Foundations

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The ability to understand cancer screening data does not require an extensive background in biostatistics, biology, or oncology. Rather, it requires clear thinking, an open mind, and knowledge of a small set of foundational concepts. Those concepts are presented in this chapter.

1.1 Cancer

The United States (US) National Cancer Institute's (NCI) webpage, "What is Cancer?," provides an overview of many biomedical aspects of cancer, including its definition, how it arises, and how it progresses [1]. The webpage is a great resource for those who are starting out in cancer research. In the next two paragraphs, I summarize relevant topics from the webpage.

Cancer is a complex disease [2], but for the purpose of this primer, it is sufficient to conceptualize it using its most notable features: abnormal cells whose division is usually unchecked. Tumors are collections of those cells. Tumors are classified by their ability to metastasize, that is, the ability of their cells to spread to other regions of the body. Tumors that do not and never will have metastatic potential are called benign, though they can kill by growing large enough to interfere with the proper functioning of organs. Tumors that can or have metastasized are called malignant. Malignant tumors are said to be invasive because they

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have broken through the basement membrane, the barrier structure on which those cells normally sit. The disruption of that membrane allows cells to utilize the circulatory or lymph systems as routes to spread. Precancer refers to cells that have not broken through the basement membrane but are abnormal in some way that suggests they could break through in the future given the right (though generally unknown) circumstances. The terms precursor, pre-invasive, and pre-malignant sometimes are used instead, but precancer will used in this primer. Strictly speaking, the word cancer (minus the prefix) refers only to malignant tumors and will be used as such in this primer. Be aware, however, that the word cancer often is used in conjunction with precancer. For example, cervical cancer screening rarely leads to the detection of malignant disease; instead, it usually leads to the detection of early cellular changes that are consistent with our understanding of the natural history of cervical cancer.

Cancer is not one disease; it is many diseases. Cancer behavior differs, for example, by and within organ site, by the type of cell that gave rise to the tumor, and by DNA mutations found in the tumor cells. Treatment and prognosis often vary by these characteristics. In the past it was assumed that all cancer would be fatal if left untreated, but we know now that some tumor types regress, stall, or grow so slowly that they are of no clinical relevance.

It is expected that about 1.8 million people in the US will be diagnosed with cancer in 2019, and about 607,000 will die of the disease [3]. A little under half the deaths will be due to cancer of the lung and bronchus (143,000), colorectum (51,000), female breast (42,000), prostate (32,000), and cervix uteri (typically referred to as cervix; 4300). Cancer screening activity in the US is focused on those five organ sites, although screening for other organ sites does occur, often in high-risk populations.

1.2 Cancer Statistics

The first step in characterizing the extent of any public health problem is to collect data. In the US, our go-to source for cancer data is the Surveillance, Epidemiology and End Results

Program, known world-wide simply as SEER [4]. SEER was established by the 1971 National Cancer Act [5] and has provided authoritative data on US cancer incidence, survival, and mortality for the years 1975 and later. SEER collects data on every cancer in 19 geographic areas, covering about 34% of the US population [6]. SEER data are available in both summary and raw form [7–9].

Cancer data also are collected through the National Program of Cancer Registries, which was established by the Centers for Disease Control and Prevention (CDC) in 1992. Through this program, high-quality cancer registry data has been collected for 97% of the US population and Puerto Rico, the US Pacific Island Jurisdictions, and the US Virgin Islands [10].

1.3 Cancer Screening

Cancer screening refers to routine, periodic testing for signs of cancer among individuals who have no symptoms. It is a form of secondary prevention. In the context of cancer screening, the goal of secondary prevention is to improve outcomes by shifting stage at diagnosis to one that is less advanced and deleterious, relative to what occurs in the absence of cancer screening.

Cancer screening is a sorting process. Screenees are sorted into two groups: those with a negative test and those with a positive test. A negative test finds nothing suspicious for cancer and does not require additional medical attention. A positive test reveals something that is suspicious for cancer or with unknown significance regarding cancer; it requires additional medical attention, referred to as diagnostic evaluation. That process is intended to definitively determine whether cancer is or is not present, but in practice can range from active surveillance to the removal of an abnormality. Active surveillance (sometimes called watchful waiting) refers to a schedule of minimally- or non-invasive testing to monitor for clinically important changes. Resection of an abnormality is considered diagnostic evaluation rather than treatment if a definitive diagnosis has not yet been made or cannot be made otherwise.

Cancer screening is not intended in and of itself to provide a definitive diagnosis. Its intent is to identify abnormal medical conditions, such as growths, occult blood, or a biomarker that may suggest cancer. Cancer screening aims to lead to the detection of cancers whose prognosis will improve with earlier detection, and it needs to lead to the detection of enough of those cancers to make screening a worthwhile public health activity. Cancer screening is neither intended to nor is able to lead to detection of every cancer, as the natural history of cancer is erratic, technology has limitations, and frequent screening is impractical.

In the United States, lung and prostate cancer screening tend to detect invasive cancer and not precancer. Screening for colorectal and breast cancer leads to the detection of invasive cancer and precancer. Cervical cancer screening leads to the detection of precancer, certain human papilloma virus (HPV) infections (the causal agent), and on occasion invasive cancers. Cervical cancer screening also can detect cellular changes that occur very early in the cancer process. Those abnormalities are classified as precancer in this primer.

The reader may come across the phrases early detection and early diagnosis in discussions of cancer screening and wonder how the two differ. Early diagnosis refers to a strategy of symptom awareness to lead to a change in the time of diagnosis. The phrases symptom-aware detection and symptom-vigilant detection are more descriptive than early diagnosis but are rarely used. Early detection comprises early diagnosis and screening. Other phrases that can be confusing are cancer prevention screening and early detection screening. Cancer prevention screening refers to cancer screening that leads to the detection of precancer, and early detection screening refers to cancer screening that leads to the detection of invasive cancer.

Principles of early diagnosis will not be discussed in this primer. The remainder of this primer, with the exception of Chap. 8, is written for the assessment of early detection screening, though the material is equally applicable to cancer prevention screening in nearly all instances. Any material that is not is noted as such.

1.4 Population-Based Cancer Screening

Population-based cancer screening refers to a cancer control practice in which all individuals who meet certain minimal criteria can choose to receive cancer screening. The term population-based is intended to connote that nearly everyone – that is, almost the entire eligible population – is targeted for cancer screening. Sometimes the phrase mass cancer screening is used instead.

In population-based cancer screening, individuals who are eligible for screening are offered a relatively standard screening regimen, standard in terms of the test and frequency. Population-based screening regimens are not intended for individuals who are at extremely elevated cancer risk due to an unusual exposure or a personal or family history of cancer. When we speak of population-based cancer screening, we exclude the aforementioned individuals, because these individuals usually employ a more intense screening regimen than that employed in population-based cancer screening. These individuals are a very small fraction of the entire population.

The focus of this primer is population-based cancer screening, but principles regarding methodology and assessment still apply when screening individuals at unusually elevated cancer risk. Individuals at that level of risk may weigh benefits and harms of cancer screening differently than those at average risk. Oftentimes more intense cancer screening regimens are offered to individuals at extremely elevated cancer risk. For those individuals, the term surveillance, rather than screening, typically is used.

The phrase population-based often will be excluded as a modifier of the phrase cancer screening in this primer when it is clear that population-based cancer screening is under discussion. The phrase is excluded for reasons of conciseness. Therefore, the reader should assume that population-based cancer screening is being discussed unless otherwise noted.

Readers who are interested in the features of ideal population-based disease screening programs can consult Principles and Practice of Screening for Disease, published in 1968 by Wilson and Jungner [11].

1.5 Choosing the Cancers for Which We Screen

Population-based cancer screening occurs routinely in the US for five cancers that, in the absence of screening, typically present as invasive cancer: female breast, cervical, colorectal, lung, and prostate. We screen for these cancers because their invasive forms can lead to morbidity and premature mortality. We also screen because there is evidence, or in some instances suspicion, that cancer screening is beneficial. The fact that cancer screening is recommended by professional organizations or has become established in community settings does not necessarily mean that conclusive evidence of a benefit exists. Adoption of unproven cancer screening tests has occurred in the US and elsewhere.

This primer will not delve into the evidence that supports (or does not support) population-based cancer screening for the five aforementioned cancers. Many well-respected and up-to-date resources for that information already exist [12, 13]. This purpose of this primer is to teach the reader how to assess and interpret cancer screening through the use of data, not to provide a review of literature on the benefits and harms of screening for specific cancers.

1.6 Choosing Who to Screen

Consideration of who to screen begins with identification of the factors that are known to meaningfully increase cancer risk. Next, prevalence of the risk factors is considered. Sufficient risk and sufficiently prevalent risk factors are necessary to affect an absolute reduction in cancer morbidity and mortality that is large enough to justify population-based cancer screening (assuming, of course, that cancer screening is of benefit). Population-based cancer screening is a resource-intense cancer control method and generally is not used for rare cancers.

Age is the strongest risk factor for adult cancer and as such cancer screening recommendations are based on that factor. For lung cancer screening, smoking history also is a criterion because

of its prevalence and strong association with the disease. We do not screen males for breast cancer or never smokers for lung cancer because the chance of individuals in those groups developing the respective cancers is very low. The day may come when age is augmented by genomic or other biologic information to drive cancer screening recommendations, both for and against screening. We are not yet in that era of personalized cancer screening for individuals at average risk, however.

We choose to screen those for whom we believe the benefit outweighs the harm, though we can only assess that for a population, not for an individual. The term individual refers to the person who is offered screening, while the term population refers to the entire group of individuals who have been offered screening. At the population level, we can examine changes in beneficial outcomes and harmful experiences with the advent of screening. At the individual level, we can never know who will or did benefit from screening, as we do not know what will happen or what would have happened in the absence of screening.

1.7 The Cancer Screening Process

Cancer screening cannot result in benefit without the successful completion of other components of the screening process, which encompasses all activities that lead up to and come after application of the screening test. The screening process begins when potential screenees are notified of the option to be screened and ends, at the earliest, when results of the screening test are relayed to the screenee. For those who receive a positive result, the process will extend to diagnostic evaluation and may include cancer diagnosis and treatment.

The resources that are needed to carry out a successful cancer screening effort include more than just those required to administer the cancer screening test. Consideration of resources employed in population-based cancer screening must include, at a minimum, those associated with screening invitation, assessment of eligibility, informed decision making, test interpretation, reporting of results, and diagnostic evaluation and cancer treatment as

needed. Other considerations include time and wages lost by individuals who are attending screening, and other manners, perhaps more critical or economically efficient, in which screening resources could be used. Readers who would like to learn more about the screening process can consult Zapka et al. [14] and Beaber et al. [15].

1.8 Cancer Screening Tests

Cancer screening tests also are known as cancer screening modalities. The screening tests we use in the US are either image-based or biospecimen-based. Imaging tests are used for breast cancer (mammography, digital tomosynthesis), colorectal cancer (sigmoidoscopy, colonoscopy, virtual colonography), and lung cancer (low dose computed tomography (LDCT)). Biospecimen-based tests are used for cervical cancer (pap smear, HPV testing), colorectal cancer (fecal occult blood testing (FOBT)), and prostate cancer (prostate-specific antigen (PSA)).

Some cancer screening tests also are used as diagnostic tests. Colonoscopy is used as a colorectal cancer screening test as well as for evaluation of symptoms or follow-up of a positive FOBT. A positive PSA screening test may lead to serial PSA tests to monitor for changes in PSA. The term indication refers to the reason for performing a test.

1.9 Organized Screening Programs Versus Opportunistic Screening

Cancer screening practices vary from country to country. Reasons include cultural differences, differing interpretations of evidence, and varying public health needs. Central to these choices, however, is the manner in which health care is administered and delivered. Organized screening programs are found in countries with nationalized health care, a setting in which a government body decides on the best medical practices, including cancer screening, and offers and administers, free of charge, only those services

deemed appropriate. Infrastructure usually exists to facilitate screening and to manage the experiences of those individuals who receive a positive screening result. Opportunistic screening occurs in the US and in other countries without nationalized health care. Opportunistic screening provides more choice, but individuals typically are left on their own to navigate the process. Opportunistic screening also occurs in countries with organized screening programs if the primary care physician arranges it or the screenee requests it, but in some jurisdictions the costs of the test must be borne by the individual.

The methods described in this primer can be used to interpret data from organized or opportunistic screening settings. Readers who wish to learn more about organized screening can consult Raffle and Gray's Screening: Evidence and Practice [16].

1.10 Benefit Versus Harm

Assessment of cancer screening tests can be contentious because disagreements exist regarding what constitutes benefit, what constitutes harm, and how to balance the two. We can measure and have measured the impact at a population level by looking for reductions in cause-specific mortality rates. Cause-specific refers to the cause of death that we aim to prevent by cancer screening. Reduction in cause-specific incidence rates is employed for tests that detect precancer and will be discussed in Chap. 8. As the reader will learn, a reduction in cause-specific incidence rate will lead to a reduction in cause-specific mortality rates in most instances.

Cause-specific mortality rates are unable to reflect any harms other than those that affect length of life or cause of death. Yet there are many potential harms of screening, including psychological impact of screening results, diversion of resources away from other health care needs, and late effects (also known as downstream effects) of diagnostic evaluation or cancer treatment. These harms often are difficult to measure, difficult to attribute to the screening process, and vary by screenee. Nevertheless, they are real, and metrics need to be developed that can incorporate

them so the net impact of population-based cancer screening programs can be measured.

Benefits and harms can occur at an individual level or a population level. Individual-level harms are more perceptible than population-level harms, but it is at the individual level that the trade-off between benefit and harm is most murky. Acceptable benefit-to-harm ratios differ by individual, because fear of cancer, risk tolerance, risk illiteracy, and other factors vary from person to person.

Reduction in cause-specific mortality rates remains the standard by which most organizations and researchers judge the benefit of population-based cancer screening programs, as it reflects advances in reducing the rates of cancer death, as well as extension of life among those who die of the disease. Lack of a reduction in cause-specific mortality is typically interpreted to mean that cancer screening does not result in benefit.

Breast and colorectal cancer screening have been shown to reduce cause-specific mortality in randomized controlled trials (RCTs), though the tests examined in those trials are now outdated. Newer tests have become the cancer screening standard of care, based on those tests' improvement in performance measures (Chap. 3) relative to the previous and RCT-tested cancer screening standard of care, and without evidence that the newer tests reduce cause-specific mortality rates. The methodological issues involving the adoption of a newer test based on a comparison with the current standard of care test are discussed in Chap. 9.

1.11 Efficacy and Effectiveness of Cancer Screening

Efficacy refers to the ability of cancer screening to reduce cause-specific mortality rates in an experimental setting. Effectiveness refers to the ability to affect the same reduction in a community setting, one in which individuals choose whether to be screened as part of their usual health care. Ideally, efficacy is studied first, and

the cancer screening test does not disseminate into community settings until it is known to be efficacious.

Efficacy does not guarantee effectiveness. Given their rigor and intense oversight of patient experiences in experimental settings, efficacy studies are considered to provide the best-case scenario regarding cancer screening's ability to reduce cause-specific mortality rates. In community settings, failures in the screening process, such as delayed communication of screening results, inadequate diagnostic evaluation, and lack of access to appropriate cancer treatment can hinder the realization of a cause-specific incidence or mortality reduction. However, cancer screening can be effective even in the presence of challenges and imperfections.

1.12 Cancer Screening: Turning Healthy People Into Cancer Patients

Individuals who present for cancer screening are healthy for all intents and purposes; neither they nor their doctors have any reason to believe they have cancer. A fraction of those screened will be diagnosed and become cancer patients. The diagnosis may lead to prevention of death from cancer. However, it may reflect screen-detection of a cancer that never would have been life-threatening. To say the latter is unfortunate is an understatement. Cancer is a disease that significantly affects every aspect of life.

There is evidence that screening for breast, lung, cervical, colorectal, and perhaps prostate cancer reduces cause-specific mortality relative to the absence of screening, even if there is disagreement regarding the extent of benefit or for whom the benefit exists. In addition to possible benefits, potential screenees need to be informed of the possible harms when the option of cancer screening is raised. Some individuals may opt out of cancer screening; for them, the possible harms outweigh the possible benefits. The choice is reasonable, as it reflects what matters to them.

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