estimates of regular detection procedures' chance of reducing mortality through early detection, and the expected reduction in mortality (14).

The probable usefulness of early diagnosis through various forms of screening has been weighed against the disadvantages (32,38), especially the problem of false positive results: a positive result of the screening test in a person without cancer. The number of people requiring follow-up because of a positive test is always considerable when there is a low prevalence of the disease in the population being screened. This is true even if the screening test has a high specificity, i.e. a high proportion of negative tests among the persons without the target disease. Follow-up is necessary and may exclude disease before treatment in most cases, but many people will be scared and invasive procedures are often necessary. Some of the women operated because of a positive mammogram do not have breast cancer, and the number of cervical conisations per year in Sweden is about ten times the incidence of cancer of the cervix (32). In Norway Hoff (32) in 1987 concluded that no form of screening for cancer has proved its value within preventive medicine if it is not combined with research purposes. Hoff calls for a better definition of high- and low-risk groups, for a better definition of "premalignant" lesions and investigation of further possibilities for primary prevention. Siem ([51]) comments that structured, computer-based screening programs should replace "wild" screening and may be the clue to reaching populations at risk.

Fig. 2. Probability that early detection in asymptomatic people reduces mortality. From Eddy (14).

All testing assumed to be annual except BSE (monthly), sigmoidoscopy (every three years), Pap test (every three years).

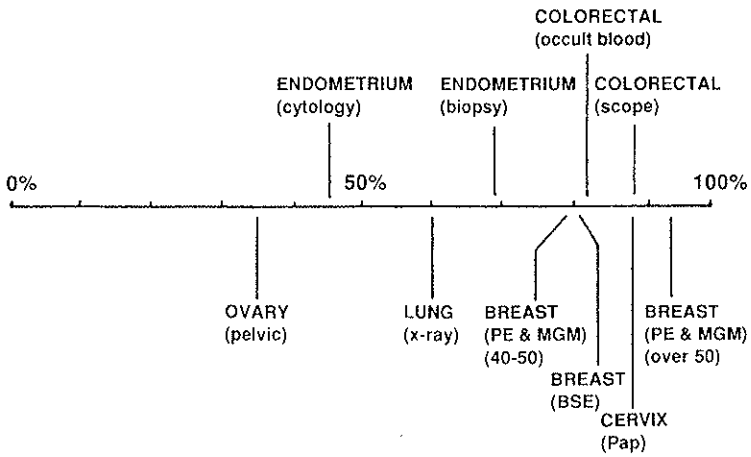
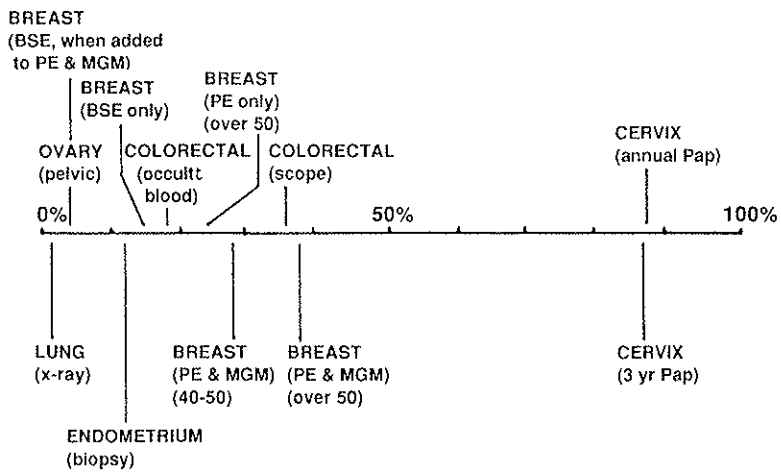


Fig 3. Expected reduction in mortality by early detection in asymptomatic people. From Eddy (14).

All testing assumed to be annual except BSE (monthly), sigmoidoscopy (every three years), and Pap test (as indicated).



In symptomatic and even in asymptomatic persons consulting a general practitioner the prevalence of the target disease may still be low, but necessary follow-up of persons with a positive test concerns fewer persons and often is more limited because the doctor can use previous knowledge about the patient. The contact with the physician is initiated by the patient. All of this contributes to making the problem of false positive tests easier to deal with in general practice than in separate screening programs, and early diagnosis is still possible in many cases. Some of the people who would be non-attenders in a systematic screening program do consult their general practitioner. Health checkups ([52,53]) or more or less systematic case-finding for certain categories of patients ([54]) is possible in addition to ordinary diagnostic work in patients with symptoms. Diagnostic possibilities are not limited to the most common forms of cancer. Whether or not systematic screening programs are initiated in the general population, much attention should be given to the possibility of diagnosing cancer through ordinary consultations.

1-4. Attitudes in general practice

Ideally, the general practitioner has a unique opportunity to detect cancers **early:** Most often he is the first doctor a cancer patient would consult. Very often the general practitioner has a general knowledge about the patient, his family and his social environment which may be helpful in making a diagnosis.

Available diagnostic methods will be used less if physicians are unaware of their potential benefit for the patient ([55]). Therefore doctors' attitudes about the usefulness of early detection are important.

In an English survey medical students, nurses and general practitioners were asked to estimate five-year survival rates for several forms of early cancer. The answers indicated a degree of pessimism unsupported by survival data ([56]).

American studies have shown that physician scepticism about the efficacy of early diagnosis and the value of aggressive treatment increased from the 1960s to around 1980 ([57]). On the other hand, in an American study resident and faculty physicians in a Depart-

ment of Family Medicine and Practice had a significantly higher belief in the benefits of risk management, early detection and screening, and treatment, than their specialty peers in internal medicine and oncology (58). An American study from 1982 suggested that most family physicians believed that early cancer detection can favourably influence patient prognosis (55).

A report from Australian discussion groups focused on doctors' involvement in public education about cancer (59). There was a broad consensus among participating general practitioners on how difficult it is to communicate health information to patients, and how difficult it is to make people follow physicians' advice. Smoking habits were mentioned as one example. A minority of the physicians expressed profound doubt about the value of early diagnosis, most often based on personal experience of individual cancer cases rather than on good statistics. Reliable facts were solicited by all the doctors participating.

A survey among French general practitioners (60) showed limited oncologic knowledge and a high degree of therapeutic pessimism. Several doctors in the survey wanted more information concerning the diagnosis of cancer.

1-5. Attitudes in the general population

To a layman, cancer is most often the name of a dangerous, even deadly disease, and so it raises unpleasant emotions. It is probable that many people's knowledge about cancer is limited to this conception of a frightening, almost unmentionable disease.

There is little information available concerning the knowledge about cancer in the general public. The American Cancer Society has sponsored two interview-based inquiries concerning such public knowledge (61,62). A summary of the findings has been presented in a separate article (4). Generally women knew more than men, and people with higher education knew more than those with less schooling. Younger people knew more than older people. Organ locations most frequently associated with cancer were breast and lungs, while the incidence-increasing cancers of colon and rectum were less well-known. Like general practitioners, people made prognostic estimates which were more pessimistic than reality: On

the average, people thought that only one of five cancer patients survives more than five years (4). An exception to this was smokers' unduly optimistic wiew of their possibility to be cured of lung cancer if it was detected early: seven of ten believed that there is a good chance of being cured (4).

2. AIMS OF THE PRESENT INVESTIGATIONS

There is good evidence that relatively more cancers are discovered in early stages now than a few decades ago (chapter 1). Whether the prognosis has improved is more open to discussion because of the difficulties in eliminating bias and controlling confounding by statistical analysis. However, most investigations point in the same direction and suggest that prognosis has improved, and that early diagnosis has contributed to this and is potentially useful for many cancer patients. Public and professional attitudes seem to be more pessimistic than necessary, and this may be an obstacle to early detection. The following considerations and questions directed my investigations:

1. Diagnostic delay is an important problem in cancer ([63]). My professional experience agreed with the literature. What is the quantitative importance of such delay in my municipality, and what are the reasons for delay?

2. Some of the diagnostic delay has been attributed to patients waiting for a long time before they consult a doctor with important symptoms of cancer. Cancer associations in many countries for many years have been encouraging the public to consult rapidly for certain symptoms, from the 1960s known as the "Seven warning signals of cancer". How appropriate and how useful are these signals?

3. General practitioners are the doctors most often consulted by yet undiagnosed cancer patients. What are the cancer diagnostic tools and strategies available to general practitioners? Can their present strategies be improved?

3. MATERIALS AND METHODS

The present investigations were conducted between 1978 and 1985. The questions I wanted to answer were the same from the beginning, but all the investigations were not planned at once. As the first projects were analysed I found that further investigations were needed to complete the answers and test the methods. The sequence of thinking and investigations is described below. The investigations are numbered and are summarized in table 1 and in figure 4.

For a general practitioner the study of cancer patient careers in general practice and after referral was the most obvious way of elucidating the delay problem:

1. MATERIAL 76: Medical records of all 108 patients from the municipality of Tromsø registered by the Norwegian Cancer Registry in 1976 were examined to estimate the importance of diagnostic delay and of the seven warning signals of cancer. All available records from general practice and hospitals were examined. All recorded symptoms considered relevant for the cancer diagnosed later on were recorded with no retrospective time limit.
Tromsø is a mixed urban/rural town in Northern Norway and had approximately 45 000 inhabitants in 1976.

One retrospective study like this could not answer how cancer patients differ from other patients with similar symptoms. It became apparent that to evaluate the importance of a cancer-related warning signal it was necessary to know more about those who presented warning signals without having cancer. And who experienced warning signals without consulting any doctor? Furthermore, do laymen and doctors agree on what a warning signal is? These questions led to the planning of a study recording warning signals in general practice patients regardless of their diagnoses (GP-MATERIAL). This study was supplemented towards the end of the registration period with interviews of people in the general population (INTERVIEWS-POP) and of patients in general practice (INTERVIEWS-PAT):

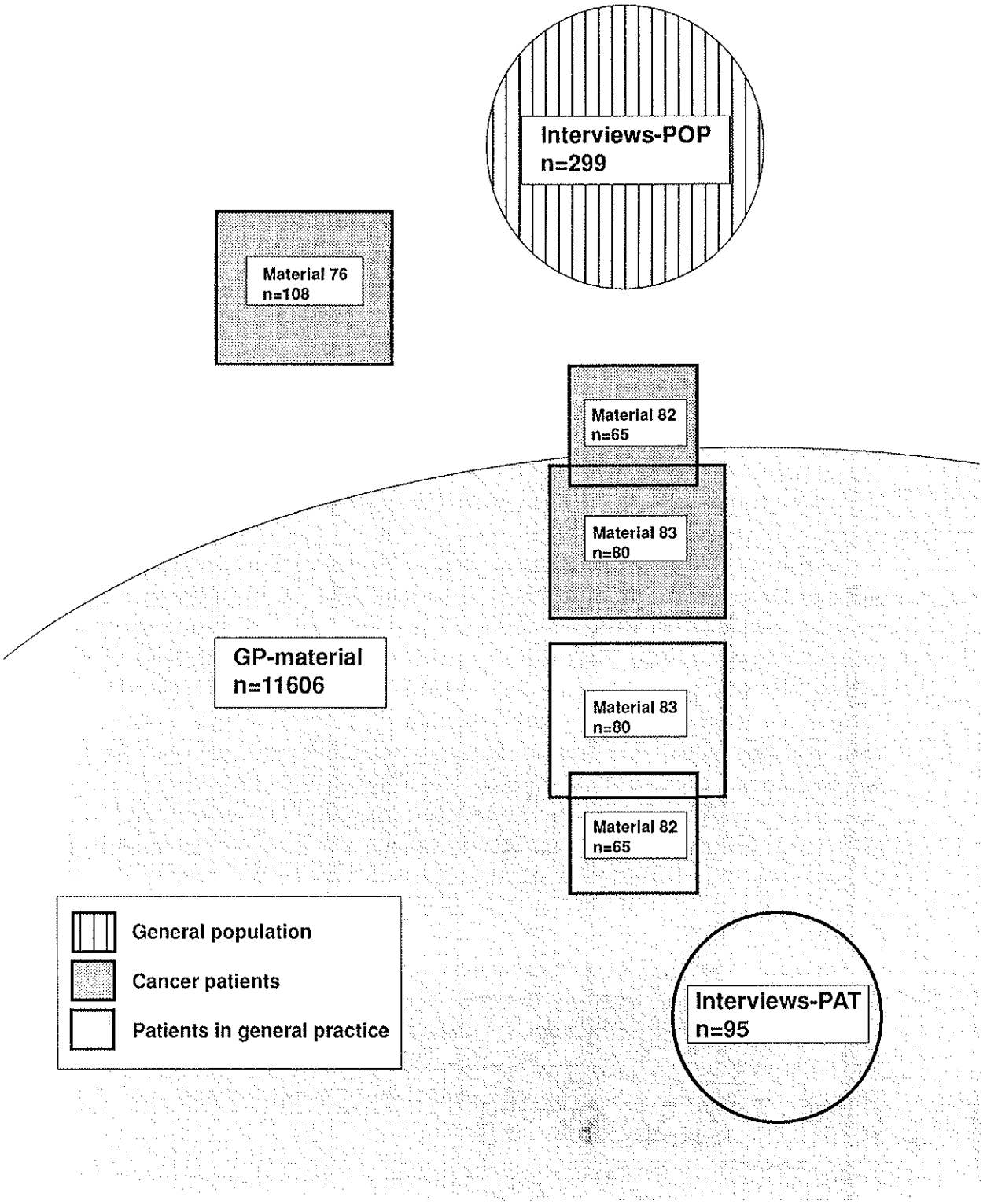
Table 1. Investigations, Tromsø, Norway 1978-1985

	Corresponding tables
MATERIAL 76 108 cancer patients registered in 1976. Study of diagnostic delay and of the Seven warning signals of cancer	2-8, 10, 19-24, 29
GP-MATERIAL 11 606 consultations in general practice, October 1st 1981 -March 31st 1982. General practitioners' recordings of warning signals after consultation	13-15, 24
INTERVIEWS-POP 229 persons, door-to-door interview about warning signals experienced last three months, March 1982	11-12, 24
INTERVIEWS-PAT 91 patients in general practice, interview about warning signals presented during preceding consultation, March 1982	16-18
MATERIAL 82 65 cancer patients registered October 1st 1981-March 31st 1982, 65 matched control patients from the GP-material. Study of warning signals.	10, 20, 22, 25-27, 29
MATERIAL 83 80 cancer patients from the GP-material, diagnosed 1-18 months after their consultation in general practice, 80 matched control patients from the GP material. Inter-observer study of warning signals.	10, 20, 22, 25-26, 28-42

Material 76 analysed 1978
GP-material, Interviews, Material 82 analysed 1982
Material 83 analysed 1985

Fig.4

The six different materials:
Material 76, Interviews-POP, GP-material, Interviews-PAT, Material 82, Material 83



2. GP-MATERIAL: Fourteen general practitioners in Tromsø recorded the presence or absence of warning signals after the end of each consultation during a six month period starting October 1st 1981). An eighth symptom "pain which does not move or disappear" was recorded along with the seven warning signals in this and later investigations to estimate its possible relevance as an additional warning signal.

3. INTERVIEWS-POP: Towards the end of the six month period, in March 1982, a door-to-door survey in the urban part of Tromsø examined the frequency of symptoms corresponding to the warning signals during the preceding three month period.

4. INTERVIEWS-PAT: In March 1982 interviews with some of the patients in general practice were carried out immediately after their consultation with a general practitioner. The patients were asked if they had presented symptoms corresponding to the warning signals during the consultation. Their answers were compared with the recordings made by the general practitioners.

The recording of warning signals in consecutive patients consulting in general practice gave a possibility of finding a control material of patients matched for age and sex with cancer patients from Tromsø, registered by the Norwegian Cancer Registry during the six month period when warning signals were recorded. Comparison with such a control material - a case-control study with matched pairs - seemed to harbour more information than mere comparison with the total pool of consultations registered. Moreover, comparison between the 1976 (Material 76) and a new 1981-1982 (Material 82) material of cancer patients would permit comparisons which might reveal inconsistencies in the registrations:

5. MATERIAL 82: During the six month period from October 1st 1981 to March 31st 1982, 65 persons from Tromsø had been registered by the Cancer Registry of Norway by mid-1982. Sixty-five control patients matched for sex and age and without cancer were found among the patients in the GP-material. The closest in age was

chosen. Medical records served to register the presence of symptoms corresponding to one or more warning signals in cancer patients before diagnosis, and in the control patients. Warning signals considered cancer-related were classified as having occurred early or late in the course of disease. This was decided according to the following definition of "early symptom": "a symptom arising early enough in the course of the disease that a cure or a relatively long remission period is still possible. The symptom must be supposed to be due to the primary tumour or to a metastasis which may well be solitary". - All symptoms which did not fit within this definition were considered as late symptoms.

Information in the medical records as far back as six months before the start of the registration period was considered. Less recent information seemed unnecessary because delay was not studied. The time period studied for each patient then varied from six to twelve months according to when their diagnoses had been made. For each control patient the period studied in the records corresponded to that of the matching cancer patient, including the month of the cancer patient's anatomo-pathological or other best possible diagnosis.

Matching was chosen to improve study efficiency in terms of the amount of information per patient studied ([64]), because close scrutiny of each medical record was necessary. At the same time confounding by age and sex could be controlled. Of the matched control patients 51 were born the same month as the cancer patient. The other cancer patients had controls less than three months younger or older, except for the oldest patient who had as control a patient 16 months older.

It seemed reasonable to think that a high proportion of patients registered with cancer during the weeks and months immediately following October 1st 1981 would be among the consulting patients included in the GP-material. The GP-material could be considered as a cohort where each member was classified either with or without a recording of warning signals. This furnished an opportunity for a combined retrospective and prospective study of whether patients with new cases of cancer had presented any warning signal when consulting a general practitioner a few weeks

or months earlier. The usefulness of any such warning signal could be considered more in detail when more was known about the diagnosis and the outcome for individual patients:

6. MATERIAL 83: During the eighteen month period from October 1st 1981 to March 31st 1983, 331 cancer patients from Tromsø were registered by the Cancer Registry of Norway. Comparison with date of birth and initials in the GP-material showed that eighty-two of the cancer patients were registered in the GP-material. Two patients were excluded because their medical records had been lost. Sixteen of the remaining 80 patients already were included in Material 82. Matched control patients for each of the 80 cancer patients were found in the GP-material. Matching was done as in Material 82.

Medical records served to analyse the presence of symptoms corresponding to one or more warning signals in cancer patients before diagnosis, and in the matched control patients. The time period studied was like in Material 82, except that the maximum was twenty-four instead of twelve months. In Material 76 and Material 82 warning signals in cancer patients had been registered only if they were thought to be related to the cancer diagnosed later on. In Material 83 warning signals thought to be unrelated to cancer were registered as well, to give a more relevant comparison with warning signals in the control group.

Warning signals thought to be cancer-related were classified as early or late, like in Material 82.

The medical records in Material 83 were analysed independently by two other general practitioners in addition to myself. This inter-observer approach was chosen to test the reliability of warning signal registrations from medical records. From other branches of medicine it is well known that inter-observer agreement may vary in different kinds of diagnostic and evaluation-type settings. Observed agreement always includes some agreement occurring by chance. The calculated kappa coefficient ([65,66]) measures agreement beyond chance. This method has been used to compare observations in pathology (46), endoscopy ([67]), neurology ([68]), as well as many other kinds of observations including the

quantification of pyuria ([69]), the general condition of hospital patients ([70]) and the medical benefit from hospital stay ([71]).

The observers[2], one female and two male, worked at three different group practices in Tromsø. The author had 12 years of experience as a general practitioner, the colleagues three to five years. They were selected by the author not at random, but because he knew them as dedicated and conscientious practitioners who would carry out the task as accurately as possible.

For the 16 patients included both in Material 82 and Material 83 and their matched controls an intra-observer comparison was possible, because these two materials were collected two and a half years apart.

The warning signal recordings previously given to some of these patients by their general practitioner were not known to the observers. I had seen the consultation recordings during previous analysis, but I neither could nor tried to remember consultation recordings pertaining to individual patients while studying the records of Material 83.

When all three observers had finished the study of records, I went back to the consultation recordings. For patients with a cancer-related warning signal recorded at consultation I made a separate estimation of how useful these warning signals had become or might have become for these patients, given that no error delayed diagnosis after the first consultation. The warning signal or warning signals were related to the diagnosis. Potential usefulness was classified on a three step ordinal scale: "useful", "somewhat useful" and "not useful, or palliation of short duration".

In Material 83 low values of the haemoglobin concentration (Hb) and high values of the erythrocyte sedimentation rate (ESR) also were recorded by the author. All patients with a haemoglobin concentration below 110 g/l (females) and 130 g/l (males), and all patients with a sedimentation rate above or equal to 20 mm/h, were registered when the measurements were made before diagnosis,

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[2] Observer 1 = Knut Arne Holtedahl
Observer 2 = Leif Bjarte Rolfsjord
Observer 3 = Terese Fors

and within the time period where the seven warning signals were recorded.

Source and treatment of data

The Norwegian Cancer Registry furnished data about cancer patients from Tromsø. Permission to study medical records was obtained from the keepers of each of the 25 different patient files of general practitioners or hospitals in Tromsø. Each file was searched for medical records concerning all patients in the different studies.

Patient initials, date of birth and other relevant information were punched by two medical secretaries on a microcomputer. The study has been approved by the Norwegian Data Inspectorate.

Reliability and validity

Reliability refers to precision, or reproducibility, of the findings ([72,73]). Valid results should be accurate, i.e. without systematic error, or bias ([72,74]). The main concern in validity discussions is whether our measurements really measure what we want to measure. A distinction is made between internal validity, which refers to validity for the actual subjects in the study, and external validity which is validity for people outside the study population ([75]). Internal validity is a prerequisite for external validity.

The first discussions about reliability and validity in medicine focused on the ability of a laboratory test to reveal disease. Today several authors have agreed that any kind of clinical information can and frequently should be understood and analysed in terms of reliability and validity ([76,77]). A symptom elicited from the medical history, a clinical finding based on the physical examination of the patient or the result of any supplementary tests may be subject to such considerations. This is important in general medicine because the medical history often is the most important diagnostic element with the physical examination a good number two ([78]). Laboratory tests more rarely contribute deci-

sively to diagnosis in general practice . This is true for cancer diagnostics as for the diagnosis of other diseases [79].

Traditional ways of estimating reproducibility include repeated history taking or testing to see whether the same results are obtained, comparison of observations made independently by more than one person, or consideration of internal consistency, i.e. whether different paths lead to the same information (72).

Common ways to approach the validity problem include qualitative consensus between experts or a quantitative comparison with a criterion or gold standard (72). Such a criterion must in turn be both reliable and valid. If accurate assessment is not possible, the criterion is not good enough to represent a standard for other ways of measuring the same phenomenon (72).

Acceptable reliability contributes to good validity (72). Validation should consider how results may change through possible bias or confounding. Vain efforts of falsifying results may strengthen conclusions. Consistent results through different methods or in different studies may increase validity [80].

Statistics

Chi-Square for comparison of percentages in independent populations [81].

Median, range and Mann-Whitney U test for comparison of interval data which do not come from a normal distribution (81).

Cochran-Mantel-Haenszel statistics for population samples stratified by sex and age intervals [82]. Linear trend is tested with Mantel-Haenszel Chi-Square (82)

McNemar test for matched pairs (81). Calculation of odds ratio [83] with a 95% confidence interval [84].

Kappa based on observer pairs (65). Standard error according to Fleiss (66).

Differences are considered statistically significant when there is less than 5% probability of obtaining the result if a null hypothesis is true.

Further details

Details of materials and methods are added in chapters 4 and 5.

4. DIAGNOSTIC DELAY — A REALITY FOR MANY CANCER PATIENTS?

Introduction

I started up in general practice in 1973. During the first couple of years I saw a few cancer patients who made me reflect upon my own practice. Looking back I thought that I should have arrived at the diagnosis in less time, and that my inadequate action delayed appropriate treatment. I also saw patients with cancer symptoms which must have bothered them for weeks before they came. Apparently, delayed detection of cancer was an important problem in my own practice.

Delayed detection of cancer may be attributed to the patient, to the general practitioner, or to waiting list or other administrative problems. Of course, specialist practitioners and hospital doctors may delay diagnosis as well. Gray (85) gave several examples of different kinds of delay. The problem was discussed as early as 1912 by Wainwright (86). Apart from casuistic descriptions there are few investigations from general practice, but several hospital studies throw light on the delay problem. Definitions of delay vary in different studies. Usually the definition chosen does not vary from one type of cancer to another. Pack and Gallo (87) in 1938 initiated the modern approach to the problem. They defined patient delay as failure to seek medical advice within three months of onset of symptoms, a definition which has been used by a number of other authors as well (63). Physician delay was defined as failure either to reach a diagnosis or to make a proper referral within one month of the first visit. In random samples of 1000 cancer patients from all social classes from two American cancer clinics over a ten to fifteen year period, patient delay but no physician delay was found for 44,3%. Among patients who promptly sought medical advice there was 17% physician delay. Delay of both kinds was found for 18%, which added up to a total delay of almost 80% (87).

Robinson & al (88) defined delay as an interval of more than six weeks between the first appearance of symptoms and the diagnosis. No delay was noted for 35% of the patients in 1974 and for 58% in 1980. Patient delay was unchanged in this period while

there was less delay due to physicians and administrative procedures. This study also investigated the relationship between delay in diagnosis, stage of disease, and survival. The survival rate was higher in patients in whom the disease was diagnosed earlier. It was also higher in clinical stages I (localized disease) and II (locally advanced disease) in patients who had no delay compared with patients with delay in diagnosis.

In a study of patient delay from 1970 ([89]) one third of the patients consulted a doctor within one month. Cobb et al. ([90]) compared fifty cancer patients who delayed more than three months after cancer was suspected with 50 patients who presented themselves promptly. Through repeated interviews and psychological tests, education about cancer was found to be an important motivational agent toward action. The delay patients were older, with a lower class way of life as estimated from an index of value orientation. Psychologically the delay patients had greater difficulties in utilizing fear as an organizing agent toward rational help-seeking (90). They more often had tragic or unpleasant experiences from cancer treatment of close family members. For general symptoms not particularly related to cancer it is known that highly educated people try to cope with their symptoms without seeing a doctor at least as long as people with less education ([91]). For cancer symptoms this is different; educated people hesitate less before they consult (90).

Seven British general practitioners ([92]) made estimates of system delay, patient delay and "retrospective delay". Retrospective delay was defined as the least possible or "ideal" delay had ideal conditions prevailed. System delay was defined as the difference between "actual" and "ideal" delay. Patient delay was defined as the interval between the onset of symptoms and the first consultation, but the author comments that in most cases it would be unreasonable to expect any diagnosis as soon as the symptoms started. Fifteen of 36 cancer patients consulted their doctor more than one week after the onset of symptoms; only a few came immediately. System delay was found for ten of the 36 patients. The author thinks that possibilities of improvement exist, but are limited by the pressures of clinical practice. The study demonstrates the problem of making an appropriate definition

of delay, and the difficulties attached to defining a date of diagnosis. Diagnosis may be based on clinical judgement, radiological or biochemical confirmation, or histological proof.

Starey (93) found that 51% of his general practice patients waited more than four weeks before consulting him, and that the diagnosis was made more than four weeks after the first consultation for 29% of his patients.

In a more recent study from an Australian general practice (94) the intervals are called Symptom interval (Si=the time in weeks the patient had symptoms before he consulted the doctor) and Diagnosis interval (Di=the time in weeks that elapsed after the patient first mentioned the symptoms until the time of diagnosis). The sum of Si and Di is called the Clinical interval (Ci). In this study the overall mean symptom interval was 17 weeks and the mean diagnosis interval five weeks. Thirteen of 73 cancer patients had a diagnosis interval greater than four weeks. The process of denial contributed to delayed presentation in several patients.

4-1 **2-1.** The delay study. Material 76

Material and method, details

The Cancer Registry of Norway provided a list of all patients from Tromsø with new cases of cancer registered in 1976, a total of 108 (Material 76). The sex and age distribution is shown in table 2.

Table 2. Age and sex distribution of 108 cancer patients. Material 76

Age	Females	Males	Both sexes
1-19	1	1	2
20-29	1	-	1
30-39	2	3	5
40-49	3	3	6
50-59	12	8	20
60-69	13	14	27
70-89	23	24	47
Total	55	53	108

The medical records (Appendix 1) were examined in 1978. From the records were noted the number of weeks from the onset of symptoms to the first consultation, and from the first consultation to cytological or histological diagnosis. The number of consultations in general practice the last year before diagnosis, the number of practices visited and the number of general practitioners seen were noted. The municipal emergency ward was counted as a general practice.

No standard definitions exist for different types of delay. The intervals noted above have been used to define delay in many studies, but make no distinction between the various forms of cancer and do not consider the great variation in symptoms for individual patients. In the present study it was decided to make a subjective assessment of whether or not delay had occurred based on individual characteristics of each neoplasm and of each patient. In this estimate were included the nature, localization, stage and cytological or histological characteristics of each neoplasm as well as the kind, duration and intensity of the symptom experienced by the patient, such as it could be interpreted from the records. The actions of each patient and each physician were also considered. The importance attributed to each factor was individualized. Such a subjective estimate of delay was made in addition to and independent of the time between the first symptom and diagnosis. Patient delay was noted when records indicated symptoms which seemed to have bothered the patient for an unreasonably long period before consultation took place. Delay between the first consultation and diagnosis was noted when the records suggested insufficient or inadequate diagnostic activity by the general practitioner, the hospital specialist or intern, or when administrative routines in primary care or in the hospital seemed to have caused delay.

Such an approach to delay in terms of what might be reasonable and practical is in accordance with Makover's recommendations ([95]), and supported by Antonovsky & Hartman (63). To some extent this approach also may avoid delay-labels for slow-growing, non-aggressive tumours where a long period from the first symptom to diagnosis may appear reasonable and probably have no negative

effect on prognosis. This would be in accordance with Feinstein's recommendation that the clinical as well as the anatomical stage should be considered (43).

The delay criteria followed may be summed up like this:

Delay from the first symptom to the first consultation (patient delay):
With one exception delay was noted only if there was at least two weeks and usually more than four weeks between the first symptom which in retrospect was judged to be cancer-related, and the first consultation. The more intense and the more uncommon the symptom, the shorter the period accepted for classification in the "No delay" group, and vice versa. The patient who was exceptionally classified with delay despite only a one week interval did not turn up to a control appointment two days after the first consultation.

Delay from the first consultation to diagnosis (doctor's delay and/or administrative delay):
Delay was noted only if there was at least two weeks and usually more than four weeks between the first consultation and diagnosis. Usually at least one delaying event (inadequate action by the physician, or hospital waiting list) which prolonged the time to diagnosis with at least one week was required but not in itself sufficient for a delay classification. A palpable lump in the breast was considered as a special symptom deserving rapid action both by the patient, the general practitioner and the hospital. In these cases and some other cases with particularly alarming symptoms the two-week intervals were applied.

Waiting list time after referral was assessed according to what seemed to be a reasonable priority-giving on the basis of the written referral from the general practitioner. A lapse of more than four weeks before the patient was seen in the hospital outpatient clinic was usually classified as delay.

Five case histories, not among the most easily classifiable, illustrate the classification criteria:

Male, 85 years old. For three weeks diarrhea and meteoristic symptoms before first consultation. Physical examination was initially negative, but was repeated one week later. The patient was then hospitalized because of jaundice and a palpable liver. Discharged with a diagnosis of pancreatitis after two weeks in the hospital. Biligraphy had shown a stenosis in the distal part of the biliary tract. It was decided not to pursue investigations but repeat the biligraphy in three months. Shortly before the end of this interval the patient was readmitted with epistaxis, jaundice and anaemia. Operation showed pancreatic cancer.
Classification:
No delay first symptom - first consultation
No delay first consultation - diagnosis

Male, 71 years old. In four weeks he developed generalized oedema and pallor. Hospitalized immediately when his wife returned home after one month's absence. Died after three weeks in the hospital with clinical diagnosis cor pulmonale, transitory atrial fibrillation and emphysema of lungs. On autopsy discovered stomach cancer and a carcinoid lung tumour.
Classification:
Delay first symptom - first consultation
No delay first consultation - diagnosis

Female, 55 years old. Painful defecation starting four weeks before the first consultation. Proctoscopy showed haemorrhoids. Another three consultations in the following five months, the patient complained about constipation. At the last of these consultations the general practitioner found an abdominal tumour and noted a weight loss of 11 kilograms. The patient was operated for a metastasizing sigmoid cancer one month later.
Classification:
No delay first symptom - first consultation
Delay first consultation - diagnosis

Male, 51 years old. Dyspepsia for several years. Insidious change of character, more constant pain after meals instead of relief from eating. Consulted when this had lasted about four months. The general practitioner found a palpaple hepatic margin of uncertain significance, requested X-rays of thorax and stomach which were negative when performed two months later. After this a consultation with a negative test for occult blood in stool. Same subjective complaints. Six months after the first consultation the patient was referred to a gastroenterologist, who found a large stomach cancer.
Classification:
No delay first symptom - first consultation
Delay first consultation - diagnosis

Female, 49 years old. Consulted two weeks after having felt a lump in the breast, confirmed by the general practitioner. Biopsy two weeks later.

Classification:
Delay first symptom - first consultation
Delay first consultation - diagnosis

Independent of delay evaluations the thoroughness of the medical history and of the clinical examination made by the general practitioner were evaluated and classified. Definitions were made for "rather brief", "adequate" or "detailed" history, and for "inadequate", "adequate local/regional" or "complete" clinical examination. Furthermore, it was estimated which elements of the consultation contributed positively to the diagnosis: medical history, clinical examination, laboratory tests, X-rays. A delaying event or "mistake" was noted when the description of the investigations and the clinical course suggested that the physician had made specific omissions or inappropriate diagnostic actions prolonging the time before diagnosis.

Some subjective judgment also was necessary in deciding which symptoms were related to the cancer and which were not. Symptoms in cancer patients may be due to cancer or to other diseases or ailments. If there was considerable doubt about the origin of a symptom it was not accepted as cancer-related.

It was noted whether the patient lived alone, in a family household or in an old people's home. Urban or rural residence was noted as well.

All recordings were made on a special form (Appendix 2).

Results

1. Delay from the onset of symptoms to the first consultation

Patient delay as it had been defined in relation to the nature, duration and intensity of symptoms was found for 48 patients (44% of the 108 patients in the material). No patient delay was noted in 55 patients (51%) (table 3). In five patients no such estimate was possible.

Table 4 shows the number of weeks from the onset of symptoms to the first consultation for the various diagnostic groups. Classification is according to the Norwegian Cancer Registry. Such information was found for 98 patients. Thirty-three patients

Table 3. Cancer patients distributed according to delay from the first symptom to the first consultation (patient delay) in three different age groups

Age	Patient delay	No patient delay	Insufficient information	Total
-39	-	7	1	8
40-59	13	12	1	26
60-	35	36	3	74
Total	48	55	5	108

Table 4. Cancer patients distributed according to the number of weeks from the onset of symptoms to the first consultation in the various diagnostic groups

Information available for 98 of 108 patients

Number of weeks Diagnostic group	0-1	2-4	5-12	13-52	53-	Total
Buccal cavity, pharynx	-	1	0	3	2	6
Digestive organs	6	9	7	10	-	32
Respiratory system	1	4	2	2	1	10
Breast and genital organs	6	7	8	2	1	24
Urinary organs	1	-	1	-	-	2
Other and unspecified sites	3	3	3	6	5	20
Lymphatic and hemopoietic tissue	2	1	-	1	-	4
Total	19	25	21	24	9	98

(31%) consulted more than twelve weeks after the onset of symptoms, which was Pack & Gallo's limit for patient delay. Forty-four patients (41%) saw a doctor within four weeks, 65 patients (60%) consulted within 12 weeks.

Intervals in relation to delay classification were:
Delay: Males: Range 10-400 weeks, median 25 weeks. Females: Range 1-150 weeks, median 13,5 weeks. The difference in intervals within the delay group between males and females is statistically significant ($0.05<p<0.01$ with two-tailed Mann-Whitney U test). This difference is due to the strict criteria for lump in the breast in cases of breast cancer.
No delay: Males: Range 0-30 weeks, median 4 weeks. Females: Range 0-50 weeks, median 3 weeks. The difference between males and females is not significant.

Patient delay was estimated to have occurred in almost all patients (97%) who waited more than 12 weeks before consulting, but only in 27% who consulted within 12 weeks.

For ten patients there was insufficient information about intervals in weeks, but in some of them a delay estimate could still be made. An example is the case of a patient with prostatic cancer which had been symptomatic for an uncertain but considerable number of weeks. The ten patients had cancers of the breast, stomach, prostate, skin (three patients), thyroid (two patients), and two had abdominal cancers of unknown origin. The five patients where no delay estimate was possible were the three skin cancer patients, one old woman with a thyroid cancer discovered at autopsy and another old woman who died at home with an abdominal tumour.

Cancer in the breast and genital organs made women see a doctor rather quickly. Lesions of the lip usually were present for months before a biopsy showed cancer. For other forms of cancer the interval between first symptom and first consultation was variable. Eight of the 108 patients had basal cell carcinomas. These appeared as skin lesions not less than half a year before the first consultation. Excision and diagnosis then were either rapid within four weeks, or several months passed until the diagnosis was made. No recurrences were noted in the records about two years after diagnosis for the eight cases.

Males had no more or less patient delay than females.

The patients were divided in three age groups (table 3). Seven of the eight patients less than forty years of age had no patient delay. For the eighth patient information was insufficient. Above 40 years 48 patients had delay and 48 no delay, and patients more than 60 years of age did not differ significantly from patients younger than 60 years of age.

The 22 patients living alone did not have any more patient delay than people living with a family, and there was no difference in delay between people living in urban or rural areas.

All four patients with lip cancer had patient delay, otherwise no diagnostic group had more or less patient delay than the others.

Six patients had had cancer two to 39 years previous to the new case of cancer diagnosed in 1976. For one of these patients information about consultations was lacking. Among the other five, four had patient delay.

In the year before diagnosis the average number of consultations for all reasons was 3.2 for both males and females. Range for males was 0-9, median three consultations. Range for females was 0-15, median two consultations. Twenty-four of the patients made five or more consultations in general practice. Twenty-seven patients saw more than two different doctors, and 37 patients visited more than one practice. Females had less patient delay if they had made more than five consultations ($p=0.03$ with Yates correction) or had visited more than one practice ($p=0.03$ with Yates correction). For males there was no such association.

2. Delay from the first consultation to diagnosis

Delay after the first consultation was found for 52 patients (48% of all the 108 cancer patients). Doctor's delay was responsible in most cases. No delay after the first consultation was noted in 53 patients (49%) (table 5). For three patients information was insufficient.

Table 6 shows the time from the first consultation to diagnosis for 103 patients. In 60 patients (56%) the diagnosis was established more than four weeks after the first consultations, which approaches Pack & Gallo's definition of delay after consultation.

Table 5. Cancer patients distributed according to delay from the first consultation to diagnosis in three different age groups

Age	Delay	No delay	Insufficient information	Total
-39	4	4	-	8
40-59	14	11	1	26
60-	34	38	2	74
Total	52	53	3	108

Table 6. Cancer patients distributed according to the number of weeks from the first consultation to diagnosis in the various diagnostic groups

Information available for 103 of 108 patients

Number of weeks Diagnostic group	0-1	2-4	5-12	13-52	53-	Total
Buccal cavity, pharynx	2	-	2	1	1	6
Digestive organs	8	5	8	11	1	33
Respiratory system	-	2	4	4	-	10
Breast and genital organs	6	8	5	4	3	26
Urinary organs	1	-	-	1	-	2
Other and unspecified sites	5	6	4	4	3	22
Lymphatic and hemopoietic tissue	-	-	1	2	1	4
Total	22	21	24	27	9	103

Within 12 weeks from the first consultation the diagnosis had been established for 67 (62%) patients. For nine patients it took more than half a year.

Intervals in relation to delay classification were:
Delay: Males: Range 4-100 weeks, median 22.5 weeks. Females: Range: 2-100 weeks, median 12.5 weeks.
No delay: Males: Range 0-90 weeks, median 2.5 weeks. Females: Range 0-300 weeks, median 1 week.

The differences between males and females are not statistically significant.

When diagnosis was made within 12 weeks 30% of the patients had delay. Among the patients diagnosed more than 12 weeks after the first consultation 89% had delay.

For five patients no interval registration was possible. All five were among the ten patients with insufficient information before consultation: the two patients with thyroid cancer, one diagnosed at autopsy, the other discovered incidentally during hospital referral for another reason, the two old women who died at home with abdominal tumours, and one of the skin cancer patients with a spinocellular cancer removed at the otorhinolaryngological outpatient ward, where no referral letter could be found. For the last three patients no subjective delay estimate could be made, either.

There was no significant delay difference between males and females.

None of the three age groups differed significantly from the others.

Eight of the eleven persons with breast cancer had delay from the first consultation to diagnosis, including all six women with breast cancer in the age group 40-59 years and the only old man with cancer of the breast. Of the breast cancer patients four had general practitioner's delay alone or in combination with specialist or administrative delay. Four had isolated hospital administrative delay and two more had such delay in addition to delay caused by the general practitioner and/or administrative delay in the primary health care. One had isolated specialist delay. Apart from the breast cancer patients no diagnostic group had more or less delay after the first consultation than the others.

Three of the five patients with previous cancer and sufficient information about consultation had delay from the first consultation to diagnosis. Considering patient delay as well, all five patients with previous cancer had delay either before or after the first consultation, and two of them had both kinds of delay.

Patients who made more than five consultations in general practice in the year before diagnosis had not significantly more or less delay from the first consultation to diagnosis than patients who made less than five consultations. Visiting more than one practice was not associated with such delay, either.

General practitioners made mistakes in 43 patients (40%) and thereby contributed to doctor's delay in 38 patients (table 7). Hospital specialists/interns made mistakes in 19 patients (18%), most of them after referral, and for 16 of these patients they contributed to doctor's delay. Administrative mistakes were of the same magnitude, most of them due to hospital outpatient waiting lists. Similar problems in the primary health care may have been underestimated because information about how long time passed between the appointment reservation and the consultation was rarely found in the medical records.

Table 7. Delay from the first consultation to cancer diagnosis: Number and source of mistake in the various diagnostic groups.

n = Number of patients
GP = General practitioner
SPEC = Hospital specialist or intern
ADM-P = Primary health care administration
ADM-H = Hospital unit administration

	Number of mistakes										
	Delay					No delay					
		Mistake caused by:					Mistake caused by:				
Diagnostic group	(n)	GP	SPEC	ADM-P	ADM-H	(n)	GP	SPEC	ADM-P	ADM-H	Total
Buccal cavity, pharynx	(3)	1	2	-	1	(3)	-	-	-	-	4
Digestive organs	(16)	14	4	2	3	(18)	2	-	-	-	25
Respiratory system	(8)	7	4	-	1	(2)	-	-	-	-	12
Breast and genital organs	(15)	10	4	1	8	(11)	-	1	-	1	25
Urinary organs	(1)	-	-	-	1	(1)	-	-	-	-	1
Other and unspecified sites	(6)	4	1	-	1	(17)	3	2	-	-	11
Lymphatic and hemopoietic tissue	(3)	2	1	-	1	(1)	-	-	-	-	4
Total	(52)	38	16	3	16	(53)	5	3	-	1	82

A total of 80 patients (74%) had patient delay, doctor's delay or administrative delay, or combinations of these.

Information about the various elements of consultation in general practice was found for 102 patients. The medical history was important for diagnosis of 47 of these patients and contributed somewhat less for 34 others. Six of seven "detailed", 32 of 52 "adequate" and nine of 43 "rather brief" medical histories were important.

The clinical examination was important for diagnosis for 41 and contributed somewhat less for 35 other of the 102 patients. Eight of nine "complete", 24 of 51 "adequate local/regional" and nine of 42 "inadequate" examinations were important.

Laboratory tests were performed in general practice for 73 patients. They contributed to diagnosis in 22 patients. In five cases the doctor was misled by low erythrocyte sedimentation rates or negative examinations of occult blood in stool in cases of gastrointestinal cancer. Sedimentation rates higher than 20 millimeters per hour were not further investigated in several cases.

Table 8 is based on the recorded mistakes and lists suggested actions which might have reduced doctor's delay for individual patients. For some patients several kinds of improvement in the work of the general practitioner seemed possible (table 8).

Table 8. Possible improvement in the diagnostic handling of 43 cancer patients which might have reduced or eliminated doctor's delay

	Number of possible improvements
Control appointment	15
More complete medical history	20
Better clinical examination	24
Better choice of laboratory tests	13
Better choice of X-ray examinations	6
Better choice of referral	13
Total	91

1 improvement suggested in	18 patients
2 improvements suggested in	11 patients
3 improvements suggested in	7 patients
4 improvements suggested in	5 patients
5 improvements suggested in	2 patients
Total	43 patients

Discussion

There are many methodological pitfalls in this study, and conclusions should be drawn with care. An important problem is the uncertainty concerning the completeness of the notes in the medical records. This will be discussed more thoroughly in chapter 6.

Reliability

Intervals in weeks for most patients could be double checked by comparing medical records from one or more general practice with medical records from one or more hospital department. Different records for one patient did not always agree, but consultation dates were unequivocal and often settled uncertainty from notes based on second-hand information. Generally, there was not much doubt about the three crucial dates: onset of symptoms, date of first consultation, and date of anatomo-pathological diagnosis. Only the two women who died with abdominal tumours and had no autopsy had no histological or cytological diagnosis. In case of doubt intervals in weeks were usually not noted. In one patient with both lung cancer and heart disease an interval was noted despite some difficulty in deciding which symptoms were attributable to which disease. A recent Norwegian study concerning otorhinolaryngological cancer patients noted similar intervals from hospital records and did not comment on any difficulty in recording such data ([96]).

The subjective part of the estimates reduce the reproducibility of the figures for delay and for the classification of the various diagnostic procedures. However, subjective estimates have proved reliable and practical in other studies. In a Dutch study ([97]) three observers examined the same four to ten written lung cancer case reports and rated identically the adequacy of the initial problem definition, the carefulness of further diagnostic methods and how the suspicion of malignancy originated. Subjective probabilities for symptom-disease relationships have been shown to perform as well as actuarial probabilities based on abstracts from the literature ([98]). Subjective probability assessment and subsequent sensitivity analysis for different subjective probabilities have become part of modern decision analysis ([99]).

Subjectivity in the delay estimates has not been extreme in the sense that it has resulted in many examples of delay in spite of short intervals and no delay in spite of long intervals. Estimates of delay after the first consultation depended in part on mistake classifications during the diagnostic procedure, and there is no evident inconsistency between mistake figures and delay figures.

More reproducible classifications might have been obtained if several general practitioners before the study had obtained consensus on weights assigned to intervals and diagnostic procedures for each form of cancer. This would reduce but not eliminate the need for subjective judgment, and bias caused by omission of information in the medical records would be unchanged.

Interval registrations like those in tables 4 and 6 are made by the Norwegian Cancer Registry as well, based on information given on a formula sheet by the physician who diagnoses and/or treats the patient; most often a surgeon, an oncologist or a pathologist. The intervals are given in months. Copies of these forms were found in the hospital records. Spaces on the forms were often left blank, and the information given deviated substantially from what could be read in the record notes. Much of the interval information given on the registry forms was unreliable and could not be used to check interval recordings in the present study.

Validity. Possibilities of bias and comparison with other studies

Validity of information from medical records poses important problems and will be considered in more detail in chapter 6. However, retrospective information through medical records is a common approach to the study of the delay problem (63). Most such studies use hospital records. The few studies from general practice (92-94) used special record cards to analyse cancer cases in the practices and did not compare their own notes with hospital records. Some studies combine interviews of patients or relatives and retrospective study of medical records (88,94). Macadam (100) in a study of patients with gastrointestinal cancer also interviewed their general practitioner. This gave three sources of

information concerning the time of onset of a symptom and intervals similar to the intervals in the present study. There was little discrepancy between the sources, and the differences which were found could not have changed the findings of the study (100). In the present study information in medical records from different sources was combined. Together they usually appeared to produce a fairly realistic impression of what had happened to the patient during the consultations.

In the absence of any generally accepted definition of delay the present delay estimates cannot be compared to any gold standard. Pack & Gallo's intervals (87) form a basis for comparison between different studies, but an acceptable gold standard of diagnostic delay should define different intervals for different forms of cancer, and perhaps even different intervals for different stages of each form of cancer (95).

The use of the word delay may be criticized because patients without cancer may have symptoms which for a long time period resemble those of a cancer patient. If this is very common it may seem unrealistic or unjust to expect a patient to consult rapidly or a physician to perform the diagnostic procedures which are necessary to approach a rare diagnosis like cancer. This perspective will be elucidated more in the following studies, but in this first study it was natural for me as a general practitioner to use a "what went wrong"-approach through the study of cancer patients. This is also the common way to approach the problem (63).

There is a possibility of expectation bias on my part. Three of the patients in the study had been my own patients, and I chose not to exclude them from the study. It is perhaps easy to judge one's own actions as reasonable, but two of them were classified as having delay from the first consultation to diagnosis. Another possibility is that frustrating diagnostic experiences may have made me too severe in my judgments. Of course I tried to be as neutral as possible, but it is difficult to completely exclude such bias.

Going through the delay classifications on the basis of the notes in each patient form there appears to be more doubtful cases of "no delay" than of "delay". Although this is a very rough estimate, it suggests that the proportion of delay classifications is not too low. However, waiting lists in the primary health care in some cases may have prolonged the interval after the first symptom with two to four weeks, contributing to a classification of patient delay in a few patients who would have consulted more promptly.

Whether what has been measured in the present investigation is a valid expression of cancer diagnostic delay probably also can be judged by comparing with results from other studies. This approach has some limitations because my judgements may have been affected by the findings of other authors. Such an influence is, however, probably quite limited. The investigation was prompted by experience in my practice, not from literature studies. Part of my criteria for delay were the intervals in weeks which could be determined without much doubt in most cases. Several of the other criteria like which tests that had been performed by the general practitioner also could be recorded without much doubt.

In a 1974 review of the literature on delay in the detection of cancer (63) comprising 49 studies starting with Pack & Gallo (87), it is stated as a very rough generalization that at least three quarters of the patients postpone visiting a physician for at least one month after they have become aware of a symptom, and that somewhere between 35 and 50 per cent of the patients delay for over three months. At least one month elapses in some 25% of the cases between the first visit to a doctor and the initiation of appropriate treatment (63). In the present study more than four weeks passed from the onset of symptoms to the first consultation for 54 patients (50% of the 108 total) and more than 12 weeks for 33 patients (31%) (table 4). More than four weeks from the first consultation was noted for 60 patients (56%). In other words, patient delay defined in number-of-weeks was somewhat less pronounced in the Tromsø patients, while delay after the first consultation was much more important on the basis of the rather strict criterion of one month from the first consultation. Compa-

risons with the rough estimates based on literature from other countries should not be drawn too far, especially for delay after the first consultation where interval definitions vary and 25% is quoted as a minimal estimate. Possibly the average number of weeks from a first symptom to a first consultation has decreased a little in later years. Such a tendency was demonstrated for patients in one hospital over a twenty year period before 1947 ([101]). However, the more subjective delay estimates suggest that for many forms of cancer consultation within twelve weeks from the onset of symptoms is not enough to avoid delay. That doctor's delay affects as many patients as patient delay is in accordance with a relatively recent Israelian study (88), but in many cases it would be rather severe to expect the initiation of appropriate treatment within four weeks after the first consultation.

Thoroughness of the medical history and completeness of the physical examination is important to arrive at an early diagnosis (97). The findings in the present study concerning the various elements of the consultation seem to confirm this. The findings are consistent with other studies of the relative importance of history-taking and laboratory tests (78,79). The physical examination made a greater contribution to diagnosis in the Tromsø cancer patients than what has been shown for all kinds of diseases in general practice (78). This is perhaps not surprising and is an interesting finding if the physical examination actually has almost the same importance as the medical history for the diagnosis of cancer. However, only in six of the cases where the physical examination was classified as important the medical history was not classified as important. The thorough and important physical examination therefore in most cases probably was the consequence of a thorough medical history which already had given some clue to the diagnosis. Leach & Robbins (101) say there is no substitute for a careful medical history and physical examination in the practice of medicine, and they quote an old saying: "More is missed in medicine by not looking than by not knowing".

It has been shown that doctors too often omit examinations like rectal exploration and gynecologic examination even if local symptoms are present ([102,103,104]). The present material is not

without examples of such omissions. The problem has preoccupied many authors at least since the beginning of the century (86). McIntyre & Popper ([105]) say that errors need to be recorded and analysed to discover why they occurred and how they could be prevented. The identification of mistakes in the present study was made in the spirit of McIntyre & Popper; linked to the improvement of all doctors and not to the punishment of those who err (105). Strategies to reduce doctor's delay will be further discussed in chapter 8.

The finding that there was no overall delay difference between the sexes is in accordance with most studies trying to define a sociodemographic profile of the delayer (63). In the majority of such studies older cancer patients have been found to delay more than younger patients (63). This was not found in the present study. However, patients below 40 years of age seem to have little patient delay. Possibly this is associated with the better public cancer knowledge of younger persons (4). Another possibility is that young people have fewer ailments and that a new symptom therefore make them more motivated for consultation.

Altogether, there is important agreement between the present investigation and previous studies of the delay problem. It is probable that the findings are really measuring this problem and that the results are valid. Some variation is inevitable when this problem is studied in different places. There are regional ([106]) and national (50) variations in cancer incidence, and ethnicity, social class and religion are among the factors affecting people's illness behaviour ([107]). Almost all studies of the delay problem have in common the demonstration of quite important delays in cancer detection, and the present investigation is no exception.

It is interesting that consultation in more than one practice could not be shown to result in more delay. On the contrary females who consulted in more than one practice the last year before cancer diagnosis had less patient delay than females consulting in one practice only. Females who consulted five times or more the last year before diagnosis also had reduced delay. Since this was not shown for males, three explanations seem pos-

sible: Either this effect is limited to cancer in the female breast and genitals, or women use their better knowledge about cancer (4) and consult if necessary several times and in several practices if they feel there is something wrong with their bodies. It is also possible that some women who avoided delay did so because they are generally frequent consulters.

Looking at individual cases with no delay and frequent consulting as described, there are three cases of rather advanced ovarian cancer, known to produce few symptoms in the early stages. Apart from this there is no overrepresentation of cancer in the female breast or reproductive organs. Possibly women know their bodies better and are able to insist more on appropriate investigation than men when they get cancer.

Frequent consultations also may be part of the explanation of why patients less than forty years of age had little patient delay. Seven patients younger than 40 years old had an average of 5.1 consultations in the year before diagnosis, but statistically this is not significantly different from the other cancer patients.

The average number of consultations the last year before diagnosis, 3.2 for both males and females, is higher than Nylenna's ([108]) calculated yearly contact rates for patients in general practice, 1.7 for men and 2.5 for women. For patients who once got a cancer diagnosis and are still alive Nylenna calculated a yearly contact rate of 4.3 and concluded that there is broad contact between cancer patients and the general practitioners. Even if the two studies are not comparable the present study suggests that this broad contact starts before diagnosis.

Perspectives

The incidence of cancer in a general practice population is very low (108). Symptom variation is wide for different forms of cancer and even for one type of neoplasm. Many common conditions have similar symptoms. It would be very unreasonable to expect that all the doctor's delay estimated to have occurred in the present study could be eliminated, or that cancer patients never should hesitate before consulting a doctor. But the main criteria for delay were deviations from what might be considered reasonable

action on the part of the patient or the doctor, and it seems unnecessary that such large proportions of cancer patients are affected by delay. There may be realistic possibilities of major reductions of the delay. This must be done by educating the public, training the general practitioners and improving administrative routines. Further investigations are needed to see how this work can best be done.

Conclusion

1. Delay in cancer detection is an important phenomenon in Tromsø. Eighty of 108 cancer patients (74%) had some kind of delay. Other studies have shown that delay in the detection of cancer is an international phenomenon.
2. Delay from the first symptom to the first consultation (patient delay) was found in 48 of 108 patients (44%).
3. Delay from the first consultation to diagnosis was found in 52 of 108 patients (48%). The general practitioner has a large responsibility in taking appropriate diagnostic action and was at least partly responsible for delay at this stage in 38 of the 52 patients. Some of the delay occurs after the general practitioner has made an appropriate referral. Specialists in various medical fields contributed to delay in 16 of the 52 patients. Administrative factors also contributed in 16 patients.
4. The physical examination contributed almost as much as the medical history to the diagnosis of cancer, but a thorough physical examination often seems to have been performed after the medical history had given some clue to the diagnosis.
5. The problem of patient delay was less important in patients younger than 40 years of age, but there are few patients in this group.
6. Some women have avoided patient delay by consulting often and/or using more than one practice.
7. Areas of possible reduction of the delay problem exist.

5. A WORD OF *CAUTION* TO THE PUBLIC: SEVEN WARNING SIGNALS OF CANCER IN A GENERAL POPULATION AND IN A GENERAL PRACTICE POPULATION

Introduction

a. Public cancer education: goals and means

Public education about cancer should contribute to the prevention of cancer on an individual and on a collective level, and early detection should be encouraged. Another aim may be to relieve unrealistic anxiety in the population. At least the anxiety which many people feel in relation to cancer ([109]) should not be reinforced. A special case is the information needed by cancer patients. Cancer patients should have considerate individual information about their disease ([110,111]), but public information may complete individual information to them and their relatives.

Mass media is very concerned with cancer. A large part of public information is derived from magazines, newspapers, television etc. ([112]). In spite of this, people may not possess adequate knowledge of significant symptoms, and this may be responsible for a considerable part of patient delay ([113,114]).

In this and the next chapter the focus will be on a means of cancer education which primarily aims at encouraging early detection in symptomatic patients, and which for years has been considered as one of the main weapons of cancer associations all over the world: the **seven warning signals.** The present chapter starts with the historic background of the warning signals. Thereafter, three studies are presented describing the frequency of warning signals in a general population and in a population of patients in general practice. In the population of patients from general practice the conceptions of some patients are compared to recordings made by general practitioners.

b. The warning signals of cancer: History, function and unanswered questions

Today there are national cancer societies or associations fighting against cancer in most countries. "Danger signals" quickly became popular several decades ago as a means of coordinated

international information about cancer. The idea arose in the United States during World War I (Gerry de Harven, Director of International Activities, American Cancer Society, personal communication). Medical resources were scarce. Texas State Council on Defense edited a booklet on the theme "Help win the War by preventing unnecessary sickness". People were asked to see a doctor if they experienced "a lump or scab or an unhealed wound or sore. Lumps in the breast.. Persistant indigestion with loss of weight..".

Fifteen years later the three original danger signals were spread in 22 different languages. In 1942 the number of danger signals were increased to five. In 1952 the number became seven. A new revision was made by the American Cancer Society after its first study of public attitudes and knowledge in 1966 (61). At that time the American Cancer Society every year distributed some 50 million copies of pamphlets or posters listing the danger signals (61). The 1966 study (61) compared active or "overt" knowledge, i.e. the ability to mention without any help one or more warning signals, with passive or "latent" knowledge, i.e. the ability to recognize warning signals from a list. Passive knowledge was on the average three times as great as active knowledge. "Lump or thickening in breast or elsewhere" was best known, mentioned by half of the people interviewed.

After 1966 the symptom descriptions were called warning signals, and the first letter of each signal together form the word CAUTION (table 9). No scientific study of symptoms has validated the

Table 9. Seven Warning Signals published by the American Cancer Society (1983)

1. Change in bowel or bladder habits
2. A sore that does not heal
3. Unusual bleeding or discharge
4. Thickening or lump in breast or elsewhere
5. Indigestion or difficulty in swallowing
6. Obvious change in wart or mole
7. Nagging cough or hoarseness

The first letters form the word CAUTION

Signals (de Harven, personal communication). The 1978 study (62) found knowledge relatively unchanged, but "persistent cough or continuing hoarseness" was better known than in 1966. This was thought to reflect the anti-smoking campaign over the preceding 12 years. For some other warning signals awareness had decreased, and continued efforts to publicize cancer's warning signals were advocated (4). People who used to go for physical check-ups knew more warning signals than people who did not go for check-ups. Two thirds of those interviewed said they would see a doctor if they experienced a warning signal. "Unusual bleeding or discharge" was most motivating, while many people would not bother about "change in bowel or bladder habits".

There is no doubt that the warning signals have an empirical basis in that cancer sometimes gives rise to such symptoms, but several of the warning signals are among the most common symptoms in general practice and must reflect many other diseases and ailments than cancer. The usefulness of knowledge about warning signals is mainly a function of whether they make people with cancer see a doctor earlier than they would have done without this knowledge.

There are many unanswered questions about warning signals. Cancer giving rise to a warning signal may be thought to have less patient delay than cancer giving rise to other symptoms. Paradoxically, Kutner & Gordan ([115]) and Goldsen ([116]) came to the opposite conclusion. Why, if their findings can be confirmed? What proportion of cancer patients experience warning signals? Like other patients cancer patients probably experience some warning signals which have nothing to do with their cancer - how important is this? Is it possible to relate individual warning signals to high risk groups, instead of telling everybody to consult a doctor whenever a warning signal is experienced and regardless of which one? Are there other symptoms than the warning signals which should raise the suspicion of the public and of doctors? Or more fundamentally: Can any kind of information to the public be expected to reduce patient delay?

In the following investigations and reflections I hope to approach some of the answers.

5-1. The study of warning signals in a general population in Tromsø, Norway, and in a general practice population

I wanted to get some information about the frequency of warning signals in two populations in Tromsø: a general population, and a general practice population. Information about the quantitative importance of warning signals in a general practice population might come from two sources; the patients, and the general practitioners. Even if the warning signals have been made for the public and not for doctors, general practitioners frequently suspect cancer when a patient presents a symptom corresponding to a warning signal ([117]). If warning signals contribute to reducing doctor's delay, general practitioners should be able to identify patients who present such symptoms. But it is not evident that doctors and patients have the same conception of the warning signals. A small study of patient-doctor agreement about the presentation of warning signals during the consultation therefore was included.

Materials and methods, details

1. Warning signals in a general population. Intervews-POP

Two medical students[3] were instructed in how to interview people in a door-to-door survey in two housing districts of Tromsø. One was an old housing area with one- or two-family dwellings, many old people and some younger families living there. The other was a newer housing area with apartment buildings where mainly younger families and people living alone were lodging. Children were included by interviewing the parents of children who opened the door, but only every tenth child since we assumed that children would be eager door-openers. Interviews were carried out after regular working hours.

The survey had been presented in the local newspapers as a health survey, and people had been asked to answer some questions if one of the students visited them. The students introduced themselves in a standardized manner with a specially made

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[3] Raymond Teigen, Per Allan Stenberg

identification card and a copy of one of the newspaper articles. After consenting to participate people were asked to answer "yes" or "no" as to whether they had experienced particular symptoms after last Christmas, which corresponded to the last three months. The time period was chosen as a compromise. It was supposed that most people having experienced a given symptom would be able to remember whether it occurred before or after Christmas.

The seven warning signals were read out one by one, without mentioning the words "cancer" or "warning signal". Those who confirmed having had any such symptom the last three months were asked if they had seen a doctor or telephoned to have a medical consultation because of this symptom.

The list of symptoms used was that of The Norwegian Cancer Society. This list (table 10) differs slightly from the American list, especially in its inclusion of weight loss and its omission of change in bladder habits. In the following text the abbreviations in table 10 will be used for the seven warning signals.

Table 10. Seven Warning Signals published by Landsforeningen mot Kreft, Norway, 1983. The author's translation

	Key word (abbreviation) used in text
1. Any sore which does not heal	Sore
2. Lumps anywhere in the body, especially in the breasts, and even if they are painless	Lump
3. Abnormal bleeding from body orifices	Bleeding
4. Changes in colour or size of warts and moles	Mole
5. Indigestion or change in bowel habits if this is not rapidly normalized	Indigestion
6. Hoarseness or coughing without any apparent reason	Cough/hoarseness
7. Weight loss without any apparent reason	Weight loss

2. Warning signals in a patient population. Recordings by general practitioners (GPs). The GP-material

Most general practitioners[4] in Tromsø, working in four group practices and one solo practice, consented to participate in an investigation of warning signals in their patients. From October 1st 1981 to March 31st 1982 the general practitioners at the end of each consultation recorded whether or not they thought that the patient had presented one or more warning signals. The participating physicians were instructed to perceive the words of the warning signals quite literally, disregarding any thought about which diagnosis to make. The symptom, not the disease was to be recorded. Instructions said the warning signal was not necessarily the patient's presenting complaint, but in order to justify recording the patient's words or behaviour should suggest that the warning signal was at least part of the reason why the doctor had been consulted.

A small pilot registration showed a relatively uniform way of recording for the participating general practitioners.

Two kinds of small registration blocks (size A6) were distributed to the doctors. One was to be used for patients without warning signals. Initials, sex and date of birth was to be recorded for each patient (appendix 3-A). The same registrations were done on the other kind of card (appendix 3-B) for the patients thought to have presented warning signals. On this card the type of warning signal or signals was noted as well. At the end of the registration period two medical secretaries punched the recordings. A numeric code identified the office of the general practitioner who had made the recording.

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4 Bjørg Haugslett, Knut Holtedahl, Gustav Jacobsen, Christiane Kolberg, Hasse Melbye, Gunnar Moe, Inger Njølstad, Øystein Pedersen, Sissel Ringnes, Sigurd Sodeland, Ann Mari Steinnes, Odd Storstein, Bernt Stueland, Ivar Aaraas

3. Warning signals in a patient population as the patients see it. Interviews-PAT

In March 1982, just before the end of the registration period and at the same time as the door-to-door interviews were carried out, one of the medical students[5] was present one day in each of the four group practices. This day all the patients in the group practice at the end of each consultation were asked by the doctor whether they would be willing to answer a few questions concerning the consultation. Nobody refused, and each patient was then asked to see the student immediately in a separate room. The patients came in one at a time. They were asked to say yes if they recognized a symptom which they had presented to the physician during the consultation immediately preceding. The student then read out the warning signals one by one. The words "cancer" or "warning signal" were not mentioned. The answers were compared to the physician's recordings.

Results.

1. General population. Interviews-POP

Three hundred and one persons were interviewed. Two persons did not answer all the questions and were excluded (table 11).

Seventy-four persons (25%) said they had experienced one or more of the seven warning signals during the last three months. There was no significant overall difference between males and females (table 12), but in the subgroup of the middle aged (40-59 years) the percentage of women who said they had experienced a warning signal was about the double of the percentage of men. In each of the three age groups in table 12 about one quarter of the persons said they had experienced warning signals.

Altogether 92 warning signals were reported by the 74 persons

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5 Raymond Teigen

Table 11. Age and sex distribution of 299 persons interviewed in door-to-door survey. Tromsø, Norway, 1982. Interviews-POP

Age	Females	Males	Both sexes
0-19	26	9	35
20-29	42	34	76
30-39	34	29	63
40-49	26	21	47
50-59	20	16	36
60-69	12	15	27
70-	8	7	15
Total	168	131	299

Table 12. Consultations in three different age groups based on personally experienced symptoms corresponding to warning signals. 168 women and 131 men. Door-to-door survey. Interviews-POP

A. Number (and percentage) of persons who experienced warning signals

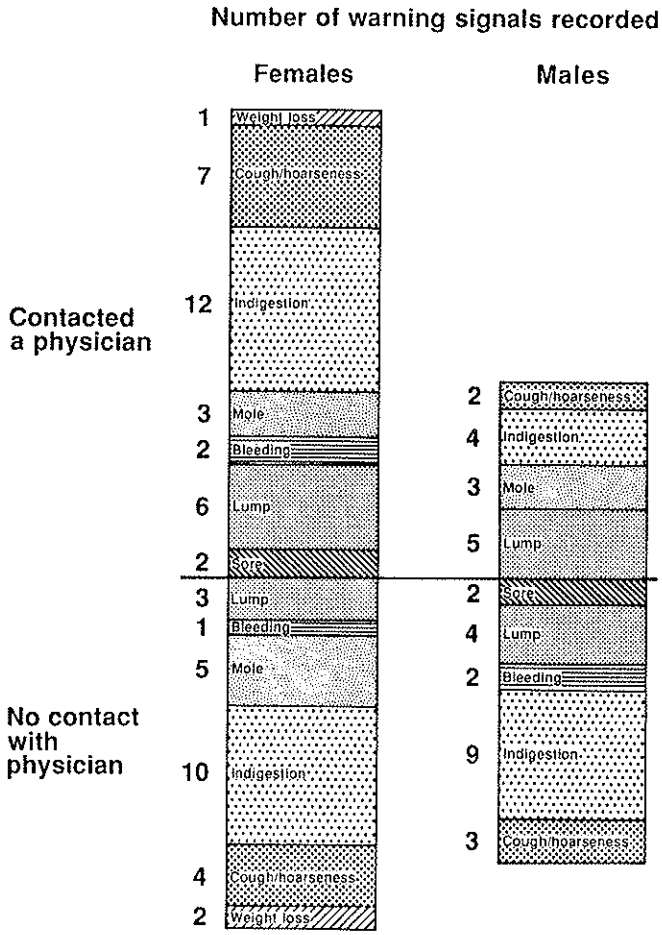
Age (years)	Females	Males	Both sexes
0-39	26 (25)	16 (22)	42 (24)
40-59	16 (35)	5 (14)	21 (25)
60-	5 (25)	6 (27)	11 (26)
Total	47 (28)	27 (21)	74 (25)

B. Number (and percentage) of persons who consulted a doctor because of warning signals

Age (years)	Females	Males	Both sexes
0-39	16 (16)	5 (7)	21 (12)
40-59	7 (15)	3 (8)	10 (12)
60-	4 (20)	4 (18)	8 (19)
Total	27 (17)	12 (9)	39 (13)

(fig 5). Indigestion[6] was the most frequent warning signal, confirmed by 22 females and 13 males. Nine females and nine males said they had experienced Lump. Other frequent warning signals were Cough/hoarseness in eleven females and five males, and Mole in eight females and three males (fig 5). The most common combination of two warning signals were Indigestion + Cough/hoarseness; four women and three men gave this answer.

Fig. 5. Consultation for 92 warning signals in 74 of 299 interviewed persons from a general population. Tromsø, Norway 1982.



[6] Abbreviations of the warning signals: see table 10

Thirty-nine persons (13%), or 53% of all persons with warning signals, had consulted or taken practical steps to consult a doctor for this reason (table 12). Fifty-seven per cent of females and 44% of males had sought a doctor's advice, but the difference is not statistically significant. Eight of 11 persons (73%) 60 or more years old and 31 of 63 persons (49%) younger than 60 years had contacted a doctor, but this difference is not significant, either.

Eleven of the 18 persons who had experienced Lump contacted a doctor, and so did nine of the 16 with Cough/hoarseness and 16 of the 35 with Indigestion. The contact rate for each of these individual symptoms is not significantly different from that of all the other symptoms, nor is the contact rate for Lump significantly different from the contact rate for Indigestion.

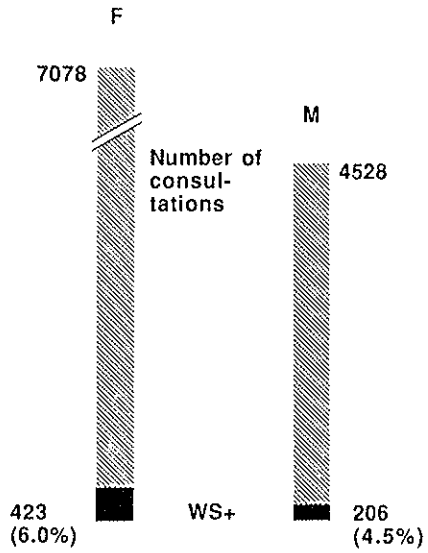
2. Patient population. GP-material

11 606 consultations in general practice were registered. In 629 (5.4%) of these one or more warning signals were recorded (fig 6). The distribution of age and sex is presented in table 13. Table 14 and figure 7 show the rate of warning signals presented per thousand consultations. Altogether 649 warning signals were recorded (table 15).

Females presented warning signals in 423 of 7078 consultations (6.0%) and males in 206 of 4528 consultations (4.5%) ($P<0.001$ controlling for age). This sex difference was most important for patients 30-59 years of age.

For individual warning signals females had more recordings of Lump ($P<0.001$), Bleeding ($P=0.001$) and Cough/hoarseness ($P=0.04$ without and $P=0.05$ with Yates correction) (table 15). Three of the warning signals, Lump, Bleeding, and Indigestion, occur far more often than the others. The warning signals Sore, Mole, Weight loss occur less frequently. Cough/hoarseness lies between these two groups (table 14).

Fig. 6. Warning signals recorded by general practitioners.
11 606 consultations.
Tromsø, Norway 1981-1982. GP-material.



Females + Males 5.4% WS+

Fig. 7. Rates of individual warning signals recorded by general practitioners. GP-material.

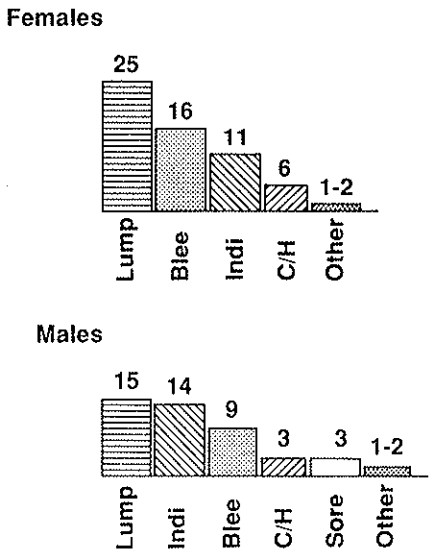


Table 13. Number of consultations distributed according to whether a warning signal was recorded or not by the general practitioner, and by age and sex of the patient.
11 606 consultations in Tromsø, Norway, 1981-1982. GP-Material

	Warning signal(s) recorded		No warning signal recorded		All consultations	
Age	Females	Males	Females	Males	Females	Males
0-19	40	33	1190	924	1230	957
20-29	72	25	1812	836	1884	861
30-39	95	30	1137	695	1232	725
40-49	64	22	646	440	710	462
50-59	45	22	698	579	743	601
60-69	51	39	635	522	686	561
70-	56	35	537	326	593	361
Total	423	206	6655	4322	7078	4528

Table 14. Warning signals recorded per thousand consultations according to age and sex. GP-Material

F = Females
M = Males

	Sore		Lump		Bleeding		Mole		Indi-gestion		Cough/ hoarse-ness		Weight loss		Total	
Age	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M
0-19	0	0	21	25	6	3	1	0	3	2	1	4	1	0	33	34
20-29	1	0	16	9	15	3	1	3	3	13	3	0	2	0	38	29
30-39	2	0	34	17	23	8	2	0	13	14	6	1	0	1	77	41
40-49	1	4	38	17	30	11	0	2	14	15	7	0	1	2	90	48
50-59	4	2	26	7	9	12	0	2	12	10	9	3	3	2	61	37
60-69	1	11	26	11	12	16	1	2	22	23	12	7	1	4	74	70
70-	7	11	20	17	22	19	2	3	30	39	10	6	5	8	94	97
Total	2	3	25	15	16	9	1	2	11	14	6	3	2	2	60	45

Table 15. Sex distribution of the different warning signals. Recordings by general practitioners. 11 606 consultations. GP-Material

Warning signal	Females	Males
Sore	13	13
Lump	175	68
Bleeding	113	40
Mole	8	7
Indigestion	78	63
Cough/hoarseness	39	13
Weight loss	11	8
Total	437	212

There is a significant linear increase in warning signal frequency with increasing age ($p<0.001$). This tendency appears in table 14 through an increasing rate of warning signals with advancing age. For males this is most marked after the age of 60 years, but the consultation rate for Lump is high in all age groups. Warning signal rates in females are highest in the old and the middle aged, and rates for Lump and Bleeding are highest in the fertile age groups. Rates for Indigestion are about equal for males and females 30-69 years of age, while males have higher rates in the very old and in the age group 20-29 years. Rates for Cough/hoarseness are generally higher in females. Lump is recorded quite often in children and young people (table 14).

Fourteen women and six men had two warning signals recorded. The combinations varied. Three women had Lump + Bleeding, three other women Indigestion + Weight loss.

3. Patient population. Interviews-PAT

On the four days when the student questioned the patients, the general practitioners recorded warning signals in nine of 63 female patients and in none of 32 male patients. The recordings in the nine women were: Bleeding + Indigestion: one woman. Lump: four women. Bleeding, Mole, Indigestion: one recording each.

Far more patients, 27 (28%), answered that they had presented one or more warning signals at the consultation. Twenty females thought they had presented 27 warning signals and seven males thought they had presented ten warning signals. Table 16 shows the distribution of age and sex for all patients and for the ones with warning signals recorded. Table 17 shows the poor agreement between patients and doctors. Table 18 shows which warning signals were indicated by the patients. Lump is more frequent than the others and was indicated by 11 females and three males.

Table 16. Number of patients interviewed immediately after a consultation, distributed according to warning signal recordings, age and sex. Interviews-PAT

	Patients interviewed		Warning signal recorded by doctor		Warning signal presented according to patient	
Age	Females	Males	Females	Males	Females	Males
0- 9	7	2	-	-	-	1
10-19	9	5	-	-	1	-
20-29	17	8	3	-	7	3
30-39	6	5	2	-	2	-
40-49	10	3	2	-	5	1
50-59	8	5	1	-	3	2
60-69	4	3	-	-	1	-
70-	2	1	1	-	1	-
Total	63	32	9	-	20	7

Table 17. Warning signals in 63 female and 32 male patients interviewed immediately after a consultation. Recordings by general practitioners, and the patients' own opinion. Interviews-PAT

	Number of patients (n=95)		
	Females	Males	Both sexes
Same warning signal recorded by doctor and patient	4	0	4 (4%)
Partial agreement between doctor and patient on the warning signals recorded	3	0	3 (3%)
Doctor and patient have recorded different warning signals	2	0	2 (2%)
Only patient indicated warning signal	11	7	18 (19%)
	20 (32%)	7 (22%)	27 (28%)

Table 18. Number of individual warning signals indicated by 27 patients immediately after their consultation, distributed by sex. Interviews-PAT

	Females	Males
Sore	-	2
Lump	11	3
Bleeding	4	2
Mole	4	-
Indigestion	5	2
Cough/hoarseness	3	1
Weight loss	-	-
Total	27	10

Discussion

The three studies show that warning signals are common in the general population as well as in the population of a general practitioner. The frequency distribution of warning signals is somewhat different in the two populations. In the population from general practice people seem to have a much broader conception than general practitioners of how warning signals should be interpreted. These findings will be discussed with respect to the representativity of the populations, the reliability and validity of the findings and possible consequences for consultation behaviour and cancer detection.

Representativity of the populations

None of the populations are random samples, and they cannot be considered representative of the general population of Tromsø or of all patients in general practice in Tromsø.

By selecting housing areas with a mixture of young and old people and with people from all social classes some effort was made to interview a general population sample not too different from the Tromsø population (Interviews-POP). However, only people in the urban part of the municipality were interviewed. Compared to the population of Tromsø ([118]) there is an underrepresentation of the age group 0-39 years ($P<0.001$). There is an overrepresentation of females ($P=0.03$), mainly due to differences in the younger age groups. Few people refused to be interviewed, but the exact number was not noted.

The sample of the population from general practice (the GP-material) was collected during six autumn and winter months of the year and is not necessarily representative for the whole year. The intention was to record every consultation in the doctor's office which was not part of routine examinations like groups of school children or infants. This goal was not achieved. Not all the general practitioners in Tromsø participated in the registration, and those who did, forgot the registration for days at a time. Usually they started over again when one of the frequent oral or written reminders were received. If we assume that Tromsø patients in general practice are not very different from

those of the whole country, we may compare sex and age distribution in the GP-material with figures from Rutle's nationwide study in spring and autumn 1978 ([119]). There is no significant difference in the sex distribution, but the GP-material has fewer patients 60 years old or more, and more people of both sexes in the age group 20-29 years. Six per cent of Rutle's "direct contacts" were home visits, which were frequent especially among the oldest patients. This may explain at least part of the difference for old people. The increase in the proportion of old people in the general population from 1978 to 1981-1982 is probably less important, but works in the opposite direction. Both in Rutle's study (119) and in the GP-material the number of encounters were recorded rather than the number of patients, but Rutle's registration period is much shorter. Young people have relatively high consultation rates (119), and repeated consultations may account for some of the difference between the two materials in the age group 20-29 years.

The age distribution in the GP material may also be affected by bias. If forgetfulness mostly concerned whole days there would hardly be any selective forgetfulness of old or young patients or of patients with or without warning signals. However, it is possible that on some days the general practitioner has started by forgetting to record, but that a patient with a warning signal in the middle of the day has served as a reminder and made him record for the rest of that day. A general practitioner with twenty patients a day would see on the average one patient with a warning signal per day since a warning signal was recorded in 5,4% of the consultations. If this type of selective forgetfulness was frequent, relatively more people with than without warning signal would have been recorded. The warning signal rate increases with age, and such an explanation would tend to favour registrations in relatively many old people. Compared to Rutle's material it was found that old people were underrepresented rather than the opposite. Bias of this type is therefore probably not very important in this study. The overrepresentation of the age group 20-39 years in the GP-material compared to the nationwide material cannot be explained by such bias either, because both genders are

overrepresented but the rates of warning signals are quite low in this age group, especially for males.

The patients in general practice who were interviewed by the student (Interviews-PAT) had a sex distribution which was not significantly different from that of the GP-material. The number of patients interviewed is too low to make comparison of age distributions meaningful, but patients from all age groups were interviewed (table 16). Nobody refused this interview.

Reliability

The interviews and the GP-recording were made only once. No re-testing can confirm the recordings. Robra & al. ([120]) have asked patients from general practice and from a corporate health insurance fund to answer the same questionnaire with symptom descriptions twice with an interval of three to four months. Kappa values for symptoms corresponding to the warning signals were generally low, but this may at least in part be explained by the time interval between the first and second questionnaire. One question concerning cumulative life prevalence (of black, tar-like stools) had a kappa value of 0.50. This rather low value may be explained in part by the low prevalence of the event (65).

In the present study some measures were taken to increase the reliability of the findings. The interviews were performed in a standardized and simple manner. The only answers which were accepted were yes or no. The general practitioners had been given detailed instructions with examples telling them how to interpret the warning signals, and the pilot study had shown only small differences in warning signal frequency recorded by different general practitioners. The phrasing of the warning signal does not seem to suggest that interpretation would be more difficult for some warning signals than for others.

Validity

a. Possibilities of comparison with a gold standard

There is no gold standard defining warning signals. Ideally one might think that true warning signals are limited to the warning signals actually caused by cancer. Such a definition would be absurd in public health education, because people usually cannot

distinguish between cancer-related and not cancer-related warning signals.

Nor is it possible to consider the recordings made by general practitioners as a gold standard for non-medical populations. Warning signals published through posters, magazines, radio or television introduce or advocate topics of conversation and debate. Only the way such topics are accepted, reflected upon and discussed by individuals and groups of people will decide what becomes a meaningful interpretation of such signals for most people ([121],[122]). Johannessen & al. ([123]) have shown that doctors, nurses and patients have very different conceptions of the meaning of some common gastrointestinal symptom terms.

People's interpretation of warning signals has to be accepted as such, and this must be the point of departure in discussing the possible role of warning signals in reducing patient delay in cancer. At least both people and doctors distinguish between "Hoarseness or coughing without any apparent reason" (=Cough/-hoarseness) and just any coughing due to the common cold: Coughing & sneezing was, together with fever, the most frequently recorded presenting symptom in cases of new illness in a Norwegian material from general practice ([124]). Cough/hoarseness is less than half as frequent as Indigestion in the general population interviews, is not particularly frequent in the GP-material and is among the least frequent warning signals mentioned by the patients in general practice who were interviewed.

For the general practitioner an effort was made to define criteria through explanations and examples. A very literal interpretation of each warning signal was chosen. The instructions still left room for individual interpretation by the general practitioners.

b. Possibilities of bias

Recall bias may be important when people are trying to remember whether or not they have had a symptom during the last three months. People may be selective in what they remember, and some groups of people may be more attached to certain events and remember them better than other groups ([125],[126]). An effort to minimize recall bias was made by selecting Christmas time as the

point of reference rather than asking people about events during a specified number (three in this case) of months. Recall bias was thought to have minor importance when general practitioners recorded warning signals once the patient had left the office, and in the patient interviews immediately following the consultation. However, some forgetfulness cannot be excluded even in these situations.

Expectation bias ([127]) may have influenced the increasing rate of warning signals with age. Cancer is associated with old age and the doctors may have been more eager recording warning signals in old people. On the other hand the tendency toward higher rates of warning signals in old people is quite strong. Probably it reflects a true tendency even if part of it may be explained by expectation bias.

On the day of the patient interviews the general practitioner knew and helped announce to the patient that a student wanted to interview the patients before they left the medical center. The doctor also knew that the interviews had to do with the warning signal registration. It seems probable that the general practitioners might have been especially vigilant in recording warning signals that day. The great discrepancy between doctors and patients is the more striking. A gap between general practitioners' and patients' understanding and interpretation of possibly cancer related symptoms and signs was found also in a Norwegian questionnaire study in general practice ([128]). For most symptoms the patients did not intend to consult as quickly as the doctors recommended. Differences in medical knowledge was thought to be at least part of the explanation. It is possible that doctors hesitate to classify as a warning signal symptoms which to their knowledge have an apparent relationship with specific benign conditions while non-medical people include more such cases. On the other hand, when a doctor has classified a symptom as a warning signal, his general attitude to rapid consultation is less ambiguous than that of a patient whose decision concerns his own person.

In the interviews the word cancer was not mentioned. It is possible that a smaller fraction of young people would have said they experienced or presented warning signals if these had been

presented as warning signals of cancer, like in the public information of the cancer associations.

c. Other aspects of validity

The findings should make sense biologically and epidemiologically, and the various findings should not be inconsistent.

In both populations some warning signals were more frequent than others. Biologically this is not surprising. The American studies (61,62) also found very different frequencies for different warning signals in the general population. In the present study Indigestion was the most frequent warning signal in the general population. In a Norwegian questionnaire survey (129) one or both of the abdominal symptoms of "bloating and rumbling" or "cramping abdominal pain" were found in 28% of middle aged men and 35% of middle aged women. A four weeks diary study in The Netherlands (130) was performed with members of randomly selected families with a male and a female adult and at least one child 16 years old or more, from four general practices. Most complaints concerned disorders of the musculo-skeletal system, psychological disorders, and disorders of the upper respiratory tract and the digestive tract. The warning signals which probably are most relevant in these conditions are Indigestion and Cough/hoarseness, Lump probably to a lesser extent. All three signals are frequent in our general population.

The most striking difference between the two populations is that Indigestion is most frequent in the general population while Lump is most frequent in the GP-material as well as when patients in this material were interviewed. It is quite possible that this reflects a true difference. No significant difference in consultation thresholds for individual warning signals were found in the interviews of the general population (fig 5), but numbers are small. Some symptoms may represent a stronger iatrotropic stimulus (43) than others. The non-significant tendency for relatively fewer consultations for Indigestion than for Lump may hide a real difference. Lump, and Bleeding in particular, are relatively more frequent in the GP-material than in the general population sample. (table 15, fig 5). In the Dutch diary material (130) only two of 73 complaints from the digestive tract were presented to a general

practitioner, while ten per cent of all complaints led to contact with a general practitioner. Nylenna & Hjortdahl (128) presented descriptions of symptoms to patients in general practice and asked for which symptoms they would see a doctor, and how quickly. "Lumps and bumps" and "visible bleeding" gave the quickest response. In the American population interviews (62) 80% reported intention to consult a doctor in case of unusual bleeding or discharge, and 59% in case of a change in bowel or bladder habits.

The finding of more warning signals in women 30-59 years of age in the GP-material was expected, since lumps in the breast and irregular menstrual bleeding are common causes for women's consultations in general practice. It is consistent with the similar sex difference found for the middle aged in the general population. This population experiences both the warning signals which lead to a consultation and those which do not lead to a consultation, and this tends to level out any overall difference between males and females. That Cough/hoarseness was more frequent in consulting women than in consulting men was perhaps more surprising.

Lump is the only warning signal in the GP-material with high rates in all age groups and for both sexes. But even if GPs frequently have recorded Lump, they have confirmed such a recording in only four of fourteen patients who said they had presented this symptom during the consultation. Lump seems to be a very strong iatrotropic stimulus.

Implications

It seems difficult for doctors to predict how people will interpret descriptions of symptoms aimed at increasing consultation rates. Such predictions are probably not much easier for other health educators. It is equally difficult to imagine how to give the warning signals a higher level of precision without making their description much more complicated.

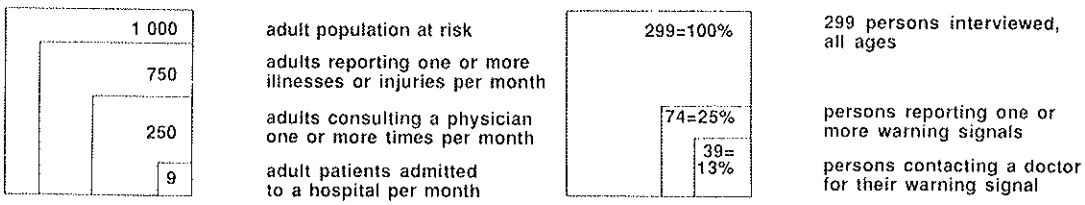
Very ardent publicity efforts aimed at increasing consultation rates for warning signals run a high risk of increasing the triviality burden of general practice. What happens if our publicity has such a success that all patients experiencing a warning signal go to see a doctor? If one quarter of the Tromsø population

were to see a general practitioner during a three month period in 1982 it would mean approximately two hundred consultations per month for each of the approximately twenty general practitioners in Tromsø at that time. It is about half of the consultation capacity in the local primary health care. This is consistent with the impression from the interviews of patients in general practice. If the twenty-seven patients reporting warning signals represent one half of the potential consulters with warning signals at that time, it gives a maximum of 54 patients consulting for warning signals out of 95+27=122 patients, or almost half of the 122 patients.

In the general population there was no predominance of warning signals in old people. Two thirds of the warning signal patients would be less than forty years of age, as this was the case in the Tromsø population of 1982. A flood of consultations should not be the goal of our information, and in particular the majority of our respondents should not be young people who have the lowest incidence of cancer. Already around 1960, compared with tumour clinic patients, patients in cancer detection centers in the United States included disproportionate numbers of young people (116).

Different persons have different consultation thresholds for apparently identical symptoms (124). Common symptoms occurring in a general population have consultation rates of about 20-35% ([131,132,133]). Consultation for warning signals in half of the cases in the general population interviews suggests that warning signals in general have a low consultation threshold (fig 8).

Fig. 8. Consultation for warning signals of cancer compared to consultation for symptoms in general.



Monthly prevalence estimates of illness in the community and the roles of physicians and hospitals in the provision of medical care. Adults 16 years of age and over. Simplified from White et al. (133)

Three months incidence of warning signals and the role of physicians in the provision of medical care (chapter 5)

There was a non-significant tendency for older people to consult more readily, but numbers are small and do not permit any conclusion about this. In the light of the increased cancer incidence in older persons a low consultation threshold appears desirable for old people, but of dubious value for young people. Even with a low consultation threshold it is difficult to know whether the people with cancer are among those who consult for warning signals before more widespread symptoms force them to some medical service.

For individual warning signals it may be that Lump and Bleeding quite often are interpreted as symptoms which require professional explanation or therapy, while the more common Indigestion more frequently calls for self-care in the form of dieting or prescription-free medication. But we do not know whether people conform their consultation behaviour to this if their Lump or Bleeding appears particularly severe and scaring, even if it has been found for some other common symptoms that increasing severity is associated with an increasing probability of consultation in general practice ([134]).

Even if it is true that many people with Indigestion practice self-care, the number who consult is considerable. Abdominal complaints in patients is everyday work for any general practitioner. Two problems with common symptoms will be mentioned here: First, they make a lot of people with rather innocent ailments consult. This is part of general practice and has diagnostic and therapeutic challenges of its own, but it carries a potential for a steady increase in work load and may be felt as a triviality burden by the general practitioner. Second, the more common a symptom is in an individual or in a population, the more probable it is that a cancer patient would disregard it for quite a while. An inverse relationship has been shown between how frequent a situation was experienced among patients in general practice and how serious it was interpreted to be (124). It is known from several cultures that disease symptoms are not necessarily regarded as such if they become common enough (91,[135]), especially if the disease does not cause subjective illness in the early stages. In parts of Africa where urinary schistosomiasis is very common,

red urine has been considered as a normal phenomenon. An example from our own culture is irregular genital bleeding as a symptom of internal genital cancer in females. Not all women consult for this, and in many cases previous experience with similar bleeding which became regular without any therapy may contribute to non-attendance. A similar tendency to put little weight on common symptoms in the absence of subjective illness has been shown for symptoms ressembling side effects from beta-blocking agents ([136]).

The problem of the iceberg ([137]), i.e. important diseases unknown to the general practitioner, is very important and has been shown to be quantitatively a bigger problem than the triviality burden in general practice ([138]). But the present study shows that the iceberg of hidden cancer must be rather small in the group of people experiencing warning signals, and even in patients consulting for warning signals. Some of the iceberg of hidden cancer does not even carry the red flag of warning signals and must be sought elsewhere.

General practice must live with some triviality burden. Cartwright ([139]) says that minor illness can only be eliminated from the consulting room by adding to the iceberg of more serious untreated illness and at the expense of good patient-doctor relationships. Our challenge is to melt some of the iceberg without drowning in the surrounding water. Further investigations are needed to determine the part that warning signals should play in cancer detection.

Conclusion

1. Twenty-five per cent of a general population sample in Tromsø said they had experienced one or more warning signals during the preceding three months. There was no difference between young (0-39 years of age), middle aged (40-59 years) or old (60 years or more) persons. There was no overall difference between males and females, but middle-aged females reported more warning signals than middle-aged males. The sample has some similarities with but is not representative of the population of Tromsø.

2. General practitioners recorded warning signals in 5,4% of 11 606 consultations in general practice during a six month period. Females had more recordings than males. On the level of individual warning signals females had more recordings of Lump, Bleeding and Cough/hoarseness.

Lump, Bleeding and Indigestion were recorded far more often than Sore, Mole and Weight loss. Cough/hoarseness had a middle position.

The rate of warning signals gradually increased with age. Rates for Lump and Bleeding in females were highest in the fertile age groups. Lump was frequent in all age groups in both males and females.

This material of patients in general practice (GP-material) has a sex distribution which is similar to that of Rutle, a nationwide patient material from general practice in 1978, but there are fewer old patients and more patients in the age group 20-29 years in the present material. The GP-material probably has important similarities with a hypothetical material of all patients in general practice in Tromsø at that time, but cannot be considered representative of such a population.

3. Patients in general practice have a much broader interpretation of warning signals than general practitioners, even if this finding may have been accentuated by the instructions intended to make recordings by different general practitioners more uniform.

4. Indigestion was the most frequent warning signal in the general population, Lump the most frequent in the population from general practice. Lump and Bleeding probably are stronger stimuli for consulting in general practice than Indigestion, even if this could not be shown on a significant level for the limited number of persons interviewed in the general population.

5. If every person who experiences a warning signal consults a general practitioner it would take up a very important part of the consultation capacity in primary health care; in Tromsø in 1982 it would have taken about half of the consultation capacity. Especially in young people such consultation behaviour should not be encouraged.

6. WARNING SIGNALS AND OTHER RELEVANT INFORMATION IN CANCER PATIENS AND CONTROL GROUPS

Introduction.

a. The warning signals

It has been found (chapter 5) that warning signals are common symptoms in the general population as well as in a population of patients from general practice in Tromsø.

From these findings we would expect to find cancer-related as well as not cancer-related warning signals in many cancer patients. The median age of all cancer patients is higher than that of the general population, and higher than the median age of a general practice population. In elderly people warning signals are at least as common as in young and middle-aged persons. A control group without cancer but matched for sex and age with a general sample of all cancer patients therefore would be expected to experience at least as many warning signals as were found in the population samples. An important question is whether cancer more than non-cancerous illness causes warning signals.

Individual assessment of each recorded warning signal, related to the cancer patient's medical history and clinical course, is needed to distinguish between warning signals with and without a probable relationship with subsequent cancer disease (43). It is not evident that warning signals unrelated to cancer occur or are recorded with the same frequency in cancer patients as in age- and sex-matched control patients from general practice. Different consultation rates and cancer-associated morbidity are among the factors which may influence the frequency of warning signals classified as not cancer-related. Careful judgment also is necessary to decide whether a warning signal classified as cancer-related occurred when the disease was still localized, and whether it retrospectively can be said to have contributed to an early diagnosis and to longer or better survival. Medical records, in spite of methodological problems which will be discussed, often are appropriate tools for such evaluations (43).

Each patient in the GP-material (chapter 5) was classified with or without a warning signal. The recordings were made by a general

practitioner at the end of each consultation. Unfortunately the mode of punching only permits counting of consultations, but it is possible to make approximate estimates of the number of patients in the cohort groups. A cohort study may show how many patients in each group who develop cancer in a limited time period after the consultation.

Further analysis of data may suggest whether a warning signal is recorded at consultation in a higher proportion of cancer patients than of patients without cancer, expressed as the likelihood ratio ([140]) of warning signals in relation to cancer. Calculation of positive predictive value (76) will suggest how probable cancer is in a patient with a warning signal recording. Analysis of age- and sex-matched pairs of cancer and control patients may give the odds ratio (83) as an estimate of the relative risk of cancer according to whether a warning signal had been recorded at consultation or not .

In addition, the case-control study based on medical records may give the odds ratio for cancer according to whether a cancer-related warning signal had been experienced or not during the weeks and months preceding cancer diagnosis. Although in general more possibilities for bias are inherent in retrospective than in prospective studies, information from a combined cohort and case-control study may strengthen conclusions.

b. Other cancer relevant information

Of the 108 cancer patients in Material 76, 35 experienced symptoms other than those corresponding to warning signals. These 35 patients had very different symptoms as well as diagnoses (table 19). The only fairly common denominator seemed to be "pain which does not move or disappear" (abbreviation: "Lasting pain"). At least 12 of the 35 patients had such a symptom if all locations were grouped together. In subsequent materials it was decided to record this symptom along with the seven warning signals. The intention was to see whether Lasting pain was as good a warning signal as any of the other warning signals.

Measurements of haemoglobin concentration (Hb) and erythrocyte sedimentation rate (ESR) are among the most frequently performed laboratory tests in general practice. A low haemoglobin concen-

Table 19. 35 patients with cancer-related symptoms other than warning signals. Material 76

* = Symptom due to a metastasis
F = Females, M = Males

Diagnosis	Symptoms before diagnosis	Sex	Age
Stomach cancer	Precordial pain	F	66
	Dyspnea, cyanosis*	M	71
	Sore throat. Anemia	F	76
	Depression. Long lasting constipation	M	83
Cancer of stomach and gallbladder	Icterus	F	79
Cancer of sigmoid colon	Inguinal "hernia", headache*	F	52
	Pelvic pain	F	77
Cancer of ascending colon	Bouts of fever	F	69
Pancreatic cancer	Thoracic pain	F	61
	Icterus	M	69
Maxillary cancer	Facial pain	F	83
Bronchial cancer	Back pain*	M	52
	Tachycardia, dyspnea on exertion	M	60
	Headache*	M	62
	Precordial pain	M	65
	Precordial pain	F	79
	Epistaxis, headache/facial pain	M	83
Cancer of ovary	Acute pain in right hypochondrium*	F	65
	Ileus	F	72
Prostatic cancer	Pain in the hip*	M	70
	Nocturia	M	73
	Low back and pelvic pain	M	73
	Weakness, anorexia	M	78
	Weakness, anorexia	M	83
	General prostatic symptoms	M	85
Cancer of penis	Phimosis	M	71
Cerebellar tumour (astrocytoma)	Headache, walking difficulties	M	2
Cerebral tumour	Epileptic fits, increasing frequency	F	56
	Rapid mental reduction	F	59
	Apoplexia	M	85
Malignant melanoma of chorioid (eyeball)	Reduced vision after a fall	M	74
Myelomatosis	Thoracic pain	F	63
	Back pain*	M	64
Abdominal cancer, unknown primary site	Acute abdomen	F	65
	Weakness, fever	F	86

tration discovered in a patient generally requires an explanation. Cancer is one of several possible causes of some forms of anaemia. Cancer also is one among many different diseases which may accelerate the ESR. The diagnostic value of these parameters therefore was considered separately in Material 83.

c. Problems with medical records

Medical records are often accessible and are commonly used for retrospective studies. Such studies are not influenced by current registration or control. However, results depend on several other factors:

I. How the notes are taken:
- -the patient's ability to describe -verbally or not verbally- his or her symptoms.
- -the doctor's ability to listen to and communicate with the patient.
- -the extent of the doctor`s examination.
- -the completeness and accuracy of what the doctor writes in the medical record.
- -legibility of notes.

II. How the medical record is interpreted:
- -the interpreter's personal and educational background.
- -the nature of the data to be interpreted and recorded.
- -the awareness and patience of the interpreter.

In the present study most records from general practice were unstructured, with no problem list or titling of progress notes ([141]). Hospital records sometimes contained problem lists. The number of patients in each material with medical records from general practice and hospitals, is shown in Appendix 1. An inter-observer approach could reveal important differences in the interpretation of records (II). This was why three observers independently examined Material 83. How the notes are taken (I) decides whether it is possible at all to find relevant information in the records. This will be discussed in connection with the validity of the findings in the different patient materials.

6-1. The study of warning signals in cancer patients and in matched control patients

Order of presentation
Materials and methods mainly were described in chapter 3. In the present chapter some details have been added in the introduction. The results are described for each material (Material 76, Material 82 and Material 83) concerning: a. warning signals, including the inter-observer study of Material 83, and b. other cancer-relevant information recorded from the medical records. The reliability and validity of these results and the conclusions which may be drawn are discussed in the final part of chapter 6.

In chapters 7 and 8 consequences of the findings in the present chapter are discussed in relation to the findings in the GP-material, Interviews-POP and Interviews-PAT from chapter 5 and the delay study in chapter 4. Chapter 7 gives a general discussion of all findings and relevant literature in relation to public health information about cancer. Chapter 8 focuses on possible strategies of early cancer diagnosis and reduced doctor's delay in general practice.

Results.

a. The warning signals

a-1. Cancer patients, 1976. Material 76
Sixty-eight patients (63%), 36 female and 32 male, presented warning signals. Table 2 shows the age and sex distribution of the 108 patients, 55 female and 53 male. The proportion of patients with warning signals is not significantly different for males and females. Sixty-two patients presented one warning signal and six patients two warning signals (table 20).

Lump and Indigestion were the most frequent warning signals recorded. Indigestion almost always suggested cancer in the digestive organs. Lump was most frequent in breast cancer. Skin cancers always manifested warning signals but were classified as Mole, Sore or Lump according to the description of symptoms. Bleeding was found to be relatively rare in these cancer

Table 20. Cancer patients and control patients by sex and by the number of warning signals recorded

Material 76 (Cancer patients only)

Warning signals per patient		0	1	2	3	4
Females	(n= 55)	19	33	3	-	-
Males	(n= 53)	21	29	3	-	-
Both sexes	(n=108)	40	62	6	-	-

Material 82

Warning signals per patient		0	1	2	3	4
Cancer patients						
Females	(n= 37)	8	21	6	2	-
Males	(n= 28)	8	16	4	-	-
Both sexes	(n= 65)	16	37	10	2	-
Control patients						
Females	(n= 37)	23	10	4	-	-
Males	(n= 28)	19	7	2	-	-
Both sexes	(n= 65)	42	17	6	-	-

Material 83

Warning signals per patient		0	1	2	3	4
Cancer patients, all warning signals						
Females	(n= 52)	12	27	10	3	-
Males	(n= 28)	6	14	8	-	-
Both sexes	(n= 80)	18	41	18	3	-
Cancer patients, only cancer-related w.s.						
Females	(n= 52)	20	24	7	1	-
Males	(n= 28)	9	12	7	-	-
Both sexes	(n= 80)	29	36	14	1	-
Control patients						
Females	(n= 52)	39	12	-	-	1
Males	(n= 28)	20	7	-	1	-
Both sexes	(n= 80)	59	19	-	1	1

patients (table 21a).

There was more patient delay (chapter 4) in the patients with than in the patients without a warning signal. Thirty-eight of 65 patients who experienced a warning signal had patient delay, but only ten of 38 patients with no recording of warning signal (p=0.002). The tendency was a little stronger for females than for males.

Within 12 weeks from the first symptom 37 of 64 patients (58%) who experienced a warning signal and 27 of 32 patients (84%) who had no warning signal had seen a doctor (P=0.02).

The sex distribution of warning signals in the various diagnostic groups is shown in table 22.

Combinations of warning signals in single cancer patients varied and are shown for all three materials in Appendix 4.

Thirty-five patients presented a heterogenous group of other main symptoms (table 23a, table 19). For seven of these 35 patients a metastasis was the cause of the initial symptom. Abdominal cancer was found to start with thoracic symptoms in a few cases. Persistant back pain occasionally stems from cancer.

Table 21a. Number of cancer-related individual warning signals recorded in the various diagnostic groups. 68 of 108 cancer patients

Material 76

Warning signal Diagnostic group	Sore	Lump	Bleeding	Mole	Indi-gestion	Cough/ hoarse-ness	Weight loss	Total
Buccal cavity, pharynx	5	1	-	-	-	-	-	6
Digestive organs	-	1	2	-	19	1	5	28
Respiratory system	-	-	-	-	-	3	1	4
Breast and genital organs	-	12	4	-	-	-	1	17
Urinary organs	-	1	1	-	-	-	1	3
Other and unspecified sites	4	3	-	7	1	-	-	15
Lymphatic and hemopoietic tissue	-	-	-	-	-	-	1	1
Total	9	18	7	7	20	4	9	74

Table 22. Number of cancer-related warning signals in the various diagnostic groups by sex of the patients

n = Number of patients with cancer-related warning signals
x = Number of cancer patients in the material

	Material 76			Material 82			Material 83		
	Females	Males	Both sexes	Females	Males	Both sexes	Females	Males	Both sexes
n/x Diagnostic group	36/55	32/53	68/108	29/37	20/28	49/65	32/52	19/28	51/80
Buccal cavity, pharynx	2	4	6	2	-	2	-	1	1
Digestive organs	11	17	28	15	13	28	11	10	21
Respiratory system	2	2	4	5	-	5	4	4	8
Breast and genital organs	15	2	17	8	-	8	17	2	19
Urinary organs	2	1	3	-	5	5	3	4	7
Other and unspecified sites	7	8	15	9	6	15	3	5	8
Lymphatic and hemopoietic tissue	-	1	1	-	-	-	3	-	3
Total	39	35	74	39	24	63	41	26	67

Thirty of the 35 patients with non-warning signal symptoms were more than 60 years of age (table 19). The proportion of patients with warning signals was significantly higher in patients below 60 years than in patients 60 years of age or more ($p=0.03$), but the difference is not significant for males or females separately.

The four patients with a brain tumour and six of seven patients with prostatic cancer did not present any warning signal. Several persons with stomach cancer or bronchial cancer experienced no warning signal (table 19).

Table 24 compares the quantitative importance of the warning signals in the general population (Interviews-POP, chapter 5), the patient population (GP-material, chapter 5) and the cancer patient population in Material 76. The distribution of the different warning signals differs significantly in all materials ($P<0.001$ except for the difference in warning signal distribution between the general population and the cancer patient population, where $P=0.02$).

Table 23a. Number of cancer patients with warning signals and with other cancer related symptoms in the various diagnostic groups

Material 76

Diagnostic group	Warning signal	Other symptom	No symptom/ no information	Total	Per cent
Buccal cavity, pharynx	6	-	-	6	5,6%
Digestive organs	24	10	-	34	31,5%
Respiratory system	3	7	-	10	9,3%
Breast and genital organs	17	9	-	26	24,0%
Urinary organs	2	-	-	2	1,9%
Other and unspecified sites	15	7	4	26	24,0%
Lymphatic and hemopoietic tissue	1	2	1	4	3,7%
Total	68	35	5	108	100,0%

Table 24. Quantitative importance of warning signals in various population groups. Tromsø, Norway, 1976 and 1982

n = number of persons/consultations/cancer patients
x = size of the population sample

Number of warning signals recorded, in decreasing frequency

General population **Interviews-POP, 1976** n/x = 74/299		Patient population **GP-Material, 1982** n/x = 629/11 606		Cancer patients **Material 76, 1976** n/x = 68/108	
Indigestion	35	Lump	243	Indigestion	20
Lump	18	Bleeding	153	Lump	18
Cough/hoarseness	16	Indigestion	141	Sore	9
Mole	11	Cough/hoarseness	52	Weight loss	9
Bleeding	5	Sore	26	Mole	7
Sore	4	Weight loss	19	Bleeding	7
Weight loss	3	Mole	15	Cough/hoarseness	4
Total	92		649		74

a-2. Cancer patients and matched control patients 1981-82.

Material 82

Sixty-five patients, 37 female and 28 male, are included in each group. The age and sex distribution (table 25) does not differ significantly from that of Material 76.

Warning signals, all of them related to the cancer disease, were recorded in 49 cancer patients (75%), 29 female and 20 male patients (table 20, table 23b). In 41 of these cancer patients at least one warning signal was recorded as an early warning signal (table 26). The sex distribution of cancer patients with warning signals or of cancer patients with early warning signals is not significanctly different from that of all patients.

Table 25. Age and sex distribution of each of the two groups of patients, cancer patients and matched control patients

Material 82

Age	Females	Males	Both sexes
1-19	1	-	1
20-29	2	-	2
30-39	3	1	4
40-49	4	1	5
50-59	7	6	13
60-69	5	10	15
70-89	15	10	25
Total	37	28	80

Material 83

Age	Females	Males	Both sexes
1-19	1	-	1
20-29	7	-	7
30-39	13	2	15
40-49	4	2	6
50-59	4	2	6
60-69	11	12	23
70-89	12	10	22
Total	52	28	80

Table 26. Number of individual cancer-related warning signals according to early/late estimations and by sex of the patients.

F = Females
M = Males
n = Number of patients with 1-3 warning signal recording(s). Patients with both early and late warning signals are counted as "early", patients with only late warning signals as "late"
x = Number of patients in the material

Material 82

	Early warning signals			Late warning signals		
	F	M	F + M	F	M	F + M
n/x	22/37	19/28	41/65	7/37	1/28	8/65
Warning signal						
Sore	2	3	5	-	-	-
Lump	12	3	15	4	-	4
Bleeding	7	5	12	-	-	-
Mole	-	-	-	-	-	-
Indigestion	4	5	9	3	3	6
Cough/hoarseness	2	-	2	-	-	-
Weight loss	2	4	6	3	1	4
Total	29	20	49	10	4	14

Material 83

	Early warning signals			Late warning signals		
	F	M	F + M	F	M	F + M
n/x	26/52	16/28	42/80	6/52	3/28	9/80
Warning signal						
Sore	-	-	-	-	-	-
Lump	10	4	14	2	1	3
Bleeding	11	9	20	2	-	2
Mole	-	1	1	-	-	-
Indigestion	6	4	10	1	1	2
Cough/hoarseness	1	1	2	1	1	2
Weight loss	4	2	6	3	2	5
Total	32	21	53	9	5	14

In the matched control patients warning signals were noted in 14 female (38%) and nine male (32%) patients. This is a considerable proportion of the control patients, but it is significantly less than in the cancer patients ($p<0.001$ for all patients, $p<0.01$ for females, $p<0.05$ for males, all with McNemar test with Yates' correction). Table 27 shows the sex distribution of individual warning signals among cancer patients and control patients. The distribution of the different recorded warning signals in cancer patients and control patients is significantly different for females ($p=0.047$), but not for males or for males and females together. The sex distribution of all the warning signals is not significantly different for cancer patients and the matched control patients. The proportion of patients with warning signals was not different for patients 60 years of age or more compared with patients less than 60 years of age, neither for cancer patients nor for control patients.

Tables 21-23 deal with the various diagnostic groups.

Table 21b shows the distribution of each warning signal in the diagnostic groups. There is no significant difference from Material 76 in the distribution of the different warning signals, or in the distribution of the number of warning signals in the different diagnostic groups.

Table 22 shows the sex distribution of warning signals in the diagnostic groups. There is no significant difference from Material 76.

Table 21b. Number of cancer-related individual warning signals recorded in the various diagnostic groups. 49 of 65 cancer patients.

Material 82

Warning signal Diagnostic group	Sore	Lump	Bleeding	Mole	Indi-gestion	Cough/ hoarse-ness	Weight loss	Total
Buccal cavity, pharynx	1	1	-	-	-	-	-	2
Digestive organs	-	-	5	-	14	-	9	28
Respiratory system	-	1	1	-	1	2	-	5
Breast and genital organs	-	6	2	-	-	-	-	8
Urinary organs	-	-	4	-	-	-	1	5
Other and unspecified sites	4	11	-	-	-	-	-	15
Lymphatic and hemopoietic tissue	-	-	-	-	-	-	-	-
Total	5	19	12	-	15	2	10	63

One patient had two separate cancers belonging to different diagnostic groups; see text

Table 23b. Number of cancer patients with warning signals and with other cancer-related symptoms in the various diagnostic groups

Material 82

Diagnostic group	Warning signal	Other symptom	No symptom/ no information	Total	Per cent
Buccal cavity, pharynx	1	-	-	1	1,5%
Digestive organs	18	2	1	21	32,3%
Respiratory system	2	-	-	2	3,1%
Breast and genital organs	8	4	2	14	21,5%
Urinary organs	5	1	-	6	9,2%
Other and unspecified sites	15	1	4	20	30,8%
Lymphatic and hemopoietic tissue	-	1	-	1	1,5%
Total	49	9	7	65	99,9%

Table 27. Number of individual warning signals recorded from the medical records of 65 cancer patients (cancer related warning signals only) -and 65 matched control patients. Distribution by sex of the patient. Material 82

F = Females
M = Males
n = Number of patients with 1-3 warning signal recording(s)
x = Number of patients in the material

	Cancer patients			Matched control patients		
	F	M	F + M	F	M	F + M
n/x	29/37	20/28	49/65	14/37	9/28	23/65
Warning signal						
Sore	2	3	5	-	-	-
Lump	16	3	19	1	3	4
Bleeding	7	5	12	5	1	6
Mole	-	-	-	-	1	1
Indigestion	7	8	15	9	5	14
Cough/hoarseness	2	-	2	1	-	1
Weight loss	5	5	10	2	1	3
Total	39	24	63	18	11	29

Table 23b shows the distribution in diagnostic groups of cancer patients with and without warning signals. This distribution does not differ significantly from the distribution of diagnostic groups in Material 76, neither for all patients nor when such analysis is limited to the patients with warning signals.

Symptoms other than warning signals in nine patients (table 23b) were weakness and general symptoms for a leukaemic child, a woman with cancer of the colon and a man with bladder cancer. Four men had prostatic cancer, three of them with ordinary prostatic symptoms similar to symptoms of adenoma patients, the fourth had back and sternal pain because of bone metastases. One woman with a thyroid cancer complained of throat irritation at swallowing. One woman with ileus died, and the autopsy showed a sigmoid cancer and breast cancer.

In the group of patients with no symptoms (table 23b) there were two cervical carcinomas. Two thyroid cancers were discovered at autopsy. Two other thyroid cancers were discovered during routine seamen's medical controls without having been suspected by the patient. There was insufficient information about one woman with stomach cancer who died in an old people's home.

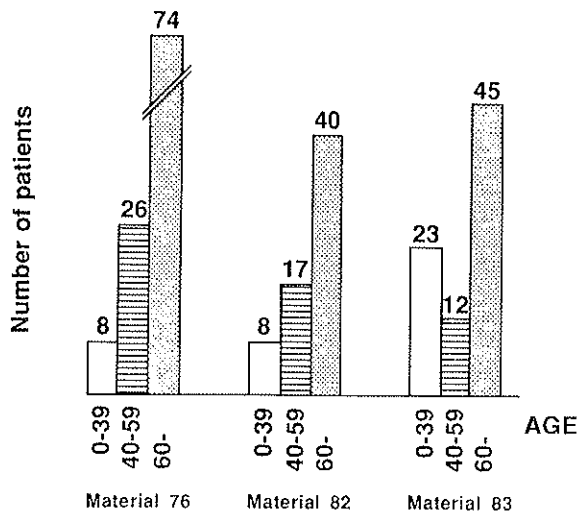
a-3. Cancer patients and matched control patients 1981-83. Material 83.

a-3-A. The case-control study based on warning signals in medical records.

Age and sex distribution of the patients is shown in table 25. Material 83 differs in several respects from Material 76 and Material 82. This will be discussed later, but it should be kept in mind that Material 76 and Material 82 are complete or almost complete registrations of cancer patients for a specified time period, while Material 83 includes only patients who consulted a general practitioner previous to the cancer diagnosis. People who consult directly in specialized services and have their cancer diagnosed there, and people whose cancer is diagnosed post-mortem, are not included in Material 83. All three materials deal with patients from the same limited geographical area. The sex distri-

bution in Material 83 is close to significantly different from Material 76 ($p=0.054$), but not from Material 82 ($p=0.32$). The age distribution of Material 83 is significantly different from Material 76 ($p<0.001$) and close to significantly different from Material 82 ($p=0.056$). Figure 9 shows the age distribution in the three materials when the five-year age groups have been combined to form three different age groups. Compared to all registered cancer patients in Norway in 1982 ([142]) there are no significant differences in age or sex distribution for Material 76 or Material 82, while Material 83 differs significantly from the national material (sex distribution: $p=0.02$ with relatively more female patients in Material 83, age distribution: $p<0.001$). Material 83 differs from Material 76 and from the national material in that there are relatively more female patients aged 20-39 years and relatively fewer females in the age groups 50-59 and 70-89 years. The national material like Material 76, Material 82 and Material 83 includes stage 0 cancer of the uterine cervix, papilloma of the urinary bladder, basocellular carcinoma and skin cancer not histologically verified.

Fig. 9. Age distribution of cancer patients in Material 76, Material 82 and Material 83.



Individual diagnoses in the three materials have been listed as subgroups of the main diagnostic groups in Appendix 5. One patient in Material 76, two patients in Material 82 and three patients in Material 83 had two new cancer diagnoses during the registration period. For one patient in Material 82 and two patients in Material 83 two main diagnostic groups were involved. In tables 21-23 only the diagnoses considered the most productive of symptoms and/or important for the prognosis are included for these three patients; a symptom-giving sigmoid cancer rather than an asymptomatic breast cancer, stomach and bladder cancer rather than cancers of the prostate. Included in Appendix 5 is sex distribution and whether individual patients had warning signal recordings.

Most recordings for all three observers are described in part a-3-C of this results section. For warning signal comparison with Material 76 and Material 82, and comparison between cancer and control patients, my own recordings from Material 83 are presented here:

Table 21c. Number of cancer-related individual warning signals recorded in the various diagnostic groups. 51 of 80 cancer patients

Material 83.

Warning signal Diagnostic group	Sore	Lump	Bleeding	Mole	Indi-gestion	Cough/ hoarse-ness	Weight loss	Total
Buccal cavity, pharynx	-	1	-	-	-	-	-	1
Digestive organs	-	-	8	-	10	-	3	21
Respiratory system	-	2	1	-	1	2	2	8
Breast and genital organs	-	8	9	-	1	-	1	19
Urinary organs	-	-	4	-	-	-	3	7
Other and unspecified sites	-	5	-	1	-	1	1	8
Lymphatic and hemopoietic tissue	-	1	-	-	-	1	1	3
Total	-	17	22	1	12	4	11	67

Two patients had two separate cancers belonging to different diagnostic groups; see text

Table 23c. Number of cancer patients with warning signals and with other cancer-related symptoms in the various diagnostic groups

Material 83

Diagnostic group	Warning signal	Other symptom/ no symptom/ no information	Total	Per cent
Buccal cavity, pharynx	1	-	1	1,3%
Digestive organs	13	5	18	22,5%
Respiratory system	4	1	5	6,3%
Breast and genital organs	18	18	36	45,0%
Urinary organs	7	-	7	8,8%
Other and unspecified sites	7	4	11	13,8%
Lymphatic and hemopoietic tissue	1	1	2	2,5%
Total	51	29	80	100,2%

Table 28. Warning signals from medical records in matched pairs of 80 cancer patients and 80 control patients. Material 83

		Cancer patients	
		Warning signal	No warning signal
Control patients	Warning signal	15	6
	No warning signal	47	12

Odds ratio = 7.8 (3.3 - 22.4)

I noted warning signals in 62 cancer patients (78%) and in 21 control patients (26%) (table 28). The difference is significant ($p<0.001$). Odds ratio is 7.8 with a 95% confidence interval from 3.3 to 22.4. Cancer-related warning-signals were recorded in 51 cancer patients (64%) (table 20, table 23c). This is also significantly more than in the control patients ($p<0.001$ for all patients and for females separately, $p<0.05$ for males with McNemar test with Yates' correction).

The proportion of patients with warning signals, or with cancer-related warning signals only or early cancer-related warning signals only, did not differ significantly for males and females. Nor were there any such differences between patients below 60 years and patients 60 years of age or more.

Like in Material 82 most cancer-related warning signals in Material 83 are estimated to have occurred early (table 26). Only Weight loss is classified as late almost as often as early in both materials.

The various diagnostic groups are considered in tables 21-23. Material 83 differs significantly from Material 76 ($p=0.008$) and from Material 82 (0.046) in the distribution of patients in the different diagnostic groups, but not in the distribution of patients with cancer-relevant warning signals in the different diagnostic groups, or in the distribution of the total number of cancer-relevant warning signals in the different diagnostic groups. This is mainly due to a low rate of warning signals in the diagnostic group which is overrepresented in Material 83 compared to the two other materials; Breast and genital organs (table 23c). Within this group cervical cancer is the disease which causes the overrepresentation (Appendix 5). Analysed separately for males and females there is a significant difference in the distribution of warnings signals in the different diagnostic groups between Material 83 and Material 82 for females ($p=0.02$), but this difference is not due to one diagnostic group in particular (table 22).

Furthermore, in the distribution of patients in the different diagnostic groups there was no significant difference between the national material of cancer patients in 1982 and Material 82. There is a difference in relation to Material 76 ($0.01<p<0.001$)

and Material 83 (p=0.04), but analyzed for each sex these differences are not statistically significant. Material 76 has relatively more patients in the "Buccal cavity, pharynx" and "Digestive organs" groups than the national material. Material 83 has relatively more female patients in "Breast and genital organs", mostly because of cervical cancer, and relatively fewer female patients in "Other and unspecified sites", mostly because there are few cases of basocellular carcinoma.

Table 29 (and table 21a-c) compare the distribution of the different warning signals in the three materials of cancer patients. There is a significant difference between Material 83 and Material 76 (p<0.001) mainly due to differences in the recordings of Sore, Bleeding and Mole. Between Material 83 and Material 82 there is no significant difference in this distribution.

Table 29. Quantitative importance of cancer-related warning signals in three groups of cancer patients

n = Number of cancer patients with cancer-related warning signal recording(s) from medical records
x = Number of cancer patients in the material

Number of warning signals recorded, in decreasing frequency

Material 76 n/x = 68/108		Material 82 n/x = 49/65		Material 83 n/x = 51/80	
Indigestion	20	Lump	19	Bleeding	22
Lump	18	Indigestion	15	Lump	17
Sore	9	Bleeding	12	Indigestion	12
Weight loss	9	Weight loss	10	Weight loss	11
Mole	7	Sore	5	Cough/hoarseness	4
Bleeding	7	Cough/hoarseness	2	Mole	1
Cough/hoarseness	4	Mole	0	Sore	0
Total	74		63		67

Figure 10 (like table 23) compares the number of cancer patients in each material with and without a cancer-related warning signal. Differences in the diagnostic distribution between the three materials will be considered in the discussion.

The patients had their diagnoses registered during an eighteen month period. This period was divided into three six months periods. Patients diagnosed during the last half year have a longer observation period and might be expected to have experienced more warning signals. For control patients there was a non-significant tendency in this direction, but not for cancer patients. For cancer related symptoms there were fewer patients with warning signals in the last six-month period, probably due to an over-representation of younger women with symptom-poor cancer of the cervix in this period.

Fig. 10. Number of cancer patients in each material with and without cancer-related warning signal(s) recorded from the medical records.

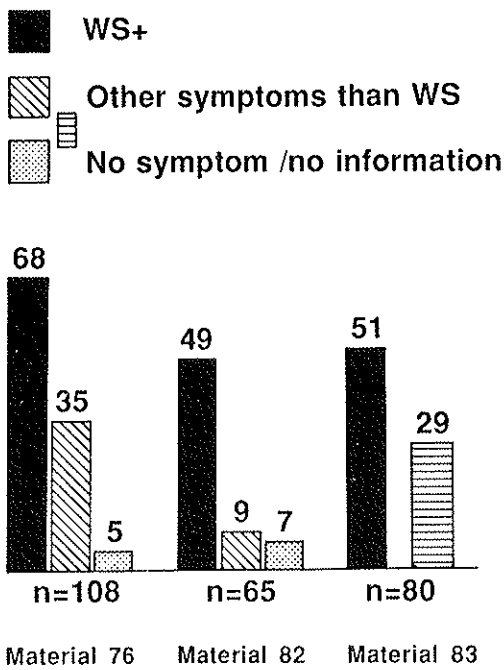


Table 30. Number of individual warning signals which were probably **not** cancer-related, distributed by sex of the patient. Material 83

F = Females
M = Males
n = Number of patients with such warning signals
x = Number of patients in the material

	Cancer patients			Control patients		
	F	M	F + M	F	M	F + M
n/x	12/52	4/28	16/80	13/52	8/28	21/80
Warning signal						
Sore	2	-	2	-	1	1
Lump	2	1	3	2	1	3
Bleeding	5	-	5	8	2	10
Mole	1	-	1	-	1	1
Indigestion	3	3	6	4	3	7
Cough/hoarseness	2	-	2	1	2	3
Weight loss	-	-	-	1	-	1
Total	15	4	19	16	10	26

Table 30 compares not-cancer-related warning signals in cancer patients and control patients. The distribution of the different not-cancer-related warning signals is not significantly different in cancer patients and control patients. There are twice as many recordings of Bleeding in control patients as in cancer patients. Otherwise recordings are very similar for the two groups. The sex distribution of patients with not-cancer-related warning signals is not significantly different for cancer patients and control patients.

a-3-B. The cohort study and the case-control study based on warning signals recorded at consultation

As to warning signals recorded **at consultation** prior to diagnosis, ten of 28 male cancer patients and ten of 52 female cancer patients had one or two warning signal recordings. This difference between the sexes is not significant (P=0.18). Ten female control patients and three male control patients had one or two warning signal recordings (table 31-32). Cancer patients have more recordings but the difference is not significant (0.10<P<0.20). Odds ratio is 1.9 with a 95% confidence interval from 0.8 to 5.1.

I estimated that 10 000 patients made the 11 606 consultations (GP-material, chapter 5). From my knowledge of the material I think this is fairly close to the true number. It corresponds to 542 patients having contributed to the 629 consultations where warning signals were recorded, assuming that the number of repeat consultations is not different in patients with and without warning signals. Given these approximations the following results are obtained: Sensitivity is 25%, specificity 95%. The prevalence of cancer or prior probability of disease is 0.8%, and positive predictive value of a warning signal recorded at consultation is 3.7%. The likelihood ratio is 4.8, which suggests that the proportion of patients with warning signals was almost five times higher in cancer patients than in patients without cancer.

The likelihood ratio for **no** warning signal recording in a cancer patient is 0.8.

If we consider how many of the matched control patients who had a warning signal recorded by a general practitioner, we may calculate the specificity of warning signals in this group as 67 out of 80 patients, or 84%. An estimate of the likelihood ratio for the two matched groups using the sensitivity of 25% found in the cohort study then would be 1.5.

Calculations may be made for individual warning signals. Lump has a positive predictive value of 3.3% and Bleeding 5.3% when the consultation-based figures in table 15 are converted to an estimated number of patients (tables 15 and 31). For the other warning signals the number of recordings in table 31 are too small to make such calculations meaningful. Table 33 gathers some

Table 31. Number of warning signals recorded **at consultation** before diagnosis in cancer patients and in their matched control patients, by sex of the patients. Material 83

F = Females
M = Males
n = Number of patients
x = Number of patients in the material

	Cancer patients			Control patients		
	F	M	F + M	F	M	F + M
n/x Warning signal	10/52	10/28	20/80	10/52	3/28	13/80
Sore	1	-	1	-	-	-
Lump	5	2	7	4	1	5
Bleeding	3	4	7	1	2	3
Mole	-	1	1	1	-	1
Indigestion	-	4	4	2	1	3
Cough/hoarseness	2	-	2	1	-	1
Weight loss	-	2	2	2	-	2
Total	11	13	24	11	4	15

Table 32. Warning signals recorded **at consultation** in matched pairs of 80 subsequent cancer patients and 80 control patients. Material 83

		Subsequent cancer patients	
		Warning signal	No warning signal
Control patients	Warning signal	5	8
	No warning signal	15	52

Odds ratio = 1.9 (0.8 - 5.1)

Table 33. Some indexes of diagnostic usefulness of warning signals of cancer. Material 83

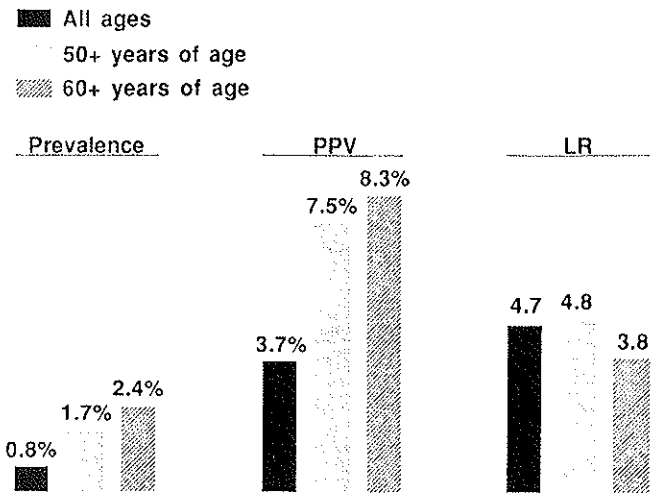
yrs = years of age

	All seven warning signals			Lump	Bleeding
	All ages	50+yrs	60+yrs		
Prevalence of cancer (%)	0.8	1.7	2.4		
Positive predictive value (%)	3.7	7.5	8.3	3.3	5.3
Likelihood ratio	4.7	4.8	3.8	4.4	6.8

indexes of diagnostic usefulness of warning signals. With increasing age there is an increase in the positive predictive value of a warning signal, reflecting the higher prevalence of cancer in old persons. The likelihood ratio for warning signals in patients with and without cancer does not increase with age (table 33, fig 11).

A total of 20 cancer patients had warning signal recording(s) at consultation. For these 20 cancer patients, consultation recordings and the corresponding recordings from medical records made by all three observers are compared in table 34. The diagnosis, and my estimation of how potentially useful the warning signals recorded before diagnosis had been for each patient, are also noted in table 34. Only two warning signals recorded at consultation were not recorded from the medical records by any of the observers. One of these two was Mole in a patient with a squamous cell carcinoma of the skin, and it was presumably the same lesion which was recorded by all three observers as Lump. Of the remaining 22 warning signals noted at consultation 17 were found in the records by all three observers, two by two observers and three by one observer (table 34).

Fig. 11. Changing diagnostic indexes with increasing age: Positive predictive value (PPV) of a warning signal in relation to cancer, and likelihood ratio (LR).



Among these 20 patients with warning signal(s) at consultation, there were three women for whom no observer found any connection between the warning signal and the cancer. For the remaining 17 cancer patients, warning signals might have been useful for nine (three women and six men), somewhat useful for five (four women and one man), and of little or no use for three (all men). This means that 14 out of 80 (17,5%) may have been helped by warning signals at consultation. As might be expected from the delay study (chapter 4), the diagnostic procedure after the first consultation did not appear to have been the best possible for all of the 14 patients. Whether any potential benefit from the warning signals thereby was lost, was not further evaluated.

Five of the 17 remaining cancer patients had low-grade malignancies with uncertain spontaneous evolution. Their warning signals were estimated as useful (one woman and three men) or somewhat useful (one man).

For the 13 control patients with warning signal recording(s) at consultation, seven of 15 warning signals at consultation were not found in the medical records. Only four warning signals were found by all three observers.

Table 34. Usefulness of warning signals occurring before diagnosis. Recordings at consultation before diagnosis, and from medical records after diagnosis, in 20 cancer patients

F = Female
M = Male
WS = Warning signal
GP = General practitioner
Obs = Observer
Abbreviations, warning signals: Bl = Bleeding
Ind = Indigestion
C/H = Cough/hoarseness
W.L.= Weight loss
(warning signal in brackets = "probably not cancer-related WS")

Usefulness: 0 = not useful, or palliation of short duration
1 = somewhat useful
2 = useful
* = usefulness uncertain because of low-grade malignancy with uncertain spontaneous evolution
- = recorded warning signal probably not cancer-related

Year of death: Patients with a blank space were alive in 1989

Sex	Age at dia-gnosis	Year of death	WS recorded by GP	WS recorded by Obs1	Obs2	Obs3	Diagnosis	Usefulness
M	78	1982	Weight loss	W.L.	W.L.	W.L. Ind	Clear cell adenocarcinoma of kidney	0
F	77	1982	Sore	(Sore) Lump	(Sore) Lump	Lump	Papillary adenocarcinoma of thyroid gland	-
F	76		Bleeding	(Bl)	(Bl)	Bl (Ind)	Tubular adenoma of colon, dysplasia	2*
F	74		Lump	Lump	Lump	Lump	Ductal adenocarcinoma of breast	2
M	73	1985	Lump Indigestion	Lump (Ind)	Lump (Ind)	Lump	Adenocarcinoma of sublingual gland	2
M	69	1982	Indigestion	Ind	Ind	Ind W.L. (Lump)	Stomach cancer	0
F	68		Bleeding	Bl	Bl	Bl	Squamous cell carcinoma of cervix uteri	2

Table 34 (cont.)

Sex	Age at dia-gnosis	Year of death	WS recorded by GP	WS recorded by Obs1	Obs2	Obs3	Diagnosis	Usefulness
M	68	1990	Bleeding	Bl	Bl	Bl	Adenoma/highly differentiated adenocarcinoma of prostate	1*
M	67	1988	Bleeding	Bl Ind	Bl (Ind) (W.L.)	Bl	Tubular adenoma of colon, dysplasia	2*
M	67	1982	Bleeding Indigestion Weight loss	W.L. C/H	Ind W.L. (C/H)	W.L. C/H	Adenocarcinoma of abdomen -unknown primary focus	0
M	64		Mole	Lump	Lump	Lump	Squamous cell carcinoma of skin	2*
F	63	1983	Cough/ hoarseness	(C/H) W.L. (Mole)	(C/H) W.L. (Mole)	(C/H) W.L. (Mole)	Clear cell adenocarcinoma of kidney	-
M	62		Bleeding		Bl	(Lump)	Adenocarcinoma of prostate, highly differentiated	2*
F	57	1984	Lump	Lump	Lump Bl Ind	Lump Bl Ind	Adenocarcinoma of ovary	1
M	57		Indigestion	Ind	Ind	Ind	Adenocarcinoma of stomach	2
F	50	1984	Bleeding	Bl	Bl Lump	Bl	Papillary cystadenoma of ovary	1
F	48	1982	Lump Cough/ hoarseness	Lump C/H	Lump C/H	Lump C/H	Bronchial carcinoma (oat cell)	1
F	33		Lump	(Lump)			Carcinoma in situ of cervix uteri	-
F	33	1988	Lump	Lump	Lump	Lump	Adenocarcinoma of breast	1
M	32		Lump	Lump	Lump	Lump	Teratocarcinoma/ seminoma of testicle	2

Table 35. Inter-observer variation of warning signal recordings, sex distributed

F = Females
M = Males

		Number of patients					
		Observer 1		Observer 2		Observer 3	
		F	M	F	M	F	M
Cancer patients	Warning signal(s) recorded	40	22	43	23	39	21
	No warning signal recorded	12	6	9	5	13	7
Control patients	Warning signal(s) recorded	13	8	18	9	11	9
	No warning signal recorded	39	20	34	19	41	19

a-3-C. The inter-observer study

Table 35 shows inter-observer variation as to how many patients were registered with at least one warning signal. Significantly more warning signals were recorded in cancer patients than in control patients ($P<0.001$ with McNemar's test for each of the three observers).

Table 36 shows inter-observer variation in the number of warning signals recorded per patient. Altogether 360 warning signals were recorded by the three observers, ranging from 86 to 97 warning signals per observer in the cancer group and from 26 to 33 in the control group.

The proportion of patients with warning signals was on average for the three observers, 78% of cancer patients and 28% of control patients. In 63% of the cancer patients warning signals had a probable[7] cancer relationship.

[7] "probable" is omitted in the following text

Table 36. Inter-observer variation in number of warning signals recorded per patient in 80 cancer patients and 80 matched control patients. Number of patients

Warning signals per patient	0	1	2	3	4
Cancer patients					
Observer 1	18	41	18	3	-
Observer 2	14	42	17	7	-
Observer 3	20	34	20	6	-
Control patients					
Observer 1	59	19	-	1	1
Observer 2	53	24	1	1	1
Observer 3	60	16	3	-	1

Inter-observer agreement on the presence or absence of warning signals is shown for each of the five most recorded warning signals in table 37. For the two remaining signals "Sore" and "Mole" there were too few recordings to justify such analysis separately; no doctor had more than two recordings in each patient group for any of these two warning signals. They are, however, included in the figures for all seven warning signals in tables 37-39. Figures include overall agreement, agreement expected by chance, and kappa. Figures are given as average values for the three observer pairs[8], with range values for kappa, calculated for each observer pair. For the group of cancer patients agreement is good and consistent; "Indigestion" and "Lump" having the lowest average kappas of 0.59 and 0.64 respectively. For control

[8] Observer pair A = Observers 1+2
Observer pair B = Observers 1+3
Observer pair C = Observers 2+3

Table 37. Inter-observer agreement on the presence or absence of five warning signals, and on all seven warning signals together. All patients

	Overall agreement	Expected agreement	Kappa	Kappa range
Lump				
Cancer patients	0.85	0.60	0.64	0.61-0.68
Control patients	0.94	0.87	0.59	0.39-0.88
Bleeding				
Cancer patients	0.89	0.55	0.78	0.76-0.80
Control patients	0.93	0.83	0.57	0.42-0.74
Indigestion				
Cancer patients	0.84	0.62	0.59	0.56-0.61
Control patients	0.93	0.81	0.62	0.56-0.68
Cough/hoarseness				
Cancer patients	0.97	0.87	0.77	0.61-0.85
Control patients	0.98	0.96	0.40	0 -0.60
Weight loss				
Cancer patients	0.97	0.75	0.88	0.80-0.92
Control patients	0.97	0.95	0.51	0.26-1
All seven warning signals				
Cancer patients	0.93	0.73	0.74	0.72-0.75
Control patients	0.96	0.90	0.55	0.49-0.60

patients there is about the same overall agreement, but with lower registration rates for warning signals agreement by chance is enhanced. This, then, is reflected in lower kappa values and greater differences between observer pairs.

In table 37 no observer pair had any tendency of constantly scoring the highest or the lowest kappa values.

For cancer patients the same analysis was carried out separately for warning signals with and without a probable connection with the cancer disease (table 38). Observer pair B tended to have the highest kappa values for cancer-related symptoms, but there were several exceptions.

Table 38. Inter-observer agreement on the presence or absence of five warning signals, with and without a probable relationship with the patient's cancer disease, and on all seven warning signals together. All cancer patients

	Relation to the cancer	Overall agreement	Expected agreement	Kappa	Kappa range
Lump	likely	0.95	0.66	0.87	0.83-0.94
	unlikely	0.89	0.88	0.10	-0.04-0.19
Bleeding	likely	0.91	0.63	0.76	0.73-0.80
	unlikely	0.89	0.83	0.34	0.23-0.46
Indigestion	likely	0.89	0.72	0.62	0.56-0.70
	unlikely	0.90	0.83	0.41	0.40-0.42
Cough/hoarseness	likely	0.98	0.91	0.73	0.53-0.88
	unlikely	0.97	0.95	0.54	0.31-1
Weight loss	likely	0.98	0.75	0.91	0.84-0.96
	unlikely	0.99	0.99	0	0
All seven warning signals	likely	0.95	0.79	0.78	0.76-0.81
	unlikely	0.95	0.91	0.38	0.34-0.43

The most important kappa differences between patient groups, based on average values for all three observer pairs, are summed up in table 39. Approximate 95% confidence intervals are found by subtracting and adding 2SE to the calculated kappa (65). Observer agreement is significantly higher for cancer patients than for control patients. So is the case for warning signals which are cancer related compared to those not cancer related. The differences between the sexes based on all seven warning signals are not significant neither for cancer patients nor for control

Table 39. Analysis of kappa differences, based on average values for all three observer pairs

N = Number of warning signal pairs for each observer pair
Kappa is given with approximate 95% confidence intervals in brackets

Warning signals in:	N	Kappa	P-value
cancer patients	560	0.74 (0.66-0.82)	P<0.001
control patients	560	0.55 (0.49-0.61)	
cancer patients, probably cancer related	560	0.78 (0.70-0.86)	P<0.001
cancer patients, probably not cancer related	560	0.38 (0.34-0.42)	
female cancer patients	364	0.76 (0.66-0.86)	P=0.4
male cancer patients	196	0.68 (0.54-0.82)	
cancer patients: "lump", probably cancer related	80	0.87 (0.65-1)	P=0.1
cancer patients: "indigestion", probably cancer related	80	0.62 (0.40-0.84)	

patients (Separate calculations for female and male patients, corresponding to tables 37-38, are added in Appendix 6). One might suspect from the kappa values that agreement on "Lump" is better than agreement on "Indigestion", but comparison of kappas gives P=0.11.

Warning signals noted by all three observers are presented in table 40. Among cancer patients two men and seven women had no recordings at all. Fifteen male and 28 female control patients had no recordings.

Most of the cancer-related warning signals were estimated by all three observers to have occurred early. One observer had only two "late" classifications, while the two others had about one fourth of the warning signals classified as having occurred late.

The author's repeated recordings three years apart included 16 cancer patients and 14 control patients common to Material 82 and

Table 40. Agreement between all three observers. Number of warning signal triplets with complete agreement, or with complete or partial disagreement

WS = Warning signal
N = Number of patients = number of warning signal triplets
F = Females
M = Males
Dis = Disagreement, complete or partial
(not) CR = Probably (not) cancer-related

	Cancer patients							Control patients				
	Agreement all three observers				Dis	N		Agreement all three observers			Dis	N
	WS, CR		WS, not CR		No WS			WS		No WS		
WS	F	M	F	M				F	M			
Sore	-	-	-	-	77	3	80	-	-	77	3	80
Lump	11	4	-	-	47	18	80	2	1	70	7	80
Bleeding	8	7	1	-	46	18	80	3	1	67	9	80
Mole	-	-	1	-	78	1	80	-	1	78	1	80
Indigestion	5	2	2	1	49	21	80	3	2	66	9	80
Cough/ hoarseness	2	-	1	-	72	5	80	-	-	77	3	80
Weight loss	5	4	-	-	66	5	80	1	-	75	4	80
Total	31	17	5	1	435	71	560	9	5	510	36	560

Material 83. Kappa values based on such a low number of patients with a limited number of warning signals have limited meaning. The overall impression is that agreement in this intra-observer approach is about as in the inter-observer study: good for cancer-related warning signals and less good for warning signals not related to cancer.

b. Other cancer relevant information

b-1. Lasting pain

From the medical records of the 65 cancer patients in Material 82, Lasting pain was recorded in eight women and six men. In four of the women and four of the men it was recorded as an early symptom. One of the women and two of the men also had one or two warning signals. Control patients had Lasting pain recordings in 15 women and six men. Two women and two men had a warning signal as well.

The recordings based on medical records in Material 83 were similar to those of Material 82.

A general practitioner's recording of Lasting pain had been made for four of the 80 cancer patients and eight of the 80 control patients. For one cancer patient two observers of medical records thought this was a cancer-related symptom, for another cancer patient one of the observers thought so. For control patients seven of the eight Lasting pain recordings also were noted from the records; in five cases by all three observers.

In the population interviews (Interviews-POP) Lasting pain had been experienced during the last three months by 15 of 299 patients (5%). In these interviews Indigestion and Lump were more common than Lasting pain. Six of eight women and five of seven men had consulted a doctor for Lasting pain.

In the registrations by general practitioners Lasting pain was recorded in 2.9% of the 11 606 consultations, more often than any warning signal. In the patient interviews (Interviews-PAT) 24% said they had presented Lasting pain.

b-2. The haemoglobin concentration and the erythrocyte sedimentation rate

In Material 83 12 cancer patients (15%) and five control patients had recorded measurements of Hb <110 g/l (females) or <130 g/l (males) before diagnosis. This difference is not significant ($0.05<P<0.10$) (table 41). Odds ratio is 2.4 with a 95% confidence interval from 0.8 to 8.7.

Twenty-six cancer patients (33%) and six control patients had an ESR >20 mm/hour ($P<0.001$) (table 42). Odds ratio is 11.0 with a 95% confidence interval from 2.7 to 96.1.

Table 41. Low hemoglobin values in matched pairs of 80 cancer patients and 80 control patients. Material 83

F = Females
M = Males

		Cancer patients			
		Females Hb<110g/l	Males Hb<130g/l	Females Hb>110g/l	Males Hb>130g/l
	Females (Hb<110g/l)	0		2	
	Males (Hb<130g/l)		0		3
Control patients					
	Females (Hb>110g/l)	7		43	
	Males (Hb>130g/l)		5		20

Odds ratio = 2.4 (0.8 -8.7)

Table 42. High erythrocyte sedimentation rates (ESR) in matched pairs of 80 cancer patients and 80 control patients. Material 83

F = Females
M = Males

		Cancer patients			
		Females ESR>20 mm/hour	Males	Females ESR<20 mm/hour	Males
	ESR>20 mm/hour:				
	Females	3		1	
	Males		1		1
Control patients					
	ESR<20 mm/hour:				
	Females	9		39	
	Males		13		13

Odds ratio = 11.0 (2.7 - 96.1)

b-3. A special patient

One of the 80 cancer patients in Material 83 turned out to be identical with a control patient in Material 82. Material 82 had already been analysed and the patient and the matching cancer patient were not excluded. The patient illustrates that cancer sometimes is an incidental finding, that apparently aggressive tumours are no exception, and that iatrogenic complications sometimes may ruin any benefit of early detection:

Female, 73 years of age. For several years angina pectoris and hypercholesterolemia. No warning signals recorded from the records studied in the autumn of 1982, when the patient was a control patient in Material 82. January 1983 routine X-ray as part of a control for her heart condition. A tumour in the hilar region was demonstrated. The patient did not feel ill. Physical examination revealed a paresis in the right arm. The patient was hospitalized and died the next day when inhalation anaesthesia for bronchoscopy was initiated. The death was thought to be due to an anaphylactic reaction. Autopsy showed widespread atherosclerosis, a small cell anaplastic bronchial carcinoma with hilar metastases and a brain tumour diagnosed as glioblastoma multiforme.

Discussion

A high proportion of cancer patients, probably between 60% and 75%, experience a cancer-related warning signal which is communicated to a doctor some time before diagnosis. Approximately five to ten per cent are asymptomatic before diagnosis, but this proportion may increase if systematic screening for breast cancer and cancer of the uterine cervix is initiated. A small fraction of people with registered cancer have their diagnosis made at autopsy. That leaves an important fraction, probably between 20 and 30 percent of cancer patients who have to be alerted by other symptoms than the seven warning signals.

The finding in previous studies (115,116) that there is a positive association between experiencing a warning signal and patient delay has been confirmed by the present study. The high proportion of warning signals recorded in patients without cancer confirm the low specificity of all warning signals. Before the implications of these findings are discussed any further, reliability and validity of the findings will be considered.

Sixteen cancer patients and 14 control patients were identical in Material 82 and Material 83. This overlap tends to reduce differences when these two materials are compared.

Reliability

The inter-observer study shows that cancer-related warning signals in cancer patients are well reproducible when medical records from both general practice and hospitals are available. The relatively low prevalence of each warning signal strengthens this conclusion when kappa is high (65). Warning signals which are not related to the actual cancer disease are less reproducible. So are warning signals of cancer in non-cancer patients. Agreement on early-late analysis is uncertain.

Retrospective recordings of symptoms from medical records seem to give reproducible results when there is a precise definition of what to look for and the data are relevant to the patient's disease. This is in accordance with Koran's ([143]) views of how the reliability of clinical data can be increased.

Validity

In chapter 5 the validity of warning signal recordings made by general practitioners at consultation was discussed in the light of possible bias during recording and consistency with biological and epidemiological knowledge. For warning signals recorded from medical records the most important question concerning validity is whether the general practitioner gave the patient a possibility to present any warning signals, and whether those warning signals which general practitioners recognized in their patients were actually written down. The conclusions about diagnostic delay

also are affected by these questions. In the abscence of direct observations of what happened during the consultations, possible indirect measures of completeness or incompleteness of warning signal recordings will be discussed.

In retrospective studies there is often no substitute for studying medical records. While it is evident that medical records in many respects contain very imperfect data, they also offer a unique opportunity to review an entire clinical course (144). The records are not designed to be notebooks of etiology or pathogenesis, but for surveys of prognosis and therapy they are appropriate and logical media (145). Medical records are used for many different purposes. The most evident kind of use is clinical problem-solving during consultation (146). Many kinds of reports about single cases or groups of patients are based on medical records (45,147,148,). Some authors have made functional (149) or prognostic (150) ratings from medical records. Several studies use medical records to evaluate the quality of care (151,152,153), and some are inter-observer studies (143). There are inconsistent results regarding the relationship between good record keeping and quality of care (151,152). In general there seems to be a positive association (154,155), but a physician who spends very much consultation time studying or writing in records might have spent some of this time more profitably in further communication with the patient (156).

For most purposes, the problems attached to the use of medical records are of the kind already mentioned, related to how the notes are taken during the consultation. Most records are not standardized. Problem-oriented records (141) might have facilitated finding standard information, but good present-day records often present a modified version of problem-orientation with problem-structuring within the old frame of chronologic free text (156).

Records are often a mixture of primary-source and derivative-source data, and the latter may have more errors (145). The problems with the interval data on the forms of the Norwegian Cancer Registry (chapter 4) is an example of this. Physicians who record medical data usually do this as an aid to problem-solving and rational therapy, not to create a tool for administration,

research or quality-control. Records have missing data (145,149). Negative findings probably are omitted more often than positive findings. No mentioning of important examination procedures makes it impossible to know whether they have been performed. Abbreviations and illegible writing may create interpretation problems. Prior probability of disease may influence what is investigated and thus noted; an examination performed in an old person may be omitted in a young person with the same complaint or the same kind of disease. Some kinds of data are noted more or less often than other kinds of data. The proportion of missing items usually is higher for social and emotional problems than for somatic problems (151,157). There are also important differences between what is noted in records from general practice and in hospital records (158). Finally, the tremendous amount of data in many medical records may be confusing (159).

In the present studies, what was looked for were specific symptoms known by the physician to have important clinical meaning in many cases. There are few studies looking specifically at the recordings of symptoms. Dawes (160) in a sample of records from eight English general practices found that less than half of the episodes of disease had any symptoms recorded. At an American paediatric university medical center the chief complaint was among the items which were uniformly well-recorded (151). In Nylenna's material of 113 Norwegian cancer patients (161) there were 11 patients with insufficient information about how they were diagnosed. Apart from this, symptoms were identified from the records when it was not evident that other roads had led to diagnosis. Norwegian recording traditions in general practice probably imply recording more details than what is usual in England.

In addition to its existence, various properties of symptoms can be reported. In the present study the existence and the duration of the warning signal were the most important items, while the quality of the symptoms such as severity, location or colour helped attribute the symptom as cancer-related or not. Decisions about this were made during the extraction procedure, as recommended by Feinstein (145). Symptoms may be reported as descriptions ("black, tar-like stool"), designations ("melaena"),

or may be noted as an interpretation of what the physician observed ("gastro-intestinal bleeding"). Usually these different ways of describing would not pose problems about the existence of the warning signal ("Bleeding").

The most important difference between the present study and studies listing missing items in medical records, is that in the present study warning signals were searched for in more than one medical record per patient. Obtaining all the records of each patient is the ideal for this type of study (144), and this was practically achieved in the present study. In most cases, especially for the cancer patients, records were both from general practice and hospital departments, completing each other (158). Omissions in one medical record therefore may have been corrected to a considerable extent in another record. Shortcomings in one medical record which were thus corrected include variability of investigations due to different prior probabilities of disease, and more personal habits and characteristics of physicians reflected in the records. Descriptions of non-cancer co-morbidity in different records facilitated decisions about cancer-relevance.

Most important, almost all the information was available from the primary source. The amount of data was important for many patients, but there was never any rush in examining the records. The time spent on the records of each patient was not recorded but probably varied from ten minutes to about an hour. Knowledge of the outcome for each cancer patient may have influenced recording and may be partly responsible for the greater inter-observer variation in warning signal recordings for control patients than for cancer patients. Although each observer was aware of this possibility of assessment bias (^{162}), a relative loss of warning signals in the control patients may have happened. Underreporting of warning signals in the records of healthy-looking control patients also would tend to reduce the number of warning signal recordings in this group. Patients who became cancer patients may have appeared more sick and have been more thoroughly examined. This may to some extent have been balanced by a similar underreporting in the 60 future cancer patients who did not get a warning signal recording at consultation.

Cancer patients had more hospital records than control patients, and hospital records generally contain more detailed information than do records from general practice. Overall, some underestimation of the occurrence of warning signals in the control group is probable. That would tend to make the odds ratio of 7.8 in the case-control study based on medical records too high. A 20% increase in warning signal recordings in control patients would reduce this odds ratio to around 5-7, depending on the distribution of concordant and discordant pairs. This would hardly change any conclusions about the association between warning signals and cancer. A 50% increase in warning signal recordings in control patients would reduce odds ratio to about 3-4, but the bias is probably not that important.

The materials are quite complete; patients who died soon after diagnosis or who moved away are not missing from the materials, although a few records had been lost in such cases. The 80 cancer patients in Material 83, with the exception of the two excluded patients, probably represent all the cancer cases diagnosed during the one and a half year period among the persons having made the 11 606 consultations.

Altogether, many of the factors mentioned because they are known to reduce the completeness of what is noted in a medical record, had been reduced in importance through the study design. It would be surprising if an important proportion of warning signals actually presented during the consultations had no mention in any of the records examined. There are, however, more ways to verify or falsify this assumption. One rather coarse method is trying to show inconsistencies between the findings and ordinary clinical experience. There are hardly any such inconsistencies regarding the frequency of the different warning signals. The results also may be compared with those of other authors. Nylenna, (161) using records from general practice, found warning signals before diagnosis in 60% of the cancer patients from one municipality in the 1970s, and this compares well with 63% in Material 76 and 75% in Material 82. There is of course the possibility that the same kind of information may have been omitted in the records of all these studies, but such systematic omissions seem improbable for the kind of symptoms studied.

A better impression is obtained by comparing studies of the same question by different methods. The recordings of warning signals by general practitioners at consultations were made on separate forms and were not necessarily noted in the medical records. Almost all the warning signals recorded in twenty patients with a subsequent cancer diagnosis were later found in the medical records of Material 83, in most cases by all three observers, while only about half of the warning signals in 13 control patients were found. The numbers are small, but it seems as if a warning signal perceived by a general practitioner and actually related to some form of cancer is noted in the medical record in the great majority of cases, while this is much more uncertain for other warning signals.

There is another way of suggesting variability as to which warning signals were noted in the records by the physicians, given that the reproducibility of what can be read in the records is acceptable. Material 76 and Material 82 were studied four years apart. Being complete or almost complete materials of cancer patients in one municipality during a specified time period, there were no significant differences in the distribution of sex, age or diagnostic groups between the two materials. Variable recording of cancer-related warning signals could then be revealed by differences in their frequencies. However, there were no statistically significant differences between the two materials in: the distribution of patients with or without warning signals (table 21), the distribution of patients with warning signals in the different diagnostic groups (table 21), the distribution of all recorded warning signals in the various diagnostic groups (table 22), the distribution of individual warning signals (table 22). There was one difference in that older cancer patients had relatively fewer warning signals than younger patients in Material 76 ($p=0.03$), but not in Material 82. There is sufficient variation in the distribution of individual forms of cancer (Appendix 5) to explain at least part of this difference between the two materials. Among the patients without any warning signal there are for example more old patients with bronchial cancer in Material 76 and more younger patients with thyroid cancer in Material 82.

In relation to Material 83 some differences in the different distributions would be expected and were actually found (chapter 6 a-3-A).

Thus, important variability in recording cancer-related warning signals has not been demonstrated.

For warning signals considered **not** cancer-related (table 30) a statistically significant difference between cancer patients and control patients in Material 83 could be expected if variability in writing down such warning signals were very important. No significant difference was found, although Bleeding was recorded twice as often in control patients. Lump was recorded relatively more often in the patient population from general practice in table 24, but this may reflect that the patient population is a younger population, and that many patients with Lump are young patients.

Finally, a look at the symptoms in cancer patients with other symptoms than warning signals (table 19) shows a broad range of more or less well-known first symptoms of cancer. It is not unreasonable that no warning signal was found in these patients. Important diagnoses on the list are: bronchial cancer, known to be diagnosed more or less incidentally in many cases (161) and where the present and other investigations ([163]) show that only half of these patients present Cough/hoarseness; prostate cancer, where the first symptom often stem from metastases or ressemble the symptoms of prostatic adenoma but rarely any warning signal; stomach cancer and pancreatic cancer where vague but constant pain plays a greater role than in many other forms of cancer; brain tumours which also show a wide variety of first symptoms, but rarely any of the warning signals. The proportion of cancer patients with and without warning signals showed no statistically significant differences neither between males and females in any of the three materials, nor between the different materials for all patients or for males or females separately. This strenghtens the conclusion that some cancer patients experience no warning signal before diagnosis and shows that it depends more upon the kind of cancer than upon the sex of the patient.

Altogether, it seems reasonable to conclude that the results concerning cancer-related warning signals are valid in the meaning

that they are based on most such warning signals which are presented by the patient and perceived as warning signals by the general practitioner during the consultation. Warning signals which are unrelated to cancer are noted with less consistency, and their existence is a little more difficult to interpret from the medical records. Conclusions about warning signals unrelated to cancer should therefore be drawn with care.

The delay estimates in chapter 4 rely on many kinds of information, and it is probable that some relevant information has not been written down. However, the conclusions were based on what was actually found in the records. With quite reliable interval classifications and in most cases a good overall impression of what had happened at the different consultations for each cancer patient (chapter 4), it is unlikely that supplementary information would have changed many of the classifications into delay or not delay. The overall conclusions about delay are probably not much influenced by the kind of possible bias discussed here.

The secretaries punching the GP-material may have made some mistakes. The fact that a few medical records concerning initially selected control patients in Material 82 and Material 83 could not be found, suggests that some such errors were made. However, most records were found in the appropriate files. Punching mistakes must have been made haphazardly. There is no reason to believe that the use of some alternative control patients have altered the results in any systematic way.

Control groups should be free of the disease studied. Subclinical cancer usually develops over many years, and Material 82 presented an example of such a patient where cancer became manifest soon after the study period. But by definition and for practical purposes the control groups are satisfactory. They were not registered by the Cancer Registry of Norway at the time of the study, and nothing in their medical records suggested detectable cancer. Records from Material 83 were analyzed in 1985, more than two years after the diagnoses of cancer had been made. The controls to the relatively few patients with asymptomatic cancer detected by cervical screening, in many cases had had cervical smears which were negative.

Material 76 and Material 82 have important similarities with the national material of cancer patients in 1982. The external validity for most conclusions about cancer-related warning signals are probably quite high as far as Norwegian cancer patients are concerned. The findings which relate to the selection of patients in Material 83 are the ones which are most apt to depend on local peculiarities in the organization of health care.

Explications and implications

a. The association between warning signals and cancer

The odds ratio of 7.8 (case-control study based on medical records) and the likelihood ratio of 4.8 (based on warning signal recordings at consultation) consistently show a quite important association between warning signals before diagnosis and cancer. At the same time they show how common warning signals are in the non-cancerous. When the patient groups are matched for sex and age, the median age of the control group increases and the likelihood ratio falls to 1.5. This illustrates a dilemma. We may acknowledge the fruitlessness of making all the young people with warning signals consult a doctor, and we may then choose to concentrate our information concerning warning signals on the older fraction of the population. But the proportion of cancer patients with warning signals is not particularly high in old age. The probability of having cancer is only slightly raised if a warning signal appears. It is the age rather than the warning signal which makes cancer a realistic possibility. Even if the odds ratio of 7.8 is statistically significant, it is doubtful whether it is clinically significant ([164]) as long as recommendations for consultation behaviour are made difficult by the high proportion of patients with warning signals among the non-cancerous.

The higher likelihood ratio of 4.8 in the population from general practice is of course somewhat more encouraging and may appear more correct to use when discussing public health information. After all the information aims at an unknown group of cancer patients hidden in the general population.

The lack of difference in warning signal recordings at consultation between female cancer and control patients (table 31) may

be due to small numbers. This assumption is strengthened by the observation that for warning signals other than Lump and Bleeding female controls have six recordings and male controls one recording. In the main material (table 15) differences between males and females were small for these five warning signals. Still the lack of difference in table 31 further weakens the faith in the warning signals as an aid to distinguish between cancer and not cancer, particularly in women.

Some individuals seem to have profited from a rapid diagnostic process after the appearance of a warning signal. But this has to be weighed against the discrimination (^{165}) of the warning signals; i.e. their ability to separate the cancerous from the non-cancerous. It is in this light a general practitioner must consider the warning signal once a patient has presented it. The specificity of the warning signals is much lower than what is usually required for a good diagnostic test. The sensitivity is fairly high if we consider the occurrence of a cancer-related warning signal some time before diagnosis, probably between 60 and 75% according to the present investigations. If we talk about sensitivity at a single consultation, sensitivity is much lower, and this is where the general practitioner must take decisions about further examination and referral.

If the proportion of patients with warning signals is five times higher for cancer patients than for other patients, this may have some importance. But despite the five times rise, the probability of cancer after the general practitioner has observed a warning signal remains very low, because it relates to a very low prior probability in the patient population of general practice. The low prevalence of cancer in the GP-material, like in most general practice populations, limits the diagnostic value of warning signals. Positive predictive values of single warning signals ranging from three to six per cent show that the physician must try to combine warning signal information with other information about the patient. Table 33 shows that a fair increase in the positive predictive values may be obtained merely by being conscious of the patient's age. Similarly, notions about risk groups may be assumed to increase positive predictive values. This will be further discussed in chapter 8.

The positive predictive values of Lump and Bleeding (table 33) correspond fairly well with Nylenna's findings of 2.5% and 3.8% respectively ([166]). Nylenna made his calculations on the basis of three "Lump" and six "Bleeding" cancers developing over a two-year period after 121 "Lump" and 156 "Bleeding" consultations where these symptoms were recorded as the main reason for encounter. In the present study the warning signal was not required to be the main reason for encounter in order to be recorded. This may account for the slightly higher positive predictive values, but the number of cancer cases is small in both studies.

The most important bias in this cohort design probably is that an unknown number of the 60 patients with no warning signal recording at consultation, probably consulted for other reasons than for their subsequent cancer disease. A first warning signal may have occurred several months after the consultation which started the registration period. This would tend to decrease sensitivity, perhaps considerably. True sensitivity for a warning signal at consultation in relation to cancer probably is in between the minimum figure of 25% and the figure of 60-75% for all warning signals occurring before diagnosis. If we imagine that 35% is the true sensitivity, likelihood ratio would change from 4.8 to around 7. The odds ratio of 1.9 in the case-control comparison based on warning signals recorded at consultation might also have increased, perhaps to around 3-3.5, but this depends upon the distribution of discordant and concordant pairs.

The warning signal specificity of 84% in the matched group is probably too low when compared with warning signal rates in table 14, even if these figures are based on consultations rather than on patients. This may be due to random error because of the low number of patients in the control group. A specificity of 90-92% for the matched group, which looks more correct from the figures of table 14, would have increased the corresponding likelihood ratio from 1.5 to 2.5-3.1.

It is probable that the association between warning signals and cancer is somewhat stronger than the likelihood ratios in the results section suggest.

In the cohort design the patients are not randomized, and the two groups are not necessarily comparable. In fact the age dis-

tribution differs. There are relatively more old people and women aged 30-49 years in the group with one or more warning signal recordings ($P<0.001$) (tables 13-14). These subgroups have more cancer than other age groups. This confounding by age and sex would tend to increase the association between warning signals and cancer and so give an artificially high sensitivity and likelihood ratio. This may balance some of the bias caused by cancer patients who consulted for other reasons than their cancers.

The consideration of usefulness (table 34) is based on recordings made by general practitioners. The doctors may have been alerted by their own recognition of a warning signal. Some doctor's delay may then have been avoided in addition to the estimated benefit from possible reduction of patient delay. We also found that patients have broader definitions of warning signals than have physicians (chapter 5). The contribution of warning signals to reducing patient delay may therefore be greater than this study indicates. The price to pay for the broad popular notions is of course that more patients without cancer see a doctor for symptoms perceived as warning signals.

Reliability for "early" or "late" classifications was uncertain, but all the observers classified the great majority of the cancer-related warning signals as "early". This reflects a dilemma as well as an opportunity in general practice which is true not only for cancer: florid disease is less common than vague symptoms, making diagnostics more difficult. But many patients consult with disease at a stage where prognosis in many cases is still good, posing an important challenge for general practitioners to recognize it.

Generally in a cohort study one looks at the association between exposure and outcome, often implying some degree of causality. In the actual study the warnings signal has been defined as the "exposure". Evidently the warning signal has not caused the cancer. On the contrary the study design makes it reasonable to assume that the disease has been the cause of most, but not all the warning signals in the cancer patients. This is the basis for the reflections concerning the association between warning signals and cancer.

The association between warning signals and cancer might have been further illustrated if patients had been matched on the basis of warning signal recordings rather than cancer, and then compared cancer incidence in the warning signal and in the matched non-warning-signal group. There would have been few cancer patients in the non-warning-signal group, and this design has not been applied.

The rate of warning signals at consultation increases with age (table 14) while the proportion of cancer patients with warning signals is not particularly high in old age (table 19). This explains the decreased likelihood ratio when we compare the relatively old cancer population with a group of patients matched for age and sex.

The approximations which were made because we do not know the exact number of patients probably has relatively little influence on the calculated values.

b. Associations between individual warning signals and different forms of cancer.

In Material 76 most cancerous Lumps were breast cancers (table 21a, Appendix 5). Material 82 (table 21b, Appendix 5) contains relatively more skin cancers and thyroid cancers than Material 76, and more of the skin cancers in Material 82 were basocellular carcinomas. Of the 15 early cancer Lumps in Material 82 four were located in the breast, one in the thyroid gland and one in the lip; the rest were skin cancers, seven of them basocellular carcinomas. Only two of the seven thyroid cancer patients in Material 82 had a warning signal recording, which was Lump in both cases. Two malignant melanomas of skin in Material 76 and none in Material 82 contribute to the shift in recording from Mole to Lump. It is possible that a few skin lesions hiding basocellular carcinomas were classified as Mole in Material 76 and Lump in Material 82 without being much different in actual appearance.

Of the four late Lumps in Material 82 one was breast cancer, two were metastases from ovarian or pulmonary cancers, the fourth patient had a thyroid cancer and possibly myelomatosis as well.

Bleeding has been recorded in four of the seven diagnostic groups and thus is a possible cancer symptom from the digestive

organs, the respiratory system, and from genital and urinary organs.

Almost all recordings of Indigestion in cancer patients were made in cases of cancer in the digestive organs. Weight loss and Bleeding also were recorded quite frequently in patients with cancer in the digestive organs. Weight loss appeared as an early symptom in more than half of the cancer cases where it was recorded in Material 82 and Material 83. It was a rather important symptom in Material 76, too. As a warning signal, Weight loss appears to defend its position as much as any other symptom on the Norwegian version of the list, although the American Cancer Society considers this as a misconception which is quite common in the population (62).

Patients with bronchial cancer may or may not have Cough/-hoarseness. In Material 76 three of eight patients with bronchial cancer had Cough/hoarseness, and one of them had Weight loss as well. In Material 82 there were only two female bronchial cancer patients who had two and three warning signals each. Cough/hoarseness was one of them. In Material 83 two of five patients with bronchial cancer had Cough/hoarseness. One had Lump and the other Weight loss as well. Two of the three others had two other warning signals each. Bronchial cancer has a wide variety of symptoms, but few of them were classified as early symptoms. Cough/hoarseness is not often a cancer symptom, although common in the population and among patients in general. This may seem surprising, but it is in accordance with findings in a five year material from general practice by McWhinney (163).

The number of recordings vary in the different patient materials and in the population material, but there is a general tendency for Lump, Bleeding and Indigestion to have more recordings than the other warning signals. In the cancer patient materials, Mole is without recordings in Material 82 and Sore in Material 83 (table 29). No warning signal satisfies the ideal: to occur frequently in people with cancer and infrequently in people without cancer. But for all the warning signals there exist forms of cancer where sensitivity is high at a time when early diagnosis is possible. At least the more rarely occurring warning signals are rather rare both in the population and in the cancer patients.

For very young persons, several warning signals have very little relevance. Three children are included in the materials. Two had no warning signal, a four year old girl with Wilms tumour had a double recording of Lump and Weight loss. These few children do not tell us which, if any, warning signals are the most relevant for children. However, the most frequent forms of cancer in children are leukaemia, brain tumours, Wilm's tumour, neuroblastoma and lymphomas ([167,168]). Among the more common forms of cancer mentioned we do not find any of the carcinomas growing from cells in contact with the outside world. Cancer in children with a few important exceptions is thought to be the result of incidental mutations not affected by environmental carcinogens ([169]). Early diagnosis seems to be at least as important in children as in adults (169). But other forms of cancer are quantitatively important in children than in adults, and this suggests that we should reconsider the relevance of each warning signal.

There are not many examples of the common children's tumours in the present material, but except for the lumps of some lymphomas no common cancer in children seems to present typically with any warning signal. It is doubtful whether any warning signal has any more than sporadic relevance for diagnosing cancer in children. As for other diseases of children parents should better be taught to react when a child manifests persisting general symptoms or any particular symptom which seems strange and unusual.

For young adults up to about 30 years of age Lump and Mole alone would cover several of the most common forms of cancer in this age group, like cancer of the testis, lymphomas, malignant melanoma and bone cancer. Testis cancer with other symptoms than Lump, like diffuse enlargement of one testicle or a relatively symptom-poor epididymitis, would usually not be covered by any warning signal. So is the case for most patients with brain tumour or leukaemia, which occur relatively frequently in this age group. Of the 14 cancer patients younger than 30 years in the three materials, only the child mentioned and a woman with choriocarcinoma after childbirth had any other warning signal than Lump.

The youngest cancer patient with Sore was 57 years old. The

forms of skin and lip cancer where this warning signal is relevant occur mainly in older persons.

c. Why do patients who experience warning signals have more patient delay?

The finding that patient delay is more important in cancer patients who experience warning signals may appear surprising. With two other investigations (115,116) arriving at the same conclusion and to this author's knowledge no investigations to contradict it, it is a very important finding which should have implications for public cancer information. We shall return to this later. If Lump and Bleeding are symptoms with a low consultation threshold and at the same time quantitatively important symptoms in cancer patients, it probably means that patients with Lump or Bleeding and cancer hesitate more than patients with Lump or Bleeding and no cancer. Patients react "correctly" to cancer information as long as they do not have cancer, but they hesitate when cancer is actually there.

A person's experience and social background is important in how fear influences action (90). Patient delay in cancer is a special case of chronic patient delay (^{170}) and is less related to the emergence of one specific symptom than to the cluster of long-standing socio-medical habits, attitudes and practices of individual persons. Goldsen (116) reexamined but maintained this conclusion because of the seemingly contradictory finding of a longer delay period when cancer symptoms were involved. Fear, anxiety and dread about cancer probably touch all social levels (90). Fear may inhibit rational action as well as triggering it (113). When fear combines with the generally low level of knowledge about cancer and warning signals (113,114), inhibition of rational action becomes the more common reaction (113). This may explain why delay is more important in patients experiencing warning signals.

In spite of this, education about cancer may reduce patient delay. Intelligent awareness of possible seriousness makes people go for help (90). Social roles including sex roles also may influence actions even for persons who understand that they have a serious disease: In a group of breast cancer patients inter-

viewed about their reaction to finding a lump in the breast, several women told the interviewer that they postponed a consultation for weeks to complete family tasks or provide substitute care for a sick husband or an old relative (Aaraas I, personal communication). One third of about 1200 women referred by general practitioners to a breast clinic and interviewed, reported reluctance to seek advice about breast symptoms ([171]). Fear, being a nuisance to the doctor, and embarrassment were the most frequently mentioned reasons for reluctance. Reluctance was associated with factors related to the women's lack of familiarity with their own breasts: No previous breast examination by a doctor and non-practice of breast self-examination.

The various non-warning signal symptoms on average could be more apparent or uncomfortable than the warning signals and thus lower the consultation threshold. From the list of symptoms in table 19 such an explanation appears unlikely, especially in the light of the low consultation threshold for important warning signals. It seems more possible that the vague and varied nature of non-warning signal symptoms less efficiently than warning signals evoke thoughts of cancer and the associated fear.

d. Differences in consultation thresholds

Lump is a warning signal commonly experienced by cancer patients (table 29), as it was common in the general population and in the material from general practice (table 24). Indigestion seems to have a higher consultation threshold than Lump (chapter 5), but has about the same quantitative importance as Lump in cancer patients (table 29). Bleeding, in spite of its particularly low consultation threshold (chapter 5) is less frequent than Lump and Indigestion in Material 76 and Material 82. However, among the cancer patients who have consulted in general practice (Material 83), Bleeding is very important (table 29).

Cough/hoarseness makes people go and see a doctor fairly often even if it is quite infrequent among the cancer patients. But people may see the doctor for Cough/hoarseness in order to get symptomatic medication, while the diagnosis may appear less important. In other words, when people see a doctor for a warning

signal it does not necessarily mean that they do so because they think their symptom may be a warning signal of cancer.

Weight loss and Sore appear rather uncommon in the general population, but not unimportant in cancer patients.

The tendency for increased rates of warning signals in old people seen in the GP-material seem to disappear when all warning signal recordings from all medical records over several months are considered. When this effect is seen in the control patients it could be due to a higher contact rate in younger persons (119), increasing the number of warning signals when there has been more consultations. When it is seen in cancer patients, or when the tendency is even reversed like in Material 76, it could mean that what looked like a promising tendency for more symptom-selective consultation behaviour in old people with high cancer incidence, actually may be of less significance than it appeared when a quite high proportion of old patients with cancer never gets any warning signal.

e. The spectrum of cancer in general practice.

In general, the number of patients in each diagnostic group in Material 83 is too low to make firm conclusions about which forms of cancer which tended to by-pass any consultation in general practice in Tromsø. However, one problem for general practitioners is that apparently they rarely get the possibility to diagnose skin cancer, even if the skin is not difficult to inspect and almost all skin cancer patients experience one of the seven warning signals (Appendix 5). There are only four skin cancers in Material 83 while Material 76 and Material 82 have 13 and 11 skin cancers each. Many of these skin cancers were removed by surgeons, dermatologists or otorhinolaryngologists without any preceding primary care consultation. This finding is consistent with findings in an investigation of the spectrum of cancers diagnosed by one American family physician ([172]). The initiative to remove the skin lesion sometimes comes from the patient, sometimes from the doctors. In both cases it happens that the consultation was initiated for some other cause. It is possible that general practitioners should have a more active attitude to inspecting and biopsying skin lesions ([173]).

The statistically non-significant female predominance in Material 83 and the statistically significant difference in age distribution with relatively many women aged 20-39 years, may suggest that younger women are more apt than other patients to have their cancer diagnoses made through a general practitioner. Nylenna (108) showed that general practitioners had a relative oversuspicion of cancer in females and in young patients when the pattern of cancer-suspicion was compared with cancer incidence. However, such an oversuspicion may be justified if cancer patients in general practice differ from the totality of cancer patients. There were two cervical cancers in Material 76 and 19 in Material 83, two urinary cancers in Material 76 and seven in Material 83. Cancer in these organs often are discovered on case-finding or screening, like cervical cancer, or they bleed, like many urinary and uterine cancers. Female cancer patients relatively more often than males may be alerted by Bleeding, with its low consultation threshold. It is noteworthy that of the 19 cervical cancers in Material 83, six had a Bleeding recording and 13 had no recording of any warning signal. With or without Bleeding a cervical smear made by a general practitioner seems to be the common pathway to the diagnosis of cervical cancer in Tromsø.

f. Would more warning signals be appropriate?

Lasting pain is unspecific as a symptom of cancer to a yet higher degree than the warning signals. Lasting pain does occur as an early cancer symptom, but sensitivity is low for most forms of cancer. The findings provide enough data to drop any thought of including this symptom in any list of warning signals for the public, but other objections should be mentioned as well: It is probably a widespread public notion that cancer always or very often is indeed associated with pain; patients sometimes say that they thought cancer was out of the question because pain did not accompany their other symptoms. Pain is probably the sensation which people experience more commonly than any other bodily symptom of malfunction, and these malfunctions vary from very innocent ones to serious diseases. Even when taking duration and constancy of localization into account we do not achieve a specificity which makes the symptom interesting for public infor-

mation. Moreover, the interviews suggest that Lasting pain already has a low consultation threshold.

For changes in bladder habits included in the American list in table 9 there are no data in the present study. It is a common symptom in benign urinary disease. Some cases of urinary cancer where changes in bladder habits might have been relevant, are signalized by Bleeding. On theoretical grounds, changes in bladder habits does not look any more practical than Lasting pain as a warning signal of cancer.

g. The cancer diagnostic value of measurements of haemoglobin concentration and erythrocyte sedimentation rate in general practice

Haemoglobin does not seem to be a good discriminator between patients with and without cancer, but the reason for a low haemoglobin measurement should still be investigated. If it is due to an iron deficiency, occult bleeding from a tumour is one possible reason. Haemoglobin can remain normal even with considerable reduction of the iron stores ([174]).

An ESR of 20 mm/hour or more discriminates cancer from non-cancer better than low haemoglobin values. However, neither sensitivity nor specificity is impressive. Other studies confirm this. About 30% of ESR measurements in a Swedish general practice were 20 mm/hour or higher ([175]). ESR was measured at every sixth to seventh consultation. About six per cent of ESR measurements were 50 mm/hour or more, most of them due to infections or musculoskeletal diseases. Neoplastic disease was less common but less evident clinically. The normal range of ESR is subject to discussion, and some authors define 15 mm/hour as an upper limit in men younger than 50 years of age, while the limits for women are defined 10 mm higher than for men ([176]).

Measurements should be made on clinical grounds although indications may be liberal. The value of such measurements in screening is highly questionable ([177,178]). It seems justified to pursue an explanation of Hb and ESR measurements in consulting adults outside the range considered normal in this investigation. To that end I have made two flow charts (appendix 7, A and B). To

limit the work load it is important to identify those patients whose ESR for years have remained stable above the defined limit.

Conclusion

1. In two materials of all or almost all cancer patients in Tromsø during specified time intervals, cancer-related warning signals before diagnosis were registered from the medical records of 63% of the cancer patients in Material 76 and 75% of the cancer patients in Material 82.

2. Most other cancer patients experience a broad range of other symptoms. "Pain which does not move or disappear" is the only single symptom other than the warning signals which is experienced by an important proportion of cancer patients, but this symptom is very unspecific and rarely an early symptom of cancer.

3. In a material of cancer patients having consulted a general practitioner prior to diagnosis (Material 83), one or more cancer-relevant warning signals were registered in 64% of the patients before diagnosis. Counting all warning signals whether or not they were considered to have any relationship with cancer, warning signals were registered in 78%.

4. Patients with warning signals in Material 76 had more patient delay than patients without any warning signal. Fear combined with limited knowledge about cancer may explain this finding, which is consistent with findings in other studies. There was no difference in delay from the first consultation to diagnosis.

5. In age- and sex-matched control patients without clinical signs of cancer, warning signals were noted in 35% in Material 82 and 26% in Material 83. The warning signals' lack of specificity is a major problem for a lay person as well as for a general practitioner who both want to know whether a warning signal may have anything to do with cancer.

6. Cervical cancer is the cancer most often diagnosed in an asymptomatic stage. In Tromsø general practitioners usually perform the first pathological smear.

7. The likelihood ratio for having a warning signal recorded at a single consultation in relation to having cancer diagnosed or not during the next eighteen months was 4.8. The positive predictive value of a warning signal in relation to cancer was 3.7%. Sensitivity was 25% and specificity 95%. The positive predictive value for Lump was 3.3% and for Bleeding 5.3%. These figures are based on an estimate of the number of patients consulting in the GP-material. When comparison was made with age- and sex-matched control patients, the likelihood ratio was 1.5 and specificity 84%. Sensitivity and with it the likelihood ratios were probably a little too low due to bias. Positive predicitive value but not likelihood ratio increases with age.

8. Odds ratio as an estimate of relative risk for cancer based on analysis of matched pairs was 1.9 (0.8-5.1) for a warning signal recorded at a single consultation less than eighteen months before diagnosis, and 7.8 (3.3-22.4) for a warning signal recorded from the medical records.

9. Of the 80 cancer patients in Material 83, 20 had a warning signal recorded at a single consultation taking place up to 18 months before diagnosis. For 17 patients the warning signal seemed to have been cancer-related, and 14 of them may have had some therapeutic benefit from consulting earlier because of their warning signal.

10. Anaemia should always be explained, but cancer is only one of several reasons for this. A sedimentation rate above 20 mm/hour is significantly more frequent in cancer patients than in age- and sex-matched control patients. The possibility of cancer is an important reason to check why a sedimentation rate is elevated, even if there are many possible explanations for this, too.

7. TEACHING THE PUBLIC

a. Symptoms for the doctors, symptoms for the public

The fact that certain symptoms occur in a high percentage of cancer cases can be used in the diagnostic process. To use such knowledge, notions about sensitivity and specificity are very important. Doctors may be expected to have such knowledge. Warning signals may be used as a cancer diagnostic tool by professional people, although the present form of the warning signals probably should be modified. This will be discussed in the next chapter.

To initiate a diagnostic process, it is essential that the patient participates. The public cannot be expected to have sophisticated notions about the specificity or the likelihood ratio of a symptom in relation to cancer. Most symptoms corresponding to warning signals are already firmly rooted in public consciousness as symptoms which should make them consult. There is, however, much confusion about when such a symptom is really experienced. The investigations have shown that most people would tend to think they have a warning signal before a general practitioner would call it so. The broad popular notion about a warning signal mingles with half-knowledge about dangerous disease. It then seems as if consultation follows more easily when there is no subjective feeling of actual disease than when cancer appears as a real, imminent threat. Only a high level of rational knowledge about the disease and possibilities of early treatment seems to encourage facing the problem rather than postponing consultation when cancer appears. Most people cannot be expected to have such knowledge today. Our natural tendency to deny danger seems to be enforced by the scaring aura of the warning signals, and lack of notions about specificity makes people with innocent ailments unable to practice rational self-reassurance and self-care.

It is possible that the warning signals have fulfilled a historic mission in making an important contribution to public awareness of the cancer problem and create a climate for prophylactic action. Undoubtedly there are also people who can think back on an early warning signal which helped them making a quick decision to consult, and who were cured of their cancer. But most cancer

patients and most people will not be able to use true associations between warning signals and cancer as a means of more rational consultation behaviour. The warning signals were introduced more than seventy years ago and may have reached the age of an honourable retirement.

It is easy to see why the seven warning signals have become so important in public cancer education. Cancer is a group of very heterogenous diseases, with some common characteristics like uncontrolled growth and a serious prognosis if left untreated. It is more difficult to find common diagnostic indicators which can be used either by doctors or by the public. However, "early diagnosis" for decades has been the light at the end of the tunnel. Its brightness has often been exaggerated and is still disputed, but it has never been extinguished as the light of hope and presently seems to radiate the word "cure" for an increasing proportion of patients. The warning signals of cancer seemed to furnish the clue to meaningful public information and have for years been written on the banners of cancer associations in most of the world. However, the results of the present study question such use.

b. Alternatives to symptoms, and symptoms in a context

Certainly, public cancer information should not be stopped. While people are no experts concerning the use of imperfect diagnostic information, they remain experts about their own body. People are able to register changes in their bodily functions, although they may have difficulty translating it into health professionals' notions about symptoms. The knowledge which is most apt to help translate bodily sensations, is basic knowledge about body function, about cell structure and organ function. People can learn the whole life long, but the age where such knowledge is easiest to acquire probably is school age. In Norway a school cancer manual for elementary school pupils ([179]) has been made based on a teacher's guide produced by the International Union Against Cancer. When basic cell and body function has been taught, like in this school manual, it is meaningful to add that "It is important to notice changes in body function" and "If we suspect having cancer, we should not postpone contacting a doctor" (179).

Teaching the public about symptoms of cancer should not be prohibited, but such teaching probably always should be subordinate to or at least associated with notions of prophylaxis, like in the recent "ten commandment"-version of cancer advice which is being published in many European countries (fig 12). Relevant symptoms may be mentioned when the teaching aims at specific groups of people who are at risk for a particular form of cancer. The Queensland melanoma project (34) is an example of this. Especially for young adults cancer education beyond basic physiologic knowledge should focus on the few forms of cancer which are common in their age group. For diseases like cancer of the testis and cancer of the uterine cervix very effective forms of therapy exist, and information about the therapeutic possibilities should always be part of the message. Somewhat more difficult to communicate, but very important is the great progress in symptom relief, whether the problems are caused by the disease or by the treatment. Pain should not be a major preoccupation of cancer patients today. Perhaps this is the information which may make an old person consult a doctor?

c. The role of the mass media

General cancer education through the mass media can be used to introduce topics of discussion among people. Natural experiments like publicity about cancer in famous persons or national cancer campaigns have shown that short-term effects of increased consultation or biopsy-taking usually do not lead to increased detection ([180],[181]). People without cancer seem to use such occasions as an opportunity to confirm what they don't have, but people with cancer stay home. To initiate good, insight-producing discussions, the search for symptoms is hardly the right focus for cancer education through mass media. Cancer information should try to avoid a public image of advice from up above, defined by experts to be "good for you". Rather, cancer information should satisfy basic personal demands, offering sound and well-founded know-how which people can use in a field of personal concern. Most people have been touched personally when a family member, a friend or an acquaintance has got cancer, and cancer information which is linked to such experiences may be well

English translation, Fig. 12.

Ten personal commandments

Reduce your risk of cancer..

1. Stop smoking.
   Do not use chewing
   tobacco or snuff

2. Avoid fat food.
   Eat ample amounts
   of fruit, vegetables
   and fiber-containing
   cereals

3. Be moderate in your
   alcohol consumption

4. Be aware of chemical
   products. Handle with
   care products marked with
   a danger symbol

5. Avoid exaggerated sunbathing

Consult a doctor if..

6. ..you discover a lump,
   regardless of where on
   your body it is located.
   Examine your breasts
   regularly

7. ..you get an unexpected
   bleeding. Have a gyneco-
   logical checkup regularly

8. ..you get long-lasting
   indigestion or lose weight
   without any reason

9. ..you don't get rid of
   coughing and hoarseness

10. ..a mole changes its
    appearance

Fig 12. 10 personlige bud
(Ten personal commandments).
Poster by
The Norwegian Cancer Society

10 PERSONLIGE BUD

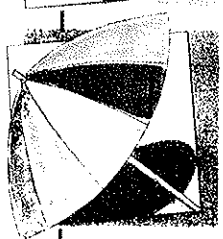
Reduser risikoen for kreft ...

1 STUMP RØYKEN. Ikke bruk skrå-tobakk eller snus.

2 UNNGÅ FET MAT. Spis rikelig med frukt, grønnsaker og fiberholdige kornprodukter.

3 VÆR MÅTEHOLDEN MED ALKOHOL.

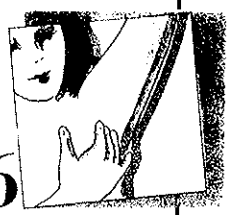
4 VÆR OPPMERKSOM PÅ KJEMISKE PRODUKTER. Håndter kreftfaremerkede stoffer med forsiktighet.



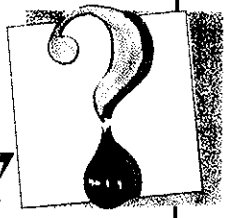
5 UNNGÅ OVERDREVEN SOLING.

Gå til legen hvis ...

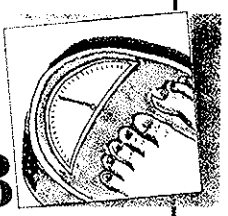
...DU OPPDAGER EN KUL, uansett hvor på kroppen den er. Undersøk brystene regelmessig selv. **6**



...DU FÅR EN UVENTET BLØDNING. Få underlivet undersøkt regelmessig. **7**

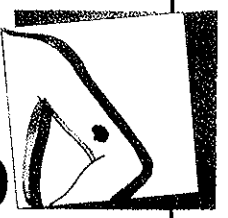


...DU FÅR LANG-VARIGE FORDØYELSES-PROBLEMER eller går ned i vekt uten grunn. **8**



...DU IKKE BLIR KVITT HOSTE OG HESHET. **9**

...EN FØFLEKK FORANDRER SEG. **10**



Mulighetene for helbredelse er størst hvis kreft oppdages tidlig.

Den Norske Kreftforening

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received. Young people often discuss how to save the environment for future generations. The pollution effect of cigarette smoking has been taught in this context ([182]), and the fact that cancer to a great extent is triggered by external stimuli may be emphasized in prevention efforts. Cancer should be put in a modern context; in the context of ecology, of anti-pollution, of democratic sharing of knowledge and social rights combined with responsibility for oneself and for one's own body.

From this point it is possible - through television, radio, magazines and booklets, but hardly through posters - to move towards more concrete teaching for the more interested, but rarely aimed at everybody at the same time. The high incidence in elderly people and an unfavourable stage-to-age relationship ([183]) make increased attention towards this age group necessary. For women between thirty and sixty years of age information about detection procedures for breast and cervical cancer should be linked with information about the diseases, and about breast self-examination. Information aimed at early diagnosis of lung cancer may be linked with information about coronary heart disease and about other forms of cancer where smoking is thought to increase the incidence. Realistic teaching about these diseases linked with various positive messages may be better than raised index fingers or talk about persisting coughing. It is not always necessary to link the message with cancer. A high intake of cereals and vegetables probably would have beneficial effects on bowel function for many people. Emphasis on this may be better than specific ties to colon cancer, where the evidence is not yet conclusive (10). Reinforcing the conviction of non-smokers and former smokers that they now do the right thing, may contribute as much to reduced future smoking as efforts to make current smokers quit their habit. Flay (121) says that "..the chances of mass media health promotion programs leading to meaningful behavior change can possibly be improved if they include considerations of values, social normative beliefs, coping skills, and reinforcement contingencies and, where possible, build in the development of appropriate behavioral skills."

d. Teaching at different levels. The role of the general practitioner

It is important to use all levels of closeness to the public and encourage talks and discussions in groups of workers, clubs, etc. (184,185). Several kinds of community health workers may be engaged in this work. The general practitioner is a link to the local population and must use the unique opportunity of face-to-face consultations to encourage lifestyle prophylaxis (186, 187). Evidence has been provided that family doctors target their efforts at those at greatest risk (188) and reach people otherwise not reached (189). Advice during the consultation will be remembered better if there are few messages which are emphasized and repeated in different ways (190). Practical procedures for how to stop smoking or eat more vegetables or dietary fiber are better than a mere recommendation to act. The patient's present state of motivation should always be the starting point (122). A follow-up appointment to check the effect of planned changes in lifestyle may tell the patient that the doctor takes a real interest in him and thinks that changes are possible. Written material also may enhance the effect of verbal advice (186).

General practitioners also may encourage rational consultation behaviour. An increased triviality burden in the primary health care would be particularly heavy if old rather than young people made "unnecessary" consultations. Nevertheless one of the clues to less cancer delay may be to facilitate older persons' access to general practice. Old people are the first to disappear from the waiting rooms if obstacles become important: waiting lists, discontinuity of doctors, high prices. Of course politicians play a role in this, and so do general practitioners in the way they administer their practices. Trust from patients also depends on the quality of the services a general practitioner can offer.

If systematic screening programs are initiated, it is important to preserve the general practitioner's role as a link to the population (191). Their knowledge of their population and of their local community may be crucial to reduce problems of non-attendance and follow-up after positive tests. The present state of unsystematic screening by cervical smears and mammography has high costs and questionable gain. For cervical cancer the unor-

ganized smear-taking in Norway probably has reached its efficiency peak [192]. Organized screening, recommended by a national commision in 1987 (29), may further reduce invasive cancer and may combine benefits from data-based population registers for invitations and smear performance in general practice. These two preconditions are essential for success (30,[193],[194],[195]), although a short teaching program for general practitioners should be included to improve the technical quality of the smears [196]. A pilot project in Tromsø showed that with two recalls of women without a registered smear the last five years, a coverage of 96% of all women in the invited age groups were attained (Thorsen E, personal communication). Well-organized, meaningful screening may increase interest in cancer in the local community.

For breast cancer screening the discussion is more complex, but the potential gain in saved lives is greater than for cervical screening. In case such screening is initiated, participating women could be activated by including a teaching session of breast self examination (BSE). This has been done in Canada with increasing compliance with BSE criteria [197], and regular performance of BSE may be more efficient in the age group invited for screening than in younger women [198]. The mammography procedure must be separated from general practice, but a parallel randomized, controlled study of BSE combined with a clinical examination in general practice has been proposed [199]. Good clinical use of new technology may increase public interest in cancer. At the same time it is important to preserve public interest for simple clinical examination methods. Links to the local community become particularly important if the technology is used for screening purposes outside the primary care setting.

Conclusion

Warning signals of cancer in previous years may have contributed to better public knowledge of cancer. Continued emphasis on warning signals seems to have a potential for doing more harm than good. The warning signals have reached the age of retirement and should retire honourably.

The present study does not tell what alternative information should be given. Current knowledge about public health information

may give some clues. Public information about cancer should be put in a modern context: ecology, anti-pollution, care for old people, democratic sharing of knowledge and social rights combined with individual responsibility. Different media may communicate messages on different levels. Some messages should aim at groups for whom the message is particularly relevant. Possibilities of prophylaxis should be an integral part of almost all cancer information. The general practitioner during the face-to-face consultation has a unique opportunity to encourage lifestyle prophylaxis.

8. CANCER DIAGNOSTIC STRATEGIES IN GENERAL PRACTICE

Introduction.

The great difference in basic medical knowledge between a doctor and a lay person should give the doctor a better foundation for interpreting symptoms, vague or clear-cut. Trying to link individual symptoms into an understandable synthesis is daily work for most physicians, and perhaps for general practitioners in particular. Doing this, the general practitioner is employing well-documented techniques which are professional although actually rather simple: pursuing a rational medical history, inspecting or palpating or performing other kinds of clinical examination of the body regions in question, estimating the person's general condition and doing simple laboratory tests. The patient may have valuable knowledge about his own body, but many people often find it difficult to interpret new or recurring bodily sensations. The possibility that a symptom may mean cancer arouses anxiety in any person. The physician can work at a distance from his patient's anxiety. Compassion towards the patient does not hinder this. Such a distance probably makes it easier to pursue rational diagnostic and therapeutic action. To aid diagnosis and treatment the doctor should also have a good knowledge of when and how to use facilities available both locally and nationally in laboratories, hospitals and other specialized services. And finally doctors should have some minimum professional insight into the value and the limitations of epidemiological and statistical information.

Relating to cancer, this way of using knowledge has an impact on what kind of knowledge to emphasize. In cancerology, as in any other field, some kinds of information are more useful than others. The selection of relevant symptoms to look for does not have to be as clear-cut as in public information. Doctors should be able to relate symptoms to anatomical structures, to think in terms of general or focal symptoms, and to know that a symptom may be felt at some distance from the organ in which it originates. It has been shown that general practitoners in a consultation situation have an amazingly similar way of thinking [200].

During the first minute of consultation the first diagnostic hypothesis is thought of. A few minutes later the general practitioner usually have thought of five or six hypotheses. These will be subjected to a problem oriented analytic process. In this process specifically aiming anamnestic questions and selected clinical examination are more important than routine questions and examinations. Positive information supporting hypotheses is sought more actively than information aimed at eliminating. If the "correct" hypothesis is among the original hypotheses, the general practitioner will most often select this hypothesis (200).

General practitioners in Material 76 were responsible for more than half of the delay taking place from the first consultation to diagnosis (table 7, chapter 4). Hospital specialists or interns and hospital waiting lists or other administrative factors were the other most important delay factors. It is beyond the scope of this monography to discuss administrative improvements, but the problem should be considered seriously in all hospital departments diagnosing or treating cancer patients. Some of the recommendations for general practitioners may be useful for hospital doctors as well. But my intention in the following pages is mainly to focus on the role the general practitioner can play to minimize delay in cancer diagnosis.

The seven warning signals have been made for the public, but it was suggested in chapter 7 that they may be of more use to the doctor. Notions about sensitivity and specificity of diagnostic tests can be applied to the warning signals and to other symptoms and signs observed by the physician. In most general practice populations the total number of new cases of cancer rarely exceeds ten per year. From this point of view, cancer is a rare disease in general practice. On the other hand, **suspecting** and **excluding** cancer is daily work. In one Norwegian material, general practitioners carried out a cancer-related follow-up in 8.5% of all contacts. In 13.2%, the patients either had some kind of malignancy, had a fear of cancer, or was subjected to a cancer-related follow-up (117). This study concluded that the general practitioner plays a central role in the overall care of cancer patients.

The study of warning signals supports this conclusion. Warning signals were recorded by general practitioners in 5,4% of the consultations (GP-material, chapter 5). A Tromsø general practitioner who sees 20 patients a day then is seeing on average one patient with one or more warning signals every day. Many general practitioners put much effort into trying not to overlook a diagnosis of cancer. Many physicians feel that this is one of the greatest challenges of daily practice. But general practitioners experience considerable dilemmas in dealing with patients who have or may have cancer (201). Doubts about the usefulness of early detection was discussed in chapter 1. Cancer-suspicion with follow-up in general practice rarely prove to be correct. Nylenna (166) found that less than every tenth suspicion was confirmed. General practitioners are aware of this every time they start their investigations. Patients who present with obviously disseminated disease may discourage doctors who put much effort into achieving early diagnosis in their patients with new cases of cancer. All the media attention focuses on technology. With due respect for modern image-making and other highly specialized technological equipment, it is important to remember that there is evidence (78,79) that the medical novice's respect for a good medical history and a thorough physical examination should remain intact. General practitioners should not be tempted to exclude diseases "belonging to" other specialties - like cancer - from their diagnostic domain.

Cancer evokes emotions also in doctors (202). It is inevitable now and then to see tragic cases with bitterness, suffering and death. These cases may colour the physician's attitude more than easily cured cases of cancer in situ or tumours more readily accessible to modern therapy. Much is still unknown about cancer; etiologic uncertainties add to difficulties in treatment, and serious interest concerning communication, pain-relieving and terminal care is fairly recent. The traditional role of the doctor as an authority on all kinds of questions about health becomes difficult (201). Probably few groups of patients make doctors feel so insecure and make them weigh their words to the extent that cancer patients do. It is possible that some of the pessimistic attitudes reflect lack of clinical routines in hand-

ling the problem of cancer diagnostics. This would seem to emphasize the need for post-graduate courses about cancer aimed at general practitioners. This kind of courses have been offered regularly in Norway from around 1985. Taking part in a well-organized, systematic screening program or another kind of cancer survey may raise the general practitioner's index of suspicion for new cases of cancer (92).

Also: consultation nowadays tends to become more complex and time-consuming than before, requiring the physician's attention towards many different health aspects. Among other factors this is due to an increased proportion of elderly patients and more attention to psychosocial factors (203).

Evidently, with one patient presenting a warning signal every day and only five to ten new cancer patients per year, there are many "false positives" if warning signals are relied on in their present form. Dealing with individual patients is difficult when relevant symptoms have high prevalence and the disease has low prevalence. Since one or two of every five cancer patients have no warning signal before diagnosis there are a few "false negatives" as well. There is no simple solution to sorting out patients with cancer in general practice. To improve current practice I see two possible strategies which should be combined:

1. Improving our knowledge about the diagnostic process: A probabilistic approach with rapid elimination of most of the false positives through the combination of several kinds of tests and information, and
2. Improving our knowledge about cancer: Improved diagnostic work with good routines and an individualized, organ-oriented approach.

8-1. Strategy 1: Improving our knowledge about the diagnostic process

In chapter 6 it was found that the positive predictive value for cancer of one single warning signal was very low, about three per cent for Lump and about five per cent for Bleeding (table 33). To exclude a possibility of cancer in general practice, a good starting point is to consider **who the patient is.** Such knowledge

can be combined with a warning signal or other presenting symptoms, but isolated concentration on the presenting symptom is insufficient in cancer diagnostics (166,[204]). The positive predictive value of a presenting symptom may increase considerably when it is combined with what general practitioners often know about their patients: age, sex, personal characteristics, former and chronic illnesses. Age 60 years or older in addition to a warning signal by itself increases the probability of cancer from four to eight percent, calculated for all warning signals (table 33). Probabilities at this level require further examination.

Williams ([205]) emphasized the importance of looking for clues or "red flags" in general practice. Such clues may be essential for forming correct diagnostic hypotheses. Usually it will be easy to get a rough estimate of whether the probability of cancer increases or decreases when the doctor has recognized any of the warning signals and this information is combined with other information about the patient and with the results of further examinations and tests. But general practitioners should be able to use a much more refined set of clues when considering cancer. Apart from symptoms, such clues may refer to personal characteristics, previous or chronic diseases, or to the course of the present illness.

In the list of "data clues" (table 43) I have collected some simple but important information which may increase or decrease the probability of finding cancer in a particular patient. In addition to various personal characteristics - age, occupation, family background, habits, etc.- the list includes some former or chronic diseases and whether there has been a progression of symptoms. Often general practitioners possess this kind of knowledge to a greater extent than hospital doctors.

There is a theoretical and practical difference in the diagnostic procedure when a person is one of many persons who are subject to population screening, and when a patient in a general practice population consults. The low prevalence of disease is common to both populations. In the population being screened it is important to get the smallest possible number of false negatives and false positives, balancing the cut-off point ([206]) for diagnostic tests according to which is the most important to avoid. One of the

Table 43. **Data clues** - for use in the early detection of cancer

A. Clues related to personal characteristics
(Age, habits, body size, skin colour, parity, sexual practice, family, profession, social class)

Increased risk of cancer	Most relevant organ or form of cancer
Increasing age	
Smoking	Bronchi Larynx Lip Oral cavity Bladder Pancreas
High intake of alcohol	Oesophagus Larynx Oral cavity Mamma Liver Pancreas Sigmoid colon
Intravenous drug abuse	Various cancers secondary to human immunodeficiency virus (HIV) infection, especially lymphoma
Low intake of vegetables	Gastrointestinal cancers Bronchi
Proneness to sunburn	Skin
No children or low parity	Mamma Corpus uteri Ovary
Early menarche, late menopause and high age at last birth, except if high parity	Mamma Corpus uteri
Large body surface (height/weight)	Mamma Corpus uteri
Low age at first birth	Cervix uteri
Many sexual partners	Cervix uteri. Indirect risk of other cancers secondary to HIV infection
Male homosexuality	Kaposi's sarcoma and other cancers secondary to HIV infection

Table 43 (cont.)

Increased risk of cancer	Most relevant organ or form of cancer
Cancer in close family members	Especially colon (polyposis), but different organ locations possible in one family. Uterus, breast, stomach are not uncommon sites. Members of "cancer families" involving two or more generations have an increased risk of cancer at a relatively young age, and of multiple cancers
Workers exposed to dust or chemicals	Bladder Bronchi Nose Liver Leukaemia
Low socioeconomic class	Cervix uteri Stomach Rectum Bronchi Bladder

B. Clues related to previous, chronic or present disease

Increased risk of cancer	Most relevant organ or form of cancer
Previous cancer	
HIV infection	Kaposi's sarcoma, lymphoma
Former gastrectomy	Stump cancer
Anacidity	Stomach
Coeliac disease	Lymphoma of small intestine
Ulcerative colitis	Colon
Hypertonia	Kidney
Gallstones/former cholecystitis	Gallbladder. In younger women also breast, internal genitals, gastrointestinal tract
Previous or ongoing immunosuppressive therapy, for instance after kidney transplantation	Lymphoma
Down's syndrome	Leukaemia
Progression of present symptoms	

problems in cancer screening is that the seriousness of the disease makes it important to avoid false negatives, which would speak against choosing a very high stringency for the positivity criterion of each test. However, in populations with low prevalence of the target disease, the number of false positives may be overwhelming if the cut-off point is not shifted in the direction of greater stringency (206). Also in screening procedures, cost in a broad sense must be reduced to a minimum. Erichsen (207) showed that for a fixed number of tests in a sequence, when a positive test means continued testing, the test with the highest specificity should be performed first to reduce the total number of tests.

Faced with an individual person who consults, the general practitioner must keep open the possibility that regardless of the test results, of symptoms or signs present or absent, both possibilities of true or false in relation to a diagnostic hypothesis should be kept open both for positive and negative results at least until a decision about treatment, referral or follow-up has been taken. Single findings are to a lesser extent basis for decisions about further investigations, it is the combined results which become a basis for decisions. This is an advantage to the extent that it makes diagnostics in general practice more subtle than in screening procedures, with more weight on detail. In clinical situations it is also less costly to pursue examinations in patients who prove to be "false positives", as their number will be limited to the number of patients who consult. This is particularly important when it is important to avoid false negatives. Testicular cancer is an example of a disease which affects relatively young people and where therapy is very effective. Examination of the testicles of a young man should be performed on very liberal indications because of this, and a high number of negative examinations should be accepted as good clinical practice in this case.

Thinking in terms of risk groups allows the complex reality in general practice (203) to be combined with probability thinking and thinking about the consequences of clinical practice. Risk groups mean higher prevalence of disease, which in most situations increases the importance of subsequent test results (76). One or

two negative tests can increase the probability of the patient being a true negative to a level where a conclusion about non-treatment or non-referral (but not necessarily non-follow-up in one's own practice) can be reached. The probability of finding cancer on the basis of a warning signal is higher in old than in young persons, because of the higher prevalence of undiagnosed cancer in old persons (chapter 6). And the probability that a patient with a positive test is a false positive in relation to the diagnostic hypothesis will be reduced in a risk group. A patient who understands that there may be reason to suspect cancer, carries a psychological burden which is considerable (208). Being cared for by a general practitioner who takes an active interest in investigating the case, may be better than being invited to follow-up because of a positive test in a population screening program. But in any case it is important to keep the number of false positives as low as possible.

An example from the case-control study based on Material 83 (chapter 6) can illustrate that an increased diagnostic probability of lung cancer is obtained by defining the patient into gradually more narrow risk groups where the prevalence is higher (table 44). This implies a sharp decline in the number of false positives. Lung cancer very often is diagnosed by chance, and we may want to find a more rational basis for diagnosing this form of cancer, starting with a patient who presents Cough/hoarseness at consultation:

In table 44 I have imagined a general population of 20 000 people and assumed that they all consult a general practitioner during one year's time. As we have seen in chapter 5, there are differences between a general population and a patient population, but in this example I have assumed that the incidence of lung cancer, the male/female ratio and the smoking fraction is the same as in the general population in 1982, when much of Material 82 and Material 83 were collected. For the age distribution I have used a figure from the patient population in chapter 5 rather than that of the general population.

In 1982 there were approximately three cases of lung cancer per 10 000 persons. The three materials of cancer patients suggest that about one half of all lung cancer patients experience Cough-

Table 44 Changing diagnostic indexes when simple information about the patient is considered together with the observation of a warning signal

PREV = Prevalence of lung cancer
PPV = Positive predictive value of Cough/hoarseness
PV-NEG = Predictive value for no lung cancer when the patient does not present Cough/hoarseness
LR = Likelihood ratio of Cough/hoarseness

	Lung cancer	No lung cancer	PREV	PPV	PV-NEG	LR
a. **All 20 000 patients**						
Cough/hoarseness +	3	87				
Cough/hoarseness -	3	19907	.03%	3.3%	99.98%	115
b. **9 000 male patients**						
Cough/hoarseness +/ Male +	2	25				
Cough/hoarseness -/ Male +	2	8971	.04%	7.4%	99.98%	180
c. **1116 male patients 60-69 years of age**						
Cough/hoarseness +/Male +/ 60-69 years +	1	7				
Cough/hoarseness -/Male +/ 60-69 years +	1	1107	.18%	12.5%	99.91%	80
d. **446 male patients 60-69 years of age, daily smokers**						
Cough/hoarseness +/Male +/ 60-69 years +/Daily smoker +	1	5				
Cough/hoarseness -/Male +/ 60-69 years +/Daily smoker +	1	439	.45%	16.7%	99.77%	44

/hoarseness before diagnosis (Appendix 5). This is in accordance with a Norwegian lung cancer material ([209]). I then assume that the warning signals recorded from the medical records actually are presented to the general practitoner at consultation. Rates for Cough/hoarseness were 30/10 000 for males and 60/10 000 for females (table 14). Assuming the female and the male population to be of the same size these rates mean that 90 of the 20 000 patients presented Cough/hoarseness (table 44 a).

In this example the patient is a man. Actually in 1982 about 45% of the population was male, and between four and five of every six lung cancer patients were males. Here I assume that four of our six lung cancer patients are among the remaining 9000 male patients. Using the rates for males in table 14 we are left with 27 patients presenting Cough/hoarseness. This means that we have eliminated 62 of 87 "false positives" merely by considering the sex of the patient (table 44 b).

Our male patient belongs to the age group 60-69 years. About ten per cent of the male population in 1982 were 60-69 years old, but 12.4% of the GP-material belonged to this age group (table 12). This latter percentage leaves 1116 male patients aged 60-69 years. In this age group there were 1.8 cases of lung cancer per thousand men, which makes it likely that two of our six lung cancer patients are among the 1116. A Cough/hoarseness-rate of seven per thousand (table 14) leaves eight patients with Cough/-hoarseness (table 44 c).

Finally our male patient in his sixties tells that he is a daily smoker. In 1982 40% of Norwegian males in this age group were daily smokers ([210]). It is quite probable that our two remaining lung cancer patients are smokers, and it is hardly unreasonable to assume that six of our eight patients with Cough/hoarseness in table 44 c are smokers (table 44 d). Of 87 false positives in table 44 a we now have eliminated 80, and calculations suggest that our 60-69 year old male patient being a daily smoker and presenting Cough/hoarseness has a one in six chance of having a lung cancer diagnosed within the next two years. I think this figure tells us to request an x-ray of our patient's thorax even if our clinical examination becomes negative. Positive clinical findings may of course strengthen the

case for rapid referral to a lung specialist rather than waiting for the result of an out-patient X-ray.

In the different hypothetical populations the likelihood ratio varies somewhat. The highest likelihood ratio for Cough/hoarseness in relation to lung cancer is found for males. Added information lowers the likelihood ratio, but in a patient included in table 44 d Cough/hoarseness is still 45 times more likely to occur when lung cancer is present than when there is no lung cancer. While the positive predictive value increases steadily as the prevalence increases, likelihood ratio is seen to vary independently of changes in prevalence.

Most single symptoms have very different origins, and estimations of probability must be part of professional thinking ([211]). In a general practice patient population there are low prevalences of almost any disease. Consequently, for almost any single test the positive predictive value for a particular disease will be low. If the general practitioner thinks in terms of risk groups, probabilities can be increased considerably. Cancer in old people is an outstanding example. Focusing on risk groups is an old idea for most general practitioners, but most such thinking is based on intuition rather than on empirical data combined with conscious thinking about probabilities and predictive values. Simpler judgmental operations may be useful in many situations, but sometimes they lead to severe and systematic errors ([212,213]). More systematic thinking about risk groups should be encouraged in the diagnostic thinking of general practitioners as well as in cancer information policy, as was discussed in chapter 7. The example also illustrates the impact of the overall consultation behaviour in a population: headache may be a symptom of a brain tumour, but the more patients with headache who consult, the more difficult it becomes to make the diagnosis of brain tumour in an individual patient.

Most general practitioners will meet one new case of breast cancer or one new case of colorectal cancer annually. Considerations of what is most frequent is part of probability thinking and is useful for a general practitioner, even if it is more useful for a hospital doctor who works with a population with a much higher prevalence of cancer.

Combining diagnostic tests with other information is and must be the general practitioner's means to overcome his low-prevalence-handicap. Even when it comes to the rare forms of cancer this approach may be fruitful. There is a multitude of cancers which are seen annually by only a small fraction of the general practitioners; perhaps once or twice in a professional career. Each rare form of cancer may not deserve the same attention as the major cancer forms. But there are many rare forms, and taken together the probability of meeting a patient with one such rare form during a year of practice is rather high (172). Which of the rarities one meets may be almost completely haphazard. Most experienced general practitioners have seen a few cases of really rare forms of cancer, or cancer occurring in unusual age groups. If they are thought of, such cancers are not necessarily particularly difficult to diagnose. The adequate diagnosing of these cancers probably require broad-based training and open-mindedness toward the possibility of cancer (172) together with an effort to increase probabilities by combining fragments of information. Consciousness about a high likelihood ratio of one single symptom may initiate the search.

In table 44 we also may note that when the prevalence of lung cancer increases, the predictive value for **no** lung cancer given **no** warning signal recording decreases, although very slightly. Still the figure of 99.77% in table 44 d is far too high to give any clue as to where to look for the three cancer patients without Cough/hoarseness. We have to consider a second strategy to avoid doctor's delay.

8-2. Strategy 2: Improving our knowledge about cancer

The process of cancer diagnostics described in the introduction depends very much on the physician's knowledge about what importance to attribute to different symptoms and data, and about what additional examinations are meaningful to carry out. The probabilistic approach in Strategy 1 therefore should be combined with a knowledge-based analysis containing three essential elements: Knowledge about symptom clues, knowledge about diagnostic traps, and ability to relate symptoms to anatomic structures.

A set of "symptoms clues" (table 45) more refined than the warning signals have been made on the basis of these reflections. Symptom clues are a physician-directed, extended version of warning signals and may be the starting point in a diagnostic process. The list tries to combine symptoms and signs which the physician meets and finds through looking, listening, feeling, smelling, imagining anatomy and physiological processes, rapidly sensing and reflecting upon the patient's general symptoms, state of mind, said and unsaid.

Table 45. **Symptom clues** - for use in the early detection of cancer

Symptom	Most relevant organ	More specific description of symptoms
Sore	Skin	
	Mucous membranes	
	Mouth	
	Nose	
	Ear	
	Genital organs	
Lump	Breast	
	Neck	
	Axilla	
	Groin	
	Bone	
	Muscle	
Pain	Sinus	
	Stomach	Epigastrial pain
	Pancreas	Vague but constant pain
	Kidney	
	Bone (especially long bones and vertebrae)	
	Central nervous system	Headache
		Backache especially when lying on the back: spinal cord, but vertebrae, pancreas, kidney as well
Stenosis/ irritation	Sinus	Nasal stenosis
	Larynx	Hoarseness
	Bronchi	Cough, dyspnoea, infection
	Oesophagus	Difficulty in swallowing
	Biliary tract	Icterus
	Cerebellopontine angle	Unilateral loss of hearing, noise in the ear, dizziness
	Pituitary	Unilateral loss of vision, sometimes endocrine symptoms
	Spinal cord	Pain usually precedes loss of sensibility. Pareses sometimes early sign
	Cerebrum	Nausea/vomiting, dizziness, mental changes, epilepsy

Table 45 (cont.)

Symptom	Most relevant organ	More specific description of symptoms
Bleeding macroscopic/ microscopic/ cutaneous	Epipharynx/nose Bronchi Stomach Colon Uterus/vagina Kidney Bladder Prostate Skin (leukaemia)	
General symptoms	Stomach	Nausea, weight loss, weakness
	Pancreas	Weight loss
	Kidney	Weight loss, weakness
	Central nervous system	Nausea, vomiting, dizziness
	Lymphoma	Weakness, moderate fever
	Leukaemia	Weakness, moderate fever
Paraneoplasias		
Polyneuritis	Most often lung	Sensibility/reflexes diminished, sometimes pareses
Endocrinopathy	Most often lung:	ACTH syndrome (Cushing)
	Most often mamma:	Hypercalcaemia, renal calculus
	Pancreas:	Gastrinoma/stomach ulcer
Cutaneous	Most often lymphomas/ myelomas/leukaemias or adenocarcinomas	Acanthosis nigrans (axilla) Acquired ichtyosis Generalized pruritus Erythrodermia Purpura Dermatomyositis (face/eyelids: erythema, oedema, telangiectases) Repeated attacks of thrombophlebitis

ACTH = Adrenocorticotropic hormone

Symptom clues necessitate: Examination
Evaluation
Control if the conclusion remains uncertain

However, statistical notions sometimes make traps. Diagnosticians have to be aware of this. A high probability is not certainty. Single laboratory or other examinations may sometimes be conclusive, but most often they are not, even if pointing in a certain direction. A patient's or a parent's own observations and reflections may be valuable, as is often the case with mothers' observations of their children. But patients' reflections may deceive as well, emphasis on former physical or psychological traumas misleading the physician. In the same way the physician's own background knowledge about the patient may mislead. Psychological particularities of a patient may be considered in a diagnostic process, but always with great prudence. A good medical history and quiet reflection probably are the best remedies to overcome the difficulties of such traps, which may make any Dr. Watson wish he knew a Mr. Holmes. The traps listed in table 46 represent tough meetings with reality for diagnosticians, with the patient as the ultimate victim. Hardly any practitioner has not fallen into one or more of the most common pitfalls. Still it is surprising how easy they are to forget in daily practice. Experience may help to avoid the fallacies, but it is no guarantee. The list of traps may have a reminder or check list function. Promising diagnostic hypotheses should be checked against such traps.

If the process of thought and practical work suggests that there is a possibility of making a positive diagnosis, the general practitioner should start to think in terms of **organ based symptoms.** Most doctors would think that this is evident, but I think that we have a tendency of limiting our imagination to the most evident locations. If we do not find disease in the patient's stomach or in his colon, it is easy to forget the other abdominal organs. Organ based thinking may contribute to limiting the number of supplementary examinations and to making appropriate referrals as rapidly as possible.

Table 46. **Diagnostic traps** - to be considered when early cancer is possible

1. **Negative results of examinations do not exclude cancer**

   Concerns laboratory tests
   X-ray examinations
   clinical examinations

2. **Pathological test values must be verified and followed up**

   Writing them down in the medical record is not enough

3. **A diagnosis of any common disease does not exclude simultaneous cancer**

4. **Increasing incidence with increasing age does not exclude cancer in younger persons**

5. **Former traumas may or may not be responsible for new symptoms**

   The quickest explanation of symptoms is not always the right one

6. **Vague symptoms sometimes may become less vague with the help of a good medical history**

   Chronology, location, intensity, progression should be considered

7. **Confusing symptoms may reveal (or hide) endocrine disorders, while endocrine disorders may reveal (or hide) a tumour**

As part of this thinking it may be useful to be aware of common fallacies for more common forms of cancer. Omission of rectal examination in spite of local symptoms was mentioned as an example in chapter 4. Another example is lack of follow-up in women presenting breast symptoms when the physician is unable to confirm the woman's findings or thinks the changes are benign ([214]). A general practitioner should not be expected to examine all patients from head to foot, and isolated concentration on cancer could lead to much wasted effort. But problem-oriented, relevant diagnostic procedures will increase diagnostic quality in general. Jenkins (92) and his group of general practitioners chose to study cancer because cancer diagnostics was thought to reflect quality of care in general. It is unlikely that a higher index of suspicion for cancer would weaken a general practitioner's diagnostic performance in other fields.

Cancer being such a heterogenous group of diseases, very different diagnostic procedures may be useful for different forms of cancer. In a previously written manual I have tried to systematize present knowledge about manifestations and useful procedures relating to cancer in a certain organ or organ system or in a specific anatomic region ([215]). An estimate of when and where to pursue controls and further examinations is included for each organ. General practitioners should routinely consider follow-up appointments with patients presenting symptoms which cannot be explained during the first consultation. Time is often a good diagnostic aid in general practice. A follow-up appointment is in itself an assurance for the patient and can counteract fear which otherwise might make him avoid a second consultation. Symptoms which have disappeared do not take up much time during the next consultation.

Cancer in children are special cases. In chapter 6 it was argued that warning signals have little relevance in the diagnosis of cancer in children. Doctors should know and actively look for the few forms of cancer which are characteristic for different age

groups in childhood. Such examinations usually are quick, simple and require little extra effort. They should be a natural part of routine examinations in mother-and-child clinics as well as of ordinary children's consultations. Examples are looking for a red reflex in the eyes of infants, abdominal flank palpation in toddlers or palpation for spleen enlargement and a few capillary blood tests in the tired child. The rare occurrence of cancer in children should assure doctors that most symptoms have other explanations. Still the prospect of seeing a leukaemic child every tenth year or so should make us prepared to exclude the possibility a few times each year.

Conclusion

Reduction of doctor's delay in cancer is possible with better diagnostic strategies. Such strategies necessitate good knowledge about the diagnostic process in general practice, and good knowledge about cancer within the frames relevant for general practice. This should be reflected in student training, and post-graduate courses about cancer aimed at general practitioners should be arranged regularly.

The often vague nature of cancer symptoms and the existence of traps prepare the ground for a minimum rule: For any patient with an uncertain diagnosis after consultation a follow-up appointment with the general practitioner should be considered if there is no referral to specialized medicine.

9. CONCLUDING REMARKS

My investigations have focused on the three topics outlined in chapter 2:

1. Cancer diagnostic delay
2. The importance of the Seven warning signals of cancer
3. Cancer diagnostic strategies in general practice

9-1. Cancer diagnostic delay

Although poorly defined in the literature, I conclude that diagnostic delay is a sad reality for many cancer patients. It has been so throughout the history of modern medicine. In the first part of the century an appreciable reduction in the duration of the delay was demonstrated, both on the part of the patient and the physician first consulted. In the late nineteen-forties some reduction of patient delay was demonstrated. It is difficult to compare the present results with previous studies, but improvement seems to be modest. The duration of patient delay may have diminished, while the fraction of patients affected by patient delay and/or doctor's delay remains very important. Conclusions from the present study should be drawn with care, as there are many methodological pitfalls. Approximately half of the cancer patients seem to consult unreasonably late, half of the patients are subject to doctor's delay, and the overlap is such that about three quarters of the patients are affected by some kind of delay. Included in this figure is a smaller fraction of patients with some kind of administrative delay. General practitioners were responsible for more than two thirds of doctor's delay, while hospital doctors contributed almost one third.

There is considerable evidence that reduction of delay in the diagnosis of cancer may reduce some of the problems associated with the disease. In addition to fewer deaths, there may be less suffering, less complicated treatment, less economic cost for the patient and the society. It would be unreasonable to expect that delay should never occur, but the present study suggests that an important reduction in delay is within reach. To that end, efforts

should concentrate on two levels: public cancer education, and training of general practitioners. A good administration of health services with continuing discussions about priorities also is important. In Norway, introduction of systematic, data-based and general practice-based screening for cancer of the uterine cervix may contribute to reduced delay, and discussions about the introduction of systematic mammography screening will continue.

9-2. The importance of the Seven warning signals of cancer

To start with the positive side, some cancer patients experience a warning signal, consult a doctor because of this, have their diagnoses made promptly and probably improve their prognosis mainly due to their adequate reaction upon experiencing a warning signal. Among 80 cancer patients in the cohort study 20 had a warning signal recorded by their general practitioner, and I estimated that 14 of them may have profited from having experienced a warning signal (chapter 6).

An association between warning signals and cancer has been demonstrated. Judged from medical records three or four of every five cancer patients experience a cancer-related warning signal during the last weeks or months preceding diagnosis. The cohort study suggests that a patient with undiagnosed cancer is about five times more likely to present a warning signal at consultation than a patient without cancer. In this case undiagnosed cancer meant cancer diagnosed up to eighteen months following the consultation. These results may encourage continued use of the warning signals in public cancer information. But there are many shortcomings of a warning signal strategy:

First of all, one or two of every five patients never experience a warning signal before diagnosis. Is it possible that some people postpone a consultation when experiencing a symptom because they think that their symptom is not a warning signal and consequently no cancer symptom? It is tempting for anybody to use any excuse for thinking that it cannot be cancer. Now, this problem may not be very important, because somewhat surprisingly delay among cancer patients not experiencing warning signals was shown to be less than when a warning signal was present (chapter

6). The two groups of patients, with and without a warning signal, are not comparable, and we cannot be certain that the warning signal contributes to the delay. But possibly it is so, and the finding is consistent with findings in other studies. A combination of fear and relative ignorance may lie behind the longer delay in patients experiencing a warning signal. Such an explanation is supported by several studies and has been discussed in chapter 6. If the understanding is particularly good, some patients may want to carry out practical matters before consulting: The female breast cancer patients who gave priority to family caring tasks before asking for help for themselves illustrate this. Possibly in some cases the postponement of the final confirmation that they had cancer helped them accept this. Generally, information may reduce ignorance and thereby delay, but cancer information can be much more than knowledge about warning signals.

Secondly, it has been shown that warning signals are very unspecific in relation to cancer (chapters 5 and 6). They discriminate poorly between cancer and non-cancer. There was no significant difference in warning signal recordings between cancer patients and control patients in the cohort study (chapter 6). In old age a person with a warning signal is only slightly more likely to have cancer than an old person without a warning signal. The interview study (chapter 5) suggested that warning signals more often than other symptoms lead to consultation, regardless of the patient's age. If all persons experiencing a warning signal promptly consulted a doctor, it would take very much of the resources of primary health care (chapter 5). For persons below 60 years of age only some of the warning signals are relevant, and for children they are hardly relevant at all (chapter 6). The very important increase in cancer incidence with age makes it very difficult to find and present a broad, consistent message aimed at the whole population. Patients below forty years of age seem to have little patient delay anyway (chapter 4). Younger people are better informed. Perhaps this makes them react more adequately when cancer symptoms appear.

Warning signals may have contributed to public cancer information at a time when health information was scarce. Today the consultation threshold for warning signals is low, and there is

hardly any need to encourage increased consulting for whoever experiences a warning signal. It is possible that insistence on warning signals may have an adverse effect through increasing fear and indirectly contributing to increased delay for some cancer patients. The role of the warning signals as a package and a pillar in public cancer information should be over, and all symptom information in cancer should be put in a context of prophylaxis, of progress in treatment methods and other information contributing to increased understanding of human biology (chapter 7).

Increased attention towards elderly people is necessary, considering the high incidence of cancer in old age. A second very important group is women between thirty and fifty years of age. Here it might be possible to focus on the nature and importance of breast cancer and cervical cancer. In countries with national screening programs, information about the screening may be linked with information about the disease. Possible symptoms could be part of a broader message.

9-3. Cancer diagnostic strategies in general practice

General practitioners in some cases may have received a useful reminder through the recognition of a warning signal in a patient. However, single symptoms are of little value when the prior probability of cancer is less than one percent. Attention towards single symptoms as a kind of cancer diagnostic awareness is sometimes appropriate but almost always insufficient. A lot more information is available to doctors, and delay figures urge us to use all the information available. In chapter 8 a two step cancer diagnostic strategy has been described.

The first step starts with the basic diagnostic problem of general practice; the low prior probability of diagnosing almost any specific disease. To overcome this, symptoms and facts about age and sex are combined with "data clues" - concerning further personal characteristics, former or chronic diseases and the development of the symptoms - to tell whether the patient is in some kind of a risk category where the prevalence of the disease is higher. Combining different pieces of information then has a

better chance of providing a rational basis for decisions about treatment, referral or follow-up in the general practitioner's own practice.

The second step is more concerned with details, even if the two strategies overlap. This step implies more accurate anatomical considerations and draws on knowledge about cancer manifestations in individual organs. Some basic "symptoms clues" are introduced inspired by the warning signals. Symptoms clues have some of the weaknesses of the warning signals, but are probably better adapted to professional thinking. "Traps" should also be considered. Some diagnostic pitfalls concern most diseases, some are more cancer specific. Follow-up of patients with symptoms of uncertain origin is very important.

9-4. The challenge

The challenge to general practitioners is not less than the challenge faced by public health authorities and cancer associations. Reducing public fear and increasing public knowledge seem to be important goals for everybody working with cancer. General practitioners must improve cancer diagnostic routines. Through rational, systematic efforts, reduction of cancer diagnostic delay should be possible.

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APPENDIX

Appendix 1. The number of patients in each material with medical records from general practice and hospitals

Medical records from:	General practice	Hospitals
Material 76:		
Cancer patients[1] (n=108)	104	107
Material 82[2]:		
Cancer patients (n=65)	33	58[3]
Control patients (n=65)	65[4]	24
Material 83[2]:		
Cancer patients (n=80)	80	75[5]
Control patients (n=80)	80	39

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[1]One old patient who died at home had no records apart from the death certificate. The records from general practice had been destroyed post mortem for two patients and mailed elsewhere for one patient who moved from Tromsø. For these three patients, referral letters from the general practitioners were found in the hospital records. All other patients had medical records from at least one hospital department and one to three records from general practice, or from an old people's home in two cases.

[2]Only records containing notes from after March 31st 1981 were considered

[3]No hospital records:
Four patients with basal cell carcinoma treated as outpatients
Two patients with thyroid cancer discovered at autopsy after sudden death
One old woman who died in an old people's home with an abdominal tumour registered as cancer

[4]Two men with diagnosed or probable cancer were excluded as controls. In a few cases the control patient's general practice record could not be found in spite of the recent encounter with a general practitioner. In these cases the second closest in age was chosen as a control.

[5]No hospital records:
Three women with in situ cancer of the cervix treated as outpatients
Two patients with skin cancer, one squamous cell and one basal cell carcinoma, treated as outpatients

Appendix 2. Registration form, material 76

Sivil-opplysninger
Navn_____ Født |_|_|_|_|_|_| Kjønn |_| 1=M 2=K
Adresse |_| 1=by, 2=distrikt.
Sivilstand |_| 1=ugift, 2=gift, 3=tidl.gift
Boligforhold |_| 1=alene, 2=med andre, 3=institutsjon

Medisinske opplysninger ved diagnosetidspunkt
Diagnosetidspunkt |_|_|_|_| (måned, år) Gruppe
Diagnose_____ |_|_|_|_|_| |_|_|
Bidiagnose(r)_____ |_|_|_|_|_| (se kode)
_____ |_|_|_|_|_|
_____ |_|_|_|_|_|
Metastaser |_| 0=ingen, 1=infiltrasjon, 2=regionale, 3=fjern

Pasient-lege-kontakt
Tid 1. symptom - 1. legekonsult. |_|_|_| uker. Kreftreg.: |_|_| mnd.
Tid 1. legekonsult. - diagnose |_|_|_| uker. kreftreg.: |_|_| mnd.
Antall konsult. hos allmenprakt. siste år |_|_|
Antall allmenprakt. konsultert siste år |_|_|
Allmenpraksis søkt siste år |_|_|_|_|_|_|_|_|_|_| (se kode)

Problempresentasjon, undersøkelser og deres betydning for diagnosen
Presentert hovedsymptom |_| (se kode) Betydning |_|
Allmenpraktikers anamnese |_| (se kode) Betydning |_|
Allmenpraktikers kliniske undersøkelse |_| (se kode) Betydning |_|
Antall lab.-u.s. rekv. av alm.prakt. si. år |_| Betydning |_|
Antall røntgen-u.s. siste år |_| Betydning |_|
Herav rekv. av almenpraktiker |_| Betydning |_|
Ant. poliklin. konsult. hos spesial. si. år |_| Betydning |_|
Antall sykehusopphold siste år |_| Betydning |_|
Allmenpraktikers mistanke om kreft |_|
0=ingen el. utilstr. opplysn., 1=mulig, 2=sannsynlig
Kreftregisterets registrerte basis for diagnosen |_|_|
1=klin.us. alene, 2=rtg., 3=op., 4=histol., 5=andre us, 6=obduksj.

Vurdering av den diagnostiske innsats og anslått konsekvens av "urimelige" forsinkelser
"Urimelig" forsinkelse 1.symptom - 1.legekonsultasjon |_|
0=ingen, 1=endel, 2=vesentlig
Hvis 1 eller 2: Anslått konsekvens for prognose |_|
0=ingen, 1=litt negativ, 2=svært negativ, 3=usikker
"Urimelig" forsinkelse 1.legekonsult. - diagnose |_| (kode over)
Hvis 1 eller 2: Anslått konsekvens for prognose |_| (kode over)
Pasientfeil |_|_| 0=ingen, 1=nøling før konsult., 2=ikke møtt til avtale
Systemfeil |_|_|_|_| 0=ingen, 1=ustabil legesit.primærhelsetj., 2=ventetid/dårlig priorit. pr.h.t., 3=do.sykehus, 4=papirer vekk
Allmenpraktikerfeil |_|_|_|_|_|_|_|_| (se kode)
Spesialistfeil |_|_| 0=ingen, 1=utilstrekkelig undersøkelse, 2=dårlig oppfølging/kommunikasjon til allmenpraktiker

Appendix 3, A and B. Registration cards

Initialer (fornavn, etternavn)	Kjønn (m/k)	Føds.dato

Merknad:

Initialer (fornavn, etternavn)	Kjønn (m/k)	Føds. dato

1. Ethvert sår som ikke vil gro . . . . . ☐
2. Knuter og klumper hvor som helst på legemet, spesielt i brystene, og selv om de er smertefrie. . . . . ☐
3. Unormale blødninger fra de naturlige legemsåpninger . . . . . ☐
4. Forandringer i farge eller størrelse på vorter og føflekker. . . . . ☐
5. Vansker ved å svelge, dårlig fordøyelse eller uregelmessigheter med avføringen, hvis det ikke går fort over. . . . . ☐
6. Hesthet eller hoste uten tydelig årsak . . . . . ☐
7. Vekttap uten forklarlig grunn . . . . . ☐
8. Smerter som ikke flytter seg eller går over . . . . . ☐

Merknad:

Appendix 4. Patients with double or triple recordings of cancer-related warning signals before diagnosis, from medical records

F = Females, M = Males
"Late" symptoms in brackets

Diagnosis	Warning signals	Sex	Age
Material 76:			
Oesophageal cancer	Lump + Weight loss	M	55
Stomach cancer	Indigestion + Weight loss	M	67
Cancer of ascending colon	Lump + Indigestion	F	56
Cancer of sigmoid colon	Bleeding + Indigestion	M	65
Bronchial cancer	Cough/hoarseness + Weight loss	F	78
Wilm's tumour	Lump + Weight loss	F	4
Material 82:			
Lip cancer	Sore + Lump	F	71
Stomach cancer	Bleeding + Indigestion	F	35
	Indigestion + (Weight loss)	M	58
	Weight loss + (Indigestion)	M	66
Cancer of sigmoid colon	Indigestion + Weight loss	F	73
	Bleeding + Indigestion	F	78
	Weight loss + (Indigestion)	M	61
Rectal cancer	Bleeding + Indigestion + Weight loss	F	56
Pancreatic cancer	Indigestion + Weight loss	M	43
	(Indigestion) + (Weight loss)	F	82
Bronchial cancer	Cough/hoarseness + (Lump) + (Indigestion)	F	47
	Bleeding + Cough/hoarseness	F	56
Material 83:			
Stomach cancer	Indigestion + Weight loss	F	60
	Bleeding + Indigestion	M	46
Cancer of colon	Bleeding + Weight loss	F	74
	Bleeding + Indigestion	M	64
Tubular adenoma of colon, dysplasia	Bleeding + Indigestion	M	67
Cancer of sigmoid colon	Bleeding + Weight loss	M	61
Rectal cancer	Bleeding + Indigestion	F	64
	Bleeding + Indigestion	F	57
Adenocarcinoma of abdomen, unknown primary focus	(Cough/hoarseness) + (Weight loss)	M	67
Bronchial cancer	Bleeding + (Lump)	M	88
	Cough/hoarseness + Weight loss	M	69
	(Indigestion) + (Weight loss)	F	65
Bronchial cancer (oat cell)	(Lump) + (Cough/hoarseness)	F	48
Cancer of ovary	Indigestion + Weight loss	F	61
Lymphoblastoma	Lump + Cough/hoarseness + (Weight loss)	F	41

Appendix 5. Organ locations of cancer in three cancer patient materials. Diagnostic groups according to the Norwegian Cancer Registry

WS+/WS- = Cancer-related warning signal(s) present/absent
F = Female, M = Male
Pairs of *,&,£,$,§,^ = Two new cancer diagnoses in the same patient during the registration period

Diagnostic group / Organ location	Material 76 WS+ F	Material 76 WS+ M	Material 76 WS- F	Material 76 WS- M	Material 82 WS+ F	Material 82 WS+ M	Material 82 WS- F	Material 82 WS- M	Material 83 WS+ F	Material 83 WS+ M	Material 83 WS- F	Material 83 WS- M
Buccal cavity, pharynx												
Lip	1	3	-	-	1	-	-	-	-	-	-	-
Buccal mucosa	1	1	-	-	-	-	-	-	-	-	-	-
Salivary gland (parotis)	-	-	-	-	-	-	-	-	-	1	-	-
Digestive organs												
Oesophagus	-	1	-	-	-	-	-	-	-	-	-	-
Stomach	2	3	2*	3	2	5	1	-	2	3	-	2$
Colon above rectum	5	3	3	-	2	1	2^	-	3	2	-	1
Rectum	1	3	-	-	3	1	-	-	2	1	1	-
Liver (primary tumour)	1	-	-	-	1	-	-	-	-	-	1	-
Gallbladder/biliary duct	-	1	1*	-	-	1	-	-	-	-	-	-
Pancreas	1	3	1	1	1	1	-	-	-	-	-	-
Respiratory system												
Sinuses	-	-	1	1	-	-	-	-	-	-	-	-
Bronchi	1	2	1	4	2	-	-	-	2	2	1	-
Breast and genital organs												
Breast	10	1	-	-	5&	-	1^	-	6£	-	-	-
Cervix	2		-		1		2		6		13	
Corpus	-		-		1		-		1		-	
Ovary	1		2		1		1&		4£		1	
Placenta/choriocarcinoma	1		-		-		-		-		-	
Vulva	1		-		-		-		-		-	
Prostate		1		6		-		4		2§		5$
Penis		-		1		-		-		-		-
Testis		-		-		-		-		1		-
Urinary organs												
Kidney	1	-	-	-	-	1	-	-	3	2	-	-
Bladder/urethra	-	1	-	-	-	4	-	1	-	2§	-	-
Other and unspecified sites												
Skin:												
Malignant melanoma	-	2	-	-	-	-	-	-	-	-	-	-
Squamous epithelial	1	3	-	-	-	1	-	-	-	1	-	-
Basocellular	4	3	1	-	5	5	-	-	2	1	-	-
Brain	-	-	2	2	-	-	-	-	-	1	-	2
Eyeball	-	-	-	1	-	-	-	-	-	-	-	-
Thyroid gland	-	-	2	-	2	-	2	3	1	1	1	-
Soft tissue/sarcoma	1	-	-	-	2	-	-	-	-	-	1	-
Unspecified	1	-	3	-	-	-	-	-	-	-	-	-
Lymphatic and hemopoietic tissue												
Myelomatosis	-	-	1	2	-	-	-	-	-	-	-	-
Leukaemia	-	-	-	-	-	-	1	-	-	-	1	-
Lymphoma	-	1	-	-	-	-	-	-	1	-	-	-
Total number of diagnoses	36	32	20	21	29	20	10	8	33	20	20	10

Appendix 6. Supplementary kappa calculations

Table A. Inter-observer agreement on the presence or absence of five warning signals, and on all seven warning signals together. Female patients

		Overall agreement	Expected agreement	Kappa	Kappa range
Lump	Cancer patients	0.86	0.57	0.68	0.66-0.70
	Control patients	0.95	0.87	0.65	0.47-1
Bleeding	Cancer patients	0.87	0.53	0.73	0.72-0.75
	Control patients	0.91	0.78	0.58	0.41-0.83
Indigestion	Cancer patients	0.88	0.64	0.67	0.62-0.74
	Control patients	0.95	0.82	0.70	0.68-0.73
Cough/hoarseness	Cancer patients	0.97	0.85	0.82	0.73-1
	Control patients	0.99	0.99	0	0
Weight loss	Cancer patients	0.97	0.77	0.88	0.82-1
	Control patients	0.96	0.92	0.59	0.38-1
All seven warning signals	Cancer patients	0.93	0.72	0.76	0.75-0.78
	Control patients	0.96	0.91	0.56	0.48-0.69

Table B. Inter-observer agreement on the presence or absence of five warning signals, and on all seven warning signals together.
Male patients

		Overall agreement	Expected agreement	Kappa	Kappa range
Lump	Cancer patients	0.83	0.65	0.53	0.44-0.65
	Control patients	0.93	0.87	0.49	0.33-0.62
Bleeding	Cancer patients	0.95	0.57	0.89	0.84-0.91
	Control patients	0.95	0.89	0.57	0.46-0.62
Indigestion	Cancer patients	0.76	0.57	0.45	0.34-0.52
	Control patients	0.88	0.77	0.51	0.44-0.64
Cough/hoarseness	Cancer patients	0.95	0.87	0.64	0.46-1
	Control patients	0.95	0.91	0.44	0.08-0.62
Weight loss	Cancer patients	0.95	0.73	0.84	0.76-1
	Control patients	0.97	0.97	0	0
All seven warning signals	Cancer patients	0.91	0.73	0.68	0.66-0.70
	Control patients	0.95	0.90	0.48	0.43-0.50

Table C. Inter-observer agreement on the presence or absence of five warning signals, with and without a probable relationship with the patient's cancer disease, and on all seven warning signals together. Female cancer patients

	Relation to the cancer	Overall agreement	Expected agreement	Kappa	Kappa range
Lump	Likely	0.96	0.64	0.89	0.84-0.94
	Unlikely	0.88	0.87	0.13	-0.05-0.24
Bleeding	Likely	0.90	0.65	0.70	0.62-0.76
	Unlikely	0.84	0.75	0.34	0.19-0.47
Indigestion	Likely	0.92	0.74	0.69	0.63-0.78
	Unlikely	0.92	0.84	0.48	0.34-0.56
Cough/hoarseness	Likely	1	0.92	1	1
	Unlikely	0.97	0.92	0.65	0.47-1
Weight loss	Likely	0.97	0.77	0.88	0.82-1
	Unlikely	-	-	-	-
All seven warning signals	Likely	0.96	0.80	0.82	0.80-0.85
	Unlikely	0.94	0.90	0.41	0.35-0.47

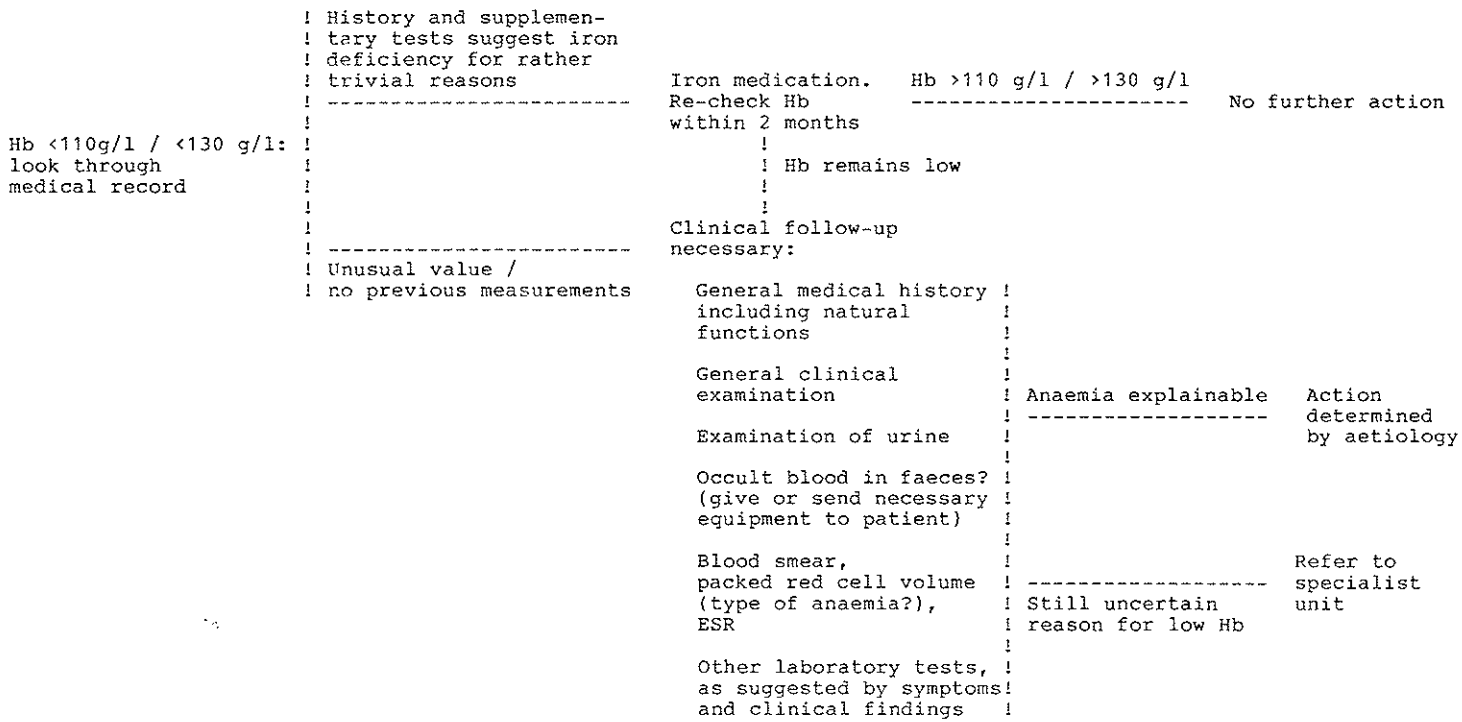
Table D. Inter-observer agreement on the presence or absence of five warning signals, with and without a probable relationship with the patient`s cancer disease, and on all seven warning signals together. Male cancer patients

	Relation to the cancer	Overall agreement	Expected agreement	Kappa	Kappa range
Lump	Likely	0.93	0.71	0.75	0.65-0.85
	Unlikely	0.90	0.91	-0.01	-0.06-0.08
Bleeding	Likely	0.93	0.58	0.83	0.74-0.91
	Unlikely	0.96	0.96	0	0*
Indigestion	Likely	0.83	0.69	0.45	0.33-0.59
	Unlikely	0.86	0.79	0.32	0.18-0.50
Cough/hoarseness	Likely	0.93	0.89	0.34	-0.06-0.62
	Unlikely	0.96	0.96	0	0*
Weight loss	Likely	0.97	0.74	0.90	0.85-1
	Unlikely	0.96	0.96	0	0**
All seven warning signals	Likely	0.96	0.78	0.72	0.63-0.79
	Unlikely	0.95	0.94	0.21	0.14-0.32

* : No registrations for pair B
**: No registrations for pair A

Appendix 7. Flow charts: A. Low hemoglobin concentration
B. High erythrocyte sedimentation rate

Appendix 7 A. Diagnostic flow chart for patients with a measured haemoglobin concentration (Hb) <110 g/l (women) / <130 g/l (men)



Appendix 7 B. Diagnostic flow chart for patients with a measured erythrocyte sedimentation rate (ESR) ≥20 mm/hour