

CHAPTER 1

Introduction to Biostatistics

1.1 INTRODUCTION

We welcome the reader who wishes to learn biostatistics. In this chapter we introduce you to the subject. We define statistics and biostatistics. Then examples are given where biostatistical techniques are useful. These examples show that biostatistics is an important tool in advancing our biological knowledge; biostatistics helps evaluate many life-and-death issues in medicine.

We urge you to read the examples carefully. Ask yourself, “what can be inferred from the information presented?” How would you design a study or experiment to investigate the problem at hand? What would you do with the data after they are collected? We want you to realize that biostatistics is a tool that can be used to benefit you and society.

The chapter closes with a description of what you may accomplish through use of this book. To paraphrase Pythagoras, there is no royal road to biostatistics. You need to be involved. You need to work hard. You need to think. You need to analyze actual data. The end result will be a tool that has immediate practical uses. As you thoughtfully consider the material presented here, you will develop thought patterns that are useful in evaluating information in all areas of your life.

1.2 WHAT IS THE FIELD OF STATISTICS?

Much of the joy and grief in life arises in situations that involve considerable uncertainty. Here are a few such situations:

1. Parents of a child with a genetic defect consider whether or not they should have another child. They will base their decision on the chance that the next child will have the same defect.
2. To choose the best therapy, a physician must compare the *prognosis*, or future course, of a patient under several therapies. A therapy may be a success, a failure, or somewhere in between; the evaluation of the chance of each occurrence necessarily enters into the decision.
3. In an experiment to investigate whether a food additive is *carcinogenic* (i.e., causes or at least enhances the possibility of having cancer), the U.S. Food and Drug Administration has animals treated with and without the additive. Often, cancer will develop in both the treated and untreated groups of animals. In both groups there will be animals that do

not develop cancer. There is a need for some method of determining whether the group treated with the additive has “too much” cancer.

4. It is well known that “smoking causes cancer.” Smoking does not cause cancer in the same manner that striking a billiard ball with another causes the second billiard ball to move. Many people smoke heavily for long periods of time and do not develop cancer. The formation of cancer subsequent to smoking is not an invariable consequence but occurs only a fraction of the time. Data collected to examine the association between smoking and cancer must be analyzed with recognition of an uncertain and variable outcome.
5. In designing and planning medical care facilities, planners take into account differing needs for medical care. Needs change because there are new modes of therapy, as well as demographic shifts, that may increase or decrease the need for facilities. All of the uncertainty associated with the future health of a population and its future geographic and demographic patterns should be taken into account.

Inherent in all of these examples is the idea of uncertainty. Similar situations do not always result in the same outcome. Statistics deals with this variability. This somewhat vague formulation will become clearer in this book. Many definitions of statistics explicitly bring in the idea of variability. Some definitions of statistics are given in the Notes at the end of the chapter.

1.3 WHY BIOSTATISTICS?

Biostatistics is the study of statistics as applied to biological areas. Biological laboratory experiments, medical research (including clinical research), and health services research all use statistical methods. Many other biological disciplines rely on statistical methodology.

Why should one study biostatistics rather than statistics, since the methods have wide applicability? There are three reasons for focusing on biostatistics:

1. Some statistical methods are used more heavily in biostatistics than in other fields. For example, a general statistical textbook would not discuss the life-table method of analyzing survival data—of importance in many biostatistical applications. The topics in this book are tailored to the applications in mind.
2. Examples are drawn from the biological, medical, and health care areas; this helps you maintain motivation. It also helps you understand how to apply statistical methods.
3. A third reason for a biostatistical text is to teach the material to an audience of health professionals. In this case, the interaction between students and teacher, but especially among the students themselves, is of great value in learning and applying the subject matter.

1.4 GOALS OF THIS BOOK

Suppose that we wanted to learn something about drugs; we can think of four different levels of knowledge. At the first level, a person may merely know that drugs act chemically when introduced into the body and produce many different effects. A second, higher level of knowledge is to know that a specific drug is given in certain situations, but we have no idea why the particular drug works. We do not know whether a drug might be useful in a situation that we have not yet seen. At the next, third level, we have a good idea why things work and also know how to administer drugs. At this level we do not have complete knowledge of all the biochemical principles involved, but we do have considerable knowledge about the activity and workings of the drug.

Finally, at the fourth and highest level, we have detailed knowledge of all of the interactions of the drug; we know the current research. This level is appropriate for researchers: those seeking

to develop new drugs and to understand further the mechanisms of existing drugs. Think of the field of biostatistics in analogy to the drug field discussed above. It is our goal that those who complete the material in this book should be on the third level. This book is written to enable you to do more than apply statistical techniques mindlessly.

The greatest danger is in statistical analysis untouched by the human mind. We have the following objectives:

1. You should understand specified statistical concepts and procedures.
2. You should be able to identify procedures appropriate (and inappropriate) to a given situation. You should also have the knowledge to recognize when you do not know of an appropriate technique.
3. You should be able to carry out appropriate specified statistical procedures.

These are high goals for you, the reader of the book. But experience has shown that professionals in a wide variety of biological and medical areas can and do attain this level of expertise. The material presented in the book is often difficult and challenging; time and effort will, however, result in the acquisition of a valuable and indispensable tool that is useful in our daily lives as well as in scientific work.

1.5 STATISTICAL PROBLEMS IN BIOMEDICAL RESEARCH

We conclude this chapter with several examples of situations in which biostatistical design and analysis have been or could have been of use. The examples are placed here to introduce you to the subject, to provide motivation for you if you have not thought about such matters before, and to encourage thought about the need for methods of approaching variability and uncertainty in data.

The examples below deal with clinical medicine, an area that has general interest. Other examples can be found in Tanur et al. [1989].

1.5.1 Example 1: Treatment of King Charles II

This first example deals with the treatment of King Charles II during his terminal illness. The following quote is taken from Haggard [1929]:

Some idea of the nature and number of the drug substances used in the medicine of the past may be obtained from the records of the treatment given King Charles II at the time of his death. These records are extant in the writings of a Dr. Scarburgh, one of the twelve or fourteen physicians called in to treat the king. At eight o'clock on Monday morning of February 2, 1685, King Charles was being shaved in his bedroom. With a sudden cry he fell backward and had a violent convulsion. He became unconscious, rallied once or twice, and after a few days died. Seventeenth-century autopsy records are far from complete, but one could hazard a guess that the king suffered with an embolism—that is, a floating blood clot which has plugged up an artery and deprived some portion of his brain of blood—or else his kidneys were diseased. As the first step in treatment the king was bled to the extent of a pint from a vein in his right arm. Next his shoulder was cut into and the incised area “cupped” to suck out an additional eight ounces of blood. After this homicidal onslaught the drugging began. An emetic and purgative were administered, and soon after a second purgative. This was followed by an enema containing antimony, sacred bitters, rock salt, mallow leaves, violets, beet root, camomile flowers, fennel seeds, linseed, cinnamon, cardamom seed, saphron, cochineal, and aloes. The enema was repeated in two hours and a purgative given. The king's head was shaved and a blister raised on his scalp. A sneezing powder of hellebore root was administered, and also a powder of cowslip flowers “to strengthen his brain.” The cathartics were repeated at frequent intervals and interspersed with a soothing drink composed of barley water, licorice and sweet almond. Likewise

white wine, absinthe and anise were given, as also were extracts of thistle leaves, mint, rue, and angelica. For external treatment a plaster of Burgundy pitch and pigeon dung was applied to the king's feet. The bleeding and purging continued, and to the medicaments were added melon seeds, manna, slippery elm, black cherry water, an extract of flowers of lime, lily-of-the-valley, peony, lavender, and dissolved pearls. Later came gentian root, nutmeg, quinine, and cloves. The king's condition did not improve, indeed it grew worse, and in the emergency forty drops of extract of human skull were administered to allay convulsions. A rallying dose of Raleigh's antidote was forced down the king's throat; this antidote contained an enormous number of herbs and animal extracts. Finally bezoar stone was given. Then says Scarburgh: "Alas! after an ill-fated night his serene majesty's strength seemed exhausted to such a degree that the whole assembly of physicians lost all hope and became despondent: still so as not to appear to fail in doing their duty in any detail, they brought into play the most active cordial." As a sort of grand summary to this pharmaceutical debauch a mixture of Raleigh's antidote, pearl julep, and ammonia was forced down the throat of the dying king.

From this time and distance there are comical aspects about this observational study describing the "treatment" given to King Charles. It should be remembered that his physicians were doing their best according to the state of their knowledge. Our knowledge has advanced considerably, but it would be intellectual pride to assume that all modes of medical treatment in use today are necessarily beneficial. This example illustrates that there is a need for sound scientific development and verification in the biomedical sciences.

1.5.2 Example 2: Relationship between the Use of Oral Contraceptives and Thromboembolic Disease

In 1967 in Great Britain, there was concern about higher rates of thromboembolic disease (disease from blood clots) among women using oral contraceptives than among women not using oral contraceptives. To investigate the possibility of a relationship, Vessey and Doll [1969] studied existing cases with thromboembolic disease. Such a study is called a *retrospective study* because retrospectively, or after the fact, the cases were identified and data accumulated for analysis. The study began by identifying women aged 16 to 40 years who had been discharged from one of 19 hospitals with a diagnosis of deep vein thrombosis, pulmonary embolism, cerebral thrombosis, or coronary thrombosis.

The idea of the study was to interview the cases to see if more of them were using oral contraceptives than one would "expect." The investigators needed to know how much oral contraceptive use to expect assuming that such use does not predispose people to thromboembolic disease. This is done by identifying a group of women "comparable" to the cases. The amount of oral contraceptive use in this *control*, or *comparison*, *group* is used as a standard of comparison for the cases. In this study, two control women were selected for each case: The control women had suffered an acute surgical or medical condition, or had been admitted for elective surgery. The controls had the same age, date of hospital admission, and parity (number of live births) as the cases. The controls were selected to have the absence of any predisposing cause of thromboembolic disease.

If there is no relationship between oral contraception and thromboembolic disease, the cases with thromboembolic disease would be no more likely than the controls to use oral contraceptives. In this study, 42 of 84 cases, or 50%, used oral contraceptives. Twenty-three of the 168 controls, or 14%, of the controls used oral contraceptives. After deciding that such a difference is unlikely to occur by chance, the authors concluded that there is a relationship between oral contraceptive use and thromboembolic disease.

This study is an example of a case-control study. The aim of such a study is to examine potential risk factors (i.e., factors that may dispose a person to have the disease) for a disease. The study begins with the identification of cases with the disease specified. A control group is then selected. The control group is a group of subjects comparable to the cases except for the presence of the disease and the possible presence of the risk factor(s). The case and control

groups are then examined to see if a risk factor occurs more often than would be expected by chance in the cases than in the controls.

1.5.3 Example 3: Use of Laboratory Tests and the Relation to Quality of Care

An important feature of medical care are laboratory tests. These tests affect both the quality and the cost of care. The frequency with which such tests are ordered varies with the physician. It is not clear how the frequency of such tests influences the quality of medical care. Laboratory tests are sometimes ordered as part of “defensive” medical practice. Some of the variation is due to training. Studies investigating the relationship between use of tests and quality of care need to be designed carefully to measure the quantities of interest reliably, without bias. Given the expense of laboratory tests and limited time and resources, there clearly is a need for evaluation of the relationship between the use of laboratory tests and the quality of care.

The study discussed here consisted of 21 physicians serving medical internships as reported by Schroeder et al. [1974]. The interns were ranked independently on overall clinical capability (i.e., quality of care) by five faculty internists who had interacted with them during their medical training. Only patients admitted with uncomplicated acute myocardial infarction or uncomplicated chest pain were considered for the study. “Medical records of all patients hospitalized on the coronary care unit between July 1, 1971 and June 20, 1972, were analyzed and all patients meeting the eligibility criteria were included in the study. . . .” The frequency of laboratory utilization ordered during the first three days of hospitalization was translated into cost. Since daily EKGs and enzyme determinations (SGOT, LDH, and CPK) were ordered on all patients, the costs of these tests were excluded. Mean costs of laboratory use were calculated for each intern’s subset of patients, and the interns were ranked in order of increasing costs on a per-patient basis.

Ranking by the five faculty internists and by cost are given in Table 1.1. There is considerable variation in the evaluations of the five internists; for example, intern K is ranked seventeenth in clinical competence by internists I and III, but first by internist II. This table still does not clearly answer the question of whether there is a relationship between clinical competence and the frequency of use of laboratory tests and their cost. Figure 1.1 shows the relationship between cost and one measure of clinical competence; on the basis of this graph and some statistical calculations, the authors conclude that “at least in the setting measured, no overall correlation existed between cost of medical care and competence of medical care.”

This study contains good examples of the types of (basically statistical) problems facing a researcher in the health administration area. First, what is the population of interest? In other words, what population do the 21 interns represent? Second, there are difficult measurement problems: Is level of clinical competence, as evaluated by an internist, equivalent to the level of quality of care? How reliable are the internists? The variation in their assessments has already been noted. Is cost of laboratory use synonymous with cost of medical care as the authors seem to imply in their conclusion?

1.5.4 Example 4: Internal Mammary Artery Ligation

One of the greatest health problems in the world, especially in industrialized nations, is coronary artery disease. The coronary arteries are the arteries around the outside of the heart. These arteries bring blood to the heart muscle (myocardium). Coronary artery disease brings a narrowing of the coronary arteries. Such narrowing often results in chest, neck, and arm pain (angina pectoris) precipitated by exertion. When arteries block off completely or *occlude*, a portion of the heart muscle is deprived of its blood supply, with life-giving oxygen and nutrients. A myocardial infarction, or heart attack, is the death of a portion of the heart muscle.

As the coronary arteries narrow, the body often compensates by building *collateral circulation*, circulation that involves branches from existing coronary arteries that develop to bring blood to an area of restricted blood flow. The internal mammary arteries are arteries that bring

Table 1.1 Independent Assessment of Clinical Competence of 21 Medical Interns by Five Faculty Internists and Ranking of Cost of Laboratory Procedures Ordered, George Washington University Hospital, 1971–1972

Intern	Clinical Competence ^a					Total	Rank	Rank of Costs of Procedures Ordered ^b
	I	II	III	IV	V			
A	1	2	1	2	1	7	1	10
B	2	6	2	1	2	13	2	5
C	5	4	11	5	3	28	3	7
D	4	5	3	12	7	31	4	8
E	3	9	8	9	8	37	5	16
F	13	11	7	3	5	39	7	9
G	7	12	5	4	11	39		13
H	11	3	9	10	6	39		18
I	9	15	6	8	4	42	9	12
J	16	8	4	7	14	49	10	1
K	17	1	17	11	9	55	11	20
L	6	7	21	16	10	60	12	19
M	8	20	14	6	17	65	13	21
N	18	10	13	13	13	67	14	14
O	12	14	12	18	15	71	15	17
P	19	13	10	17	16	75	16	11
Q	20	16	16	15	12	77	17	4
R	14	18	19	14	19	84	18	15
S	10	19	18	20	20	87	19	3
T	15	17	20	21	21	94	20.5	2
U	21	21	15	19	18	94		20.5

Source: Data from Schroeder et al. [1974]; by permission of Medical Care.

^a1 = most competent.

^b1 = least expensive.

blood to the chest. The tributaries of the internal mammary arteries develop collateral circulation to the coronary arteries. It was thus reasoned that by tying off, or *ligating*, the internal mammary arteries, a larger blood supply would be forced to the heart. An operation, internal mammary artery ligation, was developed to implement this procedure.

Early results of the operation were most promising. Battezzati et al. [1959] reported on 304 patients who underwent internal mammary artery ligation: 94.8% of the patients reported improvement; 4.9% reported no appreciable change. It would seem that the surgery gave great improvement [Ratcliff, 1957; Time, 1959]. Still, the possibility remained that the improvement resulted from a placebo effect. A *placebo effect* is a change, or perceived change, resulting from the psychological benefits of having undergone treatment. It is well known that inert tablets will cure a substantial portion of headaches and stomach aches and afford pain relief. The placebo effect of surgery might be even more substantial.

Two studies of internal mammary artery ligation were performed using a sham operation as a control. Both studies were *double blind*: Neither the patients nor physicians evaluating the effect of surgery knew whether the ligation had taken place. In each study, incisions were made in the patient's chest and the internal mammary arteries exposed. In the sham operation, nothing further was done. For the other patients, the arteries were ligated. Both studies selected patients having the ligation or sham operation by random assignment [Hitchcock et al., 1966; Ruffin et al., 1969].

Cobb et al. [1959] reported on the subjective patient estimates of "significant" improvement. Patients were asked to estimate the percent improvement after the surgery. Another indication

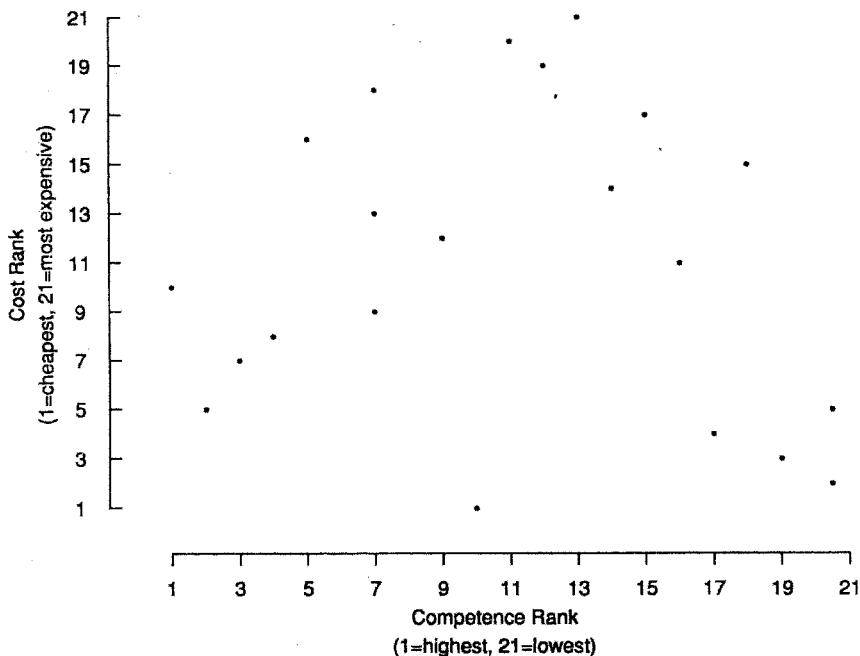


Figure 1.1 Rank order of clinical competence vs. rank order of cost of laboratory tests orders for 21 interns, George Washington University Hospital, 1971–1972. (Data from Schroeder et al. [1974].)

of the amount of pain experienced is the number of nitroglycerin tablets taken for anginal pain. Table 1.2 reports these data.

Dimond et al. [1960] reported a study of 18 patients, of whom five received the sham operation and 13 received surgery. Table 1.3 presents the patients’ opinion of the percentage benefit of surgery.

Both papers conclude that it is unlikely that the internal mammary artery ligation has benefit, beyond the placebo effect, in the treatment of coronary artery disease. Note that 12 of the 14, or 86%, of those receiving the sham operation reported improvement in the two studies. These studies point to the need for appropriate comparison groups when making scientific inferences.

Table 1.2 Subjective Improvement as Measured by Patient Reporting and Number of Nitroglycerin Tablets

	Ligated	Nonligated
Number of patients	8	9
Average percent improvement reported	32	43
Subjects reporting 40% or more improvement	5	5
Subjects reporting no improvement	3	2
Nitroglycerin tablets taken		
Average before operation (no./week)	43	30
Average after operation (no./week)	25	17
Average percent decrease (no./week)	34	43

Source: Cobb et al. [1959].

Table 1.3 Patients' Opinions of Surgical Benefit

Patients' Opinions of the Benefit of Surgery	Patient Number ^a
Cured (90–100%)	4, 10, 11, 12*, 14*
Definite benefit (50–90%)	2, 3*, 6, 8, 9*, 13*, 15, 17, 18
Improved but disappointed (25–50%)	7
Improved for two weeks, now same or worse	1, 5, 16

Source: Dimond et al. [1960].

^aThe numbers 1–18 refer to the individual patients as they occurred in the series, grouped according to their own evaluation of their benefit, expressed as a percentage. Those numbers followed by an asterisk indicate a patient on whom a sham operation was performed.

The use of clinical trials has greatly enhanced medical progress. Examples are given throughout the book, but this is not the primary emphasis of the text. Good references for learning much about clinical trials are Meinert [1986], Friedman et al. [1981], Tanur et al. [1989], and Fleiss [1986].

NOTES

1.1 Some Definitions of Statistics

- “The science of statistics is essentially a branch of Applied Mathematics, and may be regarded as mathematics applied to observational data. . . . Statistics may be regarded (i) as the study of populations, (ii) as the study of variation, (iii) as the study of methods of the reduction of data.” Fisher [1950]
- “Statistics is the branch of the scientific method which deals with the data obtained by counting or measuring the properties of populations of natural phenomena.” Kendall and Stuart [1963]
- “The science and art of dealing with variation in such a way as to obtain reliable results.” Mainland [1963]
- “Statistics is concerned with the inferential process, in particular with the planning and analysis of experiments or surveys, with the nature of observational errors and sources of variability that obscure underlying patterns, and with the efficient summarizing of sets of data.” Kruskal [1968]
- “Statistics = Uncertainty and Behavior.” Savage [1968]
- “. . . the principal object of statistics [is] to make inference on the probability of events from their observed frequencies.” von Mises [1957]
- “The technology of the scientific method.” Mood [1950]
- “The statement, still frequently made, that statistics is a branch of mathematics is no more true than would be a similar claim in respect of engineering . . . [G]ood statistical practice is equally demanding of appreciation of factors outside the formal mathematical structure, essential though that structure is.” Finney [1975]

There is clearly no complete consensus in the definitions of statistics. But certain elements reappear in all the definitions: variation, uncertainty, inference, science. In previous sections we have illustrated how the concepts occur in some typical biomedical studies. The need for biostatistics has thus been shown.

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