Cancer Prevention Screening

8

Cancer screening for certain organs leads to detection of precancer. Detection of precancer is a form of cancer prevention if one uses the word cancer to exclusively mean invasive cancer, which is customary but not universal. Bretthauer and Kalager [1] have coined the phrase cancer prevention screening to refer to cancer screening practices that aim to detect precancer, and the phrase early detection cancer screening to refer to cancer screening practices that aim to detect invasive cancer.

Much of the theory and methodology regarding the assessment of cancer screening data arose during a time when the goal of cancer screening was to reduce cancer mortality by detection of invasive cancer at early stages. The reason for that goal was that technology was not advanced enough to detect precancer. It is fair to ask whether that theory and methodology still apply in our current era, one in which both invasive cancer and precancer disease are detected through cancer screening. It does, with one exception: the interpretation of changes in cancer incidence. The remainder of the principles laid out in the first seven chapters also are applicable to cancer prevention screening. This chapter presents material of relevance to cancer prevention screening for each of the first seven chapters of this primer.

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8.1 Chapter 1: Foundations

The NCI website mentioned in Chap. 1 defines precancerous as "a term used to describe a condition that may (or is likely to) become cancer. Also called premalignant" [2]. Most researchers use those terms as well as the term pre-invasive interchangeably. I prefer precancer because I find it to be broader in meaning than pre-malignant or pre-invasive. I use precancer to mean any change that is thought to be on the pathway to invasive cancer, be it DNA mutations in one cell or a tumor consisting of mutated cells that is on the verge of breaking through the basement membrane. In general, the material presented in Chapters 1, 2, 3, 4, 5, 6, and 7 are relevant to whatever abnormality cancer screening aims to find.

Cancer prevention screening will be of value if some precancer detected through cancer screening would have become invasive and ultimately fatal cancer in the absence of cancer screening. Detection of precancer that does not meet that designation represents overdiagnosis. The definition of overdiagnosis can be modified slightly to be inclusive: screen-detected precancer or invasive cancer that never would have been diagnosed, either as precancer or invasive cancer, in the absence of cancer screening.

The overarching goal of both early detection cancer screening and cancer prevention screening is to reduce cause-specific mortality. We should not, however, assume that cancer prevention screening is merely early detection cancer screening at a very early stage, and that the benefits would be more extensive and harms less extensive than detection at a later stage. Precancer, at the time of detection, is not life-threatening as it cannot metastasize. Advances in technology have led to detection of more and more precancerous abnormalities with uncertain clinical relevance, creating quandaries for clinicians and patients. It is almost certain that overdiagnosis is more prevalent in cancer prevention screening as compared with early detection cancer screening. Even so, treatment of precancer has the potential to be less onerous than treatment of invasive cancer.

8.2 Chapter 2: Behind the Scenes

Chapter 2 presented the four phase model (Fig. 2.1). The model did not incorporate invasiveness of disease as it is immaterial to its purpose: to classify the stages of the natural history of cancer at which an abnormality, invasive or not, could be detected at an asymptomatic stage through cancer screening. While immaterial to the purpose of the model, the invasiveness of an abnormality is not immaterial to the assessment of cancer screening.

8.3 Chapter 3: Performance Measures

The building blocks of performance measures were presented in Chap. 3 (Table 3.1); a revised version that includes precancer is presented here as Table 8.1. Note that Table 8.1 does not discriminate between positive test results that are suspicious for precancer and invasive cancer. Today's cancer screening tests, with the exception of cervical cytology, do not have that level of discriminatory ability. It is questionable whether they should, as cancer

Table 8.1 The building blocks of performance measures for cancer screening tests that detect precancer and invasive cancer

Truth					
		Invasive cancer present (Phase B)	Precancer present (Phase B)	Neither present (Phase A or no cancer)	Total
Screening test result	Positive	a_i true invasive positives	a_p true precancer positives	b false positives	$a_i + a_p + b$
	Negative	c_i false invasive negatives	c_p false precancer negative	d true negatives	$c_i + c_p + d$
	Total	$a_i + c_i$	$a_p + c_p$	$b + d$	$a_i + a_p + b + c_i + c_p + d$

screening is not intended to provide that degree of information about the nature of suspicious abnormalities.

Performance measures for cancer screening tests that detect both precancer and invasive cancer can be calculated by combining the two if measuring the complete impact and performance of the cancer screening test is desired. Calculations would be the same as in Chap. 3, with a equaling $a_i + a_p$, and c equaling $c_i + c_p$. Cells b and d do not change in this instance. The interpretations do not change, although to be as precise as possible it should be said, for example, that sensitivity is the percent of individuals with precancer or invasive cancer who received a positive test, and that specificity is the percent of individuals with neither precancer nor invasive cancer who received a negative test.

C_p is somewhat of a theoretical quantity, as it is impossible to know whether a symptom-detected invasive cancer that is classified as a false negative was, at the time of the screen, a precancer or an invasive cancer. It is uncommon for a precancer to be detected due to symptoms, but when that occur, it seems fair to count that precancer towards c_p.

There are no hard and fast rules for calculating performance measures for precancer alone or invasive cancer alone when a cancer screening test detects both, though a compelling argument can be made for calculating sensitivity simply as $a_p/(a_p + c_p)$ in the instance of precancer and $a_i/(a_i + c_i)$ in the instance of invasive disease. For the other performance measures, the calculations will depend on how the outcome that is not of interest is classified and whether it is even included. If we wish, for example, to calculate performance measures for invasive disease, we have two options: precancer diagnoses could be excluded entirely from calculations, or screens that are associated with precancer diagnoses can be counted as false positives. Cells b and d are affected, which means that any performance measure that utilizes them will be different for the two methods. Both options return results of similar magnitude if precancer and invasive cancer are rare.

8.4 Chapter 4: Population Measures: Definitions

The manner in which intermediate and definitive outcomes are calculated does not change. Incidence and case survival can be calculated for precancer and invasive cancer alone or combined. A category for precancer can be added to stage distributions. Mortality calculations will not change as they do not utilize diagnoses.

8.5 Chapter 5: Population Measures: Cancer Screening's Impact

Recall from Chap. 5 that cancer screening that detects only invasive cancer will lead to an increase in invasive cancer incidence. Cancer screening that detects only precancer will lead to an increase in precancer. It also will lead to a decrease in invasive cancer incidence as long as not all precancer detected through cancer screening represents overdiagnosis. If a cancer screening test can detect both precancer and invasive cancer, the impact on invasive cancer incidence is difficult to predict. It will depend on many factors, including the ratio of precancer to invasive cancer detected through cancer screening, as well as the frequency of interval cancers and their stage (precancer or invasive).

The other measures discussed in Chap. 5 will be affected as well, though none will "flip-flop" like cause-specific incidence. Consider, for example, case survival. Detection of invasive cancer inflates case survival, and detection of precancer inflates case survival to even a greater degree, because precancer occurs earlier in the natural history of cancer.

A reduction in invasive cancer incidence is accepted as a definitive outcome in the case of cervical cancer screening and colorectal cancer screening with colonoscopy. Far more cervical precancer is detected than invasive cervical cancer. Years of widespread cervical cancer screening combined with unique aspects of cervical cancer natural history have led to extremely low incidence

rates of invasive cervical cancer in much of the US. Screening with colonoscopy has led to a meaningful reduction in the number of invasive colorectal cancers, though its impact has yet to match that of cervical cancer screening.

If cancer screening is of benefit, a reduction in invasive cancer incidence should be followed by a reduction in cause-specific mortality. If the former happens but not the latter, it is likely that detection at a precancerous stage offers no prognostic benefit compared with detection at an early invasive stage. Further discussion of benefit in the absence of a cause-specific mortality reduction can be found in Chap. 9.

The use of cancer incidence as a definitive outcome assumes that the benefit-to-harm ratio is similar or better for screen detection of precancer relative to invasive cancer. That may not be the case: precancer, at the time of detection, is not life-threatening as it cannot metastasize. Unfortunately, population-based trends in detection of precancer either are not available or are based on incomplete ascertainment of the precancer that cancer screening can detect. That limits our ability to assess the entire impact of cancer screening, a serious issue given that detection of precancer through cancer screening is becoming a relatively common occurrence.

8.6 Chapter 6: Experimental Research Designs

All study designs described in Chap. 6 can be employed to investigate cancer screening's ability to reduce invasive cancer.

8.7 Chapter 7: Observational Research Designs

Case-control studies, the most complex of the study designs presented in Chap. 7, need some modifications when detection of invasive disease is the outcome of interest [3].

A case-control study to assess the ability of a cancer screening test to reduce invasive cancer utilizes cases, individuals who have been diagnosed with invasive cancer, and matched controls. Controls must be alive at the time of the case's diagnosis and must not have been diagnosed with invasive cancer during the case's exposure window, which is the time during which the case's invasive cancer could have been detected through cancer screening as precancer. The exposure window must not include the time that the case's cancer could have been screen-detected as invasive cancer. Cancer screening activity for both cases and controls is assessed for the exposure window.

Data elements that provide information on death usually are not needed for studies of cancer prevention screening, as death occurs after the definitive outcome of diagnosis.

8.7.1 Example of a Case-Control Study of Cancer Screening with an Outcome of Invasive Disease

Newcomb et al. examined the ability of screening sigmoidoscopy to reduce colorectal cancer incidence [4]. Cases and controls resided in one of three counties in Washington State. Cases were identified using the SEER Puget Sound cancer registry, were between ages 20 and 74, and newly diagnosed with invasive colorectal adenocarcinoma. Controls were randomly selected according to the age and sex distribution of the cases (frequency-matching) using Washington State driver's license data (ages 20–64 years) and Medicare files (65 years and older). The exposure window included only those tests performed more than 1 year prior to diagnosis date (cases) or more than 1 year prior to interview date (controls). Information on cancer screening history was collected using structured telephone interviews. The authors present their findings separately for proximal and distal colorectal cancer to reflect the anatomy of the colorectum and the inability of the sigmoidoscope to reach the proximal colon.

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