

Population Measures: Definitions

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Performance measures, the subject of Chap. 3, describe the accuracy of a cancer screening test and its ability to lead to cancer detection in a set of screened individuals. They do not, however, describe characteristics of the detected cancers or experience after diagnosis. Intermediate and definitive outcomes do reflect that information. Intermediate and definitive outcomes are measured at the population level and therefore are called population measures. The term population refers to a group of individuals who are either formally offered cancer screening or for whom cancer screening is available. Though population can mean residents of a geographic region, it does not need to. Population also can refer to the types of research populations discussed in Chaps. 6 and 7. When assessing the impact of cancer screening on the population-level cancer burden, intermediate and definitive outcomes must incorporate the experience of all cancers, regardless of the method of detection, and include all individuals who were eligible to be screened. For example, assessment of intermediate and definitive breast cancer screening outcomes would need to be calculated using both screen-detected cancers and cancers diagnosed due to symptomatic presentation.

Intermediate outcomes can be measured earlier in time than definitive outcomes. Definitive outcomes are not affected by the three screening phenomena (lead time, length-weighted sampling, and overdiagnosis) that were described in Chap. 2. Favorable

intermediate outcomes are necessary but not sufficient for favorable definitive outcomes. However, intermediate outcomes that clearly are not favorable are sufficient evidence that cancer screening will not reduce cause-specific mortality.

Intermediate and definitive outcomes are defined in this chapter. Examples and associated calculations are presented. Chapter 5 will address reasons why intermediate outcomes are necessary but not sufficient to guarantee a reduction in cause-specific mortality as well as why definitive outcomes are not affected by the screening phenomena. Phenomena that can lead to inaccuracies in assignment of cause of death also will be discussed in Chap. 5.

The first intermediate outcome to be discussed, cancer incidence, is an intermediate outcome for early detection cancer screening, but a definitive outcome for cancer prevention screening. The reasons for the different classification are discussed in Chap. 8. The discussion of cancer incidence in this chapter is pertinent only to early detection cancer screening.

4.1 Intermediate Outcomes

4.1.1 Cancer Incidence

Incidence reflects the number of cancers that are diagnosed. Absolute numbers of cancers can be reported, although an incidence rate is more commonly used to allow for comparisons across populations of different sizes or with different lengths of observation. A rate incorporates a unit of time or is stated per an amount of time. Incidence rates are calculated as the number of cancers diagnosed (numerator) divided by the number of persons or person-years at risk for the cancer (denominator). Person-years are merely a measure of cumulative time, and are most often used in characterizing data from prospective research in which participants are monitored for different amounts of time. Incidence rates that do not use person-years of experience must state the unit of time over which the experience occurred. Most cancer incidence rates are age-adjusted because incidence of cancer varies by age.

There are many examples of cancer incidence rates in the literature. A widely-used and well-respected source is SEER, which was discussed in Chap. 1. SEER has been collecting data on cancer incidence, cancer mortality and other cancer outcomes in parts of the US since the early 1970s [1].

Here are two examples:

- The SEER age-adjusted incidence rate of breast cancer in 2016 was 129.81 per 100,000 women per year. SEER reports rates in that manner (rather than person-years) as its focus is on annual measures. The equivalent person-years rate would be 129.81 per 100,000 person-years [2].
- The lung cancer incidence rate in the low-dose computed tomography (LDCT) arm of the National Lung Screening Trial (NLST) was 645 per 100,000 person-years. That rate was based on 1060 lung cancers and 164,341 person-years of experience [3].

4.1.2 Calculating a Cancer Incidence Rate: A Fictional Example

Table 4.1 presents a cancer incidence rate calculation that uses person-years. The data are fictional and not reflective of the typical magnitude of cancer incidence. To calculate the incidence rate, experience (person-years) is truncated at the date of cancer diagnosis because cancer incidence is the outcome of interest. Put another way, cancer diagnosis is our endpoint for cancer incidence. Information on vital status, date of death, and cause of death are not needed yet.

The experience of 5 individuals is presented in Table 4.1. Each of the five is followed from the date of his or her 50th birthday. Two are diagnosed with cancer. The numerator is the number of cancers that were diagnosed (2 in this example). The denominator is the sum of the person-years that each individual contributed. Deborah and David were diagnosed with cancer, so person-years equals the time from the date of the 50th birthday to the date of

Table 4.1 Calculating cancer incidence

	Date turned 50	Status on 55th birthday	Date of diagnosis	Date of death or 55th birthday	Person-years contributed
Douglas	1/1/18	Alive, never diagnosed with cancer	N/A	1/1/23	5 years
Deborah	4/1/18	Dead, diagnosed with cancer	10/1/19	6/1/21	1.5 years
Don	7/1/18	Dead, never diagnosed with cancer	N/A	1/1/20	1.5 years
David	10/1/18	Alive, diagnosed with cancer	4/1/22	10/1/23	3.5 years
Dudley	1/1/19	Dead, never diagnosed with cancer	N/A	1/1/21	2 years

Number of cancers during the 5 year period: 2

Number of person-years: $5 + 1.5 + 1.5 + 3.5 + 2 = 13.5$

Five-year cancer incidence rate among these individuals: $2/13.5$, or 14.8 per 100 person-years

Data are fictional

diagnosis. Don and Dudley were not diagnosed with cancer and died prior to their 55th birthday, so person-years equals the time from the 50th birthday to the date of death. Their person-years are truncated at the date of death because they are only at risk of cancer while they are alive. Douglas was not diagnosed with cancer and was alive at his 55th birthday. He contributes five person-years, the maximum time possible in this example. Douglas was at risk of cancer for the entire period of observation.

4.1.3 Stage Distribution

A stage distribution is fashioned from a series of diagnosed cancers. It presents the number and percent of cancers that have and

have not spread. For cancers that have spread, stage distribution captures the extent of spread. The predominant staging system is the TNM system [4]. The T value indicates the size of the primary tumor and the spread into nearby tissue; the N value describes spread of cancer to nearby lymph nodes; and the M value describes metastasis (spread of cancer to other parts of the body). A T1N0M0 breast tumor is one that is invasive, smaller than 20 millimeters in its greatest dimension, and has not spread to lymph nodes or to other organs.

The TNM staging system is quite extensive, and in population-level research, TNM codes usually are combined to create the summary staging categories: local, regional, distant, and if need be unknown. Local refers to cancer that is invasive and confined to the primary site, regional refers to cancer that has spread to regional lymph nodes, and distant refers to cancer that has metastasized. An example of a stage distribution from SEER is found in Table 4.2 [5]. The TNM and summary staging systems include categories for in situ disease (the most advanced form of precancer), though that category is not included in the example.

The terms early stage, advanced stage, and late stage are frequently used when discussing cancer screening. Early stage generally refers to cancers that are curable, local-stage cancers, or cancers that are in a relatively early phase of their existence. Cancer screening aims to detect those cancers. Advanced and late stage generally refer to distant-stage cancers, cancers that are not

Table 4.2 Stage distribution of breast cancers diagnosed 2008 to 2014 and reported to the SEER 18 registry grouping

Stage	Number ^a	Percentage
Local	213,258	62
Regional	106,629	31
Distant	20,638	6
Unknown	6879	2
Total	343,965	100

^aSEER reports percentages, but not numbers, by stage. The stage-specific numbers in this table were calculated by multiplying the total number of breast cancers by the stage-specific percentages

curable, or cancers that are expected to be fatal. Cancer screening does not aim to detect cancers at late stages as their prognosis is unlikely to be improved.

4.1.4 Case Survival

Case survival is the time from cancer diagnosis to death from any cause, and in assessment of cancer screening is typically measured in months or years. Individual case survival is calculated by subtracting the date of diagnosis from the date of death. Summary measures of case survival are calculated for a series of cancers.

Case survival can be reported using medians or means, but is frequently reported as a percentage of cases alive after a certain amount of time, usually 5 years. Relative case survival is typically used; it is a measure that takes into account the hypothetical mortality the cancer patients would have had had they not been diagnosed with cancer. Relative case survival is calculated by dividing the number of cancer patients alive at the end of a given period of time by the number of individuals in a comparable but cancer-free population alive after the same period of time. It is the latter group that represents the aforementioned hypothetical mortality. A non-relative case survival percentage is calculated by dividing the number of living cancer patients by the total number of cancer patients, and is smaller than a relative case survival percentage because it does not consider that some cancer patients would have died of a cause other than cancer had they not been diagnosed with cancer. Table 4.3 presents relative and non-relative case survival percentages for a fictional sample of 100 cancer patients.

4.2 Definitive Outcomes

4.2.1 Cause-Specific and all-Cause Mortality

Mortality reflects the number of individuals who die. As is the case with incidence, rates rather than absolute numbers usually are reported. Both cause-specific and all-cause mortality rates use

Table 4.3 Calculating relative and non-relative case survival

Population	Number	Number alive 5 years later	Number dead 5 years later because of the cancer	Number dead 5 years later because of other causes
Cancer patients	100	85	6	9
Individuals who are otherwise similar to the cancer patients	100	90	0	10

Relative 5-year case survival: $85/90 = 94\%$. Non-relative 5-year case survival: $85/100 = 85\%$.

Experience is fictional

the number of person-years of individuals at risk of any death as the denominator. Cause-specific mortality rates use the number of individuals who died of the cause of interest as the numerator. All-cause mortality rates use the number of individuals who died of any cause.

It is common to confuse the meanings of mortality measures and case survival because they both involve death. The primary difference between the two is that case survival includes only those individuals who have been diagnosed with cancer. Mortality measures include all individuals who are at risk of dying from any cause. Put another way, mortality measures include those with cancer as well as those without cancer.

Figure 4.1 may help to explain. N, the number at risk of death, includes all individuals. C is the subset of the N individuals who were diagnosed with cancer. D is the subset of the C individuals who died of cancer. C minus D is the number of individuals with cancer who did not die of cancer. A mortality measure would use N (or their person-years of experience) as the denominator, while a case survival measure would use C as the denominator. As mentioned above, a cause-specific mortality measure would use D as the numerator. Figure 4.2 is a modified version of Fig. 4.1 and depicts the cascade for all-cause mortality measures.

Mortality rates reflect two measurable aspects of life: vital status and length of life. The use of person-years as the denominator

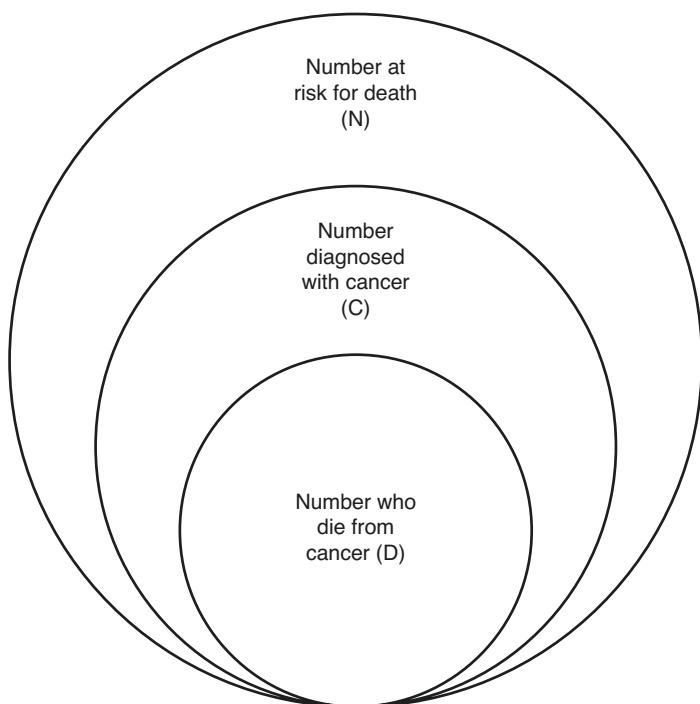


Fig. 4.1 The cascade from at risk for death to cause-specific death

enables cause-specific rates to reflect extension of life even if the cause of death is the cancer of interest. All-cause mortality rates will reflect the extension as well.

Here are two examples of cancer mortality rates:

- The SEER age-adjusted mortality rate of breast cancer in 2016 was 20.03 per 100,000 women per year or 20.03 per 100,000 person-years [2].
- The lung cancer mortality rate in the LDCT arm of the NLST was 247 per 100,000 person-years. That rate corresponds to 356 lung cancer deaths and 144,103 person-years of experience [3].

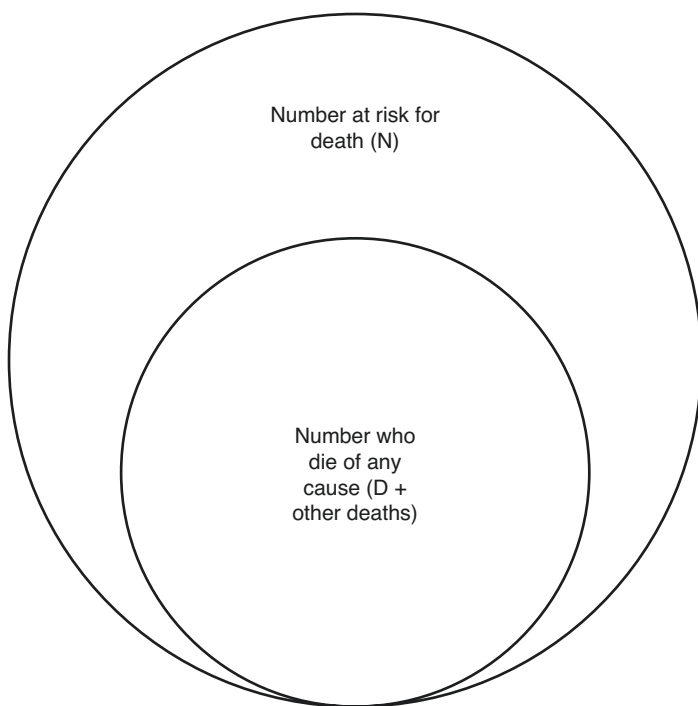


Fig. 4.2 The cascade from at risk for death to death from any cause

4.2.2 Calculating Mortality Rates: A Fictional Example

Table 4.4 displays the fictional experience of 100 individuals. All are alive on 1/1/18, twenty die on 6/30/2018, and the remaining 80 are alive on 12/31/18. Two pieces of information are needed to calculate the all-cause mortality rate: the number of individuals who died (numerator) and the collective amount of time that individuals were alive (denominator). The numerator clearly is 20, but the denominator requires some calculation. We need to separately consider those who were alive on 12/31/18 and those who died before that date. The 80 individuals who were alive on 12/31/18 each contribute a full year of time, for a total of 80 person-years.

Table 4.4 Calculating an all-cause mortality rate for 2018

	Number	Person-years contribution for 2018
Those alive on 1/1/18	100	Not applicable
Those who die on 6/30/18	20	10
Those alive on 12/31/18	80	80
Mortality rate: $20/(10 + 80) = 20$ per 90 person-years, or 22.2 per 100 person-years		

Data are fictional

The 20 who died did so half-way through the year. Each contributes half a year for a total of 10 person-years. The denominator equals the sum of the contributions from the two groups: 80 person-years plus 10 person-years, or 90 person-years. The all-cause mortality rate is 20 per 90 person-years, or 22.2 per 100 person-years.

In some instances, researchers may choose to calculate a simple percentage, reflecting the percentage of individuals who died. In the Table 4.4 example, the percentage of individuals who were alive on 1/1/18 but who died before 12/31/18 is 20%. It is smaller than the mortality rate and thus suggests more favorable experience. But it does so incorrectly, as it does not take into account that the 20 individuals who died did so halfway through the year. The simple percentage treats the deaths as if they occurred on the last day of the year. While the Table 4.4 example generated only a small disagreement in the percentage and mortality rate, the two metrics, when calculated using larger numbers of individuals who have a range of life lengths, can be meaningfully different from one another.

Table 4.5 expands on Table 4.4 by including information on cause of death. Five of the individuals who died on 6/30/18 died of lung cancer, while the remaining 15 died of another cause. When calculating a cause-specific mortality rate, only individuals who died of the cause of interest are included in the numerator, although all who died contribute the amount of time they were alive to the denominator. Table 4.5 shows calculations for the lung cancer mortality rate. The numerator is now 5, yet the denominator

Table 4.5 Calculating a lung cancer mortality rate for 2018

	Number	Person-years contribution for 2018
Those alive on 1/1/18	100	
Those who die on 6/30/18 of lung cancer	5	2.5
Those who die on 6/30/18 of a cause other than lung cancer	15	7.5
Those alive on 12/31/18	80	80
Lung cancer mortality rate: $5/(2.5 + 7.5 + 80) = 5$ per 90 person-years, or 5.6 per 100 person-years		

Data are fictional

remains at 90. The numerator is smaller because not all deaths were due to lung cancer. The denominator is the same as that of the all-cause mortality rate because the same amount of time was lived. The lung cancer mortality rate is 5 per 90 person-years, or 5.6 per 100 person-years. It is smaller than the all-cause mortality rate because our goal was to measure the rate of dying of lung cancer, which is less common than dying of any cause.

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