6.1 INTRODUCTION

The World Health Organization's guidelines for preparing national cancer control programmes (WHO, 1995) emphasize the different approaches to cancer control — (primary) prevention and early diagnosis and treatment. While primary prevention reduces the incidence of cancer, early detection strategies and treatment regimes aim to improve the outcome of incident cancer cases, by curing the cancer or by improving the quality and/or duration of life after diagnosis. Alongside information on incidence and mortality, survival statistics are a means of quantifying the effectiveness of these two interventions at the population level. Thus, information on survival has long been recognized as an important component in monitoring cancer control activities (WHO/IARC).

Like all other health indices, survival statistics are useful primarily as comparative measures showing how survival differs between different populations over time, and between population subgroups (defined by, for example, age, sex, ethnicity or socioeconomic status). It is these comparisons that help us to suggest possible reasons for the variations and provide targets for improvement and a means of monitoring progress towards them.

Population-based survival cannot normally be used to assess the efficacy of specific anticancer therapies. That is the role of the randomized controlled clinical trial, in which the effect of therapy can be evaluated irrespective of other prognostic factors. Population-based cancer registries also provide very limited information on variations in survival with
respect to different prognostic factors (size and spread of the tumor, presence or absence of tumor markers, etc.) compared with data derived from specialized oncology services.

In the context of population based cancer registry data, the aim of survival analysis is to estimate the probability of survival expressed as time elapsed since diagnosis, for individuals within groups defined by, say, type of cancer diagnosed, sex, age and place of residence. Even though it is common practice to use the term survival rate to describe this quantity, it is important to realize that we seek to estimate an individual probability rather than 'rate'. This Chapter sets out some basic concepts in survival analysis, and describes how these have been used to estimate the survival of subjects from the developing country populations.

6.2 TYPES OF SURVIVAL

If we were able to obtain complete follow up information for each individual in a group under study, then the probability or survival during a period t could be estimated simply from the proportion of survivors at the end of the period among all subject alive at the beginning of t. It would be sufficient to know each individual’s survival status at the beginning of the period, \( t_i \) and at its end, \( t_{i+1} \). With cancer registry data, we are usually concerned with periods of elapsed time between the date of incidence and some fixed point of follow up time such as five years after the date of incidence (five-year survival). In practice, follow up of persons registered with cancer is not complete, either because subjects become ‘lost to follow up during the period t (say by moving out of the area of surveillance of the cancer registry), or because the end of the period of possible follow up by the registry occurs before the end of t. This is
illustrated in following figure, which shows follow up of three subjects A, B and C.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Calendar time</th>
</tr>
</thead>
<tbody>
<tr>
<td>y4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[-----Period of registration-----]</td>
</tr>
<tr>
<td></td>
<td>[---------------Period of follow-up-----------------]</td>
</tr>
<tr>
<td>A</td>
<td>i---------------d</td>
</tr>
<tr>
<td>B</td>
<td>i-----------------If</td>
</tr>
<tr>
<td>C</td>
<td>i-----------------w</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subject</th>
<th>Follow-up time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[-----------------Period of follow-up-----------------]</td>
</tr>
<tr>
<td>A</td>
<td>i------------------1</td>
</tr>
<tr>
<td>B</td>
<td>i-----------------0</td>
</tr>
<tr>
<td>C</td>
<td>i-----------------0</td>
</tr>
</tbody>
</table>

Above figure is divided into two parts, The first shows follow up of the three subjects in terms of calendar time, while the second shows the same information in terms of the duration of follow up. Subject A is diagnosed with cancer during the first year of the period of registration, with the date of incidence shown as i, and dies between y3 and y4, shown as d which is within the period of possible follow up by the registry. In the second part of the figure, this is shown in terms of the duration of follow up as three units of time t between incidence and death. Subject B is diagnosed at the beginning of y1 but is lost to follow up (If) between y2 and y3 after a duration of follow up 1.5 units of t. Finally, subject C is diagnosed between y1 and y2 and is still alive at the end of the follow up period of the study y4 subject C is thus said to be withdrawn alive after 2.5 units of
follow up time $t$. It will be seen that the characters $d$, $I_f$ and $w$ have been replaced with the values 1, 0 and 0, respectively in the second part of the figure. This reminds us that, when we come to enumerate the number of deaths during follow up only subject A's death is known to us. Subjects B and C have incomplete follow up and will be censored from the analysis at the point in follow up time at which they were either lost to follow up or withdrawn. We are not aware of the deaths of subjects B and C but we can use the information that they did not die during the period in which they were being followed up in estimating the probability of survival for the study group as a whole. This indeed, is the key to formal survival analysis.

In practical terms, to prepare data for survival analysis, we require the time elapsed between the date of incidence and the date of death or date of loss to follow up or date of withdrawal for each individual in the group under study whichever occurs first. The accuracy of these survival times calculated from cancer registry data depends on the method of follow-up used by the registry. Some registries employ passive follow up, which relies on notifications of deaths of cancer patients to the registry by national statistical organizations. Other registries use active follow up in which information on the survival status of patients is sought by the registry at fixed points in time after the date of incidence, usually on the anniversaries of this date. Active follow up in cancer registries can be achieved by using clinical follow up systems by contacting patients' physicians or by contacting the patients or their families directly by means of postal enquiries or even home visits. Most registries used a mixture of active and passive methods. Typically, registries undertook special follow up exercises specifically for this study, in order to augment incomplete passive notification systems. The mixture of active and
passive follow up methods means that the data for analysis were composed of exact survival times for some subjects and less precise data representing cases censored as a result of follow up Enquirer.

6.3 FACTORS ASSOCIATED WITH CANCER SURVIVAL

In order to describe completely the experience of cancer in a population, it is necessary to know not only its incident and mortality, but also the survival of cancer patients. There are three main sources of information about survival: the randomized controlled clinical trial, which represents the 'gold standard' for the evaluation of forms of treatment; the hospital-based study, which aims to provide information about the outcome of treatment in particular settings; and population based survival from cancer registries, which reflects a broader range of cancer control activities, including screening and the organization of treatment services. Each of these has its limitations; survival information from trials and published hospital series is often biased by patient selection, whereas population-based survival data may lack the details of stage and treatment which are of particular interest to the clinician. Following are the factors associated with cancer survival.

DATA QUALITY FACTORS

Inevitably, the quality of cancer registration data will vary according to the availability of source data, the experience of registry staff and other factors. This variation complicates the interpretation of survival data based on routine cancer registry data (Hanai & Fujimoto, 1985). The probability of being registered tends to be correlated with prognosis: for example, elderly patients not seen in hospital are less likely to be registered than younger patients, for whom curative treatment may have
been attempted. Estimates of survival may therefore be artificially raised for a particular registry area if ascertainment is not complete. Similarly, the accuracy of diagnostic information for cancer patients tends to be correlated with prognosis. For example, a registry relying exclusively on a particular pathology laboratory for diagnostic information might tend to classify cases from other sources in nonspecific categories for primary site. Such cases would be excluded from tumour-site-specific survival analyses, whereas data for another registry might include cases with clinical diagnoses. Again, the effect of this aspect of data quality would be to increase the survival estimate for a registry, which allocated a large proportion of cases to nonspecific diagnostic categories.

In cancer registry data, there are usually some subjects for whom the registration of cancer was based on information from the death certificate only (DCO). By convention, such cases are excluded from survival analyses since – by definition – their survival time is zero. This convention was adopted in the present study. If the proportion of DCO cases is relatively low, say less than 10%, then excluding them from the analysis does not greatly influence survival estimates. Under either active or passive follow-up systems, individuals can be lost due to migration, breaking off contacts with local authorities or other changes in living conditions. Normally, registries assume that a subject is alive until a notification of death is received, or active follow-up results in a confirmation of death. Many of the individuals who are lost to follow-up will, in fact, have died, so that a registry with a large proportion of individuals with whom they have lost contact will report artificially high survival. However, the direction of the bias is unpredictable, and will depend on local circumstances. For example, loss to follow-up may occu
when subjects with a relatively good prognosis are obliged to move away from their original cancer registry area to receive treatment.

HOST FACTOR
Age at diagnosis is an independent prognostic factor for many types of cancer. This operates in two ways: age may be correlated both with the risk of dying from a particular type of cancer and with the risk dying from some other cause.

Sex is less commonly associated with variations in survival and, for this reason; many registries combined data for males and females in the interests of increasing the precision of survival estimates. However, survival from some cancer, such as malignant melanoma, has been seen to be greater for women in some developed countries, which is probably due to a greater recognition of early symptoms and a willingness to seek medical attention.

Berg et al. (1977) propose a host vulnerability hypothesis in which the poor nutritional status, general health and immunological status (related to alcoholism) of some social and racial groups leads to lower survival from cancer. Clearly, socioeconomic conditions in developed and developing countries are grossly different to the extent that inequalities in access to medical care are likely to be of particular significance in the present study.

TUMOUR-RELATED FACTORS
The stage of disease at diagnosis is generally the most important factor determining the survival of cancer patients. This is because certain treatments may be available only for early stage tumors and any treatmen
is more likely to be successful if initiated before metastasis has occurred. Therefore variations in the stage distributions of tumors in populations being compared are of particular concern.

HEALTH CARE-RELATED FACTORS
Factors relating to the health care of cancer patients in developed and developing countries are of particular concern. There are a number of ways in which the availability of, and access to, screening services and diagnostic and treatment facilities can influence survival. Screening programs aim to detect early stage cancers or pre-malignant tumors so that the disease can be treated at an early stage, which is generally more effective. However, interpreting survival statistics in terms of the benefit to patients resulting from screening is problematic, since one consequence of early detection is to bring forward the date of diagnosis of a condition: whether or not this has the desired effect of reducing risk of death from the disease. This is called lead-time bias. (Morrison, 1985). This latter will necessarily result in a marked improvement in survival, and one that is independent which, theoretically at least, could be monitored in cancer registry data. Over diagnosis almost certainly accounts for the huge increases recently observed in the reported incidence of prostate carcinoma in the USA, and the corresponding changes in survival (Kosary et al., 1995).

Diagnostic facilities may also influence survival by ensuring that a specific and correct diagnosis can be made. Improvements in the sensitivity of diagnosis may have the effect of inducing stage migration in which for example, tumors of limited metastatic activity which at one time would have been inaccurately described as simply invasive may be reallocated to the metastatic category, thus in both metastatic and the non
metastatic groups (Feinstein et al., 1985). This phenomenon can operate on a geographical as well as temporal basis (Forrow et al., 1995).

The availability of treatment facilities for cancer patients affects the survival of those for whom curative treatment would have the potential to succeed. Survival data from registries cannot be used to make direct comparisons of populations in terms of the quality of care available although some studies have shown that the survival of some cancer patients is prolonged after treatment at specialized cancer centres (Stiller, 1994). However results of this kind are difficult to interpret because of selection criteria for specialized care, which may determine the apparently better results rather than the quality of care received.

Cancer patient survival is influenced by age in two ways the risk of dying as a result of the cancer with which a patient has been diagnosed tends to be greater for elderly persons, and elderly subjects tend to be at greater risk of death from other causes. In comparing two groups of subjects, one of which has a larger proportion of elderly patients than the other, the relatively greater risk of death from causes other than the cancer under study will be reflected in a lower value for expected survival in the older group.

Obtaining adequate information about the vital status of registered cancer patients is as challenging as case finding. In general active measures to obtain follow up information must be pursued if reliable cancer survival analysis is contemplated in developing country settings. Death registration in developing countries is often incomplete not all deaths are registered and the recorded cause of death may be inaccurate or missing thus any follow up effort that relies only on matching the incident cancer
database with death certificates mentioning cancer as the cause of death will be grossly inadequate.

6.4 TECHNIQUES FOR SURVIVAL ANALYSIS

Calculation of survival rates depends mainly on three fundamental notions, namely starting date, status and indicators at common closing date (CCD).

The starting date is the date of the beginning of the observation period (zero point) of a group of individuals with some common morbidity experience. This varies according to the purpose of the study and various reference dates are commonly used such as (i) date of first symptom (ii) date of diagnosis (iii) date of first visit to physician or clinic (iv) date of hospital admission (v) date of beginning of treatment and (vi) date of randomization in clinical trials. For studying the natural history of a particular cancer the starting date might be defined as the date of appearance of the first symptom. The date of initiation of therapy could be used as the starting time for evaluating therapy (AMJC 1977,1982) Peti et al. (1976, 1977).

The second notion is the status of the patient at the end of follow-up in terms of alive or dead. When the period of observation ends, there will usually remain a number of individuals for whom the mortality data is incomplete information for survival. All others are censored observations. There are three ways in which censoring of an individual can occur during follow-up (Chiang 1968).

i) By death due to cause other than the outcome of interest so that the chance of dying from the specific cause cannot be determined directly; the date of death corresponds to the end of follow-up
ii) By the individual being lost to follow-up, the date at which the individual is lost to follow-up corresponds to the end of the period of observation; the available information on this date provides the status indicator.

iii) By withdrawal from the follow-up due to closure of the study and these patients are still be alive at CCD; the calendar time, the date of closure of the study corresponds to the end of the period of observation.

In addition to the above mentioned types, in clinical trials censoring may occur due to side effects of treatment i.e. patient may discontinue the treatment or may still be in contact, but he or she refuses to continue the treatment. This type of censoring is termed as drop-out (Miller 1981).

In a survival study, the group of individuals may form a closed or an open group. A closed group consists of individuals in which there are only complete observations. An open group is one in which observation can be incomplete. In practice, it is rare to find a closed group except in the artificial situation of the construction of a life table. In most real situations, the group is open because there are subjects either lost to follow-up or withdraw from follow-up. When only one cause of mortality is taken into consideration, the group can be treated as an open group.

FOLLOW-UP TIME

The follow-up time is defined as the time between the date from the beginning of the observation period and the date at which observation
ends (Chiang 1968). The follow-up time is expressed in terms of months (AMJC 1982).

Methods for recording and updating follow-up have been extensively discussed by several researchers (Armitage 1973, Cornel 1984, Hani and Fujimoto 1985, Parkin and Hakulinen 1991, Esteve et al. 1994). Different follow-up methods are used to confirm the patients' status, depending on the social setup and the requirements of the study.

ACTIVE FOLLOW-UP

Many population-based registries collect follow-up in formation through the collaborating registries or hospital; record departments which in turn conduct annual follow-up surveys of registered cases through the patient's own doctor (Hani and Fujimoto 1985, Parkin and Hakulinen 1991, Esteve et al. 1994). American college of surgeons (1981) recommends that through this kind of follow-up, the quality as well as duration of survival may be assessed.

Most population-based registries elsewhere do not have a follow-up system for individuals. Different active follow-up methods are used to confirm the patients' status indirectly by utilizing surveys or registers, setup for other purposes. Many registries therefore use sources such as population registers, registers of the national health insurance or social security registers, voters lists, etc. Telephone Enquirer contacts through motor vehicle department's medical insurance, general practitioners and personal enquiry are some of the other methods to assess the patient's status. This type of active follow-up provides useful information on number of patients whose vital status is unknown (Hani and Fujimoto 1985, Parkin and Hakulinen 1991, Esteve et al. 19994).
In hospital based registries, the patients follow-up is mainly maintained through referral system. The disease status of the patients is collected from where the patient was referred back upon discharge. The primary contact is generally maintained through the physician responsible for patient care. It may not be always possible to get the status of the patient from the physician responsible for the care as the patient may lose contact with the physician or the physician may move out from the area. In such situations, an attempt can be made to maintain contact directly with the patient through current address or telephonic enquiry. Such enquiries can be made from the spouse, relative, or friend. Patient disease and functional status, institution of any additional therapy, and the last date seen by the physician can be collected. Such information helps to monitor the disease status of the patient over time and to trace the patient at the time of next follow-up (Young 1991).

PASSIVE FOLLOW-UP

The passive follow-up method can be adopted by collecting information on registered patients at the time of death through death certificates from the vital statistics department of the region. This method of data collection has the potential for tracing unknown losses which would affect estimates of survival. If individuals in the populations do not have an unique identification number and the death registers are not computerized, to search and locate a given patient becomes difficult. Any registered patient whose death has not been notified to the registries by the department of vital statistics or whom the linkage fails due to poor identification is considered to be alive. The results of passive follow-up may therefore be biased estimates of the true survival if the notification through the vital

6.5 METHOD FOR ESTIMATION OF SURVIVAL RATES

DIRECT METHOD

The simplest way of summarizing survival is to calculate the percentage of patients alive at the end of a specified interval when there are no censored observations. The survival probability at a given time estimates by the ratio between the number of survivors at the end of a specified interval and the number in the group at the beginning of the study (Berkson and Gauge 1950). This approach is called direct method by some authors (Mouth 1976). Obviously, in this method, survival cannot be calculated for individuals for whom the period of follow-up is less than the specified time of survival estimation being considered and survivals analysis is done only for the those who have completed follow-up up to the specified time, i.e., only those who have completed the same time interval being considered during follow-up will be included for rate calculation. The group being studied is therefore subdivided into subgroups in which the individuals have the same potential follow-up time and the survival rate is assumed to be an estimate of the survival rate for the corresponding length of time for each subgroup. Hence as each subgroup refers to different groups of patients, the survival need not necessarily decrease with time (Esteve et al. 1994).

The survival rates described above account for all deaths regardless of cause. This is a true reflection of total mortality in the patient group. The main interest is however, usually in describing mortality attributable to the disease being studied. A net interest is however, usually can be
defined as that which might occur if the risks of death other than the
disease under study were removed (Chiang 1961). The determination of
net survivor probabilities implicitly assumes that the risk of death from
the disease being studied and the risk of death from other than causes are
independent. There are two classical methods available to estimate the
probability of surviving from a given disease: the method of cause-
specific survival and that of relative survival (Estatve et al. 1994).

CAUSE – SPECIFIC SURVIVAL

When reliable information on cause of death for each individual is
available a correction can be made for deaths due to causes other than
disease being studied (cause specific survival rates). In the calculation of
the cause-specific survival rates, the cause of death is assessed and only
those deaths attributable to the disease being studied are counted. Other
deaths are considered as simply causing the termination of follow-up at
the time of death (in the same way as cases lost to follow up) (Chiang
1968). Calculation of cause specific survival can be carried out by either
the actuarial method or by Kaplan-Meier method. In either method,
Survival rates are obtained disregarding deaths from other causes
assuming that the process leading to death from the disease being studied
is independent of the process leading to death from other causes.

The method of cause-specific survival can be applied only when the cause
of death is routinely recorded, a situation which does not generally hold in
population registries. The method of cause specific comes up against the
difficulties of determining cause of death such as poor reliability of
information supplied by the certifying doctor and the arbitrary choice of
the primary cause of death when there are multiple or associated
pathologies.
AGE-STANDARDIZED SURVIVAL

It is important to realize that, when comparing survival in different groups, the method of relative survival take account of variations in the age structure of the groups only to the extent age is correlated with risk of death from causes other than the cancer under study. For many types of cancer, the risk of dying as a result of the cancer itself is clearly associated with the subject’s age at diagnosis. In the present study we were interested in comparing survival in developing and developed country populations, in which the age structures of cancer patient groups are grossly different. For this reason, we used direct standardization of age-specific relative survival estimates to derive an overall summary statistic, age-standardized relative survival (ASRS)

\[
\text{ASRS}_x = \frac{\sum r_{ix} w_x}{\sum w_x}
\]

Where \(r_{ix}\) are age-specific relative estimates at the end of the follow-up period \(t_i\) and \(w_x\) are age specific proportions from the World Standard Cancer Patient Population for the appropriate site of cancer.

RELATIVE SURVIVAL

Information on cause of death is sometimes unavailable or not reliable. In this case, it is not possible to compute a cause-specific survival rate. By mean of relative survival, it is possible to assess the risk of dying from cancer other than the disease being studied. The method of relative survival (Ederere et al 1961) does not require knowledge of the cause of death and thus avoids the difficulties associated with its determination.

Relative survival rate refers to the ration of the observed survival rate to the expected rate for a group of people in the general population.
Expected survival corresponds to the mortality of the general population, taking into account the initial distribution corresponds to the mortality of the general population, taking into account the initial distribution in the group for prognostic factors which one wishes to control for. If only age (the effects of which should always be factors which one wishes to control for) is considered, the expected survival is provided by the proportion of survivors that would be predicted at a given time in group having the same initial age structure as the group being studied, but subjected only to the force of mortality of the general population. When the prognostic factors other than age and sex are identified, it is preferable to calculate expected survival by taking them into account.

The method for estimating relative survival rate is described by Elderer et al. (1961). It is an important measure since the determination of whether or not the death which has occurred was due to the specific cause being studied is difficult to establish and in most cases it may not be possible to establish its unequivocally. The method of relative survival is based on the assumption that the general mortality, except for the specific cause being studied. This cause is considered to be negligible (usually less than 5%) in comparison to all other causes of death. Only in this condition relative survival can provide an acceptable approximation to net survival. If this assumption does not hold, net survival will be overestimated as a result of the non-negligible mortality due to other causes.

Cutler et al. (1957) noted that mortality from a specific cause constitute a negligible fraction of total mortality and hence survival rates computed from a general population life table provide satisfactory estimates of expected rates when analyzing the survival of cancer patients with turnover at specific sites. Hekulinen (1982) demonstrated that when
patterns of patients withdrawal differ from a number of subgroups of patients with equal relative survival rates, the method of derivation of the relative survival rate is biased. He proposed a method based on the concept of an “expected life table” for removal of the bias. Examples based on material from the Finnish Cancer Registry suggested that the practical performance of the proposed matter is better than that of the other alternatives, even when the relative survival rates in the subgroups are not equal.

6.6 SOURCES OF DATA FOR ESTIMATING CANCER SURVIVAL RATES

In the usual situation of an open group, calculation of survival rates requires specific variables such as date on which follow-up started, ended, as well as the status of each subject on the common closing date of the study.

The date on which follow-up ended for each individual is either the date of death, the last date at which the subject was known to be alive for those who were lost to follow up, or the date on which follow-up ended for all subjects as a result of the study being concluded. This information can be obtained either prospectively or retrospectively. Retrospective data collection refers to data, which were recorded at some previous time and subsequently selected to be used for analysis. Prospective data collection occurs in a well–designed study. In such situation, specified information is identified to be of interest, and this information is collected as it becomes available.

In general, there are a variety of sources to collect data due on survival. These sources are rarely complete and can give rise to selection biases of different kinds, especially when they involve routine forms of data
reporting. Often cancer registry are main source of data for estimating cancer survival rates (Owleney 1985) If the registry are the main source of data for follow up information of patients routinely, retrospective analysis on survival can be done.

Population based survival results are generated from a population based cancer registry (PBCR). A PBCR is concerned with all newly diagnosed cases of cancer occurring in a population of well defined composition and size (Jensen and Whelan 1991). A PCBR records data on all cases of cancer occurring in a defined population and at times collects follow up information on these patients. The survival rates for different cancers calculated from such data will therefore represent the average prognosis in the population and provide an objective index of effectiveness of cancer care in the region concerned (WHO 1979). The finding based on population based cancer can be generalized as this is based on a wide range of natural histories and therapeutic intervention of a given cancer in population.

Hospital based Cancer Registry (HBCR) or hospital records are generally concerned with that outcome of patents treated in particular hospital or those registered in a hospital registry or a selective group seen within a hospital such as a particular service or those involved in a clinical trial. Thus address the survival outcome of a selected group of patients. Hospital based survival rates are not representative of all incident cases in the population from which they are derived but are useful to evaluate the effectiveness of different therapies. However, descriptive analysis of survival is not sufficient for evaluating the effectiveness of different forms of treatment which can only be determined by a randomized clinical trial(Parkin and Hakulinen 1991).
The characterization of survival as a function of many clinical features can be addressed in hospital based survival studies, as these are routinely collected in hospitals. Disease free survival rates are one of the important measures to assess the quality of the patients. The status of the disease at follow up will help to measure these rates and can be assessed only through hospital based studies.

6.7 LOST TO FOLLOW UP (LFU)

Complete follow up information represents the primary goal in the conduct of an end result study. Lengthy periods of observation may be required until an event occurs, and the maintenance of surveillance on patients within the study group can be extremely costly and time-consuming. The American Joint Committee on Cancer (AJC 1982) provided several guidelines for reporting end result studies. They stressed that classification of patients status must be done and that to obtain accurate results there should be no uncertainty and ambiguity.

Mortality statistics in many countries are difficult to obtain due to incompleteness of death registration. The precise cause of death is difficult to determine. The reliability of non medical personnel to record the cause of death in some developing countries may also result in inaccuracy; the data so collected in longitudinal studies may be complex and may not lend themselves to analyze by standard methods (Colton 1974). Simple, intuitive approaches may lead to serious misinterpretations. Through scientific studies deserve proper analysis; hence it is essential to maintain organizational procedures which will enable the tracing of patients and assessing the survival of a group of patients under study that can be generalized to a larger population (Mould 1976).
A typical problem encountered in survival studies is the loss to follow up (LFU) of the subjects from the study. If the loss occurs formally, such that the characteristics of lost subject are on average similar to those in the other then no bias would be introduced. In random losses a statistical model for the data on a likelihood function of the observed data can be fitted, and the lost cases do not themselves require to be modeled in the analysis. However, the subject can be lost from the study for various known and unknown reasons. Some may die due to a cause other than the disease or some may be lost due to some other events unrelated to the outcome of interest. Hence only partial information, limited to a small interval is available on lost patients.

As the proportion of people in the study group without complete follow up in large, the potential for bias increases. Such a situation would certainly raise serious doubts about the validity of the survival rates estimated. However, the more difficult issue for interpretation is that, even if the rate of loss is not so extreme, the probability of loss may be related to the outcome of interest (non random loss). If the follow up loss is associated with the outcome of interest, survival estimates derived from the study may be biased. Hence direct application of various methods for estimation of survival of patients can not be fully accepted. Various methods discussed earlier such as the actuarial method (Berkson and Gage 1950), Cutler and Ederer 1958, Chaing 1968,) the product-limit method (Kaplan and Meier 1985), the Cox proportional hazards model (Cox 1972) which are available are based on the assumption that the loss to follow-up occurs completely at random.

COMMON CAUSES OF FOLLOW-UP LOSS IN DEVELOPING COUNTRIES:
Difficulties in establishing adequate follow-up system in the hospitals or in population registries are major factors that effect LFU rates. Poor communication facilities and frequent social upheavals makes follow-up difficulty and at best fragmented. Roads are inaccessible for most of the year. Telephones are only a selected few of the society. Postal systems are unreliable and tracing of patients are very difficult due to lack of proper permanent address. Moreover, most patients do not appreciate the importance and need for follow-ups. Some patients may be willing to report back as requested but due to monetary constraints may not report on the appointed date.

ASSESSMENT OF BIAS DUE TO LOST TO FOLLOW-UP:

Drolette (1975) while investigating the effect of subjects being lost to follow-up, showed that the inclusion of such subjects introduces a bias in conditional probability of death as earlier suggested by Berkson and Gage (1950) and Culter and Ederer (1958). Austin (1983) concluded from routine follow-up experience of the California Tumour Registry that the traditionally computed survivals rates are too pessimistic and underestimate the true rates when there are a higher proportion of lost to follow-up patients in the study. This is due to the fact that the death registration system is complete in developed countries. The dead patients could be traced more easily and included in the study.

In developed countries due to accurate death registration systems, LFU patients who die are traced more easily than those who are alive, thus a bias is created which has the effect of computing survivals rates that are lower than the true rate (Enstrom and Austin 1977). Tallis et al (1988) presented analysis for survivals data
obtained from a central cancer registry with a passive follow-up method. It was concluded that the method of data collection has the potential to produce unknown random losses which would affect estimates of survivals. If the death registration is accurate and the follow-up system is good, the reliability of survivals would increase especially for those known to have poor prognosis. It has been suggested that data collection, abstracting and coding procedures should remain uniform over time. However, in a developing country where the death registration is incomplete and follow-up is inadequate, survival rates exaggerated estimate.

Ganesh (1995) used indirect approach to describe the extent of bias introduced by loss to follow-up by assuming the most extreme situations with respect to LFU in survival estimation. One estimate was based on the assumption that all who were lost to follow-up developed the outcome of interest. While the other assumed that none developed it. The observed range was wide and provided little useful information due to high proportion of LFU.

Factors influencing lost of follow-up may be associated with the study outcome. Since it is extremely difficult to know the factors to which losses are related, ideally one should aim to keep follow-up loss to an absolute minimum. Some insight may be obtained for distinguishing the type of LFU (random or non-random) by comparing individuals who are regular in follow-up to those who are not. Mortality information using sources such as obituary listings, state vital statistics bureaus, contacts with patients, relative or neighbors by telephone and searches using the national Death Index can be used to determine whether there are systematic difference in the characteristics between those whose outcome is known and
those who have been lost to follow-up. If the two groups are similar in most characteristics, it may be assumed that there is little difference between those who are on regular follow-up compared to those who are not, and conclusion ed based on analysis of the followed-up compared to those who are not. It is assumed that the LFU patients are random losses and the only effect of LFU is that of lowering the sample size used in the study.

LOSS ADJUSTED SURVIVALS RATES (LAR)

Statistical complexities arise due to outcome related loss in follow-up studies. A great need exists to deal with non-random LFU's which are very common in follow-up studies carried out in the developing countries. Tallis et al. (1993) suggested a procedure for correcting unidentified random losses that may affect registries which use passive follow-up method for survival analysis. Considering heavy LFU ascertained in survivals studies, Ganesh (1995) proposed two methods for computing loss-adjusted survivals rates (LAR) by taking into consideration of the difference in patient loss to follow-up with respect to prognostic factors. For the illustrating of the methodology breast cancer patients reported at Tata memorial Hospital, Bombay, India were used. The method develop for computing LAR was within the general framework of the actuarial method. The main assumption of this method was that breast cancer patients lost to follow-up with respect to a specific age, stage, residence and treatment group have the same probability of death as those remaining under observation and belonging to the same group.
6.8 AN OVERVIEW OF CANCER SURVIVAL IN DEVELOPING COUNTRIES

The variations were less marked for cancer sites such as hypopharynx, esophagus, stomach, liver, gallbladder, lung, and bone tumors within the range of age standardized relative survival (ASRS) estimates. Shangri, in China reported the highest figures for all cancer sites except the hypopharynx, esophagus, liver, bone, cervix, vagina, prostate, brain, thyroid, and leukemia. Khon Kaen in Thailand reported the highest survival for cancers of the esophagus, bone melanoma, brain and thyroid, while Chiang Mai in Thailand reported the highest figures for cancers of the uterine cervix, vagina, skin, hypopharynx, and prostate. Cuba reported the highest survival for leukemia, and Rizal (Philippines) the highest survival for liver cancer.

Generally a higher survival among females was observed for cancers of the tongue, salivary gland, oral cavity, nasopharynx, and kidney, and to a lesser extent for cancers of the oropharynx, esophagus, colon rectum, lung, melanoma, brain, thyroid, and lymphoma. Lower survival among females was observed for urinary bladder cancers in all registries and for stomach, pancreas, and larynx in some. Sex differences in cancer survival have been a matter of intense discussion (Wiebelt & Hakulinen 1991). It seems likely that the observed female advantage in survival from most cancers in developed countries is the result of more favorable distributions of prognostic factors, particularly stage.

The five year relative survival rates were generally higher for young adults than for older age groups in respect of most cancer sites in most registries although this was less evident for colorectal and breast cancer.
The declining relative survival with increasing age was most marked for cervical cancer in all registries.

For all the subsites within the oral cavity and pharynx, age standardized relative survival in the developing country regions (except Shanghai) was lower than in Europe, although comparatively high survival was reported from Shanghai for all subsites except hypopharynx.

In Cuba, one third of patients presented with localized disease, compared with one tenth of patients in the other two regions. The high proportion of localized cancers and the comparatively high survival from oral cavity cancer in Cuba may be due to the ongoing oral cancer-screening programme in that country (Fernandez Garrote et al., 1995).

Age standardized relative survival in Qidong, Madras and Chiang Mai registries was lower than in the USA for 1998-91 and comparable with that reported from Europe in 1978-85 and the USA in 1967-73. Survival in Shanghai is similar to that in the USA while the reasons for the apparently high survival in Khon Kaen are not clear. They may be related to misclassification at diagnosis, in view of the high proportion of clinically diagnosed cases.

There has been some improvement in short term survival (one year and two year survival) in the USA which has been attributed to improvements in diagnosis, staging, availability of parental nutrition and increasing use of combinations of chemotherapy and radiation in the treatment of unrespectable esophageal cancer (Miller et al. 1993). Almost half the histologically verified esophageal cancers in the US SEER white patients are adenocarcinomas compared with one quarter to one third in European
registries, and less than one fifth in the developing country registries (Parkin et al., 1997). Adenocarcinomas mainly occur in the lower third of the esophagus. These cancers are more suitable for surgical therapy. Which offers the best chance for long-term survival in esophageal cancer. Hence lower third tumors have a better prognosis than other cancers located in the middle or upper third of the esophagus.

STOMACH
The five year survival rates reported from Qidong and Khon Kaen registry are comparable with those in the USA and Europe: those from Madras, Rizal and Chiang Mai are lower. The survival reported from Shanghais is higher than the US and European results: this may be related to the early detection efforts in Shanghai. Short term and long term survival rates in USA have increased only very slightly during the period 1973-89 (Miller et al. 1993). In spite of continuing worldwide decline in incidence, it is still the second most common cancer globally and the most common cancer in many developing countries (Parkin et al. 1993).

LUNG
Survival from lung cancer was low in all registries. Though five-year survival increases if the disease is diagnosed in early state, screening has not been effective in reducing mortality. (Perkin and Pisani, 1996). Mass screening with chest X-ray and sputum cytology is not recommended to control lung cancer.

FEMALE BREAST
Five-year age standardized relative survival in all registries was considerably lower than the survival rates for USA for period 1974-86 and 1986 – 91. With the exception of Shanghai, the developing country
rates were also lower than in the USA in the period 1967-73. Survival in Shanghai (in 1981-91) was similar to Europe, while other developing country regions had lower survival.

The gain in long term survival from Breast cancer in developed countries over the last three decades is probably due both to early diagnosis and to advances in treatment (Ewertz 1993; Miller et al.1993; Nab et al 1994a, 1994b; Olivotto et al. 1994; Garne et al. 1997) Wide spread use of mammography in screening for breast cancer has resulted in an increasing incidence of localized breast cancer. Clinical trials over the last three decades have also contributed considerably to the optimization and advancement of treatment in breast cancer (Bonndonna et al. 1976; Early Breast Cancer Trialist’s Collaborative Group, 1992,1995)

The rather poorer survival from localized breast cancer in developing countries, compared with the similar tumours in the USA, could be reflection both of stage misclassification (due to limited investigative facilities) and the limited availability of adequate therapy. The poor survival in women with regional disease in developing countries could be due to inadequate treatment, particularly the difficulty of providing adjuvant treatment. However, stage misclassification due to limited investigative facilities could be another important factor.

The comparative high survival from breast cancer in Shanghai (72.7% five year survival) deserved further discussion. This registry covers predominantly urban areas with several outlets for cancer diagnosis and treatment, supported by early detection activities for cancer sites such as stomach breast and cervix.
UTERINE CERVIX

Age-standardized relative reported from developing country regions, with the exception of Shanghai and Chiang Mai, was lower than Europe in 1978-85 and in the USA in 1967-73 and later. The proportion of localized cervical cancer in the developing country regions (with the exception of Cuba) was considerably lower than USA for the period 1986-91) indicating that the poor survival in developing country regions was, in part, due to advance disease at presentation.

For localized cervical cancer, survival was lower in all developing country registries (except Chiang Mai) than in the USA. However five-year survival was above 80% in Bombay, above 70% in Cuba. The outcome from regional disease in Madras, Chiang Mai and Khon Kaen was similar to that in USA. These results indicate that good survival can be achieved in developing-country regions if early detection and adequate treatment can be ensured.

Cervical cancer is the most common cancer among women in developing countries (Parkin et al. 1993) Though incidence rates are either stable or slowly declining in many countries (Coleman et al. 1993) It is still a major cause of death in young women in developing countries. (Pisani et al., 1993).

The wide variation in survival observed in these registries cannot be entirely due to differences in the mechanisms and efficiency of data collection. Factors such as clinical extent of disease at presentation, efficiency and accessibility of the cancer-related health services available, treatment received, follow-up care and patient-related factors such as socioeconomic status, attitudes and compliance with treatment and
aftercare are likely to be responsible for at least some of the observed differences. These factors may be particularly important for those cancer sites for which the outcome is influenced by treatment related to the clinical stage of the cancer at diagnosis.

There were greater differences in survival for cancer sites such as head and neck, large bowel, breast, melanoma, cervix, ovary and urinary bladder, which have a moderate to good prognosis, if detected early and treated appropriately. The differences in survival are likely to be reduced by the linking early detection with adequate treatment facilities. Some of these cancers are, of course, also amenable to primary prevention. Organized screening with cervical cytology could reduce mortality from cervical cancer.

The differences in survival between the developed and developing-country registries were even more striking for cancer sites such as testis, leukemia and lymphoma, in which improved multimodality treatment has increased long-term survival. With appropriate logistics, the available resources can be used to deliver such treatment in developing countries, which is likely to reduce the differences observed in survival. The adoption of WHO recommendations on essential drugs for cancer chemotherapy should result in improved outcome from these cancers in low-resource settings (WHO, 1994).