Birth-Cohort Phenomenon in the Time Trends of Mortality from Ulcerative Colitis

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It has been suggested that the mortality trends of ulcerative colitis in England and Wales are shaped by an underlying birth-cohort phenomenon. This pattern implies that exposure to an environmental risk factor early in life plays a crucial role in the development of the disease. The authors tested whether the birth-cohort pattern is unique to British mortality statistics or a common feature of ulcerative colitis in western countries by using the vital statistics from England and Wales, Canada, Scotland, Switzerland, the Netherlands, and the United States. Ulcerative colitis death rates from the six countries were plotted against the periods of death or periods of birth. Mortality from ulcerative colitis increased in successive generations born throughout the second half of the 19th century. It peaked in subjects born between 1880 and 1890 and has declined since then. Strikingly similar patterns were found in the six countries and when women and men were analyzed separately. The birth-cohort pattern indicates that development of ulcerative colitis is strongly influenced by one or several environmental risk factors, which act during a short period early in life. In western countries, exposure to this risk has changed in a similar fashion. Am J Epidemiol 1999;150:359–66.

Despite much speculation, the etiology of ulcerative colitis remains unknown (1–3). Knowledge of disease epidemiology constitutes a powerful tool for detecting etiologic factors. In particular, changes over time are a key element in developing hypotheses about causative associations. A previous analysis of mortality data from England and Wales and from Scotland revealed a birth-cohort pattern underlying mortality from ulcerative colitis (4). The existence of a birth-cohort phenomenon implies that exposure to an environmental risk factor early in life plays a crucial role in the development of a disease and that after exposure occurs, the risk remains for the rest of a person’s life (5). The phenomenon can be identified only when consecutive generations experience rapidly changing rates of exposure to the same risk factor. Infection with Helicobacter pylori, for instance, is thought to underlie the birth-cohort phenomenon of peptic ulcer (6–9), and acquisition of a risk factor during childhood was predicted as a possible cause of peptic ulcer before the role of H. pylori had been fully recognized (9). Similarly, a birth-cohort pattern in the time trends of ulcerative colitis would have important implications for our understanding of the etiology of the disease, indicating that childhood exposure to environmental risk factors also influences its occurrence. Hence, the aim of the present study was to test whether the birth-cohort pattern represented a general characteristic of the time trends of ulcerative colitis.

MATERIALS AND METHODS

Data sources

Age- and gender-specific numbers of deaths from ulcerative colitis were requested from the national statistics offices of 15 different countries. Eleven countries made the data available, but only six provided data from the 1950s or earlier to 1994: Canada (1931–1994), England and Wales (1921–1994), the Netherlands (1950–1994), Scotland (1921–1994), Switzerland (1942–1994), and the United States (1952–1994). The resident populations of the six countries, broken down by 5-year age groups and gender, were also supplied by the respective national statistics offices.

The formats of the death certificates from the six countries included in the present analysis were similar.
Besides the underlying (primary) cause of death, the death certificates contained entries for other contributing (secondary) causes of death. Over the years, the death certificates were modified to extend the list of secondary causes and to list other disease conditions unrelated to the cause of death. The vital statistics available to us tabulated only the primary causes of death.

Although the code “ulceration/ulcer of intestine” has existed in England since 1891 and in Scotland since 1921, only since 1931 has this code been used to reflect ulcerative colitis without dilution by other disease entities (4). The Fifth through Ninth Revisions of the International Classification of Diseases were introduced from 1931 to 1979. The following numbers were assigned to code for ulcerative colitis in England and Wales and in Scotland (corresponding revision numbers and effective dates are also listed): International Classification of Diseases (ICD), Fifth Revision (ICD-5) since 1931, codes 119 and 120(b); ICD-6 since 1940, codes 119 and 120(b); ICD-7 since 1950, code 572.2; ICD-8 since 1968, code 563.1; and ICD-9 since 1979, code 556. In Scotland, ulcerative colitis and Crohn’s disease were listed together between 1950 and 1978. Ulcerative colitis has been coded in Canada since ICD-5 was introduced in 1931. The Netherlands and the United States started listing ulcerative colitis in 1950 and 1962, respectively. For US mortality data during the period of 1952–1961, we relied on data published by Acheson (10). Until 1968, the Swiss Federal Office for Statistics used its own modified version of the ICD to record causes of death: since 1942, code 152(c); since 1951, code 557. Starting in 1969, Switzerland has also used ICD-8 (and subsequently ICD-9).

Data analyses

Age- and gender-specific death rates were calculated for consecutive 10-year periods and 10-year age groups. For instance, the total number of deaths from 1965 until 1974 among men aged 45–54 years was divided by the corresponding number of male residents of the same age group who lived during the same time that the deaths occurred. Death rates were expressed per million living population. The median for each age group and time period was labeled, for instance, 50 indicated the age group 45–54 years and 1970 the time period 1965–1974. Each time period was comprised of 10 consecutive years except for the first or last time period, which covered fewer years depending on data availability. The age-specific death rates were plotted against the period of death to obtain period-age contours or against the period of birth to obtain cohort-age contours. In the present context, the terms “cohort,” “birth cohort,” or “generation” are used as synonyms to describe a group of subjects born during the same time period of 10–20 years.

An age-standardized cohort mortality ratio (SCMR) was calculated as a summary statistic of the overall mortality associated with each consecutive birth cohort (11). Age standardization was used to control for the changing contribution of different age groups to the mortality of different cohorts. The SCMR was computed according to the method of indirect standardization, dividing the number of observed deaths in each birth cohort by the number of expected deaths in that particular birth cohort. The expected number of deaths in each cohort corresponded to the sum of the age-specific cohort population multiplied by the average age-specific death rates for all cohorts. The ratio of observed to expected was expressed as a percentage and was plotted against the year of birth.

RESULTS

The left panels of figures 1 and 2 display the period-age contours of ulcerative colitis in England and Wales among women and men, respectively. Mortality from ulcerative colitis was generally higher in the older than in the younger age groups. For both genders, the period-age contours appear to be arranged in a fan-like pattern. This pattern originates from the progressively steeper decline in the time trends of mortality from ulcerative colitis among consecutive age groups. For the oldest age group, death rates rose for a period of 30–40 years before leveling off or starting to decline smoothly. The contours for the next younger age group, those persons dying at age 65–75 years, show a shorter initial rise followed by a more pronounced decline compared with the oldest age group. As the age at death decreases, the decline in the period-age contours gradually becomes steeper.

Note that the logarithmic scale of the ordinate tends to compress large changes in death rates among the older age groups and to expand small changes among the younger age groups. However, the logarithmic scale also makes it easier to compare the relative changes in consecutive period-age contours and to visualize them on a single graph. The same age-specific death rates as those depicted in the left panels of figures 1 and 2 were plotted against period of birth, as shown in the right panels of both figures. For instance, persons who died at age 80 years between 1930 and 1990 were born between 1850 and 1910. Similarly, persons who died at age 20 years between 1930 and 1990 were born between 1910 and 1970. When plotted against the period of birth rather than the period of death, the death rates aligned as cohort-age contours covered a time period of 120 years, much longer than the 60 years cov-
FIGURE 1. Female age-specific death rates of ulcerative colitis in England and Wales, plotted as period-age contours (panel A) and as cohort-age contours (panel B). Each curve represents subjects dying from ulcerative colitis at a different age. Ages (in years) are listed vertically in panel A, and the same ages apply to the line patterns in panel B.

FIGURE 2. Male age-specific death rates of ulcerative colitis in England and Wales, plotted as period-age contours (panel A) and as cohort-age contours (panel B). Each curve represents subjects dying from ulcerative colitis at a different age. Ages (in years) are listed vertically in panel A, and the same ages apply to the line patterns in panel B.

As mentioned previously, the logarithmic plots tend to emphasize the recent decline at the expense of concealing some of the initial rise. The underlying birth-cohort phenomenon becomes more evident if the individual cohort-specific death rates are summarized as an SCMR, as shown in figures 3 and 4. A vertical line perpendicular to the abscissa would intersect the cohort-age contours for persons who were born during the same time period but died from ulcerative colitis at a different age and during different time periods. Every point on the SCMR curve thus represents an approximation of the average death rate among persons in different age groups who were born during the same time period. As shown, average mortality increased among cohorts born between 1850 and 1890. Among women...
and men alike, peak mortality occurred for cohorts born in 1890 before declining markedly.

Since the time trends for women and men were identical, we plotted the death rates for both gender groups together when we analyzed the data from other countries. Besides England and Wales, patterns suggestive of an underlying birth-cohort phenomenon were also evident from the cohort-age contours for the other countries included in the present analysis (figure 5). For all countries, the individual cohort-age contours were aligned in one hyperbola characterized by an initial rise and a subsequent decline. As shown, the initial rise was most pronounced for England and Wales, the Netherlands, Switzerland, and Scotland. It was less obvious from the cohort-age contours for the United States and Canada. However, for all six countries, the contours for older age groups were characterized by an initial rise or a flat course, whereas those for the middle-aged groups revealed a decline, which was most accentuated for the youngest age groups.

Figure 6 shows the trends in the SCMRs from all six countries that were included in the present analysis. As shown, similar trends were observed in all countries. After an initial rise, mortality of consecutive birth cohorts from England and Wales, the Netherlands, and Switzerland peaked in 1890 and declined thereafter. Peak mortality occurred around 1880 in the United States and in Scotland, and it was only poorly defined in Canada. If women and men are analyzed separately, SCMR curves of similar appearance are obtained.

**DISCUSSION**

The present study showed that mortality from ulcerative colitis increased continuously among successive generations born during the second half of the 19th century, peaked among subjects born between 1880 and 1890, and has progressively decreased since then. Such a birth-cohort pattern was identified for both women and men as well as in the vital statistics from different countries.

The mortality and incidence of ulcerative colitis in different countries were shown to correlate with each other (12). A geographic correlation was also demonstrated between mortality and hospitalization rates of ulcerative colitis in individual states of the United States (13). Disease activity tends to be the most severe at onset, and the majority of deaths from ulcerative colitis occur within the first 2 years after initial diagnosis (14, 15). Mortality from ulcerative colitis is also highest in patients with pancolitis (15). Recently, mild manifestations of ulcerative colitis, such as ulcerative proctitis or left-sided colitis, have been diagnosed with increasing frequency (16). However, these forms of ulcerative colitis contribute little to the overall mortality of the disease (17, 18), which could explain the steeper decline in mortality from ulcerative colitis as compared with the incidence data. The general parallel between the incidence and mortality rates may stem from the fact that the most severe clinical presentation and the highest mortality associated with inflammatory bowel disease tend to occur within a few years of onset of the disease (14, 15). Overall, these correlations suggest that death rates may be a reliable morbidity parameter for severe forms of ulcerative colitis.
Temporal changes in the case-fatality rate could affect the epidemiologic parallel between incidence and mortality. Changes in medical coding, diagnosis, and therapy would also influence the relation between the true time trends of ulcerative colitis and their reflection in the mortality data. For instance, introduction of a new diagnostic code would be manifest as an abrupt change occurring in all age groups during the same time period. As a matter of fact, such a phenomenon can be readily observed in Scottish data from 1950 to 1978, when Crohn's disease and ulcerative colitis were lumped together as one code. Advances in diagnostic techniques, such as endoscopy and histopathology, almost certainly would have led to greater recognition of ulcerative colitis and to an increase in its certification, running counter to the current decline in mortality.

From an epidemiologic perspective, it is difficult to reconcile rising mortality among the older age groups occurring simultaneously with declining mortality among the younger age groups. Improvements in health care, changes in diagnostic standards, and advances in medical treatment should affect all different age groups. Thus, a fan-like pattern is very suggestive of an underlying birth-cohort phenomenon. The majority of external influences, unrelated to the trends of ulcerative colitis, should have affected all different age groups. They would have occurred as period effects of the period-age contours, that is, as parallel rises and falls or as simultaneous discontinuities of all age-specific curves. These influences are far less likely to have caused the peculiar alignment of individual cohort-age contours to form one hyperbola. Overall, each of these alternative explanations appears less
plausible than a true generational effect underlying the time trends of ulcerative colitis.

On multiple occasions, cohort analyses have proven useful in developing hypotheses about disease etiologies (19–22). The similarity of the time trends of mortality from ulcerative colitis for both genders and among different countries strengthens the validity of our findings. The use of vital statistics to study the epidemiology of ulcerative colitis has several apparent advantages. Although studies from single medical centers show disease behavior in small, particular fractions of the population, vital statistics cover the entire population without selection or referral biases. Compared with statistics from an individual hospital, vital statistics are less likely to be biased by differences in diagnostic and therapeutic standards. They also tend to cover more uniformly all social classes of the entire population. Even given a low case-fatality rate, mortality statistics of ulcerative colitis include far more cases than are available at any individual medical centers. The most relevant advantage of using mortality statistics relates to the long time period that they cover consistently, unlike the statistics for any other morbidity parameter. Lastly, the general availability of mortality statistics makes it possible to compare the trends among several different countries.

Time trends of diseases are influenced simultaneously by age, period, and generation effects (5–7). Age effects refer to the aging process of an organism and its related odds of developing a certain disease. Period effects are environmental effects attributed to and defined by a given time period. Period effects exert their influence on subjects of different ages and different generations during the same time period. Typical examples are disease epidemics and the effects of wars and natural disasters. Finally, generation or cohort effects are environmental influences attributed to the singular experience of a specific cohort of subjects born during the same time period. Cohort effects can encompass exposure to an environmental agent or acquisition of a risk factor. The risk factors must operate before the disease becomes evident, that is, the environmental risk must be acquired by specific cohorts early in life. The risk must then be retained throughout a lifetime. To be associated with the year of birth, cohort effects must change relatively rapidly among consecutive generations and exert their influence within a short time period. Typical of a cohort effect are the aftereffects of rubella infection. Rubella embryopathy and its aftereffects tend to be diagnosed at different times among persons of different ages who belong to the same generation born shortly after a rubella epidemic occurs.
A birth-cohort phenomenon in the mortality trends of ulcerative colitis in England and Wales and in Scotland has been reported previously (4). The present study tested whether such a phenomenon was unique to the British population or whether it represented a general characteristic of ulcerative colitis. We planned to include as many countries as possible in the analysis. Six countries had data available that covered a sufficiently long time period for a meaningful cohort analysis. A birth-cohort phenomenon was observed in all countries, despite their diverse geographic locations, health care systems, and social and political histories. The existence of a birth-cohort phenomenon underlying all mortality from ulcerative colitis indicates that the occurrence of the disease is shaped by one or several risk factors acquired during gestation, childhood, or adolescence. The risk exposure must have varied relatively quickly during the past 120 years. The ubiquity of the phenomenon among industrialized countries also implies that the risk factor is common among western cultures and is independent of their individual national characteristics. Exposure to the unknown environmental influence occurred until 1880–1890 of the 19th century and declined thereafter.

During the 19th century, all western countries underwent industrialization and urbanization of large strata of their populations. An initial "crowding effect" associated with an increased spread of infections was followed by improved hygiene standards. It may be hypothesized that transmission of a parasite or other infectious organisms underlies the initial steps in the pathogenesis of ulcerative colitis. Contrary to most diseases, ulcerative colitis tends to affect a disproportionately high fraction of Jews and persons from urban communities with a more affluent, educated, and professional background than the rest of the population (2, 3). Such characteristics are more likely to be associated with stricter adherence to hygiene measures. It is tempting to speculate that improved hygiene was initially associated with an increased risk for germ transmission or a selection of microorganisms that precipitated the occurrence of ulcerative colitis. Many of the more advanced hygiene practices were first introduced among the more affluent strata of the population. In two recent studies from England, Crohn's disease but not ulcerative colitis was found to be more common in subjects whose household amenities during infancy included a hot-water tap and a separate bathroom (23, 24). Nevertheless, it is possible that the rise of ulcerative colitis during the 19th century was induced by a moderate increase in hygiene, first restricted to a few strata of the population. The disease may have subsequently declined when further improvements in hygiene standards affected all or most strata of the population. The birth-cohort pattern clearly demonstrates that irrespective of its particular nature, the factor modulating the occurrence of ulcerative colitis must reside in the environment outside the body. The risk factor acts during a short period early in life. In many western countries, exposure to this risk has changed in a similar fashion.

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REFERENCES