Glossary of essential terms used in cancer screening

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This short glossary defines essential clinical epidemiology parameters useful for understanding cancer screening methods. Three displays illustrate several concepts outlined in this glossary. We also added comments about the interpretation of some of them.

Asymptomatic cancer: see preclinical cancer.

Attendance rate: see participation rate.

Background incidence rate: the incidence rate of invasive cancer that would be expected in the absence of screening.

Clinical cancer: a cancer that causes symptom(s) or clinical sign(s).

Coverage (screening coverage): proportion of subjects eligible for screening who have had a test in the time period corresponding to the recommended screening schedule. For instance, for a biennial screening schedule, the coverage will be computed considering subjects who had a test during a two-year period.

Delay time: the time between when a cancer could be screen-detected and when it is actually detected (Fig. 3).

Detection rate: number of cancer detected per 1000 screened subjects. This rate will differ for initial (prevalent) versus subsequent (incident) screening examinations.

Efficacy (of screening): ability of screening to decrease deaths due to cancer under ideal conditions (e.g., in randomised trials).

Effectiveness (of screening): ability of screening to decrease deaths due to cancer in the general population, under real world conditions.

Efficiency (of screening): it is the balance between health benefits versus the side effects and the costs of implementation of screening.

False negative (FN) result: subjects having a cancer that is not detected by the screening test (Fig. 1).

False positive (FP) result: subjects without cancer that have a positive test (Fig. 1).

Incidence rate: the rate at which new cancer cases occur in a population. The incidence rate is usually expressed as the number of new cases per 100,000 per year, i.e., per 100,000 person-years or PYs. The numerator is the number of persons living in an area newly developing the disease during a year. The denominator is the number of persons at risk of developing the cancer resident in the area at the middle of the year.

Incidence rate of advanced cancer (IAC): the rate at which new cases of advanced cancer cases occur in a population. This rate is calculated as the incidence rate but the numerator includes numbers of advanced cancer only. Because screening aims at detecting cancers before they have progressed to advanced stage (through detection of precursor lesions or through detection of early cancer), the IAC should decrease before one would observe reductions in cancer mortality attributable to screening.

Incident cancer: cancer found at a subsequent screening rounds, i.e., cancers deemed to have progressed to a screen-detectable tumour after a previous negative screening round.

Initial (or prevalent) screening: the first time subjects are screened. The initial screening will find cancers sometimes present since a long time (i.e., cancers with long sojourn time). Therefore, the detection rate at initial screening round will generally be higher than the detection rate at subsequent screening rounds.

Interval cancer (IC): a cancer diagnosed in subjects who had a negative screening test within a period equal to the time interval between two screening rounds. If the interval between two screening rounds is 2 years, statistics may report interval cancers diagnosed within 1 and within 2 years after the test. Broadly, ICs are of two types: cancers present at screening but missed by the screening test, and cancers that became detectable after the last screening test. In practice, it proves difficult to distinguish between the two types of IC.

Interval cancer rate (ICR): the number of interval cancer found within a defined period of time after the last screening test divided by the number of

		Reference test results		
		Positive	**Negative**	Total of rows
Screening test results	**Positive**	True positives (TP)	False positives (FP)	Positive tests (P)
	Negative	False negatives (FN)	True negatives (TN)	Negative tests (N)
	Total of columns	Subjects with cancer (C)	Subjects without cancer (W)	Total number of screened subjects(T)
Sensitivity	=	TP/(TP+FN) =	TP/C	
Specificity	=	TN/(TN+FP) =	TN/W	
Positive predictive value	=	TP/(TP+FP) =	TP/P	
Negative predictive value	=	TN/(TN+FN) =	TN/N	

Fig. 1. Basic tabular organisation of data for the evaluation of screening test performances.

subjects who had a negative screening test (Fig. 1: ICR = FN/N or FN/[FN + TN]).

Incidence based mortality: see refined mortality.

In situ cancer: epithelial cancer that has not breached the basal membrane and does not extend in surrounding tissues, even minimally. In situ cancers are described for most epithelial cancers (e.g., breast, melanoma). The likelihood of in situ cancers to progress into invasive cancers is not well known and is deemed to be low.

Invasive cancer: epithelial cancerous lesion that extends beyond the basal membrane and has invaded surrounding tissues, even minimally.

Lead time: the time between when a cancer is screen-detected and when it would have been a clinical cancer (Fig. 3). The lead time cannot be directly measured as this would necessitate repeated screening tests without work-up of positive screening tests. Most lead time estimations found in the literature are average figures of unknown relevance since cancer of an organ is in reality a mix of different types of cancers that have highly variable aggressive potential and thus also highly variable lead time. Lead time may cause an inflation of incidence rates at the beginning of a screening programme because screen-detected cancers are found in advance, i.e., before they would be clinical. This lead time effect is expected to fade away as time progresses because cancers that were found in advance should no longer be present in subsequent screening rounds, and incidence rates should return to pre-screening levels.

Lead time bias: the overestimation of cancer survival statistics induced by screening because the lead time is added to the clinical time, what gives the spurious impression that survival of subjects with screen-detected cancer is longer than of subjects with clinical cancer.

Length time: the time between when the cancer is screen-detectable and the final outcome (e.g., death) (Fig. 3). If a pre-clinical cancer never progresses to a clinical cancer, then the sojourn time is equal to the length time.

Length time bias: screening tests have greater ability to detect cancers with longer sojourn time (slow progressing cancers or indolent cancers) than cancers with short sojourn time, that are often more aggressive. Because less aggressive cancers have long sojourn time, the length time bias has the potential to increase the survival of subjects found with cancer without reducing the mortality from cancer.

Mortality rate: the rate at which people in a population die from a cancer. The mortality rate is usually expressed as the number of deaths per 100,000 persons per year, i.e., per 100,000 person-years or PYs. The numerator is the number of persons resident in an area dying from the cancer during a year. The denominator is the number of persons at risk of dying from the cancer residing in the area at the middle of the year.

Negative predictive value: the proportion of subjects without cancer among all subjects with a negative screening test (Fig. 1). In screening, the NPV should read as the proportion of subjects with a negative screening test that will not develop an interval cancer.

Non-organised (or opportunistic) screening (NOS): screening left to the subject's or doctors' initiative, without centrally organised invitation or follow-up systems. NOS takes place outside organised screening programmes, and often, little statistics is available allowing proper evaluation of their performance.

Organised screening programme (OSP): population-based programme in which subjects of defined ages are invited to screening at regular time interval. OSP

	Population A	Population B
Total screened subjects	100,000	100,000
No. Screened subjects with cancer	400	100
Test sensitivity (SE)	90%	90%
Test specificity (SP)	98%	98%
No. Cancerous subjects with positive test result (TP)	360	90
No. Non-cancerous subjects with positve test result (FP)	2000	2000
Positive predictive value (PPV)	15%	4%

Fig. 2. Influence of cancer incidence on the positive predictive value of a screening test.

often includes a follow-up of subjects who tested positive in order to reduce as much as possible nonappearance to work-up and to treatment.

Overdiagnosis: detection of cancer that would have never progressed to clinical cancer during a subject's life.

Overtreatment: treatment of a cancer that would have never progressed to clinical cancer during a subject's life.

Participation (or attendance) rate: the number of subjects who have a screening test as a proportion of (for OSP) all subjects invited to attend for screening, or (for NOS) of all subjects expected to have a screening test. In OSP, the participation rate is also called the **"uptake rate"**.

Positive predictive value (PPV): the proportion of subjects with a cancer among all subjects with a positive screening test (Fig. 1). The PPV is directly dependent of the incidence of the cancer to be screened. For a same ability to exclude the presence of a cancer in subjects truly free of that cancer (specificity), the PPV will be lower if the cancer is rare than if the cancer is frequent (Fig. 2). In other words, for a given specificity, the proportion of false positive test results in subjects who had a positive test result will increase with decreasing incidence of the cancer.

Prevalence (cancer prevalence): proportion of subjects living in an area at a given time who have been diagnosed with a cancer at any time in their life. It can also be the proportion of subjects living in an area at a given time who have a pre-clinical cancer. For screening tests, it is the latter definition of prevalence that matters.

Pre-clinical (or asymptomatic) cancer: a cancer that is truly present but that does not cause any symptom or clinical sign.

Precursor lesion: a non-malignant lesion that may progress to invasive cancer in the absence of treatment. Precursor lesions are for instance, intraepithelial neoplasia (for the uterine cervix), adenomatous polyps (colon and rectum), and leukoplakia (in the mouth). Removal of precursor lesions detected by a screening test (e.g., endoscopic examination of the large bowel, cytology test for cervical cancer, clinical inspection for oral cancer) leads to reductions in both the incidence and mortality of cancer. The expression "pre-malignant" lesion should be omitted.

Recall rate: the proportion of all screened subjects who were recommended to have work-up exams because the screening test was positive, i.e., the test result was compatible with presence of a cancer.

Reference test or "gold standard test": test considered as providing the strongest, unbiased, evidence for the presence or absence of cancer. The reference test is crucial for evaluation of screening test performance, e.g., sensitivity and specificity. However, the reference test cannot be applied in all circumstances, e.g., all men with elevated serum prostate specific antigen test do not undergo radical prostatectomy. Biopsy results are often used as proxy reference test, but this may end up in erroneous results because biopsy is itself subject to false negative results.

Refined mortality (or incidence-based mortality): mortality associated with cancer diagnosed after that screening began. Refined mortality calculation excludes deaths due to cancers diagnosed before screening start.

Screening interval: time between two screening rounds recommended by screening programmes, public health institutions or health professional organisations.

Screening round: the time rank of a screening test. The initial screening is always the first screening round, the first subsequent screening is the second screening round, and so on.

Screening test: clinical, laboratory, or imaging test aimed at detecting pre-clinical cancer.

Sensitivity: ability to detect pre-clinical cancer, i.e., the ability to detect the presence of a cancer in

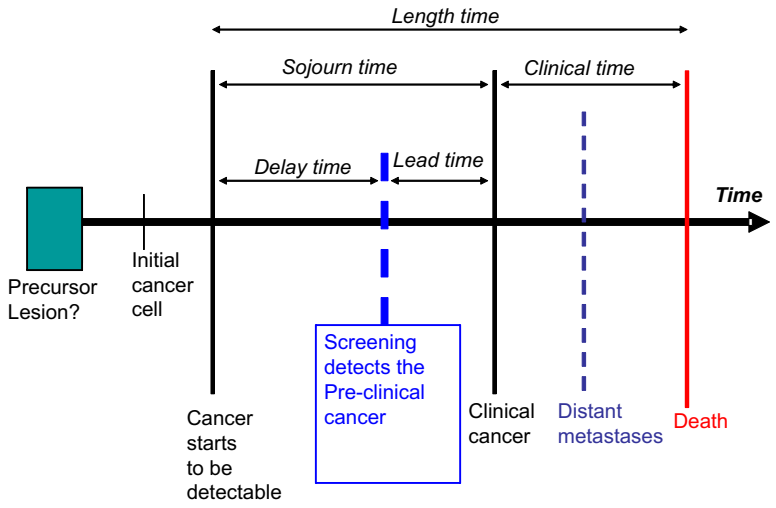

Fig. 3. Natural course of cancer (classic view based on the chronological progression from normal cell to the cancer phenotype, and then to the metastatic phenotype; the time scale is arbitrary).

subjects without symptom or clinical sign possibly associated with that cancer. Sensitivity is computed as the proportion of subjects diagnosed with cancer that had a positive screening test (Fig. 1). The sensitivity of the screening activities is often computed as the ratio of subjects with cancer correctly identified by the test (i.e., the screen-detected cancers) divided by the number of subjects with cancer correctly identified or missed (i.e., the screen-detected plus the interval cancers) by the test (Fig. 1). To establish the sensitivity of the screening, accurate identification of interval cancers is required. In this respect, in the real world, screening tests sensitivity is difficult to estimate. When the screening test is associated with overdiagnosis, a proportion of subjects with screen-detected cancer would not have been diagnosed with cancer if screening had not existed. In this situation, sensitivity computed by the classic formula is likely to be overestimated. An alternative is to compute sensitivity as the rate of screen-detected cancers divided by the background incidence rate (i.e., the incidence rate that prevailed before screening start). A limitation of this method is the absence of population-based cancer registry in many areas where screening exists. Furthermore, as time passes, the historical incidence rate may become irrelevant because the prevalence of risk factors change over time, what also influences incidence trends. Another possibility is to consider the interval cancer rate (ICR) as a proxy for sensitivity. The ICR has the disadvantage of not reflecting the underlying cancer incidence: for similar test sensitivity, the ICR will be higher in areas with high background cancer incidence, what may erroneously suggest a suboptimal sensitivity.

Sojourn time: the time between when a cancer can be detected by screening and when it is clinically apparent (Fig. 3). The sojourn time cannot be directly measured as this would necessitate repeated screening tests without work-up of positive screening tests. Most sojourn time estimations found in the literature are average figures of unknown relevance since cancer of an organ is in reality a mix of different types of cancers that have highly variable aggressive potential and thus also highly variable sojourn times.

Specificity: ability to exclude presence of pre-clinical cancer, i.e., ability to exclude the presence of a cancer in subjects without symptom or clinical sign or symptom possibly associated with that cancer. The specificity of screening test is computed as the proportion of truly non-cancerous subjects among the screened subjects who are identified as non-cancerous by the screening test (Fig. 1).

Target population: the group of subjects for whom the screening test is intended.

True cancer: two definitions of cancer co-exist: (a) lesion meeting the histological criteria of cancerous process; or (b) lesion that, in the absence of treatment, will invade surrounding tissues and/or to disseminate in distant organs. These two definitions are not necessarily synonymous, because lesions looking like cancer under the microscope may not have similar aggressive potential and some may not become clinical (the so-called “pseudo-cancer”). Pseudo-cancers are usually small with long lead and length time parameters. Pseudo-cancers are

therefore more likely to be picked up by screening tests than true cancers.

True positive (TP) result: subjects having a cancer that is detected by the screening test (Fig. 1).

True negative (TN) test: subjects without cancer that have a negative test (Fig. 1).

Work-up: additional exams done in subjects who had a positive screening test in order to confirm or exclude the presence of cancer.