

# Age Patterns of the Life Table Aging Rate for Major Causes of Death in Japan, 1951–1990

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*It has been widely supposed that human mortality from all causes increases with age nearly exponentially (at a constant rate) through adult ages except for very old ages, and that this exponential increase also holds fairly well for most major causes of death (CODs). However, the present analysis of death registration data for Japan, 1951–1990, reveals that the rate of age-related relative increase in mortality (the life table aging rate) changes with age significantly and systematically for many CODs. Above age 75, the mortality increase decelerates for most CODs; under age 75, it remains at a relatively stable pace for ischemic heart disease, decelerates for most major cancers, and accelerates for diseases related to a declining ability to maintain homeostasis (pneumonia, bronchitis, influenza, gastroenteritis, and heart failure). These results seem to suggest that significantly different types of senescent processes may underlie atherogenesis, oncogenesis, and immunosenescence.*

DEATH rates for most major degenerative diseases increase markedly with age, suggesting that the initiation and development of the diseases are closely associated with age-related changes in physiological functions and structures. It can be expected that there are significant variations in the age pattern of mortality among major causes of deaths (CODs) for the following two reasons. First, because the pathologies of the diseases differ considerably, they may interact with aging in different ways. A few theoretical schemes have been proposed for classifying diseases in terms of their relationships to aging (Kohn, 1978; Brody and Schneider, 1986; Rowe and Katzman, 1992). Second, aging is considered to involve a number of distinct physiological mechanisms (Rose, 1991). These multiple aging processes may proceed at differential paces, which will be reflected in the age patterns of incidence, prevalence, and mortality of the diseases that are linked to the aging processes.

In a number of studies, age-specific death rates for major CODs are plotted in semi-logarithmic graphs (called Gompertzian plots), and the age patterns are compared among those CODs (e.g., Simms, 1946; Kohn, 1963; many publications by Riggs cited in Riggs, 1992; Figure 2 of this article). The plotted points fall along a straight line if the death rate rises exponentially with age; the mortality curve is convex if the logarithmic death rate accelerates; and the curve is concave if the logarithmic death rate decelerates. (Hereafter, “mortality increase,” “mortality acceleration,” and “mortality deceleration” refer to increase, acceleration, and deceleration, respectively, of the logarithm of death rate with respect to age.)

In general, major CODs follow different age trajectories with respect to the mortality level and the steepness of age-related mortality increase. Nevertheless, many of the major cause-specific mortality curves appear to have relatively similar patterns: in a logarithmic scale, they look fairly linear except for very old ages. The cause-specific curves may not

be as straight as the all-cause curve, but usually the subtle curvatures do not seem significant. Thus, a number of researchers state that various cause-specific death rates increase almost exponentially with age (Simms, 1946; Johnson, 1985; Forbes and Hirdes, 1993; Gerhard and Cristofalo, 1993; Woods et al., 1994). This implies that the death rates increase at nearly constant rates without significant acceleration or deceleration.

This prevailing view may be partly attributable to use of the semi-logarithmic plot of death rate against age to examine age variations of mortality. In such a graph, mortality accelerations and decelerations can be visually detected from curvatures of the logarithmic mortality curve. This type of graph, however, has a serious limitation: although decelerations at very old ages can be seen clearly, some significant mortality accelerations and decelerations at middle ages and younger old ages (jointly defined in this article as ages between 35 and 75) may not be captured. The reason for this limitation rests in the basic trigonometry.

For example, the artificial mortality pattern in Figure 1 becomes increasingly concave with age, which may give an impression that mortality deceleration is more pronounced at older ages. The impression is wrong: the extent of the mortality deceleration in Figure 1 is actually constant over age (i.e., it is a fragment of a parabolic curve). This wrong impression comes from a nonlinear relationship between the slope, calculated as the tangent, and its angle, measured in radian or degree. A curve looks straighter if the angle of its slope varies less. However, as indicated by the shape of the tangent function (or more precisely, its inverse, the arctan function), a given numerical change in the slope of a steeper curve produces a smaller angular change of the slope — i.e., steeper curves tend to appear less bent. This may make the logarithmic mortality curve reasonably straight at middle ages and younger old ages, where the slope is usually steeper than at older old ages. Thus, the rate of mortality increase at

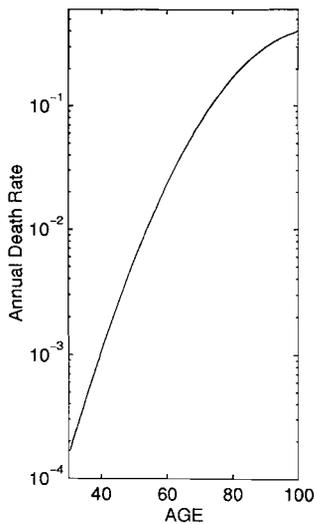


Figure 1. Natural logarithm of age-specific death rate (number of deaths per person-year at a given age): an artificial example, in which the logarithmic mortality is a quadratic function of age.

middle ages and younger old ages should not be judged to be nearly constant simply because the logarithmic mortality curve appears fairly straight.

This seems to be a reason that little attention has previously been given to human mortality accelerations and decelerations at middle ages and younger old ages. In contrast, there are a number of studies on mortality decelerations at very high ages for humans (Bayo, 1972; Manton, 1992; Hirsh, 1994; Wilmoth, 1995a) and several other animal species (Economos, 1980; Witten, 1988; Carey et al., 1992; Curtsinger et al., 1992; Brooks et al., 1994).

The insensitivity of the logarithmic mortality curve may also be related to some ambiguities in previous research on mortality patterns. The same mortality data often appear straight in both the logarithmic and semi-logarithmic plots (Forbes et al., 1993). Some functions that are not exponential but have positive second derivatives still appear to be fairly straight in certain numerical ranges in the semi-logarithmic graph. Several two-parameter mathematical functions including the exponential function often fit mortality data more or less equally well (Woods et al., 1994).

It seems possible, therefore, that the rates of age-related mortality increase for major CODs do not necessarily remain nearly constant over age but change with age significantly and systematically, even at middle ages and younger old ages. This should be tested by measuring directly the rate of age-related mortality increase, not indirectly from the semi-logarithmic mortality plot. Given that the age-related increase in cause-specific mortality is not necessarily close to exponential, the pattern of mortality acceleration and deceleration may differ significantly among CODs, reflecting a multiplicity of aging processes and aging-disease relationships.

## METHOD

*Statistical method.* — A statistical tool that is useful for studying mortality accelerations and decelerations is the age-

specific rate of relative mortality increase with age, which is defined as

$$k(x) = \frac{1}{\mu(x)} \frac{d\mu(x)}{dx} = \frac{d \ln \mu(x)}{dx},$$

where  $\mu(x)$  is the force of mortality (instantaneous death rate) at exact age  $x$  (Horiuchi and Coale, 1990). This may be briefly called the life table aging rate, or LAR (Carey and Liedo, 1995). A LAR of .08, for example, means that the death rate is rising at the exponential rate of 8% per additional year of age (which is equivalent to the geometric rate of about 8.3% in a year). The LAR is the slope of the logarithmic mortality curve. It does not vary with age if mortality follows an exponential function, and the constant rate of increase is called the actuarial aging rate (Sacher, 1978) or the Gompertzian aging rate (Johnson, 1990). The mortality rate doubling time (MRDT), obtained by dividing the natural logarithm of 2 by the Gompertzian aging rate, is used for comparing mortality patterns of various species (Finch, 1990).

The LAR approach, broadly defined, is concerned with age variations in the rate of relative mortality increase with age. The LAR approach has previously been implemented by (1) fitting the Gompertz equation separately for two or more age ranges (Pakin and Hrisanov, 1984; Riggs, 1991; Fukui et al., 1993; Hirsh, 1994), (2) calculating the ratio of death rates of two consecutive age groups (Lew and Seltzer, 1970; Lew and Garfinkel, 1984; Carey and Liedo, 1995), or (3) deriving the LAR as the logarithm of the ratio (Horiuchi, 1983). The LAR approach has been adopted for a variety of purposes, including assessment of the extent to which the Gompertz model fits data (Lew and Garfinkel, 1984; Ekonomov et al., 1989), detection of cohort mortality variations (Horiuchi, 1983), construction of model life tables (Coale and Guo, 1989), extrapolation of mortality trajectories to very advanced ages (Wilmoth, 1995a), and detailed examination of all-cause mortality patterns (Horiuchi and Coale, 1990; Carey and Liedo, 1995).

Age-related changes in mortality can be measured in either absolute or relative terms. The LAR approach focuses on relative changes, since clear patterns of age variations, trends, and risk factor effects are usually found in the logarithms of death rates (Sacher, 1977; Lee and Carter, 1992). In addition, some models of mechanisms that convert a linear or quadratic change of risk factor to a geometric change of mortality have been proposed (Strehler and Mildvan, 1960; Sacher and Trucco, 1962; Brown and Forbes, 1974; Manton et al., 1994). The acceleration of absolute mortality increase has previously been discussed by Witten (1989).

The LAR can be obtained for cause-specific as well as all-cause mortality. In this study, since the cause-specific death rates are tabulated by 5-year age groups, the LAR at age  $x$  for cause  $i$  is estimated by

$$\hat{k}_i(x) = [\ln M_i(x,5) - \ln M_i(x-5,5)] / 5,$$

where  $M_i(x,5)$  is the death rate (number of deaths per person-year) due to cause  $i$  in the age interval between  $x$  and  $x + 5.0$  years. The approximation has been shown sufficiently accu-

rate (Horiuchi and Coale, 1990). The standard error of this estimate of  $k_i(x)$  can be approximated by

$$\sigma_i(x) = \frac{1}{5} \sqrt{\frac{1}{D_i(x,5)} + \frac{1}{D_i(x-5,5)}},$$

where  $D_i(x,5)$  is the number of deaths due to cause  $i$  in the age interval between  $x$  and  $x+5.0$  (Wilmoth, 1995a).

Cause-specific LAR curves will be shown later in Figures 3 and 4. It is important to distinguish the level and slope of the LAR curve in those figures (or equivalently, the first and second derivatives of the logarithmic mortality function). A higher LAR value means that the mortality increases faster — i.e., the logarithmic mortality curve is steeper. An increasing LAR curve means that the mortality increase accelerates with age, a decreasing LAR curve means that the mortality increase decelerates with age, and a flat LAR curve implies that the mortality increases at a constant rate. Thus, mortality accelerations and decelerations can be directly measured from LAR values.

*Data.* — Death rates by sex, 5-year age group, cause, and calendar year in Japan, 1951–1990, are analyzed for this study. The data set, developed jointly by the Institute of Population Problems of the Ministry of Health and Welfare and the Department of Demography at the University of California at Berkeley, is particularly useful for aging research, because the highest age categories are 95–99 and 100+, instead of the widely used 80–84 and 85+ for COD data tabulation.

The data have 40 exhaustive and mutually exclusive COD categories. Twenty-three categories and “all causes” are

selected or constructed for this study in consideration of the number of deaths, age-dependence, clarity of the definition, and the frequency of use in previous studies (Table 1). During the four decades, the classification of CODs in Japan changed three times, following the revisions of the International Classification of Diseases (ICD), and the consistency of categories through the different revisions is approximate. Some COD categories are considered seriously inconsistent through the four different ICD periods either because some previous U.S. studies have shown their substantial changes with ICD revisions (National Center for Health Statistics, 1975; Klebba and Scott, 1980) or because their annual trends in Japan exhibit notable discontinuities at ICD shifts. These CODs are chronic rheumatic heart disease, hypertensive disease, ischemic heart disease, other heart disease, and “nephritis, nephrotic syndrome, and nephrosis.” For these CODs, LARs for the first two or three ICD periods are not shown and cohort LARs are not calculated. Unfortunately, some important renal-cardiovascular disease categories are included in this group.

LAR patterns are examined for both periods and cohorts. Although cohort analyses are generally preferred to period analyses in aging studies, we need to place more emphasis on period results in this study and use cohort results mainly for checking the consistency of period and cohort patterns, because of the following limitations of our cohort data: the age range for each cohort is 40 years long at most and does not cover the full age range of this study, which is 70 years from age 30 to 99; since the COD data are tabulated by 5-year age group but not by year of birth, cohort trajectories need to be roughly approximated by corresponding “cohort-like” sequences of age-period data; and some CODs cannot

Table 1. Causes of Death Selected for This Study and Their ICD Codes

Causes of Death	Period (ICD revision)		
	1951–1967 (ICD6 and ICD7)	1968–1978 (ICD8)	1979–1990 (ICD9)
Cancer of stomach	151	151	105
Cancer of colon	153	153	153
Cancer of rectum, rectomoid junction, and anus	154	154	154
Cancer of pancreas	157	157	157
Cancer of trachea, bronchus, and lung	162, 163	162	162
Cancer of breast	170	174	174
Cancer of uterus, cervix uteri, and placenta	171–174	180–182	179–182
Diabetes mellitus	260	250	250
Chronic rheumatic heart disease			393–398
Hypertensive disease			401–405
Ischemic heart disease		410–414	410–414
Other heart disease			415–429
Cerebral hemorrhage	331	431	431–432
Cerebral infarction	332	432–434	433–434
Pneumonia	490–493, 763	480–486	480–486
Bronchitis	500–502	466, 490, 491	466.0, 490, 491
Ulcer of stomach and duodenum	540–541	531–533	531–533
Gastroenteritis	543, 571, 572, 764	8, 9, 535, 561–563	8, 9, 535, 555, 556, 558, 562
Chronic liver disease and cirrhosis	581	571	571
Nephritis, nephrotic syndrome, and nephrosis			580–589
Motor vehicle accidents	E810–E835	E810–E823	E810–E825
Other accidents	E800–E802, E840–E962	E800–E807, E825–E949	E800–E807, E826–E899
Suicide	E963, E970–E979	E950–E959	E950–E959

be included in the cohort analysis because of the above-mentioned ICD changes. It should be noted, however, that some of the usual advantages of longitudinal (cohort) over cross-sectional (period) data in aging research (Costa and McCrae, 1995) do not necessarily apply to this study, because the data do not include any information on risk factors except age and sex.

In order to avoid large stochastic errors in the LAR estimates, data are pooled for each ICD period (about 10 years) in the period analysis, and death rates of 5-year age groups in overlapping 10-year periods are used for constructing the cohort-like sequences: for example, the mortality trajectory of the cohort born in 1926–1930 is approximated by a sequence of death rates for ages 30–34 in 1956–1965, 35–39 in 1961–1970, and so on. LARs are estimated in this way for each 5-year birth cohort, but displayed for only three selected cohorts, 1886–1890, 1906–1910, and 1926–1930, in order to avoid unnecessary complexities in the figure.

RESULTS

Figure 2 is a semi-logarithmic plot of age-specific death rates for 24 major CODs among Japanese women in 1979–

1990 (ICD9). Figures 3 and 4 show period and cohort LAR curves for those CODs in 1951–1990. All of the LAR graphs have the same scale to make visual comparisons easier, at the cost of a few extreme values that fall out of the range. The vertical axis covers a wide LAR range between  $-.12$  (mortality halving in 5.78 years of age) and  $.22$  (mortality doubling in 3.15 years of age). The MRDT in years that corresponds to the given LAR value is shown on the right vertical axis of each figure. Each LAR graph has a vertical dotted line indicating age 75.

The comparison between the logarithmic mortality curves in Figure 2 and the corresponding LAR curves for 1979–1990 in Figure 3 suggests that significant mortality accelerations and decelerations can be easily overlooked in the semi-logarithmic plot of death rates, and that the extent and age range of mortality acceleration or deceleration should be determined unequivocally by direct calculation of the LAR. For example, the all-cause curve (solid line) in Figure 2A may appear fairly straight: an ordinary least squares (OLS) regression will produce a very high  $R^2$  value. However, the corresponding LAR curve (dash-dot line) in Figure 3A exhibits a rise from  $.078$  at age 55 to  $.129$  at age 80 followed

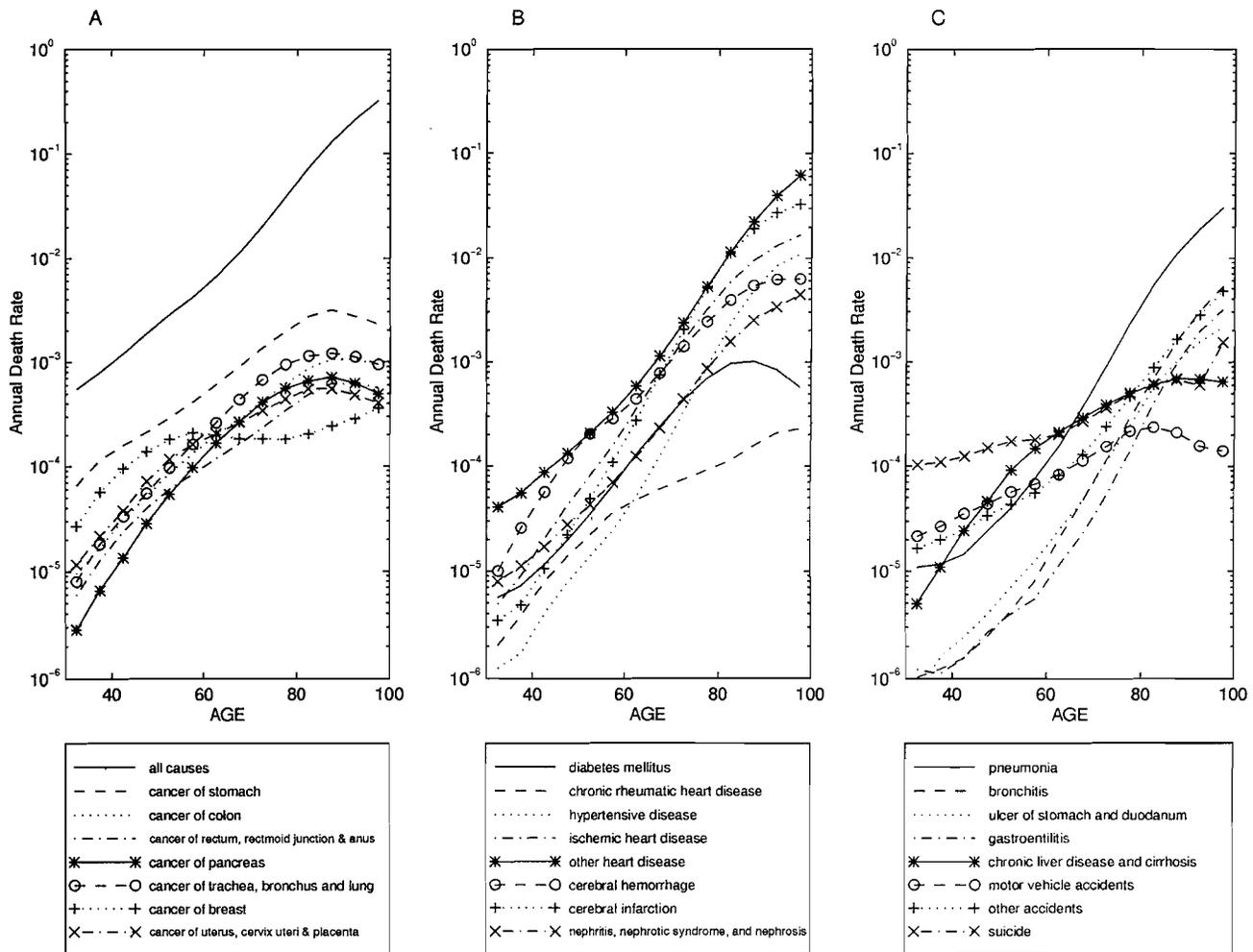


Figure 2. Natural logarithm of age-specific death rate (number of deaths per person-year at a given age) for selected major causes of death, Japanese females, 1979–1990 (ICD9).

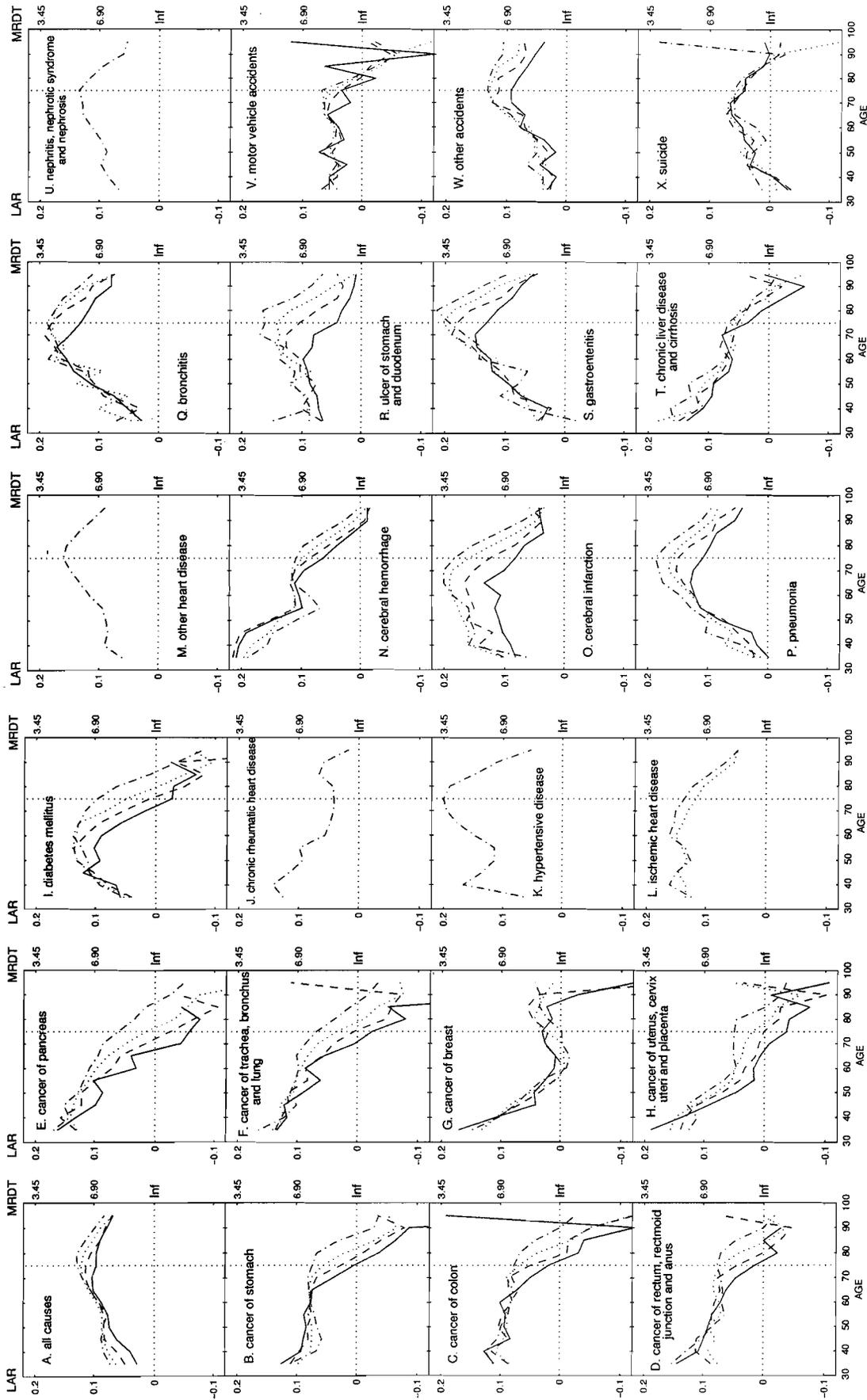


Figure 3. Period life table aging rate for selected major causes of death, Japanese females, 1951–1990. Solid lines, 1951–1957 (ICD6); dashed lines, 1958–1967 (ICD7); dotted lines, 1968–1978 (ICD8); dash-dot lines, 1979–1990 (ICD9). Early period data are not shown for some causes because of the ICD changes. The right vertical axis shows the mortality rate doubling time (MRDT) corresponding to the life table aging rate. “Inf” means infinity; a doubling would never occur.

by a fall to .083 at age 95. This is a notable variation: the mortality rate doubling times corresponding to the LARs of .078 and .129 are 8.9 years and 5.4 years, respectively. The variations with age of many cause-specific LARs are considerably greater.

*Differential LAR patterns among CODs.* — COD variations in the LAR pattern differ markedly between under age 75 and over age 75. Most of the period and cohort LAR curves decline above age 75 (on right side of the dotted line of each figure). Cause-specific LAR patterns under age 75 (on the left side of the dotted line) exhibit three major overall patterns (rise, fall, and plateau).

The age-related mortality increase accelerates continuously and steeply for pneumonia (Figures 3P and 4P), bronchitis (3Q, 4Q), and gastroenteritis (3S, 4S) and moderately for other (than rheumatic or ischemic) heart disease (3M), nephritis, nephrotic syndrome, and nephrosis (3U), and other (than motor vehicle) accidents (3W, 4W). Diabetes mellitus between ages 35 and 55 (3I, 4I) and hypertensive disease between 55 and 75 (3K) may be included as special cases. Influenza is not shown because its small number of deaths makes the LAR curve in each ICD period very erratic. However, the steepness of its LAR rise is comparable to those of pneumonia and bronchitis when data on influenza in all four ICD periods are combined. CODs in this group tend to have considerably higher LARs at highest ages (about 0.1 at age 95) than most other CODs.

The age-related mortality increase continues to decelerate through adult ages for most cancers (Figures 3B–H, 4B–H), although the steepness and the timing of the LAR decline differ among cancers. In particular, the colon cancer LAR is stable under age 75 (3C, 4C), and the LARs of both breast cancer (3G, 4G) and the cancer of uterus, cervix uteri, and placenta (3H, 4H) decline steeply up to age 50 or 55 and then remain stable at low rates afterwards. These unusual LAR patterns of the three cancers are consistent for both period and cohort data. The deceleration is clear for chronic rheumatic heart disease (3J), cerebral hemorrhage (3N, 4N), and chronic liver disease and cirrhosis (3T, 4T) as well.

LARs of some CODs are relatively stable. The LAR of ischemic heart disease (3L) fluctuates around 0.15. Hypertensive disease (3K) and cerebral infarction (period data in 3O but not cohort data in 4O) remain mostly in a high LAR range of 0.1 to 0.2 as well. LAR values of nephritis, nephrotic syndrome, and nephrosis (3U) fall in a relatively narrow range around 1.0 although its age trend of moderate increase is apparent. Stable at low LAR levels are motor vehicle accidents (period data in 3V but not cohort data in 4V) and suicide (3X, 4X).

The above classification of CODs into the three groups (acceleration, deceleration, and stable rate) is, to some extent, arbitrary. Some CODs exhibit moderate trends of acceleration or deceleration, and thus appear to fall between two categories (acceleration or deceleration on the one hand, and stable rate on the other). Some CODs are difficult to place in any group because of notable age-related changes in the LAR direction even under age 75 [stomach cancer (period) in 3B, breast cancer in 3G and 4G, and hypertensive disease in 3K], marked changes in the period LAR pattern

(diabetes mellitus in 3I, and ulcer of stomach and duodenum in 3R), or considerable inconsistency between period and cohort patterns (cerebral infarction in 3O and 4O, ulcer of stomach and duodenum in 3R and 4R, and motor vehicle accidents in 3V and 4V).

*Stability over time.* — In spite of substantial changes in the cause-specific mortality levels during the four decades, their LAR patterns remained relatively stable. The most notable trend is that LAR curves for a number of CODs tend to be at higher levels in later periods, either for the entire adult age range (cerebral infarction and pneumonia) or particularly at older ages (cancers, diabetes mellitus, ulcer of stomach and duodenum, gastroenteritis, and other accidents). This is due to the tendency for the over-time decline in logarithmic mortality of these CODs to be smaller at older ages. Death rates at very old ages actually increased for many of these CODs. However, the increase may be partly due to improved diagnosis. High proportions of deaths at very old ages were classified to "senility without psychosis" during the ICD6 and ICD7 periods of 1951–1967 (Wilmoth, 1995b). Many deaths that would have been placed in this category were probably transferred to more specific categories in later years.

*Period-cohort comparison.* — The direction of the LAR slope (upward, downward, or flat) is generally consistent between periods and cohorts for most CODs. The levels of period and cohort LAR curves, however, are significantly different for many causes mainly because of pronounced time trends in mortality level. It can be shown that a decrease and an increase of the period mortality over a wide age range tend to make cohort LARs higher and lower, respectively, than period LARs: the age-related mortality increase may be counteracted to some extent by the secular trend of mortality decrease over time, and thus the cohort LARs are lowered.

The three cohort curves appear to form a fairly continuous age trajectory for some CODs (e.g., cancer of colon in 4C) but have notable discontinuities for others (e.g., diabetes mellitus in 4I). Most of these discrepancies seem attributable mainly to considerable period variations in mortality. An extreme example is motor vehicle accidents (4V), for which the three cohort curves have similar trajectories, regardless of age, suggesting greater period variations than age variations. A detailed comparison of the logarithmic mortality curves and LAR curves for periods and cohorts indicates that most of the cohort curve discrepancies are produced in one of two ways. First, greater mortality declines in later periods (cancer of stomach, diabetes mellitus, cerebral hemorrhage, and gastroenteritis) or greater mortality rises in earlier periods (cancer of pancreas, "cancer of trachea, bronchus, and lung," cerebral infarction, and motor vehicle accidents) make the LARs of younger cohorts lower than the LARs of older cohorts when they are compared at the same ages (4B, 4E, 4F, 4I, 4N, 4O, 4S, 4V). Second, for pneumonia, bronchitis, and ulcer of stomach and duodenum, the tendency for mortality declines to be greater at younger ages makes the logarithmic mortality curve steeper in later periods, thereby making the LARs of younger cohorts higher

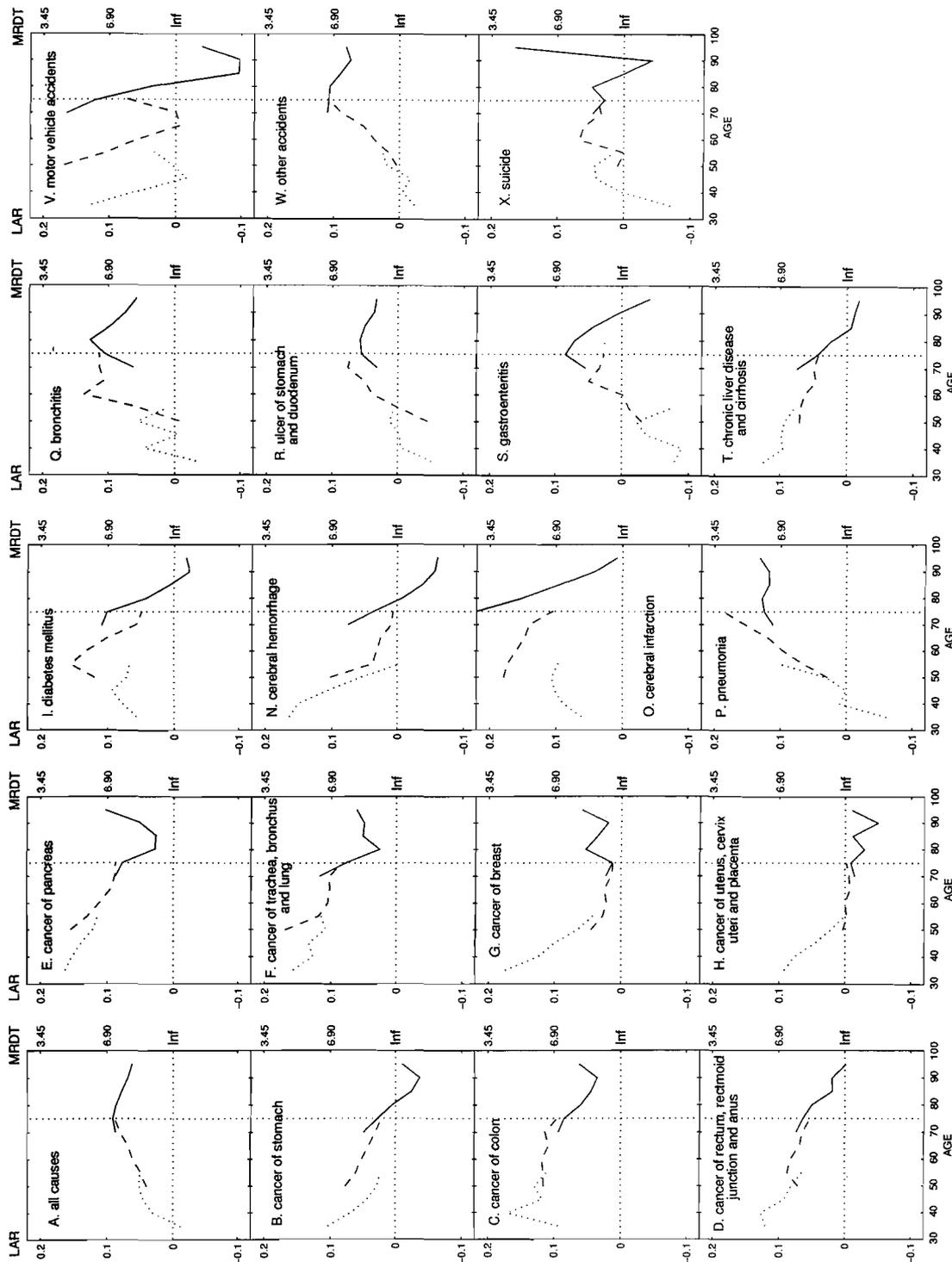


Figure 4. Cohort life table aging rate for selected major causes of death, Japanese females, 1951–1990. Solid line, the birth cohort of 1886–1890; dashed line, the birth cohort of 1906–1910; dotted line, the birth cohort of 1926–1930. Because the data are not available by year of birth, the cohort rates are estimated from a series of death rates by 5-year age groups for 10-year periods (see the text for more details). The right vertical axis shows the mortality rate doubling time (MRDT) corresponding to the life table aging rate. “Inf” means infinity; a doubling would never occur. A–X correspond to those in Figure 3. J, K, L, M, and U are missing because cohort LARs are not calculated due to ICD changes of those CODs.

than the corresponding LARs of older cohorts (Figures 4P, 4Q, 4R).

When these effects of period trends are taken into consideration, period and cohort LAR patterns appear fairly consistent for the majority of CODs. This means, for a given cause of death, that period mortality and cohort mortality may increase with age at markedly different rates, but they tend to have similar age patterns of acceleration or deceleration — i.e., periods and cohorts have logarithmic mortality curves of differing steepness but with a comparable pattern of concavity or convexity. For example, although the cohort LAR curves for cerebral hemorrhage are discontinuous and lower than the period curves, both the period and cohort curves exhibit a sharp LAR decline between ages 35 and 55, a moderate or no decline between 55 and 70, and another sharp decline over 75 (3N, 4N). Notable exceptions, however, include cerebral infarction (3O, 4O) and ulcer of stomach and duodenum (3R, 4R).

*Sex differentials.* — In this article, only female results are shown, partly because the COD variations in the LAR direction (upward, downward, or flat) seem to be fairly similar for females and males, and partly because the male LAR patterns for some CODs appear to be significantly affected by unusually strong cohort variations (Tango and Kurashima, 1987), reflecting long-term impacts of World War II on the health of the male survivors (Okubo, 1981). There are some important LAR differences between sexes, in particular all-cause mortality between ages 55 and 75, which increases at an accelerated rate for females (3A, 4A) but at a more stable rate for males. This sex difference may be due mainly to menopausal effects on the sex hormone status, and in turn, on the lipoprotein metabolism (Hazzard and Applebaum-Bowden, 1989; Gorodeski, 1994). In another article in this issue, we analyze international data to investigate the difference between sexes in LAR patterns in more depth (Horiuchi, 1997).

## DISCUSSION

*Data advantages and limitations.* — The Japanese data have three important advantages. First, Japan has a large old-age population. This reduces stochastic variations in the LAR estimate, which is calculated from the difference of two logarithmic death rates and thus tends to be erratic when the number of deaths is small. Second, reported ages of old persons and decedents in Japan are highly accurate according to some international data evaluation studies (Condran et al., 1991; Kannisto, 1994). Third, Japan has undergone a rapid mortality change during the last few decades. If the past LAR patterns in Japan are found to be stable, then those patterns may be considered relatively independent of mortality level.

The Japanese data have two limitations. First, Japan differs significantly from countries in Europe and Northern America in the COD structure and risk-factor effects, particularly with respect to heart diseases and cerebrovascular diseases (Keys et al., 1984; Yanagishita and Grulnik, 1988). Hence, their generalizability of Japanese mortality patterns to other countries may be limited. Second, as mentioned

previously, high proportions of deaths at very old ages were classified to “senility without psychosis” in earlier years (Wilmoth, 1995b). Since the apparent reduction of this cause-specific mortality is probably due to improved diagnosis, trends of other CODs might have been biased.

The results of this study should be examined with caution, taking the following COD data problems into consideration. First, a number of studies have shown that CODs on death certificates are not necessarily accurate (reviewed in Manton and Stallard, 1984, chapter 2.3). In addition, the diagnostic accuracy might have changed over time. Second, when the deceased had more than one disease, the selection of the “underlying” (primary) cause could be ambiguous. Third, a COD category usually comprises some subcategories, which may have different age patterns of mortality. Under certain conditions, however, these biases may not be significant: even if a large proportion of deaths due to a particular cause is mistakenly attributed to other categories, the age pattern of the cause-specific mortality is not distorted unless the error rate varies with age; older persons are more likely to have more than one disease (Guralnik et al., 1989), which may bias results for middle ages and younger old ages less strongly than results for older old ages; and the observed LAR pattern for a COD should reflect that of its dominant subcategory, if the other subcategories have a relatively small proportion of the deaths.

*Major patterns.* — The mortality deceleration at oldest ages, observed widely for all causes combined in humans and several other species, is found for each of the most major CODs among Japanese women and men aged 75 and over. A plausible explanation of the deceleration is selective survival due to population heterogeneity: since those who are more vulnerable to mortality risks tend to die off at younger ages, survivors to older ages tend to be relatively healthy, thereby exerting a downward pressure on death rates at advanced ages (Vaupel et al., 1979). The heterogeneity hypothesis is consistent with our finding that the deceleration occurs for almost all major CODs. Epidemiological studies have shown that there are identifiable risk factors for virtually every major disease: thus, some persons are more vulnerable to the disease than others.

Similarities and differences of the cause-specific LAR patterns under age 75 do not necessarily correspond to the conventional anatomical and pathological classification of diseases (e.g., ICD) or the previously proposed typologies of diseases with respect to aging (Kohn, 1978; Brody and Schneider, 1986; Rowe and Katzman, 1992). Thus, it is important to search for common characteristics of CODs that have similar LAR patterns.

Most CODs with mortality accelerations over long age ranges seem to be closely related to the age-associated decline in the ability to preserve homeostasis (Yates and Benton, 1995). The declining immune functions (reviewed in Miller, 1991) may be responsible for many deaths at old ages due to pneumonia, bronchitis, influenza, and gastroenteritis. The main subcategory of “other heart disease” is heart failure, which constitutes 86.1% of deaths due to “other heart disease” for females of all ages in 1989. Although 94.7% of the female heart failure deaths are

classified as "unspecified" heart failure (428.9 in ICD9), probably most of these deaths are due to congestive heart failure (428.0 in ICD9): usually the word "congestive" is not written in death certificates in Japan (Baba et al., 1994). Heart failure indicates a cardiac inability to pump an adequate amount of blood and may be considered a difficulty in maintaining homeostasis. In addition, it seems possible that mortality due to "other accidents" is partially related to physical frailty in posture and movement at old ages (Woolacott, 1993).

Mortality decelerations are seen for all of the seven cancers examined here, chronic rheumatic heart disease, cerebral hemorrhage, and chronic liver disease and cirrhosis. Although the LAR patterns differ notably among the seven cancers, all of them appear to show decelerations, suggesting that the deceleration may be related to some general characteristics of cancer. The pathologies of the other three CODs are very different from those of cancers and one another, making it difficult to find a common factor underlying all of the diseases in this group.

CODs that do not show consistent and notable acceleration or deceleration should be split into those with high stable LARs and those with low stable LARs. The high stable group possibly includes ischemic heart disease, hypertensive disease, cerebral infarction, and nephritis, nephrotic syndrome, and nephrosis. They are renal-cardiovascular disease categories. Their membership in this group, however, is questionable except for ischemic heart disease: the hypertensive LAR may rise and fall too steeply to be called stable; the cerebral infarction pattern differs markedly between period and cohort data; and the LAR for nephritis, nephrotic syndrome, and nephrosis rises with age moderately, and its LAR level is lower than the other three CODs. It should also be noted that three other cardiovascular disease categories (chronic rheumatic heart disease, other heart disease, and cerebral hemorrhage) distinctively belong to other groups. Low LAR curves of motor vehicle accidents and suicide may indicate that their relations to age-associated physiological changes are less direct than those of the other CODs.

*Frameworks for explaining LAR patterns.* — The explanation of the various cause-specific LAR patterns under age 75 may be sought in at least three different directions: age-related pathogenesis, selective survival, and competing risks.

First, the COD variations in the LAR trajectory may reflect differential age patterns of disease initiation and development. The mortality accelerates for pneumonia, bronchitis, influenza, and gastroenteritis. Although they comprise many subcategories of different etiologies, a large proportion of these deaths may involve infective agents. It has been shown that a number of important immune function indicators not only decline with age but also decline more rapidly at older ages (Wikby et al., 1994). In contrast, the cancer mortality tends to decelerate, which may be related to the age-associated decline in tumor aggressiveness observed for some cancers (Kaesberg and Ershler, 1989; Holmes, 1992; Peer et al., 1993). The relatively constant LAR of ischemic heart disease suggests that it may be worth investi-

gating if atherosclerosis tends to proceed with age at a relatively steady pace.

This type of explanation suggests the conjecture that there are substantial differences among senescent processes involved in immunosenescence, oncogenesis, and atherogenesis (Forbes and Thompson, 1990), and that these differences are reflected as accelerating, decelerating, and exponential (constant-rate) patterns of age-related mortality increase, respectively. Further research in this direction should consider linkages between age patterns of mortality and those of risk factors (Manton et al., 1994).

Second, although selective survival was mentioned earlier as a possible explanation for mortality decelerations above age 75 observed for most CODs, it may also be noteworthy as a factor possibly affecting LAR variations among CODs under age 75. The distribution of the vulnerability in a cohort may differ significantly among diseases (Weiss, 1990). Notable effects of selective survival may start earlier for diseases that have greater individual differences in vulnerability. Dynamics of cause-specific selective survival have been discussed or modeled for some disease categories (Manton et al., 1986; Vaupel and Yashin, 1986; Manton and Stallard, 1988; Manton et al., 1993; Smith, 1996).

There seems to be sufficient evidence indicating substantial individual differences in the risk of the diseases that have declining LARs. Many environmental risk factors have been identified for a variety of cancers (reviewed in Boyle et al., 1995), and genetic risk factors have strong impacts on some cancers (reviewed in Bodmer and Murday, 1995). Liver cirrhosis has close linkages with two risk factors — heavy consumption of alcohol and prevalence of hepatitis B or C. Those who had acute rheumatic fever early in life are highly susceptible to chronic rheumatic heart disease. In Japan, geographical mortality differentials are most distinct for cerebral hemorrhage and liver cirrhosis (Ministry of Health and Welfare, 1992). Unfortunately, there are no established criteria for testing if the extent of heterogeneous vulnerability is greater for these CODs than for the other CODs, which include ischemic heart disease, for which a number of risk factors have been indicated.

The selective survival explanation, if extended further from the deceleration group to the acceleration group, may lead to the conjecture that the risk heterogeneity should be relatively small for the CODs with rising LARs. This means that many old persons may be more or less vulnerable to such diseases as pneumonia, bronchitis, influenza, gastroenteritis, and heart failure, but they are more heterogeneous with respect to the mortality risk of, for example, cancers and, probably to a lesser extent, ischemic heart disease.

Third, some dynamics of competing risks may decelerate chronic disease mortality more than acute disease mortality. Risks of many diseases are high at older ages. In addition, morbidity makes the person more vulnerable to other diseases. Thus it seems more likely at older ages, for example, that a person with a slow-growing cancer suddenly dies of pneumonia before the cancer reaches the terminal stage (Inagaki et al., 1974). This could contribute to the cancer mortality deceleration.

Since this is an exploratory statistical analysis of demographic data, explanation of the cause-specific LAR patterns

awaits further work in experimental, clinical, and epidemiological research. In addition, interpretation of the disease variations in mortality acceleration or deceleration from evolutionary perspectives (Rose, 1991; Carnes and Olshansky, 1993) seems to be a noteworthy possibility, since various physiological mechanisms, whose age-associated deteriorations constitute the senescent process, might have developed through differential evolutionary pathways.

*Questions remaining.* — Comparison of cause-specific LAR patterns raises some puzzling questions. First, although there are some immune responses to tumors (Boon and Cerottini, 1995), LAR patterns of cancers (deceleration) are opposite to those of pneumonia, bronchitis, and gastroenteritis (acceleration) that frequently involve infective agents. Possible mechanisms whereby immunosenescence may favor restrained tumor growth are discussed in Ershler (1992). Second, although coronary heart disease and hypertension are the most common precursors of congestive heart failure (Eriksson et al., 1991; Ho et al., 1993), the LAR pattern of ischemic heart disease (stable rate) is entirely different from the pattern of "other heart disease" (acceleration), a high proportion of which is supposedly congestive heart failures. The patterns of hypertensive disease and other heart disease, however, are comparable after age 55. Third, cerebral hemorrhage is closely associated with hypertension (Wityk and Caplan, 1992), but cerebral hemorrhage and hypertensive disease have very different types of LAR patterns. Caution is needed, however, in interpreting data on hypertensive disease, or 401–405 in ICD9, which is essentially a "remainder" category after exclusion of most deaths due to ischemic heart disease or cerebrovascular disease in the presence of hypertension.

*Conclusion.* — In summary, the results support our conjectures that (1) the rate of relative mortality increase with age (LAR) does not remain nearly constant but changes with age significantly and systematically for all causes combined and for major CODs even at middle ages and younger old ages, and that (2) the age pattern differs markedly among the CODs. The results seem consistent with the notion of a multiplicity of aging processes and multiplicity of aging-disease relationships. Explanations of the differential cause-specific LAR patterns should be sought in future studies, in consideration of age-dependent pathogenesis, selective survival, and risk competition.

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