5 Population Measures: Cancer Screening's Impact

If assessment of cancer screening involved nothing more than calculating the outcomes described in Chap. 4, there would be little need for this primer. The challenging aspect is the interpretation of changes in outcomes, both intermediate and definitive, that accompany cancer screening. The material in Chap. 5 is presented in terms of a change from no population-based cancer screening to the establishment of population-based cancer screening, even though the same principles apply when an established cancer screening test is replaced by one with improved performance measures. Matters specific to the latter scenario are discussed further in Chap. 9.

The three screening phenomena presented in Chap. 2, lead time, length-weighted sampling, and overdiagnosis, feature prominently in Chap. 5. The reader may wish to review that material prior to proceeding.

The material on cancer incidence presented in this chapter is pertinent only to early detection cancer screening. The impact on the incidence of cancer prevention screening is presented in Chap. 8.

P. M. Marcus, *Assessment of Cancer Screening*,
https://doi.org/10.1007/978-3-030-94577-0_5

5.1 Cancer Screening's Impact on Intermediate Outcomes

5.1.1 Cancer Incidence

Cancer incidence is expected to increase when cancer screening is introduced. Lead time results in diagnosis at an earlier point in time, creating a bunching effect as the shifted screen-detected cancers are diagnosed contemporaneously with symptom-detected cancers. Also adding to the increase are the overdiagnosed cancers.

Cancer screening cannot lead to a reduction in cause-specific mortality if cancer incidence does not increase. If cancer incidence remains stable as cancer screening is introduced and uptake increases, diagnoses are not occurring earlier, and therefore prognosis cannot change. An increase in cancer incidence does not guarantee a cause-specific mortality reduction. The increase may be due to detection of overdiagnosed cancers or detection of cancers that would have the same prognosis regardless of detection in Phase B or Phase C (as defined in Chap. 2).

5.1.2 Cancer Incidence Example

Figure 5.1 displays, in a very simplistic manner, how introduction of cancer screening increases the number of cancers that are diagnosed. In the absence of cancer screening, three cancers are diagnosed due to symptoms in 2017 (the X cancers) and three cancers

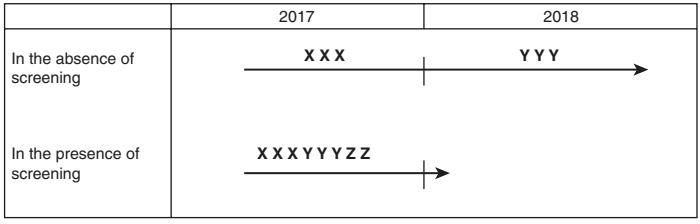

Fig. 5.1 Cancer incidence in the presence and absence of cancer screening

are diagnosed due to symptoms in 2018 (the Y cancers). In the presence of cancer screening, the three X cancers are either screen or symptom detected in 2017, the three Y cancers are screen detected in 2017, and the two Z cancers, the overdiagnosed cancers, also are diagnosed in 2017. The number of cancers diagnosed in 2017 in the presence of cancer screening is 5 more than would have been diagnosed in the absence of cancer screening. If this fictional population included 1000 individuals, the incidence rate for 2017 would be 3/1000 per year in the absence of cancer screening versus 8/1000 per year in the presence of cancer screening.

In the absence of cancer screening, X and Y cancers are symptom detected, with X cancers diagnosed in 2017 and Y cancers diagnosed in 2018. Z cancers are never diagnosed. In the presence of cancer screening, X cancers are still detected in 2017 though they may be screen or symptom detected. Y cancers are now screen detected in 2017. Z cancers (overdiagnosed cancers) are screen detected in 2017. Data are fictional.

Figure 5.1 depicts what cancer screening is intended to do: detect cancers at an earlier point in time. Screen detection of the Y cancers in Fig. 5.1 may lead to more favorable experiences for these patients, such as simpler treatment and better prognosis. Their detection could lead to a reduction in cause-specific mortality, although at the point of diagnosis, it is impossible to know. Of course, conjecture is possible and frequently happens. For example, diagnosis at an earlier point in time may be interpreted as advantageous, which can then be prematurely interpreted to mean that cancer screening will lead to a reduction in cause-specific mortality.

Figure 5.1 does not depict what happens in the presence of cancer screening in 2018, but if the graph were extended for additional years, the same general pattern of shifting should hold. The specifics of the shift depend on how cancer screening interferes with cancer's natural history, other changes in cancer's natural history, as well as changes in cancer screening uptake and performance. Barring any drastic changes in the three, the characteristics of the shift, such as degree and speed, should be fairly similar and stabilize after no more than a few screening rounds.

5.1.3 Stage at Diagnosis

Cancer screening aims to detect cancer when prognosis is more favorable than it would have been if detected due to symptoms. Prognosis usually is related to stage at diagnosis. Most local-stage cancers are curable with resection, though these days, some regional- and distant-stage cancers can be cured with surgery, chemotherapy, immunotherapy, radiation, or a combination. As more non-local-stage cancers become curable, cancers diagnosed at those stages could have similar prognosis as those diagnosed at a local stage. But in today's cancer world, it is fair to assume that cure is most likely for local cancers and that those with treated local cancers live the longest.

The number of local-stage cancers is expected to increase when cancer screening is introduced. Soon after, a decrease in the number of regional- or distant-stage cancers is expected, as some cancers that were destined to be diagnosed at a later stage in the absence of cancer screening will have been detected at an earlier stage in the presence of cancer screening. The phrases stage shift and down staging are used to describe that situation. The phrases should be used to refer to changes in numbers, not changes in percentages. While it is true that a stage shift will lead to a change in the percentage of cancers for a given stage, percentages can be misleading if the number of local-stage cancers increase absent a decrease in regional- and distant-stage cancers, which can happen when cancer screening leads to overdiagnosis.

If a stage shift does not occur, cancer screening will not lead to a reduction in cause-specific mortality. Lack of a stage shift indicates no movement in the stage at diagnosis and thus no improvement in prognosis. But the presence of a stage shift does not guarantee a cause-specific mortality reduction. A stage shift reflecting a change from one stage to another that has similar prognosis would confer no reduction in cause-specific mortality. Length-weighted sampling could produce that situation in the instance of curable disease, while lead time could produce that situation in the instance of incurable disease.

Discussion of stage shifts have typically focused on the need to observe an increase in early-stage cancer rather than a reduction in late-stage cancer. But both are necessary for a cause-specific mortality reduction to be possible, and a reduction in distant-stage cancer is unlikely to be due to lead time, length-weighted sampling, or ovediagnosis. The use of distant-stage cancer as a possible surrogate for cause-specific mortality is discussed in Chap. 9.

5.1.4 Stage at Diagnosis Example

Table 5.1 displays fictional stage experience of the Fig. 5.1 cancers in the absence and presence of cancer screening. Scenario 1 excludes overdiagnosed cancers, while Scenarios 2 and 3 include them. Scenarios 1 and 2 present a favorable change: two cancers that, in the absence of cancer screening, would have been diagnosed at a distant stage are, in the presence of cancer screening, diagnosed at a local stage. In Scenario 3, the two distant-stage cancers remain as such even in the presence of cancer screening.

The numbers of local-stage cancers increase and the numbers of distant-stage cancers decrease in Scenarios 1 and 2. The inclusion of the overdiagnosed cancers in Scenario 2 presents a more favorable picture than in Scenario 1, but it is an overly-optimistic picture, as the overdiagnosed cases cannot contribute to a cause-specific mortality reduction, should one exist. In Scenario 3, the distant-stage cancers are detected at the same stage, regardless of cancer screening. Screening cannot reduce cause-specific mortality as no stage shift occurred; rather, it has led to the unnecessary detection of the two overdiagnosed cancers. Note that in Scenario 3 the stage-specific numbers do not suggest down staging, but the percentages, when examined alone, do.

5.1.5 Case Survival

Measures of case survival will increase when cancer screening is introduced. Cancer screening leads to increased case survival

because, for screen-detected cancers, the date of diagnosis occurs earlier (by the amount of lead time) than it would have in the absence of cancer screening. Yet our ability to interpret changes in case survival in the presence of cancer screening, relative to case survival in the absence of cancer screening, is impaired because we do not know what the date of diagnosis or date of death would have been in the absence of cancer screening for a given individual. The fictional Y and Z cancers in Fig. 8, in conjunction with additional fictional experience in Table 5.2, will be used to demonstrate how case survival could change with cancer screening. Mean and median case survival are presented for ease of explanation, although relative case survival will change as well.

If case survival does not increase after cancer screening's introduction, cancer screening will not lead to a reduction in cause-specific mortality. A lack of increase indicates that diagnoses are not occurring earlier and that lives are not being lengthened. It is virtually impossible, however, for case survival not to increase when cancer screening occurs, because shifting the date of diagnosis to an earlier point in time is at the core of cancer screening. An increase in case survival does not guarantee a cause-specific mortality reduction, however. Lead time is usually responsible in that instance, but length-weighted sampling and overdiagnosis can lead to detection of cancers that will have the longest case survival because they have the most favorable prognosis.

Case survival seems to be the most frequently misinterpreted intermediate outcome. Increases in 5-year case survival are quoted as evidence that cancer screening saves lives, but lead time is rarely mentioned as a contributing factor and possible explanation for the observation.

5.1.6 Case Survival Example

Table 5.2 presents date of diagnosis, date of death, and case survival for the Y and Z cancers in the presence and absence of cancer screening. The experience of each Y cancer represents a

Table 5.1 Stage distributions in the absence and presence of cancer screening

	In the absence of cancer screening		In the presence of cancer screening	
Disease stage	Cancers	N (%)	Cancers	N (%)
Scenario 1:X and Y cancers only (non-overdiagnosed); two distant cancers are now detected at a local stage				
Local	X, Y	2 (34%)	X, Y, Y, Y	4 (67%)
Regional	X	1 (17%)	X	1 (17%)
Distant	X, Y, Y	3 (50%)	X	1 (17%)
Scenario 2:X, Y, and Z cancers (overdiagnosed and non-overdiagnosed cancer); two distant cancers are now detected at a local stage.				
Local	X, Y	2 (34%)	X, Y, Y, Y, Z, Z	6 (75%)
Regional	X	1 (17%)	X	1 (13%)
Distant	X, Y, Y	3 (50%)	X	1 (13%)
Scenario 3:X, Y, and Z cancers (overdiagnosed and non-overdiagnosed cancer); two distant cancers are detected at the same stage as in the absence of cancer screening.				
Local	X, Y	2 (34%)	X, Y, Z, Z	4 (50%)
Regional	X	1 (17%)	X	1 (13%)
Distant	X, Y, Y	3 (50%)	X, Y, Y	3 (38%)

X, Y, and Z cancers are defined in Fig. 5.1. Data are fictional

different way that lead time can change case survival. Y1 is screen detected but the date of death does not change. Case survival, which increases from 12 months to 20 months, suggests a benefit though. Y2 is screen detected but dies 3 months earlier than he or she would have in the absence of cancer screening, perhaps due to

Table 5.2 Case survival in the absence and presence of cancer screening

	In the absence of cancer screening			In the presence of cancer screening		
Cancer	Date of diagnosis	Date of death	Case survival	Date of diagnosis	Date of death	Case survival
Y1	2/1/18	2/1/19	12 months	6/1/17	2/1/19	20 months
Y2	2/1/18	12/1/18	10 months	6/1/17	9/1/18	15 months
Y3	2/1/18	10/1/20	32 months	6/1/17	12/1/22	66 months
Z1	Never diagnosed	6/1/21	Not relevant	6/1/17	6/1/21	48 months
Z2	Never diagnosed	9/1/21	Not relevant	6/1/17	10/1/20	36 months

X, Y, and Z cancers are defined in Fig. 5.1. Data are fictional

toxicity of cancer treatment. Case survival increases, though, from 10 months to 15 months because of lead time. Y3 benefits from screen detection. Case survival increases from 32 to 66 months, though the extension of life is only 26 months. The remainder of the 34-month increase in case survival, 8 months, is lead time.

The Z cancers do not have a measure of case survival in the absence of cancer screening because they were overdiagnosed. Detection of an overdiagnosed cancer cannot result in extension of life due to treatment. It can result, however, in premature death. Early death can occur in the instance of an adverse event related to cancer screening, diagnostic evaluation, or treatment. In addition, cancer patients have been shown to be at elevated risk of suicide [1].

Z1 is diagnosed due to cancer screening but his or her date of death does not change. Z2, on the other hand, dies sooner than he or she would have in the absence of cancer screening. Such a situation needs to be considered when weighing benefits and harms of cancer screening. It also is possible that the experience of having cancer will lead to lifestyle changes that improve overall health and extend life. Both situations would be reflected in mortality rates. The impact of lifestyle changes that do not affect length of

life yet lead to improved quality of life is not usually considered when evaluating cancer screening efficacy or effectiveness.

In the absence of cancer screening, the three non-overdiagnosed cancers would have a median case survival of 12 months and mean case survival of 18 months. In the presence of cancer screening, the 5 detected cancers would have median case survival of 36 months and mean case survival of 37 months. Yet only 1 of 5 screen-detected cases lived longer that he or she would have in the absence of cancer screening.

5.2 Cancer Screening's Impact on Definitive Outcomes

The two definitive outcomes in cancer screening are cause-specific mortality and all-cause mortality. The mortality outcomes are called definitive because it is impossible for them to be biased by the three screening phenomena, as is discussed in the next section of this chapter. That does not mean, however, that they cannot be affected by other factors, something that may not have been appreciated when the term definitive was bestowed upon them many years ago.

5.2.1 Mortality Rates and the Three Screening Phenomena

Cause-specific and all-cause mortality rates are not affected by lead time, length-weighted sampling, or overdiagnosis. They are not affected by lead time because date of diagnosis is not used to calculate mortality rates. They are not affected by length-weighted sampling or overdiagnosis because deaths are not restricted to those individuals whose cancer was screen detected.

Recall from Chap. 4 that the numerator in cause-specific mortality rates includes all deaths due to the cause of interest and the numerator in all-cause mortality rates includes all deaths. The denominator includes all persons at risk of death, not only those

who were screened. It is for these reasons that mortality rates reflect the impact of cancer screening on the entire population eligible to be screened. They incorporate cancer screening's successes as well as its failures, should either or both exist. Successes are extension of life among those screened. Failures are missed opportunities for early detection due to many factors, including limitations of the test, shortcomings in test interpretation, and non-adherence to cancer screening or diagnostic evaluation for a positive test.

5.2.2 Cause-Specific Mortality Rates

The calculation of a cause-specific mortality rate to assess cancer screening is straightforward, as was demonstrated in Chap. 4. The numerator includes all individuals who died of the cause of interest. The underlying assumption in the calculation is that the numerator correctly captures all relevant deaths. Unfortunately, errors in cause of death assignment are known to occur [2]. The cause of death recorded on the death certificate may not be the true cause of death.

When attempting to assess whether cancer screening can reduce cause-specific mortality, it is advised to classify any death that occurred as an adverse effect of the cancer screening process as a cause-specific death. The reason for that is to measure all screening failures. Any death that occurs due to the cancer for which screening is occurring is clearly a failure of the cancer screening process. However, any death due to an adverse effect of the cancer screening process also should be considered a failure because it would not have happened (or might have happened later) if cancer screening had not occurred. Identifying those deaths is a challenge because the death certificate is unlikely to indicate the sort of information that is necessary to link the death to the cancer screening process.

The next section addresses two phenomena that affect the ability of cause-specific mortality rates to measure what we want them to measure.

5.2.3 Sticking Diagnosis, Slippery Linkage, and Assessment of Cancer Screening

Sticking diagnosis occurs when the cancer of interest is erroneously assigned to be the cause of death, which can happen due to cancer's reputation for lethality. Sticking diagnosis can happen in the instance of screen- or symptom-detected cancer, but because incidence rates typically increase with cancer screening, sticking diagnosis generally leads to cause-specific mortality rates that are higher than they should be. In that instance, cancer screening could appear to not reduce cause-specific mortality when it actually does.

Slippery linkage occurs when death certificates do not capture a direct or downstream consequence of cancer screening, or do not capture it in such a way that it can be linked to cancer screening. Slippery linkage leads to cause-specific mortality rates that are lower than they should be and could lead to the conclusion that cancer screening does reduce cause-specific mortality when it actually does not. Slippery linkage would be at work in the instance of death due to a bowel perforation sustained during a screening colonoscopy, or development of fatal breast cancer caused by radiation from extensive imaging for an abnormality observed on lung cancer screening. In the former example, screening played a part in the death, and while the death certificate is likely to note a medical misadventure, it probably will not reflect the reason for the colonoscopy. In the latter example, it would be all but impossible to recognize the death as a downstream effect of cancer screening.

The section of the US standard death certificate that covers cause of death is presented as Fig. 5.2. Note that immediate causes, underlying causes, and significant medical conditions can be listed on the death certificate. Oftentimes a single underlying cause of death is derived using all entries according to rules set forth by the National Center for Health Statistics (NCHS); that cause of death is defined by the World Health Organization as "the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury" [3].

ITEMS 24-28 MUST BE COMPLETED BY PERSON WHO PRONOUNCES OR CERTIFIES DEATH	24. DATE PRONOUNCED DEAD (Mo/Day/Yr)	25. TIME PRONOUNCED DEAD
26. SIGNATURE OF PERSON PRONOUNCING DEATH (Only when applicable)	27. LICENSE NUMBER	28. DATE SIGNED (Mo/Day/Yr)
29. ACTUAL OR PRESUMED DATE OF DEATH (Mo/Day/Yr) (Spell Month)	30. ACTUAL OR PRESUMED DATE OF DEATH	31. WAS MEDICAL EXAMINER OR CORONER CONTACTED? ☐ Yes ☐ No

CAUSE OF DEATH (See instructions and examples)

32. **PART I.** Enter the chain of events--diseases, injuries, or complications--that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.

		Approximate interval: Onset to death
IMMEDIATE CAUSE (Final disease or condition ---------> resulting in death)	a. _____ Due to (or as a consequence of):	
Sequentially list conditions, if any, leading to the cause listed on line a. Enter the **UNDERLYING CAUSE** (disease or injury that initiated the events resulting in death) **LAST**	b. _____ Due to (or as a consequence of):	
	c. _____ Due to (or as a consequence of):	
	d. _____	

PART II. Enter other significant conditions contributing to death but not resulting in the underlying cause given in PART I	33. WAS AN AUTOPSY PERFORMED? ☐ Yes ☐ No
	34. WERE AUTOPSY FINDINGS AVAILABLE TO COMPLETE THE CAUSE OF DEATH? ☐ Yes ☐ No

Fig. 5.2 Questions 24–34 of the US Standard Certificate of Death (Rev 11/2003) [3]

In the US, researchers can obtain certain death certificate fields as long as the scientific rationale is strong. Requestors often forget, however, that death certificates are not completed with biomedical research in mind. To use death certificate data for research purposes requires an understanding of the rules used to complete them and recognition of their limitations. Additional information about death certificate completion and cause of death coding can be found at the website of the National Center for Health Statistics' (NCHS) National Vital Statistics System website [3].

5.2.4 Cause of Death Review

To arrive at accurate cause of death information, it may be necessary to review medical records that document the events leading to death. A review of every death could be done, though a thoughtfully-chosen, algorithm-driven, subset of deaths, as was done in the National Lung Screening Trial (NLST) [4], will save time and effort. Death review is usually a large undertaking, given the medical records that must be obtained and the person-power to review them. Nevertheless, death review can help to reverse death certificate cause of death assignment errors caused by sticking diagnosis and slippery linkage.

5.2.5 Cause-Specific Mortality Rates: Definitive Enough?

Given the possibility of sticking diagnosis and slippery linkage, it is fair to question whether cause-specific mortality outcomes are definitive. Obviously no outcome will be perfect, and by reviewing medical records one may be able to circumvent much of the error that is possible with assigned cause of death. The "definitiveness" for a given cancer is primarily dependent on the extent of sticking diagnosis and slippery linkage that goes uncorrected. Cause of death in the NLST was expected to be affected by slippery linkage and sticking diagnosis given comorbidities that are often experienced by heavy smokers and the perceived

lethality of lung cancer. However, a comparison of death certificate cause of death and death review cause of death indicated that disagreement was minimal [5]. The authors concluded death review may not be necessary in lung cancer screening.

It is possible to create a scenario, however far-fetched, in which a cause-specific mortality reduction could be explained by something other than cause of death errors created by slippery linkage. A reduction in mortality could be due, for example, to rapid elimination of a powerful risk factor or rapid introduction of a highly effective treatment. Such dramatic changes would have to be timed just so and be highly correlated with the act of being screened for the cancer of interest to explain away what appears to be a beneficial effect of population-based cancer screening. Given that the cancer landscape has never been a fast-changing one, that scenario is unlikely. Even cigarette smoking, an exceptionally strong cancer risk factor, took years to make its effect known, and universal smoking cessation, should it ever occur, also would take years for its impact to be realized. Certain molecularly targeted cancer therapies appear to be miracle cures, but they are available for only a few tumor types. The impact of concurrent changes on assessment of cancer screening tests is discussed further in Chap. 9.

Definitive outcomes are considered by most to be superior to intermediate outcomes when assessing the ability of cancer screening to reduce cause-specific mortality.

5.2.6 All-Cause Mortality

All-cause mortality rates are not affected by sticking diagnosis and slippery linkage because no cause of death is necessary to calculate them. Yet all-cause mortality is not a practical outcome in assessment of most cancer screening tests. Reduction in cause-specific mortality of a typical magnitude (perhaps about 20%) will lead to a small relative reduction in all-cause mortality, because death due to a single cancer usually represents a small percentage of all deaths.

The NLST was an exception: a statistically significant 20% lung cancer mortality reduction was accompanied by a statistically significant 7% all-cause mortality reduction. However, lung cancer deaths accounted for about 25% of all deaths, and when those deaths were excluded, the reduction in all-cause mortality was no longer statistically significant. Results from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) are more in line with what typically happens. The trial observed a statistically significant 26% reduction in colorectal cancer mortality, though the colorectal cancer deaths represented only about 2% of all deaths. An insignificant reduction in all-cause mortality of about 2% was observed, even with accumulation of over 800,000 person years in each arm.

Randomized controlled trials of cancer screening that utilize an all-cause mortality outcome would require extremely large numbers of individuals to have the necessary statistical power to detect typical mortality reductions. Large simple trials with an all-cause mortality outcome have been proposed [6, 7] but have their own shortcomings. Large numbers of screening centers might allow for recruitment of hundreds of thousands of participants, but would require more autonomy on the part of those screening centers, leading to challenges regarding rigor, such as uniform application of the screening protocol. A diffuse trial structure would make tracking factors that impact the outcome, such as contamination, difficult.

References

1. Zaorsky NG, Zhang Y, Tuanquin L, Bluethmann SM, Park HS, Chinchilli VM. Suicide among cancer patients. Nat Commun. 2019;10(1):207.
2. Smith Sehdev AE, Hutchins GM. Problems with proper completion and accuracy of the cause-of-death statement. Arch Int Med. 2001;161(2):277–84.
3. Revisions of the US standard certificates and reports [Internet]. Atlanta: Centers for Disease Control and Prevention. c [updated 2017; cited 2019 Oct 22]. Available from: https://www.cdc.gov/nchs/nvss/revisions-of-the-us-standard-certificates-and-reports.htm

4. Marcus PM, Gareen IF, Miller AB, Rosenbaum J, Keating K, Aberle DR, Berg CD. The national lung screening trial's endpoint verification process: determining the cause of death. Contemp Clin Trials. 2011;32(6):834–40.
5. Marcus PM, Doria-Rose VP, Gareen IF, Brewer B, Clingan K, Keating K, Rosenbaum J, Rozjabek HM, Rathmell J, Sicks J, Miller AB. Did death certificates and a death review process agree on lung cancer cause of death in the National Lung Screening Trial? Clin Trials. 2016;13(4):434–8.
6. Peto R, Collins C, Gray R. Large-scale randomized evidence: large, simple trials and overviews of trials. J Clin Epidemiol. 1995;48(1):23–40.
7. Prasad V. Powering cancer screening for overall mortality. Ecancermedicalscience. 2013;7:ed27. Available from: https://ecancer.org/en/journal/editorial/27-powering-cancer-screening-for-overall-mortality