Allgemeinmedizin (1990) 19: 74–79

ALLGEMEIN
MEDIZIN

A method of calculating diagnostic indexes for possible cancer symptoms in general practice

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Berechnung des diagnostischen Index für mögliche Krebssymptome in der Allgemeinpraxis

Zusammenfassung. Die meisten medizinischen Berechnungen beginnen mit der Aufzählung von Symptomen, die zu einer Diagnosenhypothese geführt haben. Es kann nützlich sein, die Wahrscheinlichkeit einer Krankheitsentstehung zu kennen, wenn ein Symptom in einer Sprechstunde vorkommt, d. h. der positive Prädikstionswert (PPV) eines Einzelsymptoms in Relation zu einer Erkrankung. Ein solcher diagnostischer Index muß seine Grundlage sowohl in Daten über die Symptomprävalenz und Krankheitsprävalenz in einer Patientengruppe als auch in der Empfindlichkeit (Sensitivität) eines Symptoms als Indikator einer Erkrankung zur Zeit der Sprechstunde haben. „Likelihood ratio" (LR), d. h. die Wahrscheinlichkeit, ein Symptom in Zusammenhang mit einer bestimmten Krankheit zu finden, dividiert durch die Wahrscheinlichkeit, das Symptom ohne die Krankheit zu finden, konnte auf der Basis solcher Daten auch berechnet werden. Hier wird die Berechnung des diagnostischen Indexes von Colorektalkrebs und Lungenkrebs gezeigt. Eine norwegische allgemeinmedizinische Arbeit über die sieben Verdachtssymptome für Krebs („Warnzeichen") hat die Daten für die Symptomprävalenz ergeben. Dieses Material ist mit Daten über örtliche Krebspatienten, aus der Krebsstatistik und Bevölkerungsstatistik kombiniert worden, um die notwendige Beurteilung von Krebsprävalenz und Sensivitität vornehmen können. PPV von Verdauungsstörungen im Verhältnis zum Colorektalkrebs nimmt mit dem Alter gleichmäßig zu, von <0,1% bis 2,5–4,4% für Männer 70 Jahre und älter, und 3,4–6,1% für Frauen in diesem Alter. LR variiert von 7 bis 46 und hat niedrige Werte für die ältesten Patienten. PPV von dauernden Husten im Verhältnis zum Lungenkrebs zeigt höhere Werte für Männer (3,9%–9,0%) als für Frauen (0,5%–1,2%) in der Altersklasse 60–69 Jahre. LR ist ebenfalls höher, 22–55 für Männer und 13–30 für Frauen 60–69 Jahre alt. In anderen Altersklassen hat man nicht genug Daten für Männer. LR für Frauen nimmt mit dem Alter etwas ab. Der Wert der quantitativen Annäherung an die Krebsdiagnose in der Allgemeinpraxis wird beurteilt. Einzelne Symptome können einen guten Startpunkt darstellen, geben aber selten genügend Grundlage für Entscheidungen. Die Zahlen im Berechnungsindex sollten nicht ohne Einschränkung übernommen werden, weil die Beurteilung der verschiedenen Grundlagsdaten zu verschiedenen Zeiten und in verschiedenen Orten variieren kann.

Summary. Most medical encounters start with the presentation of symptoms that lead to hypotheses about the diagnosis. It might be useful to know the probability of a disease when a symptom of it is presented in a consultation with a general practitioner, i.e., the positive predictive value (PPV) of a particular symptom in relation to a disease. A diagnostic index of this kind would need to be based on data about symptom prevalence and disease prevalence in the population studied, and on sensitivity of the symptom as an indicator of the disease at the time of the encounter. Likelihood ratio (LR), the probability of a given symptom when a particular disease is present divided by the probability of finding the symptom without the disease, could also be calculated on the basis of such data. The calculation of diagnostic indexes for colorectal cancer and lung cancer is shown. A Norwegian general practice study of the seven warning signals of cancer has yielded data about symptom prevalence. This material has been combined with information on local groups of cancer patients, cancer statistics and population statistics to produce necessary estimates of cancer prevalence and of sensitivity. The PPV of the warning signal "indigestion" in relation to colorectal cancer increases with age from <0.1% to 2.5%–4.4% for men 70 years old or more, and 3.4%–6.1% for women in this high age group. LR varies from 7 to 46 and has slightly lower values for the highest age groups. For "cough/hoarseness" the PPV range for men 60–69 years old is 3.9%–

9.0%. There were insufficient data for males in other age groups. For women, PPV for the different age groups varies from 0.1–0.2% to 0.6–1.5%, with a slight increase with age. LR in the age group 60–69 years is 22–55 for men and 13–30 for women. There is a slight tendency to lower LR values with increasing age in women. The value of a quantitative approach to cancer diagnosis in general practice is considered. Single symptoms may be a good starting point, but they rarely furnish a sufficient basis for decisions. The external validity of the figures is limited because some of the base estimates may vary with time and from place to place. However, the changes from one age group to another and differences between males and females probably would show limited variation. The method may serve as an example of a local quantitative approach to diagnostic thinking in general practice.

Modern decision analysis encourages a quantitative approach to diagnostic thinking [1]. In general practice such an approach may appear particularly difficult. The prevalence of almost any important disease is very low in general practice. Serious disease and innocent ailments may produce the same kind of symptom. General practitioners are easily blamed if they overlook new cases of cancer, but several hundred encounters take place for each case of cancer.

Fortunately, decision making does not always require high levels of probability. Therapeutic decisions usually require higher probabilities than decisions about diagnostic pursuit, which are frequent in general practice. With important diseases the search should be continued at low levels of probability, either through referral to a specialist or through a check-up appointment. Disease prevalence defines prior probabilities of disease in a patient. This may be higher in one sex than in the other, for certain age groups or for patients with some other personal characteristics.

This article demonstrates a quantitative approach to cancer diagnosis based on data from general practice combined with population and cancer statistics. Colorectal cancer and lung cancer have been chosen as examples.

The positive predictive value (PPV) [1] of a possible cancer symptom in general practice can be calculated if one knows:

1. The prevalence of the symptom in general practice encounters (P ‹Symptom› where P = probability).
2. The prevalence of diagnosable cancer at the time of encounters (P ‹Cancer›).
3. The proportion of encounters during which cancer symptoms are presented (P ‹Symptom/Cancer›).

The likelihood ratio (LR) [2] is the frequency of the symptom in patients with cancer divided by the frequency of the symptom in patients without cancer. The two diagnostic indexes complement each other because the predictive value changes with prevalence while the likelihood ratio remains much more stable when prevalence changes. General practitioners can sometimes make a good estimate of the likelihood ratio simply by asking themselves how much more likely it is for symptom X to occur in their population of 60-year-old women with the disease D than in their population of 60-year-old women without D. Reasonably good subjective likelihood estimates through consensus have been described [3]. The general approach does not exclude consideration of local population peculiarities known to the general practitioner.

Materials and methods

The various estimates necessary for calculations are based on investigations in the municipality of Tromsø, Norway, 1981–1983 and on Norwegian population and cancer statistics from 1982 [4]. Table 1 shows calculated incidence rates for colorectal and lung cancer in males and females. The Tromsø investigations include recording of warning signals of cancer in general practice as described below [5], retrospective studies of two cancer patient populations, based on medical records from general practice and hospitals [6, 7] and a prospective study of cancer patients [8] derived from the warning signals recorded [5].

P ‹Symptom›

During a 6-month period in 1981–1982, 14 Norwegian general practitioners took part in a study recording the seven warning signals of cancer presented at consultation [5]. The practitioners had been instructed to consider at the end of each consultation whether appropriate symptoms had been presented, regardless of any diagnostic hypotheses. The warning signals were to be perceived quite literally in the way they had been formulated by the Norwegian Cancer Society (Table 2). Recordings were made for 11,606 consultations. Table 3 shows the number of warning signals recorded in the different age groups for both sexes. Rates and numbers of recordings for the two warning signals considered here are shown in Table 4. The rates are used as a basis for estimates of how probable it is that a general practitioner will encounter symptoms that correspond to or are part of these warning signals.

Table 1. Incidence of colorectal and lung cancer in Norwegian adults, 1982

Age group	Colorectal cancer				Lung cancer			
	Males		Females		Males		Females	
	No	I	No	I	No	I	No	I
20–29	3	–	1	–	1	–	0	–
30–39	11	0.04	14	0.05	8	0.03	8	0.03
40–49	39	0.19	40	0.20	36	0.18	11	0.06
50–59	139	0.64	135	0.62	202	0.94	60	0.28
60–69	303	1.48	321	1.40	371	1.81	92	0.40
70+	648	3.82	681	2.71	402	2.37	107	0.43
20+	1,143	0.80	1,192	0.80	1,020	0.72	278	0.19

No, Number of cases per year; I, incidence rate per 1000

Table 2. Seven warning signals published by Landsforeningen mot Kreft, Norway, 1983

	Key word (abbreviation)
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

Table 3. Number of consultations distributed according to whether a warning signal was recorded or not by the general practitioner, and according to age and sex of the patient, based on 11,606 consultations in Tromsø, Norway, 1981–1982. (From [5])

Age group	Warning signal(s) recorded		No warning signal recorded		All consultations	
	Males	Females	Males	Females	Males	Females
0–19	33	40	924	1,190	957	1,230
20–29	25	72	836	1,812	861	1,884
30–39	30	95	695	1,137	725	1,232
40–49	22	64	440	646	462	710
50–59	22	45	579	698	601	743
60–69	39	51	522	635	561	686
70+	35	56	326	537	361	593
Total	206	423	4,322	6,655	4,528	7,078

Table 4. Warning signals recorded per 1,000 consultations, by sex and age. (Modified from [5])

Age group	Indigestion				Cough/hoarseness			
	Males		Females		Males		Females	
	Rate	*n*	Rate	*n*	Rate	*n*	Rate	*n*
0–19	2	2	3	4	4	4	1	1
20–29	13	11	3	6	0	0	3	5
30–39	14	10	13	16	1	1	6	7
40–49	15	7	14	10	0	0	7	5
50–59	10	6	12	9	3	2	9	7
60–69	23	13	22	15	7	4	12	8
70+	39	14	30	18	6	2	10	6
Total	14	63	11	78	3	13	6	39

n, number of recordings

P ‹Cancer›

The meaning of prevalence is the frequency of disease in a population at a given point in time. The prevalence that is interesting in this case is the fraction of persons in whom cancer has not yet been diagnosed, but who have sufficient signs of the disease to make a diagnosis at least theoretically possible on the day of consultation. Two assumptions are important: the estimated average period of possible diagnosis for the forms of cancer dealt with here, and whether the prevalence of cancer at encounters in general practice is the same as that of the general population. Balancing the different considerations described in the Discussion, I have used the yearly incidence rates as a measure for P ‹Cancer›.

Table 5. Age distributed positive predictive values (PPV) and likelihood ratios (LR) of indigestion (I) in relation to cancer of the colon including rectum (CC)

Age group	PPV (P ⟨CC/I⟩)		LR	
	Males	Females	Males	Females
20–29	<0.1%	–	19–35	–
30–39	0.1%	0.1–0.2%	18–32	19–35
40–49	0.3–0.6%	0.4–0.6%	17–30	18–32
50–59	1.6–2.9%	1.3–2.3%	25–46	21–38
60–69	1.6–2.9%	1.6–2.9%	11–20	12–21
70+	2.5–4.4%	3.4–6.1%	7–12	13–24
20+	1.4–2.6%	1.8–3.3%	18–33	23–42

P, probability; ⟨X/Y⟩=X given the presence of Y; sensitivity of indigestion presented at an encounter (P ⟨I/CC⟩)=0.25–0.45

Table 6. Age distributed PPV and LR of cough/hoarseness (C, H) in relation to cancer of trachea/bronchus/lung (LC)

Age group	PPV (P ⟨LC/C, H⟩)		LR	
	Males	Females	Males	Females
20–29	–	–	–	–
30–39	–	0.1–0.2%	–	25–58
40–49	–	0.1–0.3%	–	21–50
50–59	–	0.4–1.1%	–	17–39
60–69	3.9– 9.0%	0.5–1.2%	22– 55	13–30
70+	–	0.6–1.5%	–	15–36
20+	5.5–12.5%	0.5–1.2%	79–200	25–59

P, Probability; ⟨X/Y⟩=X given the presence of Y; sensitivity of cough/hoarseness presented at an encounter (P ⟨C, H/LC⟩)=0.15–0.35

P ‹Symptom/Cancer›

We need to know or estimate the proportion of the encounters in which the cancer patient will complain of the relevant symptom. This is probably lower than what would usually be described as the sensitivity (S′) of the symptom: the proportion of cancer cases in which the symptom occurs at some time before diagnosis. For each form of cancer I have started with the latter estimate, described in the discussion. From the different cancer patient materials [5–7] I have estimated the sensitivity (S) necessary for calculation purposes at $S = S' : 2 \pm 0.1$. The reasons for using this range are explained in the Discussion.

Diagnostic indexes were calculated using the 2×2 table [1]. Identical results are obtained with the alternative methods of substituting probabilities directly into Bayes' formula or through inverted probability trees [1]. Both PPV and LR are given as ranges of values, the lowest and highest values corresponding to the lowest and highest sensitivity estimates, respectively.

Calculations of diagnostic indexes have not been made when less than three warning signal recordings were made for the sex and age group in question or when the incidence rate in less than 1 in 100,000.

Results

The PPV of each symptom is presented together with likelihood ratios in Tables 5 and 6.

The PPV of indigestion in relation to colorectal cancer increases with age from <0.1% to 2.5%–4.4%

for men 70 years old or more, and 3.4%–6.1% for women in this high age group. The PPVs for aged patients tend to be higher in women even if men have a slightly higher incidence rate in this age group. The LR varies from 7 to 46 and has slightly lower values for the highest age groups (Table 5).

For cough/hoarseness the number of recordings for males was sufficient to calculate diagnostic indexes only in the age group 60–69 years. Especially the PPV range of 3.9%–9.0% is much higher than the corresponding value for females. For women, PPV for the different age groups varies only from 0.1–0.2% to 0.6–1.5%, with a slight increase with age. LR in the age group 60–69 years is 22–55 for males and 13–30 for females. There is a slight tendency to lower LR values with increasing age in women (Table 6).

Discussion

P ‹Symptom›

Some uncertainty is attached to the rates of warning signals recorded by the general practitioners. Those taking part forgot to record them for days at a time, but usually started again when one of the frequent oral or written reminders was received. This kind of forgetfulness will not influence the rates, as patients with and without warning signals were both forgotten. However, we cannot be quite certain that either patients with or without warning signals were recorded relatively more frequently. Reflecting upon which is the most probable, it seems more probable that a patient with a warning signal may have served as a reminder after a period of forgetfulness. This would tend to make the rates in Table 4 too high.

If we imagine that the "true" rates of warning signals are only half of what has been found, the PPVs for the different forms of cancer would double. For example, the range of P ‹CC/I› for a 50- to 59-year-old man would increase from 1.6–2.9% to 3.2–5.8%. Such a change would hardly alter the way a general practitioner would treat the patient. In both cases it would seem wise to test for occult blood in stool, take a more detailed medical history and perform a clinical examination to revise probabilities before deciding between referral, treatment or a period of wait and see. The LR would more than double from 25–46 to 52–96, without any more practical consequences than the change in PPV. With higher index ranges the practical consequences might be greater. However, such a gross error in the recorded rates is hardly probable, especially for the most frequently recorded warning signals.

P ‹Disease›

Population statistics and the official cancer statistics may deviate from true figures, but not to an extent that would be important for the calculated diagnostic indexes.

The period of possible diagnosis varies not only for different types of cancer, but also for individual tumours within the same organ in different persons. Most cancers start to develop years before they are diagnosed, but the period between the earliest possible diagnosis and the actual diagnosis can probably be measured in months for most forms of cancer, more rarely in weeks. The period of possible diagnosis would usually be considered to be the sum of two periods; the time from the first symptom to the first consultation, and the time from the first consultation to diagnosis. However, it seems too restrictive to consider that diagnosis is only possible when rather evident symptoms appear. In many cases screening or case-finding procedures or even a more thorough diagnostic approach in the case of vague symptoms might have revealed the cancer before the patient took notice of any more specific symptoms. In the case of screening procedures this is demonstrated by the well-known general phenomenon of increased incidence during the first phase of a new diagnostic screening programme [9].

It is quite common to make diagnoses of cancer mor than 3 months after the first symptoms appear [10, 11]. In Tromsø the majority of cancers were diagnosed within 6 months from the first symptom, but longer periods were not uncommon [6]. For most forms of cancer, including colorectal cancer and lung cancer, the diagnostic intervals varied considerably. Nylenna [12] found an average duration from first symptom to diagnosis of 8 months, but with important differences for different symptoms.

If these were the only important considerations it would seem that prevalence figures should be somewhat lower than the incidence rates. However, it is probable that people with potentially diagnosable cancer visit their general practitioner more often than people without cancer. The importance of this difference is difficult to estimate quantitatively and may vary in different localities, but the resulting increase in the prevalence of cancer diagnosed at consultations may bridge the gap to the incidence figures.

I have concluded that it is possible to use the incidence figures to express prevalence, but if there is a bias it is probable that this estimate is too high rather than too low. The PPV varies with prevalence, and if a prevalence is only half of our estimate, PPV will be half of the value shown in the corresponding table. In general, the direction of the most probable bias is the opposite of that estimated for P ‹Symptom›.

Sensitivity (= P ‹Symptom/Disease›)

The proportion of cancer patients experiencing at least one relevant warning signal (Table 2) at some time before diagnosis was 63% of 108 patients [5] and

75% of 65 patients [7] in these studies based on medical records. This gives an idea of the sensitivity (S′) of all seven warning signals in relation to all forms of cancer. Results in another patient population give an idea of the sensitivity of a warning signal presented at an encounter (S): of 80 patients in whom cancer was later diagnosed, 20 presented one ore more warning signals recorded during consultation [8]. According to the medical records of these 20 patients, for 17 of them (21%) warning signals related to their subsequent cancer diagnosis had been recorded. This is a more appropriate measure of the proportion of consultations in which the cancer patient complains of the relevant symptom. Its value is somewhat less than half of (S′) found for all seven warning signals. In this case the observation period for the subsequent cancer varied from 1 to 18 months. This is a longer period than the assumed period of possible diagnosis. The patients with a very long interval between consultation and diagnosis are less likely to have had a cancer-related warning signal recorded than patients with a shorter interval. Hence the average sensitivity (S) for all warning signals expressing the proportion needed for calculation purposes probably lie somewhere between 20% and 75%, and closer to the lower figure. This suggests that the ratio S′:S may be approximately 2:1. An interview study in the general population of Tromsø [13] suggested that the different warning signals do not differ much in their ability to initiate a medical encounter. The estimated ratio is very approximate, and estimates of S′ for the different symptoms also are based on a combination of subjective and objective data, as will be explained. I therefore use a range and not a fixed value for $S = S':2 \pm 0.1$.

S′ expressing the probability of a symptom at some time before diagnosis was estimated as follows for the two warning signals: Sensitivity of indigestion in relation to colorectal cancer:

$S' = 0.7$, $S = 0.25-0.45$

A Norwegian study [14] of 590 patients with cancer of the colon including rectum found that about half of the patients presented with constipation or diarrhoea, more frequently the farther distally the tumour was located, while one-third had abdominal pain, which was more frequent with tumours in the more proximal locations. In my study, 16 of 22 patients with cancer of the colon and 11 of 12 patients with rectal cancer experienced at least one warning signal, and indigestion was by far the most important of the warning signals in these cases [6–8].

The estimated probability $S' = 0.7$ is thus a compromise between regionally estimated probabilities which are: P ‹I/CC› = 0.5 for the right half of the colon, P ‹I/CC› = 0.7 for the left half of the colon excluding rectum, and P ‹I/CC› = 0.8 for the rectum. It may be useful for the general practitioner to keep these regional differences in mind.

Sensitivity of cough/hoarseness in relation to cancer of trachea, bronchus, lung:

$S' = 0.5$, $S = 0.15-0.35$

I have used the rates for "hoarseness or coughing without any apparent reason" directly, assuming that the coughing part is responsible for most of the entries in the registration forms. Hoarseness is rarely a symptom of cancer at a site lower down than the larynx. Seven of 15 patients with bronchial cancer presented cough/hoarseness [5–7]. This is in accordance with a Norwegian population of lung cancer patients, in which about 60% of 1,053 patients presented cough [15]. In McWhinney's 5-year material from general practice, less than half of the patients presented with cough [16].

Slight deviations in these estimates will not cause any significant alterations in predictive values. If S approached S′ the PPV for indigestion in relation to colorectal cancer in females 60–69 years old would change from 1.6–2.9% to approach 4.5%. The LR would increase from 12–21 towards a maximal value of 33. The potential change is modest, although not unimportant, but the estimated sensitivity range is fairly broad and gross deviation in either direction is hardly probable.

Positive predictive values (= P ‹Disease/Symptom›) and likelihood ratios

As might be expected, there is a tendency to gradually increasing PPV when incidence increases with age. However, for the age groups 50–59 and 60–69 years the PPV for indigestion relative to colorectal cancer is stable in both sexes in spite of three to four times higher incidence rates in the higher age group. The LR decreases. What happens is that the false-positive fraction (the proportion of patients with the symptom among disease-free patients) increases, while the true-positive fraction (the proportion of patients with the symptom among diseased patients) by our estimate remains stable. Relatively more people in the older age group consult for indigestion. The general morbidity is higher, and perhaps the consultation threshold is lower in the higher age group [12]. The importance of the false-positive fraction is also demonstrated in people 70 years of age and older: a higher false-positive fraction in men gives lower indexes than for women in spite of a higher incidence rate.

Predictive values for lung cancer in women are likely to increase with time because more women smoke and incidence rates increase. If several women and very few men have consulted for hoarseness without any coughing, the calculated diagnostic indexes may be too low for women. However, the index differences between males and females in the age group 60–69 years seem reasonable given the significant sex difference in smoking habits and incidence rates for lung cancer.

The present study confirms that predictive values based on single symptoms are quite low. The potential change in probability introduced by a single symptom may still be relatively important. A Norwegian man in the age group 60–69 years in 1982 had a 1.8% probability of getting lung cancer. If he consulted his general practitioner for cough/hoarseness this probability increased to 3.9–9.0%. We are already in the percentage range where an X-ray seems justified, unless we revise the probability through new information which again lowers the probability of lung cancer.

In general, single symptoms do not furnish sufficient information to allow decisions about referral or check-up appointments. Knowing the potentially serious diseases that may lie behind the symptoms presented, it is important to say that at this stage of analysis we are only at the beginning of our involvement with the patient. The real probability revision starts here. Maybe the medical history we elicit, our clinical examination, or our simple laboratory tests will permit us to increase the probability of colorectal cancer in our 55-year-old male patient initially presenting with indigestion from 1.6–2.9% to around 10–15%, calling for a colonoscopy or a double-contrast X-ray of the colon. Or maybe our thorough examination and a control appointment leave use with a probability of 1% or 2%. In that case we make a good clinical decision when we continue to treat the symptom, do not demand a colonoscopy "for the sake of certainty" but avoid pain, cost and labour by a wait-and-see approach.

Conclusion

A quantitative approach to diagnosis may increase the understanding of common clinical experience and improve the rational basis for decisions. Most factors influencing probabilities must be taken into account, and mistakes attributed to more intuitative thinking [17] can be avoided. The quantitative approach gives a better assurance that necessary investigation lies behind our decisions. Sometimes unnecessary and bothersome investigations may be avoided.

Cancer incidence rates are not very different in different western countries, and extrapolation of the diagnostic indexes to other places may seem tempting. However, the propensity of patients to present symptoms in general practice may vary with time and from place to place, and so may the prevalence of cancer in general practice encounters. Many different estimates based to some extent on subjective judgment lie behind the calculations. Practitioners who consider these estimates relevant for their own patient population may get an approximate idea of probability levels and of how the diagnostic indexes vary with age and sex for the forms of cancer considered here. More accurate values must be based on local estimates. For most general practitioners a single symptom may be a good starting point but rarely a sufficient basis for decisions related to the diagnosis of cancer.

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