In this chapter, the various methods to estimate age-specific (ASp), crude (CR) and age-standardized (ASR) incidence or mortality rates of cancer are provided (Section 2.1). In section 2.2, analytical approaches used for estimating time trends in incidence and mortality rates of cancer are provided. Advantages and limitations of each method are discussed. In section 2.3, the methods such as age-conditional probability and cumulative risk to estimate the probability of developing or dying from cancer, either over a lifetime or over a specified number of years are provided along with the advantages and limitations of each method. In section 2.4, the methods for estimating the burden of disease in terms of disability-adjusted life years (DALY) are provided.
2.1. Age-specific, crude and age-standardized rates

2.1.1. Introduction

Cancer incidence is defined as new cases occurring in members of a defined population in a specified time period. Mortality serve as a measure of disease severity and are defined as the number of deaths due to specific disease of interest in a population, scaled to the size of that population per unit time. Ideally, one would like to know the risk of an individual in the population of being diagnosed or died with cancer at a given age and specific point in time - \( l_{xt} \) the instantaneous incidence rate at age \( x \) and time \( t \). In practice we are only able to estimate \( l_{xt} \) by observing the rate of occurrence of new cases or deaths due to cancer in the population over a specific time period - the incidence or mortality rate.

2.1.2. Person-years at risk

In order to calculate the incidence or mortality rate, a count of the number of new cases which have occurred in the population during the period under study and an estimate of the person-time at risk are required. Denominator in the calculation of incidence or mortality rate is defined in terms of units of person-time rather than simply the number of persons in the population at a specific point of time (as enumerated in population censuses or estimated by national bureau of statistics).

2.1.3. Age-specific incidence or mortality rate

Age is the single most important determinant of risk for cancer. Mathematical models have been extensively employed to describe the steeply increasing age incidence curves observed with many cancers. The shape of the age-incidence curve relates to the accumulation of exposure to carcinogenic events throughout life and provides clues to the underlying biology. Models have been used to interpret the effects on cancer rates seen when exposure to known carcinogens takes place at different ages or for different durations or when it ceases.

Age-specific rate for age group \( x \), \( a_x \), provides our best estimate of the theoretical rate \( l_x \). It is calculated as:

\[
a_x = \frac{k_x}{m_x}
\]
where $k_x$ and $m_x$ denote, respectively, numbers of cases and the person-years-at-risk in age group $x$. For presentational purposes, it is conventional to multiply $a_x$ by $10^5$ to show a ‘rate per $10^5$ person-years at risk’. The number of cases observed, and therefore also the rate, is subject to random variation. The nature of the variation in count data is assumed through Poisson distribution. We say that $k_x$ is a Poisson random variable with a mean (or expected value) of $l_x m_x$. Age-specific rates provide an indication of the way cancer risk evolves with age in a particular population.

For many forms of cancers, it has been suggested that the relationship between log (age) and log (incidence) to be linear of the form $l_x = b * x^k$, where $l_x$ denotes the incidence of cancer at age $x$, $b$ denotes the incidence rate in the absence of exposure, and $k$ reflects the effect of age on the transition rate to cancer.

### 2.1.4. Crude incidence or mortality rate

Summary measure of incidence or mortality in a population is the crude rate, which is given by:

$$\sum \frac{k_x}{m_x}$$

Using the standard 16 age groups 0-4, 5-9, ..., 75+ so that $x = 1, ..., 16$ in the above formula, the crude incidence or mortality rate is calculated. Crude rates are, however, not satisfactory for comparing populations. This is because some of the observed variation in the crude rates might be due to differences in the age structures of the populations being compared.

**Standard error and confidence interval of crude rates**

If the number of cases that occur, during the observation period is denoted by ‘$a$’ and the quantity of person-time at risk by ‘$y$’, the estimated incidence rate ($r$) is,

$$r = \frac{a}{y}$$

An approximate standard error is calculated as, $SE (r) = \frac{r}{\sqrt{a}}$

The 95% confidence interval for the observed rate ($r$) is obtained as, $r \pm 1.96 \times SE (r)$

‘Exact method’ lower and upper limit of a 95% confidence interval,
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Lower limit = \( r \times \text{lower limit factor (L)} \)

Upper limit = \( r \times \text{upper limit factor (U)} \)

Where L & U are obtained from the confidence limit factors estimated for a Poisson distributed variable.

‘Approximate’ formulae is appropriate when the number of cases in the numerator, ‘a’ is greater than 30. If the number of cases is small, ‘exact’ confidence intervals, based on the Poisson distribution can be used.

2.1.5. Age-standardized incidence or mortality rate

Age standardization is a way of accounting for the population structures under study and a number of methods of calculation are available. The direct method involves applying the age-specific rates in the population of interest to a fixed reference population. Age standardized rate (to world standard population, Table 2.1) is calculated as:

\[
\sum_x a_x w_x
\]

where \( w_x \) is the proportion of the total world standard population in age group \( x \) of the standard 16 age groups such as 0-4, 5-9, ..., 75+. Thus age-standardized incidence or mortality rate is a weighted average of the age-specific rates, where the weights are the proportions of persons in the corresponding age groups of a standard 100,000 population. The potential confounding effect of age is reduced when comparing age-standardized rates for different age-structured populations.

**Standard error for age-standardized rates**

If the age-specific rate in age group \( x \) is estimated from \( k_x \) cases and \( m_x \) person-years, then the age-standardized rate (with \( w_x \) representing the standardization weights) has an estimated variance (based on the Poisson distribution) of:

\[
\sum_x k_x (w_x/m_x)^2
\]

and an estimated standard error of:

\[
\sqrt{\sum_x k_x (w_x/m_x)^2}
\]
Table 2.1. Age-distribution of $10^5$ World standard population

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>World standard population</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>12000</td>
</tr>
<tr>
<td>5-9</td>
<td>10000</td>
</tr>
<tr>
<td>10-14</td>
<td>9000</td>
</tr>
<tr>
<td>15-19</td>
<td>9000</td>
</tr>
<tr>
<td>20-24</td>
<td>8000</td>
</tr>
<tr>
<td>25-29</td>
<td>8000</td>
</tr>
<tr>
<td>30-34</td>
<td>6000</td>
</tr>
<tr>
<td>35-39</td>
<td>6000</td>
</tr>
<tr>
<td>40-44</td>
<td>6000</td>
</tr>
<tr>
<td>45-49</td>
<td>6000</td>
</tr>
<tr>
<td>50-54</td>
<td>5000</td>
</tr>
<tr>
<td>55-59</td>
<td>4000</td>
</tr>
<tr>
<td>60-64</td>
<td>4000</td>
</tr>
<tr>
<td>65-69</td>
<td>3000</td>
</tr>
<tr>
<td>70-74</td>
<td>2000</td>
</tr>
<tr>
<td>75+</td>
<td>2000</td>
</tr>
</tbody>
</table>

Source: NCRP (2006)

2.2. Trends in cancer incidence or mortality rates—Analytical approaches

2.2.1. Introduction

There are many reasons for studying time trends in cancer incidence and mortality. Firstly, information on risk (incidence or mortality) can generate hypothesis or confirmation of suspected associations between risk factors and disease. While the existence of geographical variation in incidence between populations might be explained by genetic changes, changes in incidence in single populations imply the introduction or disappearance of environmental risk factors much more clearly.
Comparison of development of frequency of different types of cancer is therefore profitable.

The study of time trends is of particular interest in the evaluation of primary prevention, which involves the reduction in exposure to risk factors, and of secondary prevention (screening), which is aimed at reducing mortality. Improved treatment or earlier detection of disease will cause a more or less generalized shift in the existing trend in incidence or mortality. From the public health viewpoint, the observation of changes, in risk in the recent past leads naturally to a desire to predict its future development, in order to determine budget priorities and plan necessary services.

Data on cancer incidence from population-based registries (which collect information on all cancer cases in defined areas) provide information on geographical and temporal variation in cancer risk by personal characteristics such as age, sex and racial or ethnic groups etc.. Trend analysis offers clues to the understanding causes of the disease and variation in the frequency around different geographical areas. A systematic cancer trend analysis helps to understand the questions such as how the cancer risk has been changing, why and what is likely to happen in future. Quantitative comparison of trends for different cancer sites may prompt for a future search for common risk factors. Changes in cancer pattern with the passage of time are of vital interest in cancer control activities. Cancer trends also provide of future patterns, which will be guidance for drawing future cancer patterns.

Most of the trend analysis methods rely on the assumption that ratios of incidence (or mortality) remain more or less constant with age. In fact, it is far from certain that risk alters in the same way for all age groups in a changing environment. Indeed, there are, in general, good reasons to assume that different age groups behave in different ways. In addition to real trends in risk and random variations, changes in data quality over time affect the observed trend in incidence or mortality. These effects can create apparent increases or decreases in risk, when the true risk is completely stable. For incidence data, time series partially reflect progressive improvements in the registration rate, whether resulting from the development of diagnostic techniques or improved reporting systems for the cancer registry. As a registry develops, there is also an improvement in the quality of diagnostic
information obtained for each cancer registered, and a consequent increases in the precision in coding of the site and type of the tumour. Codes corresponding to poorly defined sites are progressively less used as the percentage of histologically confirmed cases arises. An artificial increase in the frequency of well-specified sites will therefore be seen. Incidence can fluctuate as a result of changes in the stage, at which cancer is detected, particularly for slow-growing tumours. The detection of early stage disease has an even greater effect in the study of time trends in survival. All changes in classification, or even coding practices, can affect the number of cases at a given site or due to a specific cause of death and distort trends. The problem of imprecise data is accentuated by the differences in the evolution of precision with region or age. Errors in diagnosis are generally more serious in older people, and improvements in diagnostic precision can therefore have a fundamental effect on incidence rates in this age group.

Chronological patterns in incidence or mortality rates depend on the quality of the denominators over time. Population estimates provided by statistical services may be increasingly distorted further as they are from the date of the census. This distortion often results in an underestimation of the denominators, because enumeration is not as accurate for persons leaving the population as it is for those arriving.

Sometimes it is sufficient to describe long-term trends, in other situations, interest might focus on variation over a more limited time period, in particular the recent past, if the goal is to predict new directions of the phenomenon. Apart from the simple description of changes in risk over time, the study of trends involves the search for models which can describe data via plausible hypothesis about the causes of observed changes. Relevant components of the time trend can be separated from random or systematic, allowing a more complete interpretation of the data.

2.2.2. Annual Percent Change (APC)

APC is one way to characterize trends in cancer rates over time. This means that the cancer rates are assumed to change at a constant percentage of the rate of the
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previous year. Rates that change at a constant percentage every year change linearly on a log scale. For this reason, to estimate the APC for a series of data, the following loglinear model is used. The model assumes the response variable $Y$ has a Poisson distribution, and assumes the logarithm of its expected value can be modeled by a linear combination of unknown parameters. The multiplicative Poisson regression model is fitted as a log-linear regression, with an offset equal to the natural logarithm of person-time is specified.

$$\log(R_y) = b_0 + b_1 y$$ where $\log(R_y)$ is the natural log of the rate in year $y$.

The APC from year $y$ to year $y+1 = \left[ \frac{(R_{y+1} - R_y)}{R_y} \right] \times 100$

$$= \left[ e^{b_0 + b_1 (y+1)} - e^{b_0 + b_1 y} \right] / e^{b_0 + b_1 y} \times 100$$

The model gives a scale parameter as a measure of over-dispersion; this is equal to the Pearson chi-square statistic divided by the number of observations minus the number of parameters (covariates and intercept). The variances of the coefficients can be adjusted by multiplying by scale parameter. The goodness of fit test statistics and residuals can be adjusted by dividing by scale parameter.

The deviance (likelihood ratio) test statistic, $G^2$, is the most useful summary of the adequacy of fitted model. It represents the change in deviance between the fitted model and the model with a constant term and no covariates and $G^2$ is not calculated if no constant is specified. If this test is significant then the covariates contribute significantly to the model.

$$\text{Deviance} = 2 \sum_{i=1}^{n} \left[ y_i \ln \left( \frac{\hat{\mu}_i}{\mu} \right) - (y_i - \hat{\mu}) \right]$$

Where $y$ is the number of events, $n$ is the number of observations and $\mu$ is the fitted Poisson mean. The log-likelihood function is:

$$L = \sum_{i=1}^{n} y_i \ln (\mu_i) - \mu_i - \ln (y_i)$$
Adequacy of fit for the models is assessed by the likelihood ratio goodness of fit statistic, as well as a visual determination of systematic departures from the model. When the lack of fit is statistically significant but random, a quasi-likelihood approach is used in which the ratio of the goodness of fit statistic to its degrees of freedom estimated the mean squared error in the denominator of a corresponding F statistic. The Pearson goodness of fit test statistic is:

\[
\chi^2 = \sum_{i=1}^{n} \frac{y_i - \hat{\mu}_i}{\sqrt{\hat{\mu}_i}}
\]

One advantage of characterizing trends this way is that it is a measure that is comparable across scales, for both rare and common cancers. For example, it is reasonable to think that rates for a rare cancer and a common cancer could both change at 1% per year, but it is not reasonable to think that a rare cancer and a common cancer would change in the same increments on an absolute (or arithmetic) scale. That is, a cancer with a rate of 100 per 100,000 could be changing by 2 per 100,000 every year, but a cancer with a rate of 1 per 100,000 would probably not change in the same increments. However, it is not always reasonable to expect that a single APC can accurately characterize the trend over an entire series of data.

### 2.2.3. Joinpoint regression model

The joinpoint model uses statistical criteria to determine when and how often the APC changes. For cancer rates, it is fitted using joined log-linear segments, so each segment can be characterized using an APC. For example, cancer rates may rise gradually for a period of several years, rise sharply for several years after that, then drop gradually for the next several years. Finding the joinpoint model that best fits the data allows us to determine how long the APC remained constant, and when it changed.

Joinpoint models have been applied to the cancer incidence and mortality data with continuous change points. Hudson provides an algorithm to find the weighted least square estimates of the joinpoint on the continuous scale (Hudson 1966). Fitting
segmented regression models by grid search method is available and which assumes that the joinpoints only occur at discrete grid points (Lerman 1980).

Statistical software called Joinpoint is available for the analysis of trends using joinpoint models, that is, models where several different lines are connected together at the "joinpoints". The software takes trend data (e.g. cancer rates) and fits the simplest joinpoint model that the data allow. The user supplies the minimum and maximum number of joinpoints. The program starts with the minimum number of joinpoint (e.g. 0 joinpoints, which is a straight line) and tests whether more joinpoints are statistically significant and must be added to the model (up to that maximum number). This enables the user to test that an apparent change in trend is statistically significant. The tests of significance use a Monte Carlo Permutation method. The models may incorporate estimated variation for each point (e.g. when the responses are age adjusted rates) or use a Poisson model of variation. In addition, the model assumes linearity on the log of the response (e.g. for calculating annual percentage rate change). The software also allows viewing one graph for each joinpoint model, from the model with the minimum number of joinpoints to the model with maximum number of joinpoints (Kim et al., 2000).

2.2.4. Average Annual Percent Change (AAPC)

AAPC is a summary measure of the trend over a pre-specified fixed interval. It allows us to use a single number to describe the average APCs over a period of multiple years. It is valid even if the joinpoint model indicates that there were changes in trends during those years. It is computed as a weighted average of the APC's from the joinpoint model, with the weights equal to the length of the APC interval. AAPC is derived by first estimating the underlying joinpoint model that best fits the data. The AAPC over any fixed interval is a weighted average of the slope coefficients of the underlying joinpoint regression line with the weights equal to the length of each segment over the interval. The final step of the calculation transforms the weighted average of slope coefficients to an annual percent change. If we denote $b_i$ as the slope
coefficients for each segment in the desired range of years, and the $w_i$s as the length of each segment runs in the range of years, then:

$$APC_i = \{ [\text{Exp}(b_i) - 1] \} \times 100$$

and

$$AAPC = \left\{ \text{Exp}\left( \frac{\sum w_i b_i}{\sum w_i} \right) - 1 \right\} \times 100$$

**Confidence Interval for AAPC**

Denote the normalized weight as $\tilde{w}_i = w_i / \sum w_i$. We can rewrite the AAPC as

$$AAPC = \{ \exp(\sum \tilde{w}_i b_i) - 1 \} \times 100$$

An ‘approximate’ 100(1-\(\alpha\))% confidence interval for the true average annual percent change is

$$(AAPC_{l(\alpha)}, AAPC_{u(\alpha)})$$, where

$$AAPC_{l(\alpha)} = \{ \exp[\log(AAPC) + 1] - z_{a/2} \sqrt{\sum \tilde{w}_i^2 \hat{\sigma}_i^2} - 1 \} \times 100$$

$$AAPC_{u(\alpha)} = \{ \exp[\log(AAPC) + 1] + z_{a/2} \sqrt{\sum \tilde{w}_i^2 \hat{\sigma}_i^2} - 1 \} \times 100$$

are the lower and upper confidence limits of the intervals, $z_\alpha$ is the $\alpha^{th}$ quantile of the standard normal distribution, and $\hat{\sigma}_i^2$ denotes the estimate of the variance of $b_i$ obtained from the fit of the joinpoint model. If the confidence interval contains zero, then there is no evidence to reject the null hypothesis that the true AAPC is zero at the significance level of $\alpha$; otherwise, we reject the null hypothesis in the favor of the alternative hypothesis that the true AAPC is different from zero.
2.2.5. Relative advantages and disadvantages of reporting an AAPC over APCs

Reporting APCs for each joinpoint segment provides a complete characterization of the trend over time. However, sometimes a summary measure over a fixed interval may be desirable. The statistical power to determine if an APC is different from 0 is a function of the length of the interval. Thus, a short segment rising at a steep rate may not be statistically significant. Comparing the last segment of two or more series sometimes yields seemingly contradictory results when the segments are of very different lengths. Comparing AAPC’s of equal lengths from all series is usually a more meaningful comparison. Rather than reporting the APC for the final segment for a long list of cancer sites, there may be advantages to reporting the AAPCs over specified fixed intervals. If space permits, reporting both the AAPC and the final segment APC gives an even more complete picture, since each give a somewhat different perspective.

Prior to the development of the joinpoint and AAPC methodology, to characterize a trend over a fixed interval, a single regression line (on a log scale) over the fixed interval was fit, and the slope coefficient was then transformed to an APC. This older methodology has two disadvantages over the AAPC. First, the older methodology assumes linearity of the trend (on a log scale) over the interval, while the AAPC does not. Secondly, the AAPC can be used to characterize a short segment based on a joinpoint model fit over a much longer series. This is especially advantageous for situations when the data are sparse (e.g. a rare cancer or data from a small geographic area).

2.3. Probability of developing cancer

2.3.1. Introduction

Estimate of the probability of developing or dying due to cancer, either over a lifetime or over a specified number of years, is another useful summary measure of the burden of cancer in a population. Probabilities of developing or dying due to cancer can be
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estimated after removing the risk due to other causes. Using competing risk models, the probabilities of death due to various risks can be separated. There are a few approaches available for estimating these probabilities with and without considering the effect of competing risk.

2.3.2. Age Conditional Probabilities of Developing Cancer

An estimator for the age-conditional probability of cancer is derived using statistical competing risk model (Fay et al., 2003). In many situations, there are several possible risks of failure. The actual cause of failure of the individual may be any one of these risks. Hence these risks are said to compete for the life of the individual. The model for lifetime in the presence of such competing risks is known as the competing risks model.

In the competing risk method, the time until one of several events, T, and an indicator of the type of event that occurred, J is observed. T is a random variable denoting the age at death and J has one of two values, J = d means death from the event of interest (for example, breast cancer), and J = 0 means death from other causes. The cause-specific hazard function for J = j is

\[ \lambda_j(a) = \lim_{\varepsilon \to 0^+} \frac{\Pr[a \leq T < a + \varepsilon, J = j / T \geq a]}{\varepsilon} \]

Thus \( \lambda_d(a) \) is the rate of cancer deaths per person-years alive at age a, and \( \lambda_o(a) \) is the rate of other (that is, non-cancer) deaths per person-years alive at age a. The overall failure rate at age a is \( \lambda(a) = \lambda_d(a) + \lambda_o(a) \), and the overall survival function is \( S(a) = \Pr[T > a] = \exp(- \int_0^a \lambda(u)du) \). The probability of dying from cause j in the age interval \([x, y)\) given survival until just prior to x is

\[ \Pr[x \leq T < y, J = j | T \geq x] = \frac{\int_x^y \lambda_j(u)S(u-)du}{S(x-)} \]

where \( S(a-) = \lim_{\varepsilon \to 0} S(a - \varepsilon) \).
Statistically identical competing risks is also considered where $T^*$ is the age at either first cancer or death before first cancer, and $J^*$ is the indicator with $J^* = c$ denoting that $T^*$ is the age at first cancer and $J^* = 0$ denoting that $T^*$ is the age at death if death occurs before the first cancer. The cause-specific hazard functions are: $\lambda^*_c(a)$, the rate of first cancer per person-years alive and cancer free at age $a$, and $\lambda^*_o(a)$, the rate of deaths per person-years alive and cancer free at age $a$. Then, similar to the above, the probability of getting a first cancer in the age interval $[x,y)$ given alive and cancer free until just prior to $x$ is

$$A(x, y) = \Pr[x \leq T^* < y, J^* = c | T^* \geq x] = \frac{\int_{x}^{y} \lambda^*_c(u)S^*(u-)du}{S^*(x-)} \hspace{1cm} \text{(1)}$$

where $S^*(a) = \exp\{-\int_{0}^{a} \lambda^*_c(u)du\}$ and $\lambda^*_c(a) + \lambda^*_o(a)$. 

Assume that the rate of non-cancer deaths is the same for all people regardless of whether or not they have had a cancer, so that $\lambda^*_o(a) = \lambda_o(a)$. Then $A(x, y)$ can be re-written in terms of the function $\lambda_c(\cdot), \lambda_d(\cdot)$ and $\lambda_o(\cdot)$.

$$\lambda_c(a) = \lim_{\epsilon \to 0^+} \frac{\Pr[a \leq T^* < a + \epsilon, J^* = c | T^* \geq a]}{\epsilon} = \lim_{\epsilon \to 0^+} \frac{\Pr[a \leq T^* < a + \epsilon, J^* = c \text{ and } T^* \geq a]}{\epsilon \Pr[T^* \geq a]}$$

$$= \lim_{\epsilon \to 0^+} \frac{\Pr[a \leq T^* < a + \epsilon, J^* = c]}{\epsilon \Pr[T^* \geq a]} = \frac{\lambda^*_c(a)S^*(a-)}{S(a-)} \hspace{1cm} \text{(2)}$$

Using this equation the numerator of equation (1) can be written as $\int_{x}^{y} \lambda_c(u)S(u-)du$.

The denominator can be re-written as, $S^*(a) = S^*_c(a) \cdot S^*_o(a)$, where $S^*_j(a) = \exp\{- \int_{0}^{a} \lambda^*_j(u)du\}$ for $j = c, 0$. $S^*_j(a)$ does not have a survival function interpretation as it is assumed that $\lambda^*_o(a) = \lambda_o(a)$. So $S^*_o(a) = S_o(a) = \exp\{- \int_{0}^{a} \lambda^*_o(u)du\}$. 

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In the definition of \( S^*(a) \), rewrite the expression for \( \hat{\lambda}^* (a) \) using equation (2), and the recursive equation is obtained.

\[
S^*(a) = \exp \left\{ - \int_0^a \hat{\lambda}_c(u)S(u-) \, du \right\}
\]  

Recursive equation is solved in the following way, first let \( S(t) = S_d(t)S_c(t) \), where

\[
S^*(t) = \exp \left\{ - \int_0^t \hat{\lambda}_o(u)S_d(u-) \, du \right\}
\]

Take log of both sides, then differentiate with respect to \( t \) to get

\[
\frac{dS^*(t)}{dt} = \frac{\hat{\lambda}_c(t)S_d(t-)}{S^*(t-)}
\]

If \( T^* \) is a continuous random variable then \( S^*(t) = S^*(t-) \) and \( dS^*(t)/dt = -\hat{\lambda}_o(t)S_d(t-) \). Now integrate to obtain \( S^*_c(a) - S^*_c(0) = - \int_0^a \hat{\lambda}_o(t)S_d(t-) \, dt \) and \( S^*_c(0) = 1 \), so that \( S^*_c(a) = 1 - \int_0^a \hat{\lambda}_o(u)S_d(u-) \, du \). Thus, under the assumption \( \hat{\lambda}_o(a) = \hat{\lambda}_c(a) \), \( A(x,y) \) can be expressed as

\[
A(x,y) = \frac{\int_0^x \hat{\lambda}_c(u)S(u-) \, du}{S_c(x-)[1 - \int_0^x \hat{\lambda}_o(u)S_d(u-) \, du]} 
\]

To obtain an estimate of \( A(x,y) \) using cancer incidence and mortality data, the possible ages are divided into \( k+1 \) intervals, \([a_i, a_{i+1})\) where \( 0 = a_0 < a_1 < ... < a_k < a_{k+1} = \infty \), and choose a calendar interval, \([t_1, t_2)\). Although the cancer incident cases and the deaths often come from the same population, this is not necessary.

\( n_j^{(i)} \), which is \( (t_2 - t_1) \) times the estimated number of people from the same population associated with event \( j \) (where \( j = c, d \) or 0) with ages in \([a_i, a_{i+1})\) at the midpoint, \((t_1 + t_2)/2\), of the interval \([t_1, t_2)\), for \( i=0, ....k \) is observed. If \( t_2 - t_1 = 1 \),
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\( n_i^{(j)} \) corresponds to the midyear population with ages in \([a_i, a_i+1)\). The counts \( c_i, d_i, o_i \) are assumed as Poisson and the mid interval populations are fixed constants.

Assuming constant rates within age intervals, rates for ages \( a \in [a_i, a_i+1) \) by \( \hat{\lambda}_c (a) = c_i / n_i^{(c)} \), \( \hat{\lambda}_d (a) = d_i / n_i^{(d)} \), and \( \hat{\lambda}_o (a) = o_i / n_i^{(o)} = \hat{\lambda}^*_{o} (a) \) is estimated. These estimators replace their associated functions in equation (4) to obtain the estimator of \( A(x,y) \).

Using DevCan (DevCan 6.4.1, 2009), the age-conditional probabilities of cancer can be estimated using cancer incidence as well as cancer and non-cancer mortality data.

**Confidence limits for the estimator \( A(x,y) \)**

Gamma and delta method confidence intervals are developed for linear combinations of independent Poisson random variables to create confidence intervals for \( A(x,y) \) (Fay and Feuer (1997; Fay et al; 2003).

### 2.3.3. Cumulative risk

In cancer registries, non-cancer mortality data may not be available. However incidence and mortality rates due to cancer are available. Using these rates we can estimate the probability of developing cancer in terms of cumulative risk. It is defined as the probability that a particular event, such as occurrence of a particular disease, has occurred before a given time. The risk actually incurred by an individual subjected not only to the risk of cancer but also to the risk of death. For a given level of incidence, this probability will be higher when the general mortality is low and vice versa. It is equivalent to the incidence, calculated using a period of time during which all of the individuals in the population are considered to be at risk for the outcome. Thus the overall incidence of a disease observed in a population can be described as the cumulative incidence rate which provides an approximation of the risk of developing a disease before a particular age say \( b \) (or between two ages say \( a \) and \( b \)) in the absence of mortality. Thus cumulative rate over a whole lifetime is an integral of the function represented by the incidence curve.

Cumulative incidence is calculated by the number of new cases during a period divided by the number of subjects at risk in the population at the beginning of the
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study. The cumulative rate is based on the sum of age specific rates, giving equal weight to all age groups. Each age specific rate is multiplied by the length of the age group in years, which is 5 years for all age groups up to 70-74 years. The oldest age groups are excluded when we are interested in the cumulative incidence up to a specific age. Thus the cumulative rate up to age 74 years is calculated as:

\[ \sum_{x=1}^{15} 5a_x \]

from which the cumulative risk, expressed as a percentage, can be estimated as:

\[ (1 - e^{-CumRate}) \times 100 \]

The cumulative risk can be interpreted as an approximation to the cumulative 'lifetime' (age 0-74 years) risk of disease for an individual if, throughout their life, they are to experience the same age specific risks as the population from which the cumulative rates are calculated, and are free from competing causes of death. Thus cumulative risk is the probability that an individual will be diagnosed or died with cancer during a certain age period in the absence of any competing cause of death and assumed that the current trends prevail over the time period. The percentage cumulative risk is used as it is appealing because it provides a statistic which is tangible to lay people. One in number of persons at risk of developing cancer (life-time risk) is calculated as 100/cumulative risk.

**Standard error of cumulative incidence rate**

Both the standardized and the cumulative rate are a weighted sum of the age-specific rates, so the standard error can be derived in both cases from the same formula. If the age-specific rate in age group \( x \) is estimated from \( k_x \) cases and \( m_x \) person-years, then the cumulative rate has an estimated variance (based on the Poisson distribution) of:

\[ \sum_i k_i \left( \frac{w_i}{m_i} \right)^3 \]

and an estimated standard error of:

\[ \sqrt{\sum_i k_i \left( \frac{w_i}{m_i} \right)^3} \]

For the cumulative rate, the weights \( (w_x) \) are equal to the widths of the age groups.
2.4. Burden of cancer using disability adjusted life years (DALY)

2.4.1. Introduction

Morbidity including incidence rates and mortality rates are classically used to measure cancer burden. Burden of disease (BOD) is a joint measure of morbidity and mortality, which makes it easier to compare health problems in which these two components enjoy different degrees of relative importance. However, the allocation of limited health-care resources demands an agreed rational allocation principle and, consequently, the setting of priorities is of considerable importance. Health gaps are based on the premise that the best approach for measuring the burden of disease is to use units of time. Time lost due to premature mortality is a function of the death rate and the duration of life lost due to death at each age.

Several countries have estimated the burden of cancer by adding the number of years of life a person loses as a consequence of dying early because of the disease (called YLL, or Years of Life Lost); and the number of years of life a person lives with disability caused by the disease (called YLD, or Years of Life lived with Disability). Adding together the Years of Life Lost and Years of Life lived with Disability gives a single-figure estimate of disease burden, called the Disability Adjusted Life Year (or DALY).

DALY is a summary measure to assess the burden of a disease in a population. It measures health gaps as opposed to health expectancies. i.e. it measures the difference between a current situation and an ideal situation where everyone lives upto the age of the standard life expectancy, and in perfect health. DALY combines in one measure the time lived with disability and the time lost due to premature mortality. Total DALYs for each cause-age-sex group are calculated as the sum of the non-fatal burden and the burden of premature mortality:

\[ \text{DALY} = \text{YLD} + \text{YLL} \]

where YLL= years of life lost due to premature mortality, and YLD= years lived with disability.

All summary measures of population health involve explicit or implicit social value choices. In particular, the DALY measures the gap between a population’s actual
health status and some ‘ideal’ or reference status. In developing the DALY indicator, Murray and Lopez (1996) identified five value choices that should be explicitly made:

i) How long ‘should’ people in good health expect to live? (Standard life expectancy)

ii) How should we compare years of life lost through death with years lived with poor health or disability of various levels of severity? (Disability weight)

iii) Is a year of healthy life gained now worth more to society than a year of healthy life gained sometime in the future? (Discount rate)

iv) Are lost years of healthy life valued more at some ages than others? (Age weighting). Are all people equal? Do all people lose the same amount of health through death at a given age, even if there are variations in current life expectancies between population groups? (Standard age weighting).

2.4.2. Age weighting and Discounting

Age weights are a controversial value choice built into the DALY. Studies have shown that people have preferences regarding the moment at which death or disability occur (Murray and Lopez, 1996a,b; Murray and Acharya, 1997). The exponential function used to model the relative age weights adapted from Murray & Lopez (1996) is:  

\[ X_w = C \times e^{-\beta x} \]

where:  

- \( X_w \) = weighted age (years),  
- \( C \) = constant,  
- \( \beta \) = constant,  
- \( x \) = age (years)

The DALY measures the future stream of healthy years of life lost due to each incident case of disease and thus it is an incidence-based measure. If a discrete annual discount rate \( r \) is used, then the formula for the present value of a stream of life years in length ‘n’ is:

\[ V_{\text{present value}} = \left(1 + r\right)^{-0.5} \left(1 - \left(\frac{1}{1 + r}\right)^n\right) \]

If continuous time discounting at an instantaneous rate \( r \) is applied, then the formula becomes: 

\[ V_{\text{present value}} = \left(1 + r\right)^{-0.5} \left(1 - e^{-rn}\right) \]
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\[ n_{\text{present value}} = \frac{1}{r} - \left( \frac{1}{r} e^{-r} \right) \]

In order to make the discrete and continuous forms give the same result, the discount rate in the continuous form must be set equal to \( \ln (1+r) \).

2.4.3. Estimation of Disability adjusted life years (DALY)

Components of Years Lived with Disability (YLD) have been estimated by using the software DISMOD and DALY have been estimated using the templates provided in the Global Burden of Disease (GBD) study conducted by WHO (Murray and Lopez 1996a,b; Murray and Lopez 1997a,b). YLD is estimated by assuming that death due to disease under study and death due to other causes are independent. With this assumption, the disease model can be completely determined by three transition hazards viz. incidence, remission and case-fatality. However, for disease like cancer, information on remission is difficult to obtain as it requires follow-up data. Secondly, deaths due to cancer may not be independent on other causes and thus other cause mortality may also be considered. After removing the risk due to other causes (competing risks), YLD is estimated by using the indicators such as incidence, mortality and all-cause mortality.

Choices such as disability weight, discount rate, age-weighting, duration of disease and age at onset are made for estimating both YLL and YLD. Disability weight reflects the severity of the disease on a scale from “perfect health” to “equivalent to death”. This weight is derived using different methods such as rating scale or visual analogue scale, standard gamble, time trade off and person trade off. Discount rate reflects the rate at which society as a whole is willing to trade off present for future benefits. The value of a life year is set higher than the value of future life years. Discounting future benefits is of standard practice in economic analysis. Age weighting is based on a number of studies that have indicated that there is a broad social preference to value a year lived by a young adult more highly than a year lived by a young child or at older ages (Murray and Lopez 1996a,b). The formula for YLL under the various above social value choices are:
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i) Without discounting or age-weights:

\[ YLL = N \times L; \] where \( N \) is the number of deaths; \( L \) standard life expectancy.

ii) With non-zero discounting (at a rate of 3%) and uniform age-weights:

\[ YLL = \frac{[N \times (1 - e^{-0.03L})]}{0.03} \]

iii) With non-zero discounting (at a rate of 3%) and non-zero age-weights:

\[ YLL = N \times C e^{(ra)} / (L+a)^2 \left[ e^{(L+r)(L+a)} - (L+a) \left[ (L+a) \times e^{(L+r)(L+a)} \right] \right] \]

where \( r \) is the discount rate, \( C \) is the age-weighting correction constant (GBD standard value is 0.1658), \( \frac{r}{L+a} \) is the parameter from the age-weighting function (GBD standard value is 0.04), \( a \) is the age at onset, and \( L \) standard life expectancy at age \( a \).

Using DISMOD II procedure, average duration of disability and age at onset are derived based on either incidence, mortality and case-fatality rate (without considering competing risk approach) or based on incidence, mortality and RR mortality (considered all-cause mortality). The formula for YLD under the various social value choices are:

i) \[ YLD = I \times DW \times L; \] where \( I \) is the number of incident cases in the reference period, \( DW \) is the disability weight (in the range 0-1) and \( L \) is the average duration of disability (measured in years).

ii) With non-zero discounting (at a rate of 3%), the formula becomes:

\[ YLD = I \times DW \times (1 - e^{-0.03L}) \]

\[ 0.03 \]

iii) With non-uniform age weights, YLD is given by:

\[ YLD = I \times DW \times C e^{(ra)} / (L+a)^2 \left[ e^{(L+r)(L+a)} - (L+a) \left[ (L+a) \times e^{(L+r)(L+a)} \right] \right] \]

where \( DW \) is the disability weight, \( r \) is the discount rate (GBD standard value is 0.03), \( C \) is the age-weighting correction constant (GBD standard value is 0.1658), \( \frac{r}{L+a} \) is the parameter from the age-weighting function (GBD standard value is 0.04), \( a \) is the age of onset, and \( L \) is the duration of disability.

Using a parameter \( K \) that specifies whether age weighting is applied (\( K=1 \)) or not (\( K=0 \)), the non-zero discounting and non-uniform age-weighting formulae can be combined into a single general formula for YLD and which is given below.

\[ YLD = I \times DW \times \{ K \times C e^{(ra)} / (L+a)^2 \left[ e^{(L+r)(L+a)} - (L+a) \left[ (L+a) \times e^{(L+r)(L+a)} \right] \right] \times (1-K) (L/r) (1 - e^{rL}) \}\]
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References


