**Epidemiology**

The Decline in U.S. Cancer Mortality in People Born since 1925

Eric J. Kort,¹,² Nigel Paneth,³,⁴ and George F. Vande Woude²

Laboratories of Molecular Epidemiology and Molecular Oncology, Van Andel Research Institute, Grand Rapids, Michigan and Departments of Epidemiology and Pediatrics and Human Development, College of Human Medicine, Michigan State University, East Lansing, Michigan

**Abstract**

The conventional practice of analyzing overall age-adjusted cancer mortality rates heavily emphasizes the experience of older, higher mortality age groups. This may conceal shifts in lifetime cancer mortality experience emerging first in younger age groups. We examined age-specific cancer mortality rates and birth cohort–specific cancer mortality rates in U.S. mortality data recorded since 1955 to assess the effects of age, period, and cohort in secular mortality trends. Cancer mortality and population data were obtained from WHO Statistical Information System. Age-specific cancer mortality rates have been steadily declining in the United States since the early 1950s, beginning with children and young adults and now including all age groups. During the second half of the 20th century, each successive decade of births from 1925 to 1995 experienced a lower risk of cancer death than its predecessor at virtually every age for which such a comparison can be made. A major decline in cancer mortality has been occurring in the United States for the past 50 years, affecting birth cohorts born as long as 80 years ago. Excepting lung cancer, much of this decline has occurred despite relatively stable cancer incidence. These findings suggest that improvements in cancer detection, treatment, and/or prevention have reduced the risk of cancer death across the life span for individuals born in the last three quarters of the 20th century. [Cancer Res 2009;69(16):6500–5]

**Introduction**

Cancer mortality and incidence statistics are nearly universally age adjusted and are on sound theoretical grounds. Without age adjustment, the aging of the population as a whole will tend to upwardly bias trends in incidence and mortality; furthermore, age adjustment permits comparison of subgroups (e.g., gender or racial subgroups or geographic regions) that differ in age distribution (1). Secular trends in age-adjusted cancer mortality rates were central to decennial reviews of national cancer mortality rates in the United States in the 20th century (2, 3), which raised concerns about progress in the war against cancer and the balance of investment in research into prevention, early detection, and treatment. These analyses have inspired energetic discussion in both the medical and lay literature (4–7) with, on balance, more pessimism than optimism. More recent annual reports on the status of cancer from American Cancer Society, U.S. Centers for Disease Control and Prevention, U.S. National Cancer Institute (NCI), and North American Association of Central Cancer Registries have been more encouraging, documenting progress against cancer in noting that age-adjusted cancer mortality rates began to decline in the mid-1990s (8–12).

However, because the preponderance of cancer mortality occurs in older age groups, analysis of summary age-adjusted rates heavily emphasizes the experience of these groups, most of whom were born around the turn of the 20th century. Age adjustment can thus easily obscure the emergence of trends among those born more recently. An alternative to age adjustment is to examine age and birth cohort–specific cancer mortality.

We hypothesized that efforts in prevention, early diagnosis, and/or treatment have been having effects on cancer mortality risk in the United States that go back much farther than the 1990s, but that these benefits were attained first and foremost by younger individuals. As a result, this progress would not be reflected in overall age-adjusted mortality rates until long after it began. To test this hypothesis, we conducted age- and birth cohort–specific analyses of all-site cancer rates. The utility of birth cohort analysis has long been recognized (13–17) and has been applied to cancer mortality rates in the past (18, 19), as has age stratification (19, 20). To our knowledge, recent applications of birth cohort analysis in the context of cancer mortality have been limited to individual cancer sites both in the United States (e.g., ref. 21) and in other countries (e.g., ref. 22). We are aware of no age- and birth cohort–specific analyses of all-site cancer mortality in the United States published in the peer review literature within the past 20 years.

**Materials and Methods**

Mortality data from 1955 to 2004, as reported by the U.S. National Center for Health Statistics, was obtained from WHO Statistical Information System (WHOSIS). Annual U.S. population estimates for this same period were also obtained from WHOSIS. Multiple coding systems were in place at different points during the time span studied (ICD7–ICD10). Table 1 lists the codes [both WHOSIS and their International Classification of Diseases (ICD) equivalents] used from each system for calculating cancer mortality rates.

All rates were reported in 5-y age intervals, ranging from 0 to 85 y of age. We calculated mortality rates for each 5-y age group by year of death and by 10-y birth cohort. Year of birth was estimated by subtracting age at death from year of death. Because age at death is expressed in 5-y intervals in the databases used for this analysis, age at death was approximated as the midpoint of the interval. All rates were log-transformed before plotting to allow clear visualization of trends in all age groups despite the wide range of values from youngest to oldest individuals.

Whereas important shifts in the mortality trends plotted by age and birth cohort seemed subjectively obvious to us upon inspection, we desired to quantify the contributions of age, period, and cohort more systematically as well. It is well known that identification of the independent contributions of age, period, and birth cohort to secular trends is refractory to common
methods of analysis, such as multivariate regression. The reason for this is that, given any two of these factors (age, period, and cohort), the third may be calculated directly; therefore, they are confounded (23, 24). A Bayesian solution has been proposed, which uses the data itself together with a set of *a priori* assumptions to identify the most probable relative contributions of age, period, and cohort (25, 26). We chose to use this approach, previously used by others (27–31) and implemented in the BAMP software package (26), to quantitatively assess age, period, and cohort effects in cancer mortality. The first *a priori* assumption this approach requires is that the risk ratios for each effect (e.g., “age”) sum to zero over the observed interval. The second assumption required by the model is that the effects tend to be constant, such that small deviations from constant rate are favored over large ones. As a result of these assumptions, the absolute magnitude of each effect cannot be identified with certainty by the model. However, this approach does allow us to identify second-order differences: the most probable direction of change in rate and the inflection points in rate. In our analysis, we had no prior knowledge. Furthermore, the software discarded the first 5,000 iterations of the Monte Carlo simulation as a “burn in” to minimize the influence of starting values. Finally, we repeated the analysis across a wide range of starting values for the γ prior distribution (an order of magnitude or more) and found that the selection of starting values did not substantively alter the results of the analysis.

We made use of annual percentage change (APC) estimates (3, 32) to compare cumulative age-adjusted rates and age-stratified rates. To estimate the APC for each successive 5-y interval, we first fit a linear regression model to the natural log-transformed mortality rates for the given interval to obtain the maximum likelihood estimate of the slope β. Estimated APC was then calculated as \((e^\beta - 1) \times 100\). The APC calculated in this manner for age-adjusted cumulative mortality rates is denoted as APC\(_a\), because age-adjusted cumulative mortality rates represent the average rate across age groups weighted by the number of at-risk persons in each age group. For comparison, we also calculated the APC for the unweighted average rate across age groups in each interval, which we denoted APC\(_u\). Where rates are changing homogeneously across age groups, APC\(_a\) and APC\(_u\) will be the same. Where rates of change in mortality are biased with respect to age, these two rates will diverge.

### Results

Age-specific cancer mortality rates were calculated by estimated year of birth to enable direct comparison of birth cohorts. When these mortality rates are plotted with year of birth on the x axis, the age-specific mortality rates for a given cohort align vertically (Fig. 1, *solid black vertical lines*). By comparing two columns of points, shifts in the lifetime mortality experience of two cohorts can be identified (Fig. 1, *gray dashes*). Thus, we see that from 1875 to 1924 each birth cohort exhibited cancer mortality rates across the observed portions of the life span that were higher than or equivalent to (observed portions of) the preceding birth cohort. Then beginning with the cohort of individuals born after 1925, each subsequent birth cohort has experienced decreasing cancer mortality throughout the observed portion of the life span. In Fig. 1, we present only age groups for whom data were available spanning the two decadal birth cohorts (1915–1934) in which mortality began to decline. Mortality rates by year of birth for every available age group are shown in Supplementary Fig. S1. Because our mortality data set begins in 1955 and ends in 2004, not all age-specific rates are available for every birth cohort. Thus, for example, the 1925 to 1934 birth cohort includes mortality data only for cohort members between the ages of 30 and 80 years.

We also analyzed age-specific mortality rates stratified by gender in light of the fact that some exposures, screening modalities, and cancers are gender specific. Mortality rates in both males (Supplementary Fig. S2) and females (Supplementary Fig. S3) exhibited a birth cohort pattern similar to that of the combined data. Each cohort of women born since 1925 has experienced a progressive decrease in cancer mortality throughout the observed portion of the life span. The same is true for males.

To more clearly visualize the cohort-dependent shifts in mortality, we plotted mortality rates by year of death for each cohort born between 1925 and 1994 (Fig. 2). Because of the time period for which we have mortality data (1955–2004), we have successively fewer cohorts to compare as age advances. Thus,
before age of 30 y, we can compare six cohorts; for people in their 30s, five cohorts; and so on until ages 70 to 79 y, for which data is available for only one cohort. However for nearly every comparison between cohorts that can be made, the later born cohort has lower mortality at the same age. The oldest cohort, born in 1925 to 1934, has a higher mortality rate than any other later born birth cohort at every age of comparison, from their early 20s until their late 60s. Subsequent birth cohorts have experienced a substantial decline in mortality. The total number of data points available for comparison between different cohorts at the same age is 59. Of these 59 adjacent age-cohort comparisons, the more recently born cohort had the lower mortality rate 57 times, with two ties (10–14 year olds in the 1935 and 1945 cohorts and 5–9 year olds in the 1985 and 1995 cohorts; a comparison which is based on the smallest number of deaths of any comparison in the figure).

The cohorts of individuals born in the second quarter of the 20th century have aged to the point that now every age group exhibits declining rates of cancer mortality. However, mortality rates are decreasing more rapidly among younger individuals; the average rate of decrease in cancer mortality among the youngest individuals is nearly four times greater than that of the oldest individuals (25.9% per decade versus 6.8%).

BAPC analysis was used to further characterize the relative contributions of age, period and birth cohort effects. Cancer mortality risk decreases during early childhood and then increases steadily with age (Fig. 2 and Supplementary Fig. S1). The BAPC analysis identifies this pattern as well (Fig. 3A) and over the same order of magnitude, suggesting that the a priori assumptions required by the BAPC analysis are not unreasonable. Controlling for the effects of age and birth cohort, the risk of dying of cancer has exhibited a consistent downward trend over the past 50 years (Fig. 3B). Finally, the BAPC model confirmed our impression, derived from the age-stratified mortality curves, that an inflection in birth cohort–specific risk occurred among those born in the late 1920s and that cohorts born because that time period have experienced a progressive decline in cancer mortality risk (Fig. 3C). Results of BAPC analysis of mortality rates stratified by gender (Supplementary Figs. S4 and S5) yielded results essentially identical to those described above for both genders combined.
If the rate of change in mortality rates were either homogenous or stochastic with respect to age, analysis of cumulative age-adjusted mortality rates could be assumed to provide a reasonable summary estimate of trends in cancer mortality. But as we have shown above, rate of change in mortality trends are neither homogenous nor stochastic with respect to age. As a result of the birth cohort effect we describe here, rates drop first among younger individuals. To quantify the difference between cumulative age-adjusted mortality rates and age-stratified rates, we compared the APC in mortality experienced by the average person (APCw) to the APC in mortality in the average age group (APCu). As described in Materials and Methods, where rates are changing homogeneously across age groups, APCw and APCu will be the same and, where rates of change are biased with respect to age, APCw and APCu will diverge.

We calculated the APCw and APCu in cancer mortality rates across eleven 5-year intervals from 1950 to 2004 (Fig. 4). These two figures were essentially the same during the 1950s. Then, as those born after 1935 entered adulthood, the two lines begin to diverge and remain divergent for 30 years. Finally, as those born before 1935 wash out of our population, the lines are again converging. At its most severe, the difference between the two curves was nearly 1.5 percentage points per year, and worse, the rate of change had opposite signs between the two measures for almost 30 years.

**Conclusions**

It is estimated that ~41% of individuals born today in the United States will be diagnosed with cancer at some point in their lives and 21% will succumb to the disease (33). The annual national investment in cancer research in the U.S. numbers in tens of billions of dollars, in addition to which it is estimated that we spend over $40 billion annually in cancer-related health care. In light of the socioeconomic burden of cancer, it is not surprising that trends in cancer incidence and mortality receive a great deal of attention in the biomedical literature (1–3, 11, 12). These reports usually use age adjustment to remove bias related to the aging of the population and to allow comparison between populations with different age distributions.

The canonical interpretation of age-adjusted all-site cancer mortality data is that mortality rates were rising through most of the 20th century and only began to decline slightly in the mid-1990s. But because age adjustment and summarization emphasize the trends in older groups with high mortality rates at the expense of trends in younger, lower mortality groups, this interpretation conceals the fact that mortality has been systematically decreasing among younger individuals for many decades. Moreover, birth cohort analysis shows a decline in lifetime risk of dying from cancer beginning with individuals born between 1925 and 1934. As an example of the magnitude of this decrease, it is noteworthy that the cancer mortality rates for 30 to 39 year olds born between 1945 and 1954 was 29% lower than for people of the same age born three decades earlier. These observations too have been obscured by age-adjusted analyses that have largely reflected the experience of people born in the first quarter of the 20th century. The present analysis of unadjusted age- and birth cohort–specific rates shows that substantial changes in cancer mortality risk across the life span have been developing over the past half century in the United States.

An alternative to our approach would have been to analyze age-stratified incidence rates as a measure of the effects of prevention and age-stratified survival rates as a measure of the effects of earlier diagnosis and improved treatment. Such analyses are routinely reported by the NCI in their valuable annual reports on cancer rates (8–12). Such analyses, however, have two limitations. First, incidence and survival data are only available on the portion of the population covered by the SEER registries in place since 1973. Second, neither set of analyses can describe the generation-specific pattern of cancer mortality seen in birth cohort figures. Our analysis, by contrast, provides a composite picture of the net effects of changes in both incidence and survival upon cancer mortality rates.

Our analysis shows the fact that age-dependant heterogeneity in trends is revealed by divergence between weighed and unweighed average APC in mortality rates (Fig. 4). In the case of cancer mortality, a divergence between APCw and APCu has been evident since the mid-1960s. This divergence may be taken as a signal that further age-stratified analysis is required to fully describe the developing trends. Where efforts at improved prevention and treatment benefit younger individuals first, analysis of aggregate age-adjusted rates will inevitably fail to detect the results of such efforts until long after they take effect. In such cases, age-stratified analysis and age period cohort analysis will provide important additional perspectives.

This analysis and interpretation of cancer mortality trends over the past 50 years is not without limitations. Any interpretation of vital record data must acknowledge the fact that the recording of death events is subject to changes in coding (e.g., ICD-9 versus ICD-10), legislative requirements, and recording habits (20, 34). Secondly, the BAPC analysis presented requires significant a priori assumptions to be made, although this is no less true of frequentist approaches.

It is not our intention to suggest that the observed birth cohort effect in cancer mortality must result entirely from direct biological effects of very early life experience. Rather, the birth cohort effect is likely the net result of diverse behavioral, medical,
and technological factors operating throughout the life span. The value of birth cohort analysis in identifying shifts in the overall environmental milieu, including but not limited to early life experience, has long been recognized (13, 35).

Age-stratified cancer incidence data (see Supplementary Fig. S6) do not show the same pattern of decreases documented for mortality. The mortality decline we describe in this paper cannot therefore be attributed to an overall decline in cancer incidence. Rather, the net improvement in cancer mortality in birth cohorts born since 1925 seems to reflect a succession of public health and medical care efforts. For one site (lung cancer), the decline in mortality does parallel a decline in incidence. The first wave of antismoking efforts in the 1950s produced a steady decline in smoking that began to be reflected in cancer mortality in younger males as early as the 1950s and 1960s. Harris has shown that smoking in men declined in every successive birth cohort born since 1920, paralleling the decline in cancer mortality (36). However, in women, the decline in smoking was not evident until the cohort born in the 1940s. Further evidence that the birth cohort–dependent decline of cancer mortality is not purely a result of changes in smoking behavior is the fact that breast cancer mortality, for which a relationship to cigarette smoking has not been consistently shown (37), follows essentially the same birth cohort–dependent pattern as the all-site trends discussed in this report (38).

At about the same time as the hazards of cigarette smoking began to affect smoking behaviors, the first chemotherapeutic successes in childhood leukemia began to be noted (39) followed very closely by improvement in treatment of the lymphomas (40) and testicular cancers (41) of young adulthood. The final quarter of the century saw mortality reductions in older adults as a result of increasingly successful screening programs for breast (42), prostate (43), and colon cancer (44).

Whereas there are likely other contributory factors, this analysis suggests that efforts in prevention, early detection, and/or treatment have significantly affected our society’s experience of cancer risk. We are optimistic that ongoing efforts in very early cancer prevention (such as use of HB and human papillomavirus vaccines), as well as ongoing clinical trials of targeted therapies, will preserve the downward trend of cancer mortality. For the public and the health care community to be fully informed about trends in cancer mortality, we recommend supplementing time trends in age-adjusted cancer mortality with age-specific and cohort-specific analyses that provide more insight into the complex societal influences on the cancer death rate.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

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