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Risk Factors and the Study of Prevention in the Elderly: Methodological Issues

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The striking changes in the age structure of the populations of most economically developed countries, particularly with respect to the proportion of older persons, have been widely noted (Rice and Feldman, 1983; Siegal, 1980). The reasons for these changes in the age structure of the population are not well understood, but they undoubtedly involve both decreases in the fertility of younger persons and increases in the survival of older persons. These increases in survival of older persons are striking.

Figure 3-1 compares the U.S. mortality rates for those 65–74, 75–84, and 85 or more years of age during 1950–1986 (NCHS, 1989). Over this period of 36 years, mortality rates declined by 43 percent, 32 percent, and 24 percent, respectively, in the three age groups. Ninety-three percent of the decline from 1950 to 1986 in all-cause mortality rates at ages 65–74 was due to declines in the rates of cardiovascular and cerebrovascular diseases (Figure 3-2). For those 75–84 and 85+ years old, the corresponding percentages were 87 percent and 67 percent.

These substantial declines in age-specific mortality rates provide the impetus to examine the role of primary and secondary prevention in improving the health of the elderly. So does the demographic imperative of increasing numbers of older persons. Preventive approaches traditionally have been based on interventions targeting factors previously identified as associated with increased risk for a particular disease outcome or event. Unfortunately, relatively few studies have been devoted to describing the role of risk factors among the elderly, and even fewer have involved controlled interventions aimed at risk factors.

Nonetheless, the evidence that does exist offers support for the idea that preventive activities can improve the health of older persons (Castelli et al, 1989; Kaplan and Haan, 1989; Stamler, 1988). In what follows, a number of important considerations in the examination and interpretation of risk factor associations in older populations will be discussed. These issues range from the consequences of time of measurement of risk factors to the choice of analytic techniques to the biological and social nature of the outcome being studied.

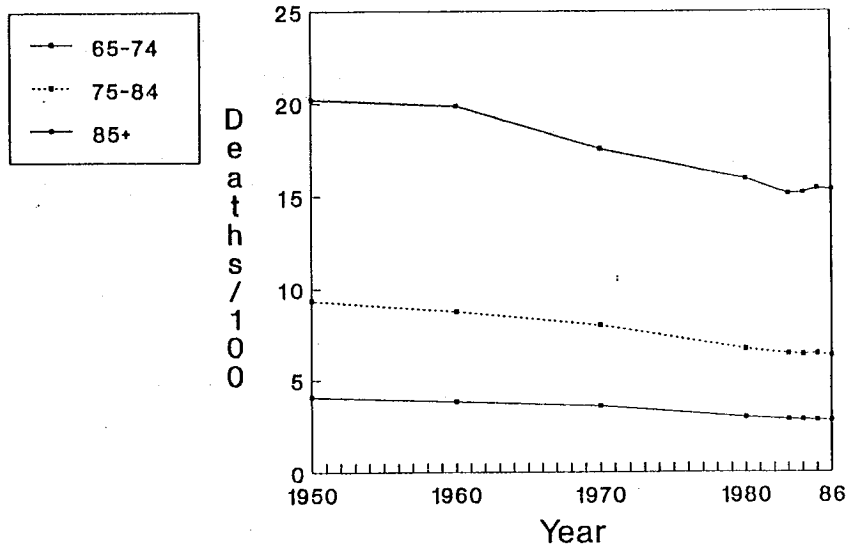

Figure 3-1 Mortality rates from all causes by age and year (United States, 1950–1986).

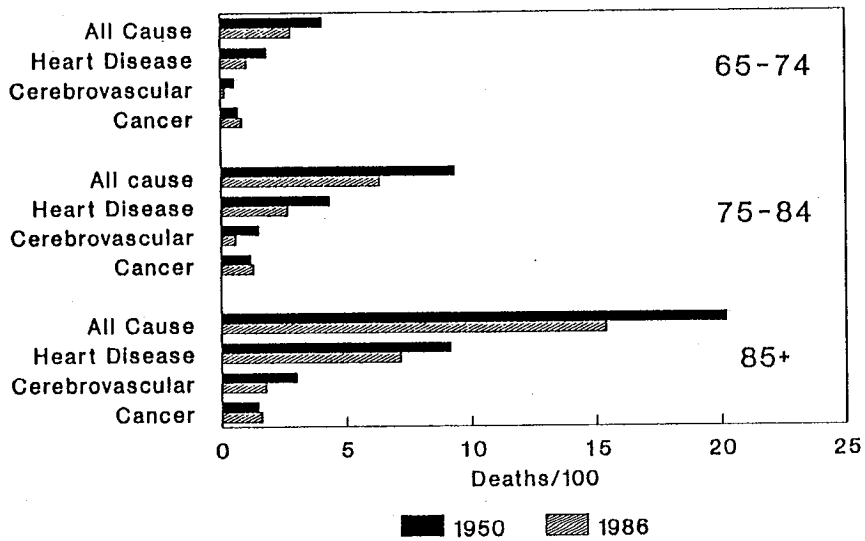

Figure 3-2 Mortality rates from various causes, 1950 vs. 1986 (United States, males and females).

A SCHEMATIC VIEW

To appreciate properly the complexities in the study of risk factors in older persons, it may be helpful to think of the disease process being studied as a stream with a particular course over time, paralleled by a road representing the aging process. With the passage of time the stream widens, indicating increased severity, and at some point there may be clinically significant events or death, which might be indicated by rapids or a waterfall. In some diseases, such as malignancies, it may be helpful to divide the course into periods of initiation, promotion, and progression (Farber, 1988). In some cases the disease may progress over long periods. For example, many cancers may have a latency period of 10–40 years, a time span also consistent with the development of many diseases of the cardiovascular system. For deaths associated with pneumonia, for example, the time course may be considerably shorter, although there may be a longer-acting process of nonspecific vulnerability, frailty, or otherwise compromised functioning that acts in the background. For most chronic diseases prevalent among older persons, there will have been a considerable period of disease progression before clinical recognition occurs, either because of the appearance of symptoms or because of a frank event. Routinely applied diagnostic tools may also result in clinical recognition without the occurrence of symptoms or events.

Also important to consider are the age-related physiologic and psychosocial changes, possibly unrelated to disease, that occur with the passage of time. This could be conceptualized as a road that moves parallel to but starts earlier than the disease stream. Although it is important to emphasize that disease effects need to be distinguished, whenever possible, from the primary, nondisease, manifestations of aging, it is also true that the development of clinically relevant disease needs to be considered in the context of aging. Aging-related changes may lead directly to alterations in disease risk, or they may interact with other factors to modify disease risk. For example, the older artery may be more susceptible to atherogenic influences (Hazzard, 1989), or age-related declines in pulmonary functioning, unrelated to disease, may lead to more severe consequences of acute bacterial pneumonias (Rowe and Wang, 1988). What is not clear is whether these age-related changes represent a "pure" aging effect or are inextricably intertwined with prior risk factor exposures and their pathophysiologic effects.

Finally, whether a prospective or retrospective study is being done, it is generally only possible to observe a limited portion of this unfolding process, ranging usually from perhaps months to a decade or so. Thus, the follow-up, or follow-back, time of a study will expose only a limited portion of the disease and aging processes to investigative scrutiny, and different parts of these processes will be exposed, depending on when the study starts. It is important to realize that the length of the study and where it begins and ends relative to both the disease and aging process may have a great influence on what is discovered with respect to risk factor–disease associations. Thus, there are three time-related processes simultaneously taking place related to (1) age-related changes not related to disease, (2) the development of disease and its consequences, and (3) the length of follow-up and the age range included in the study. Although there is currently insufficient information to understand the relationships fully between these three processes, consideration of many of the issues involved in studying risk factors among older persons will be facilitated by keeping these three processes in mind.

What Is to Be Prevented?

In chronic diseases manifested at older ages, considerable pathophysiologic changes may already have occurred. Therefore, risk factors in the elderly will be likely to accelerate transitions from preclinical disease to clinically significant disease. Most interventions traditionally focus on the prevention of pathophysiologic damage through risk factor reductions. In the elderly, although this still remains a goal, efforts may also focus on preventing or slowing the rate of disease progression and thereby influencing the rate of transition from preclinical to clinically manifested disease: Screening of asymptomatic patients and identification and prevention of risk factors that may precipitate such transitions are examples of such interventions.

To take atherosclerotic heart disease as an example, significant risk factors, such as smoking, at older ages, may be more closely related to precipitants of ischemic events than to the atherogenic process itself. Similarly, risk factors for osteoporotic-related hip fractures may be more closely related to endogenous factors, such as those related to balance and response to falling, and exogenous variables affecting the opportunities for falling, such as those related to physical hazards, than to the exact degree of osteoporosis.

Thus, the goal of prevention might be conceptualized, in the elderly, as the prevention or delay of the further progression of disease to a clinically significant event (e.g., the prevention or delay of the precipitants of such events). Such a view means that the notion of "pure" disease incidence in older persons may not be meaningful.

In addition to attention to the progression of chronic disease and their transitions, preventive approaches (and the associated search for risk factors) can profitably focus on many other aspects of the health of older persons. Foremost among these are those related to functional health. Functional health outcomes reflect the ability of individuals to perform activities and roles that are part of living independently and productively. These abilities strongly influence quality of life, which is so critical to the continuing health and well-being of older persons. Because functional health involves a complex mix of physiologic, behavioral, cognitive, and social factors, it is likely to be multifactorial in causation, and involve considerable interaction between determinants.

Some functional outcomes, such as urinary incontinence, may develop over shorter periods of time but are likely to reflect the influence of other long-acting chronic processes that increase vulnerability or susceptibility. In the case of infectious diseases, the same pattern holds, with susceptibility being influenced by the impaired functioning of damaged organ systems and compromised immune functioning (Garibaldi et al, 1988). In addition to being influenced by traumatic causes, functional changes often result from age-related physiologic limitations interacting with chronic debilitating disease. With respect to the "stream" metaphor, one might think of tributaries that join with other ongoing disease processes or exposures to precipitate additional clinical events.

Finally, there is a broad set of biopsychosocial outcomes that may be preventable to a significant extent. Examples of these include institutionalization, depression, frailty, social isolation, and cognitive declines. As with functional outcomes, these are likely to have several causes, reflecting complex admixtures of physiologic capacity; physical health; motivation; economic, social, and psychological resources; and social policy. Again, there is likely to be considerable interdependence and interaction between these different classes of risk factors.

Issues Related to Risk Factor Measurement

Time of Measurement

Ideally, one would like to have complete risk factor information for an individual, obtained by repetitive measurement and/or surveillance covering the total period of time relevant to the disease process being studied. This is seldom, if ever, possible. Without such a comprehensive evaluation, a series of tradeoffs must be made, the consequences of which have not often been studied. Risk factor levels obtained at older ages may not necessarily reflect characteristic values over the preceding years, having been influenced by changes in underlying function, by undetected disease, or by social processes. Thus, an 80-year-old who reports being physically inactive may have been active previously and changed because of poor health or for other reasons. Since this important issue of the correlation, or tracking, of risk factor levels over time has not been well studied in older persons, it is impossible to assess the extent of misclassification of risk factor levels that arises from lack of data on constancy or change in risk factor levels. Presumably, such effects are minimized if the follow-up period is short. However, the general impact of such misclassification is to dilute the magnitude of the association between risk factors and outcomes.

One possible solution is the retrospective recall of risk factor exposure levels. However, the validity of retrospectively reported risk factor information obtained from older persons is probably variable, and the collection of such data would be lengthy and complex, so such information will not necessarily help. Given the possible link between levels of cognitive functioning and underlying chronic diseases, unreliability and recall bias are likely to be introduced. Information on blood pressure, cholesterol, and many other laboratory measures is usually not available retrospectively.

In some cases such information is available, for example, for long-term participants in a study or for long-term members of a health maintenance organization. However, it is a complex choice to determine whether it is more accurate and effective to use information on risk factors collected earlier or later, an average level or a cumulative level, or measures of change or rate of change. Only a few studies have examined this issue in any detail, and few have studied older persons (Harris et al, 1985). The most important issues may involve consideration of which underlying disease processes and outcomes are being examined. For disease outcomes that involve chronic, cumulative processes it may be best to use as much information as is available, while recognizing at the same time that the current level may be more closely related to the triggering of clinical events. For example, if one were examining the impact of relative weight on development of osteoarthritis, it is probably more relevant to use measures

that reflect cumulative exposure than it is to use current weight, particularly given the weight changes that occur with aging. On the other hand, current weight might be a stronger predictor than previous weight of current level of physical functioning.

To add complexity, it should not be assumed that exposures simply accumulate and "spill over" one day into a clinical event when some maximum tolerance has been reached. Although this may be true, it is also possible that that exposure may interact with endogenous susceptibility, which may change with age.

Quality of Risk Factor Measurement

Another area in which little information is available is that of quality of risk factor measurement. Although it has not been well documented, there is some reason to believe that, for some measures, there is an increase in within-person variability in some physiologic functions that reflects a pattern of increased "homeostenosis" (Besdine, 1988a). For example, it is believed that attenuated baroreflex sensitivity, perhaps related to arterial stiffening, may lead to increased lability in blood pressure in older persons (Rowe and Lipsitz, 1988). Without careful standardization, attention to repeated measurements, and control to reduce this variability, greater imprecision in the measurement of blood pressure in older persons would result.

Impact of Health Status on Risk Factors

The high prevalence of existing chronic diseases among the elderly (Irvine, 1990) means that the magnitude of risk factor levels may often reflect the impact of disease on the risk factor. For example, one would have to be very cautious in interpreting data for older persons that indicated that sedentary levels of physical activity were associated with decreased pulmonary functioning, unless it was possible to eliminate the possibility that low levels of pulmonary function led to reductions in physical activity. Similar problems would apply to a study that indicated that obesity was associated with greater risk of osteoarthritis, since osteoarthritis could lead to decreased levels of physical activity, which could lead to higher rates of obesity. Measures of weight, lipids, dietary intake, immune functioning, metabolic activity, hormones, depression, and many other risk factors can be influenced by diagnosed or occult disease. With diagnosed and treated disease, there may be considerable impact of medications on risk factor levels. In addition, behavioral changes associated with aging, such as becoming a widower, may alter risk factor levels as well. Where information is available on diagnosed diseases, several analytic strategies are available (cf. the later sections "Selection of Study Subjects" and "Issues Related to Analysis and Interpetation"); however, the high burden of preclinical disease at older ages leads to great difficulty in properly accounting for the impact of disease on risk factors. Information that suggests monotonic relationships between risk factor levels and disease severity can be helpful in this regard. For example, if information on the level of a risk factor is available for a population of older persons for whom a good deal of information on cardiovascular status is available and if the risk levels do not vary by cardiovascular status, then an association between that risk factor and some outcome is not likely to reflect the impact of cardiovascular disease on that outcome.

Issues Related to Study Design

Length of Follow-up

In a prospective study, the length of follow-up can have considerable impact on the observed association between a risk factor and an outcome. In fact, the assumption of a constant risk association over time, which underlies some of the currently favored analytic techniques such as proportional hazards regression (Cox, 1972), may not be appropriate. To the extent that information is only available on risk factor levels at the beginning of the study and the follow-up time is long, misclassification bias, as mentioned earlier, is a potential problem. Although the subject has not been carefully studied, it is logical to postulate that short follow-up periods, such as the two-year incidence periods used in many analyses of the Framingham study, may be more likely to reflect recent effects on late-stage pathophysiologic processes than long-acting chronic processes. Of course, if the risk factor "tracks" strongly over both the long and short term, it would be very difficult to distinguish between "early" and "late" effects.

There has been very little examination of these potential biases in studying risk factor–disease associations among older groups. In one study using the follow-up experience of 49–82-year-old members of the Framingham cohort, there was considerable diminution in the strength of the association between high-density lipoprotein cholesterol (HDL-C) and systolic blood pressure and the incidence of coronary heart disease when follow-up times of four and 12 years were compared (Castelli et al, 1986). The strength of the association between HDL-C and coronary heart disease incidence decreased by 36 percent and 22 percent for men and women, respectively, when the two follow-up periods were compared. For systolic blood pressure, the corresponding figures were 39 percent and 14 percent. These diminutions in the strength of the association, with increasing follow-up time, may stem from a variety of factors, including those related to lack of tracking of the risk factor, selective mortality of those at high risk (to be discussed later), changes in the physiologic impact of the risk factor, and changes in the clinical manifestations of the disease.

Selection of Study Subjects

It is commonplace in the design of epidemiologic studies to caution that choice of subject or patient population can have a major impact on whether associations are observed between a risk factor and an outcome. Such considerations become even more important in studies of the elderly. Foremost among these are concerns that involve inclusion or exclusion based on the health status of the study participants. Although it will be possible to find individuals free of a specific disease at older ages, disease-free persons represent an increasingly selected group, and the associations observed in such a group may not characterize the majority of individuals of that age. The impact of such selection on the observation of a disease–risk factor association could be considerable. Furthermore, there is substantial increase in the prevalence of co-morbidities among older persons. Persons apparently free of one disease may be likely to suffer from another that could have an impact on the risk factor–disease association being considered. Even those who have not suffered a clinically defined event may have considerable preclinical disease. Also, the existence of subclinical illness increases with age.

In short, prevalent illness and its treatment may confound the risk factor–disease association, if the study includes older persons with prevalent chronic disease. Carefully collecting illness history and treatment and assessing clinical and subclinical disease states can help mitigate this confounding influence. With such information, analyses can be stratified on health status information and/or risk factor–health status interactions can be examined. Where possible, it is also informative to conduct analyses on a series of graded outcomes. Thus, Guralnik and Kaplan (1989) were able to show that a set of risk factors was associated with risk of death, with low and intermediate levels of physical functioning, and with high levels of physical functioning.

Case-Control Studies

Although for a variety of outcomes, such as Alzheimer's disease, there may be no practical alternative to the use of case-control studies, there can be methodological problems in such studies. For example, Sackett (1979) identified a very large number of potential biases in case-control studies. Here we will only mention briefly some of the more important issues. Measurement of current risk factor levels in cases will always include the possibility of the disease affecting the risk factor. Assessment of previous exposure levels may be even more problematic among older populations because of age- and disease-related increases in memory problems, or the need to use proxies as a source of information. There does not seem to have been any direct examination of these issues with respect to older populations, although age-specific analyses of some studies would present such opportunities. In cases where the disease itself interferes with the ability to report risk factor information, proxy informants are necessary, and there is beginning to be an empirical base for evaluating the validity of such information (Magaziner, Chapter 8).

With respect to choice of controls, the usual controversies arise. The most important biases with respect to older populations are probably those related to the health status of the controls. Although it is tempting to use controls that are identified by virtue of their contact with the health care system, the high rates of morbidity in such groups and the fact that many chronic diseases share common risk factors and pathophysiologic processes will tend to bias the measure of association toward the null. With respect to population samples for controls, the choice of the population needs to be carefully considered. For example, inclusion or exclusion of age-eligible persons who are in nursing homes may affect the observed association. The issue of the representativeness of controls in an elderly population is more profoundly influenced by consideration of health status than it is in younger populations. Indeed, it may be difficult, it not impossible, for some studies to obtain older controls who are disease-free.

Issues Related to Analysis and Interpretation

Choice of Analytic Method and of Measure of Association

As in any epidemiologic study, the choice of analytic method and measure of association should be carried out carefully, mindful of the underlying assumptions. A number of such issues are particularly relevant to studies of older populations. High event rates in some studies of older persons, because of advanced age and/or long follow-up, will negate the useful approximation of the relative risk by the odds ratio. In mortality

studies, high rates of competing causes will lead to substantial censoring. Thus, survival techniques that can accommodate such losses are preferable. However, the assumptions of survival techniques such as the proportional hazards model (Cox, 1972) should be tested whenever possible. For example, as noted earlier, the assumption by the proportional hazard model of a constant relative hazard over the entire follow-up period may not be appropriate when used with older groups and high event rates.

Because of the high rates of chronic conditions and medication use, careful consideration of confounding or effect modification by co-existing conditions and their treatment needs to be carefully considered. The structure of multivariate models used to assess the impact of potential confounders or effect modifiers needs to be considered. Analyses utilizing stratification of co-morbidity status or risk factor interaction with morbidity status may be useful. Although it is tempting to use indices that summarize the presence or absence of a large number of possible co-morbid conditions, such techniques can lead to an underestimation of the extent of confounding or effect modification due to these conditions. The use and construction of such indices should be informed by biologic and physiologic knowledge whenever possible.

The choice of which measure of association to use will follow from the selection of a study design and particular analytic tools. However, it should be recognized that different measures of association can reveal different age-related patterns. Figure 3-3(a,b) presents the results of six years of follow-up, by level of total serum cholesterol (<182 mg/dl vs. ≥ 182 mg/dl), for the over 350,000 persons who were screened for the MRFIT study (Stamler, 1988). As can be seen in Figure 3-3a, the six-year risk of coronary heart disease death rises monotonically as a function of age at entry into the study. Although the slope is steeper for the high-risk group (≥ 182 mg/dl), inspection of Figure 3-3b shows that the relative risk is decreasing, from 3.3 to 1.8, with increasing age for those over age 40. When the difference in risks between the high- and low-risk groups, the excess risk, is considered, the opposite pattern is seen. Excess risk rises, almost linearly, from 124.8 per 100,000 at age 35–39 to 705.0 per 100,000 for the oldest group. Thus, very different conclusions would be drawn concerning the association between levels of serum cholesterol and risk of coronary death, depending on which measure of association is used.

Both the relative risk and the excess risk can obscure potentially important relationships that are seen when the data in Figure 3-3a are examined. The interaction between age and the risk factor may be important information that would be missed if only the relative risk was considered. Since different approaches to modeling the interaction test particular forms of interaction, they should not replace actually inspecting the absolute risks. Therefore, it is important to consider the absolute risk levels. While the relative risk is lowest in the 55–57-year-old group, the excess risk is highest. This increase in the excess risk is of great importance from a preventive point of view, because it implies that for each 100,000 persons in a particular age group, more coronary deaths could be prevented by cholesterol control in the oldest age group.

The Meaning of Age

It is important to remember the fundamental interrelationships between age, period, and cohort (Kleinbaum et al, 1982; Susser, 1973). Exposure levels to a given risk factor

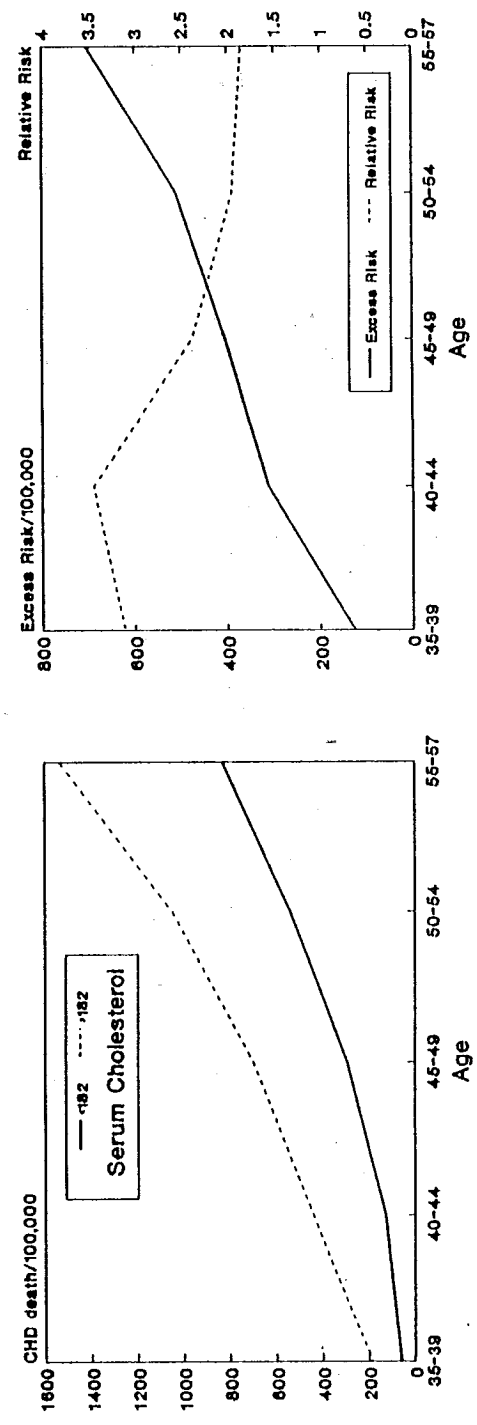

Figure 3-3 Absolute, excess, and relative risk of coronary death (6 yr) elevated serum cholesterol (356,222 MRFIT screenees, 35–57 years old).

in a given age group are also a function of the historical period and birth cohort to which that group belongs. Changes in the strength of an association with increasing age may be confounded by the effects of period and cohort. In general, any observation of one of the effects will involve confounding of the other two. Although various statistical techniques have been proposed to deal with these interdependencies, they are fundamentally inseparable because of the linear dependence of each variable on the other two. This can create problems in the interpretation of age-related changes in the association between a risk factor and an outcome because it is not known if a cohort or period effect is being observed. If there are period or cohort effects, then analyses based on the accumulated age-specific experience of a fixed cohort moving through time may misrepresent the nature of the association. For example, to accumulate enough persons in each age group, some analyses of the Framingham study data have examined biennial incidence of coronary heart disease accumulated for two-year periods starting when a person reached a particular age (Kannel and Vokonas, 1986). This means that someone who reached 70 years old in 1960 is considered the same as someone who reached that age in 1980. Interpretation of an age-related decline in the association between a risk factor such as smoking and coronary heart disease is clouded by the real possibility of cohort–period effects. Potentially informative approaches to this problem involve explicit modeling of period effects (Kleinbaum et al, 1982) or examination of age-specific risk factor–disease associations at different points during the extended follow-up. It also may be informative to compare period and cohort differences in exposure to particular risk factors, especially when considering changes in the strength of an association and outcome with increasing age.

Co-morbidity

With increasing age, there are increasing levels of co-morbidity. For example, in the Alameda County Study, 41 percent of those 60 years old or older reported three or more chronic conditions and symptoms (Seeman et al, 1989). Many symptoms and conditions were found to have substantial rates of co-occurrence. For example, although high blood pressure was reported by 26 percent of those over 60 years old in 1965, in 70 percent of the cases it was mentioned along with two or more other conditions or symptoms. These levels of co-morbidity have significant consequences. In the same analyses, those who were over age 60 and who reported three or more chronic conditions and symptoms, compared to those who reported none, had 25 percent higher risk of death over the next 17 years, 680 percent higher risk of reporting two or more additional morbidities nine years later, and 224 percent higher risk of reporting high levels of depressive symptoms nine years later.

These high levels of co-morbidity complicate the examination of risk factor associations with particular disease outcomes for a variety of reasons. Treatment of a co-morbidity can often have an effect on the morbidity under examination, changing its mode of presentation or timing. In addition, there may be disease–disease interactions (Besdine, 1988a; Korenchevsky, 1961). Also, a given risk factor may be associated with more than one outcome, and the presence of the co-morbid condition may influence the severity or progression of the outcome under study. The end result is that it is difficult to study the "pure" association between a particular risk factor and a "single" disease end point in older populations. Indeed, given these interconnecting patterns of

morbidities, some of which are consequences of one another, it may be misleading to look for associations with single end points. For example, although it would be statistically possible to model the impact of a particular risk factor on functional ability while adjusting for the impact of various prevalent chronic and acute conditions, one would, in effect, be studying impaired functioning independent of many of the factors that simultaneously present themselves.

Related concerns apply to the examination of risk factors associated with deaths from particular causes among the aged. In one autopsy study of decedents older than 85 years old, no acceptable cause of death was found in 26 percent of the cases (Kohn, 1982). The reporting of co-morbidities on the death certificate is quite high and appears to have risen over time (Israel et al, 1986; Manton and Stallard, 1984). In 1979, more than one cause of death was mentioned on over 70 percent of U.S. death certificates (Israel et al, 1986). (This topic is discussed more fully in Chapter 17.) These patterns reflect the extensive amount of co-existing disease that make assignment of an underlying cause of death at the older ages so difficult. Risk factor associations based on analyses of multiple causes of death information or on all causes may more adequately reflect the nature of the terminal process in a substantial proportion of deaths in the elderly.

It may also be important to consider as an important outcome the co-occurrence of symptoms and conditions that may be indicative of a general systems breakdown leading to frailty and, ultimately, death. Studies of risk factor associations with systemic, overarching changes in functioning, across organ systems, might prove valuable.

Competing Risks

In any prospective epidemiologic study, the observation of an association between a risk factor and an outcome is potentially influenced by other outcomes that might remove (censor) the individual from observation. For example, an individual participating in a study of risk factors for lung cancer might die from cardiovascular causes and therefore not live long enough for an underlying tumor to be detected. Other sources of censoring include institutionalization or dementia, making the collection of data impossible. This problem of competing risks can be handled in a number of ways. If the risk of the competing cause is quite low relative to the risk of the cause under study, then the competing cause will have very little effect. Life table approaches to the competing risk problem have typically assumed, for computational simplicity, that causes of death are independent. In older populations, the high rates of interrelated co-morbidities make such assumptions unreasonable. Fortunately, other life table–based methods that do not assume independence of causes are available (Manton and Stallard, 1988).

The censoring of individuals from a study due to competing risks can be dealt with using other survival methods, such as the Cox proportional hazard model, which allow an individual to remain at risk so long as they have not contracted a competing cause. Thus, until the time of diagnosis or death from the competing cause, they contribute person-years of exposure to the analysis. Although this is a convenient solution to the problem of censoring, as mentioned earlier, the assumption of a constant relative hazard in the proportional hazards model may not be appropriate for some studies with

older persons. If the overall risk level is high either because of age or because of long follow-up time, the assumption of proportionality will need to be formally or graphically tested (Kalbfleisch and Prentice, 1980).

Competing outcomes can also introduce problems due to what could be called "interfering risks." In these cases, which might be quite common among older populations, contracting another disease and/or treatment for that disease may have an impact on the relationship between the risk factor and the index disease under study. Analytically, this is a much more difficult issue. One solution is to use a form of the proportional hazard model that includes information on a potentially interfering cause and allows for time-dependent covariates. Thus, if and when the individual contracts the interfering cause, the value of that covariate is altered to reflect that change. Another possibility is to use techniques, such as the Grade of Membership model, that would allow various combinations of primary and competing or interfering causes to form separate sets (Manton and Stallard, 1988). Whatever approach is taken, it should be recognized that the interdependence of disease outcomes may be an important part of the chronic disease process in older persons, in itself worthy of study.

Reasons for Declines in Risk Factor–Disease Association with Increasing Age

A number of prospective studies have indicated that the strength of association between a risk factor may decline with increasing age. Although other patterns have also been found (Kaplan et al, 1987), the pattern is common enough to warrant discussion. There are four major reasons that such a pattern of declining strength of association with increasing age might occur. The first and most widely offered explanation one can call a "survivor" explanation. Figure 3-4 presents, schematically, the nature of this explanation. Consider two groups, one that is exposed to the risk factor and one that is not. Rather than viewing the exposed group, and for that matter the unexposed group, as homogeneous, they are seen as heterogeneous, composed of subgroups. In the simplest case, the exposed group is considered to consist of two groups, one that is "susceptible" to the risk factor and one that is not. The risk level of the nonsusceptibles in the exposed group is assumed to be equivalent to that of the unexposed group. Over

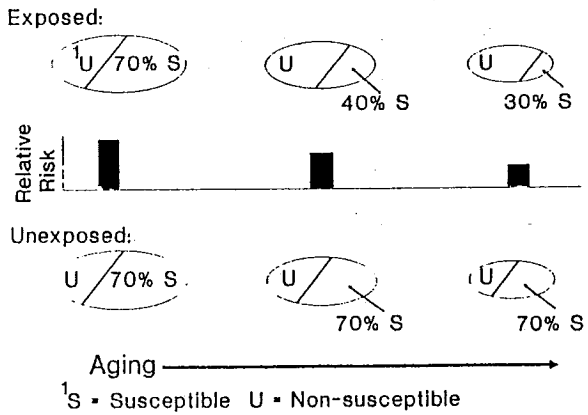

Figure 3-4 Reduction in relative risk with deletion of susceptible.

time, with aging, there is a progressive elimination of the susceptibles from the exposed group, leaving a group that becomes more and more like the unexposed group with respect to level of risk. As the two groups become more and more alike, the risk factor association weakens accordingly, ultimately reaching the null level if all the susceptibles are removed from the exposed group.

If a risk factor is associated with a fatal, or otherwise censoring, disease outcome, then over time, with increasing age, there will be a selective removal of the exposed from the population. However, this fact does not, in itself, account for diminished strength of association between a risk factor and an outcome with increasing age. The critical element of the selection explanation for decrements in strength of association with age is a postulation of susceptible and unsusceptible persons in the exposed group. Although factors related to susceptibility may exist, without their specification, the explanation becomes unprovable. That is, the lack of a risk factor effect in the exposed group is "explained" by postulating that the group comes to be composed more and more of persons who are not affected by the risk factor. What is needed to make the selection argument useful in understanding decreases in the strength of an association with increasing age is a specification of the genetic, biological, behavioral, social, psychological, and other factors associated with variations in susceptibility to a risk factor. This could be conceptualized as the identification of "risk factors" for susceptibility and can be studied using stratification or interaction approaches.

There are other possible explanations for declines in strength of association with increasing age. Figure 3-5 shows two situations in which the risk factor would have weaker association among older persons. In each of these, the risk level as a function of age for an exposed and unexposed group is presented. In Figure 3-5a, although the absolute level of risk is lower for the unexposed group, risk is rising faster with age in the unexposed group. Although it indicates a situation in which the risk factor effect declines with increasing age, this interaction with age could be interpreted as suggesting that the risk factor actually "protects" against the effect of aging. Figure 3-5b presents a common example of a ceiling effect that can be found when risk measures are used. If a high proportion of the exposed group is contracting the disease, then the ability of the risk level to rise further is severely constrained. In the extreme example, if everyone who has been exposed has contracted the disease, then the relative risk will have to decrease with increasing age, as more and more of the nonexposed persons get the disease. Depending on the age of the population being studied, the length of follow-up, and other factors, substantial death and event rates have been observed in prospective studies of older populations. For example, in a study using the Alameda

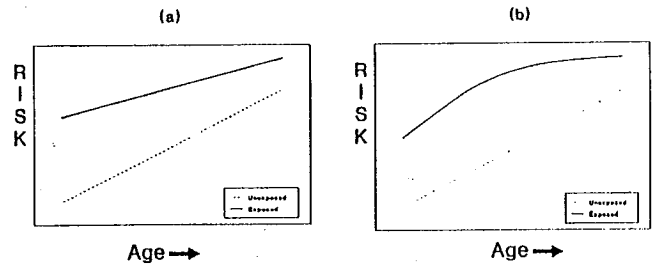

Figure 3-5 Hypothetical increases in risk in two groups.

County cohort, there was an 80 percent mortality rate in a 17-year follow-up of persons 70–94 years old (Kaplan et al, 1987). In the Framingham study, the eight-year risk of incident cardiovascular disease in 70-year-olds who smoked and who had a systolic blood pressure >195 mm, serum cholesterol >335 mg/dl, positive response to a glucose intolerance test, and evidence of left-ventricular hypertrophy was 82 percent (Kannel and Gordon, 1978). Inspection of the examples in Figure 3-5 should emphasize the importance of examining absolute levels of risk by age and risk factor status, rather than only ratio or difference measures of association. Without inspection of the risk or rate levels that contribute to such age-related measures of association, it is difficult to interpret changes in the measures.

Fourth, reductions in the strength of a risk factor's association with a disease end point with increasing age may also represent the changing impact of the risk factor on the progressing disease process. This changed impact may be related to progression of the diseases or concomitant aging. For example, a given risk factor might have a different effect on tumor promotion and progression. Similarly, the impact of factors that increase sympathetic activity on various disease outcomes may be reduced because of reduction in beta-adrenergic activity with aging (Weber et al, 1989).

When considering reductions in factors associated with increasing age, it is important to realize, as pointed out earlier in the example from the MRFIT study, that these trends may depend on the measure of association being used. Similarly, it is possible to have a decrease in the relative hazard with increasing age, accompanied by an increase in the odds ratio. Thus, the examination of age-related change in the association between a risk factor and an outcome needs to be seen as conditional on the measure of association chosen.

Choosing between these alternative explanations for observed declines in risk factor associations with increasing age is not easy. To the extent that no information is available to characterize the factors related to susceptibility, the "survivor" explanation needs to be seen as a heuristic to prompt a search for such factors. Inspection of the actual risk levels and how they vary by age and exposure group can help to direct attention to processes that are accelerating risk as a function of age in one group but not another, or can identify ceiling effects. However, few studies will have sufficient sample size to allow the calculation of stable age-specific and risk factor–specific risks. The third approach appears promising, although compromised by an inadequate understanding of both the pathophysiology of disease progression in older persons and the aging process. Given these limitations in our knowledge, interpretation of age-related changes in associations between a risk factor and an outcome should be carried out very cautiously.

Causal Interpretations

As in all analyses of observational data, great care is required in the interpretation of evidence for and against a risk factor being associated with an outcome in older persons. By far the biggest caution may be related to understanding the role of chronic conditions. Consider that urinary incontinence is an outcome that results from any number of acute and chronic diseases prevalent among the elderly. If a given risk factor is associated with one of these diseases, it is in part a risk factor for the development of incontinence. However, in the usual form of multivariate modeling, the disease might be detected as a confounder of the association between the risk factor and incontinence. Without a clear understanding of the mediating role of the disease, the risk factor would not emerge as an antecedent, causal factor (Susser, 1973). Thus, it is very important to bring knowledge of the potential pathophysiologic processes to bear on the interpretation of apparent patterns of confounding. Without such informed interpretation, a potentially modifiable risk factor related to the development of incontinence would be overlooked.

CONCLUSIONS

The substantial changes that have occurred in the mortality rates at the older ages suggest that there may be a considerable role for prevention among the elderly. However, the identification of associations between risk factors and disease outcomes in the elderly suffers from a number of methodological and conceptual challenges, some of which apply to epidemiologic studies in general and some of which are particularly germane to studies of the elderly. What little evidence there is supports a role for a number of modifiable risk factors in the health experience of older persons. However, this area of epidemiologic investigation is in its infancy, and much work remains to be done. Such work should be carried out with full awareness of the interrelationships between aging, pathophysiology and disease progression, and study design. Although the challenges are great, the impact of information gained from such studies could have a significant impact on both the duration and quality of life.

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II

ISSUES IN SURVEYING OLDER PERSONS