A Cohort Study of Twins and Cancer

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Abstract

Given the current explosion of knowledge of the genetics and molecular biology of cancer, the possibility of widespread testing for inherited predisposition to cancer has been raised. The main objective of this study was to assess the effect of inherited predisposition on cancer mortality among the National Academy of Sciences-National Research Council Twin Registry. The twins were white male United States veterans of World War II, who were born during the period 1917–1927. The follow-up period was from 1946 to 1990, and cause of death was determined with the use of death certificates. We compared concordance for death from cancer among 5690 monozygotic twin pairs to that among 7248 dizygotic pairs. A possible effect of inherited predisposition to death from cancer was considered present if concordance for cancer mortality among monozygotic twin pairs was greater than it was among dizygotic twin pairs. Among monozygotic and dizygotic twins, a total of 1918 cancer deaths was observed. Concordance for death from cancer at all sites among monozygotic twins was higher than it was among dizygotic twins (overall rate ratio, 1.4; 95% confidence interval, 1.0–2.0). For each zygosity group, two or fewer pairs were observed to be concordant for death from cancer of a specific site, with the exception of lung cancer. A cohort analysis, taking duration of follow-up into account, found that the risk of cancer death among monozygotic twins who survived the death of their cotwin from cancers not associated with smoking was greater than among dizygotic twins (overall rate ratio, 1.9; 95% confidence interval, 1.0–3.5); the corresponding ratio among survivors of death of a cotwin from smoking-associated cancer was 1.4 (95% confidence interval, 0.9–2.3). The moderate excess concordance for all cancer mortality that we observed among monozygotic compared with dizygotic twins probably reflects both greater environmental similarity within monozygotic twin pairs than within dizygotic twin pairs, as well as a true effect of inherited predisposition on cancer mortality. Nonetheless, our results for monozygotic twins demonstrate that knowledge of the cancer mortality experience of an individual will not commonly have strong predictive value for the experience of another individual who has identical genes.

Introduction

Numerous single gene traits have been found to be associated with cancer, and in addition it has been suggested that combinations of multiple genes that predispose to cancer may be important in the development of cancer in individuals (1–2). Although the currently known predisposing genes do not explain a large proportion of cancers, increasing recognition of such genes would likely lead to calls for screening of germline DNA among the general population for cancer prevention and early diagnosis (3).

The potential benefit of any approach to cancer prevention that is based on population-wide screening of germline DNA of healthy people will be related to the proportion of cancer deaths that can be attributed to inherited predisposition. Large twin studies can help to put in perspective the magnitude of this proportion. Although precise quantification of the effects of the genes that predispose to cancer is beyond the power of epidemiological studies using existing twin registries (1), the virtually identical genetic makeup of monozygotic twins makes them particularly suitable for evaluating the possibility that the presence of single or multiple predisposing genes in an individual commonly will be strongly predictive of the development of cancer.

Prior studies in twins have not demonstrated that monozygotic twins are substantially more likely than dizygotic twins to be concordant for cancer or cancer death (4–7). However, the number of cancer cases and the number of sites studied have been limited in some studies. Our study of the NAS-NRC2 Twin Registry reports the largest number of cancer deaths yet studied in a twin cohort.

Materials and Methods

The creation of the NAS-NRC Twin Registry and the methods for determining zygosity of the twins have been described elsewhere in detail (8, 9). White male multiple births occurring in the general population of the United States during the period 1917–1927 were identified through a search of birth certificates. Approximately 93% of the estimated number of twin births were ascertained. Of these, the Master Index file of the VA indicated that both members of 15,924 pairs of twins had served in the armed forces of the United States during the World War II era. These veterans compose the NAS-NRC Twin Registry.

Zygosity has been determined for 13,486 pairs of twins in the panel. Approximately 11,000 of the zygosity determinations

2 The abbreviations used are: NAS-NRC, National Academy of Sciences-National Research Council; VA, Veterans Administration; BIRLS, Beneficiary Identification and Records Locator Subsystem; CI, confidence interval; O/E, observed/expected.
were based on questionnaire data about the similarity of the twins as children. In addition, zygosity was determined for approximately 1950 pairs based on blood typing and for approximately 800 pairs based on physical characteristics, primarily fingerprints. Cross-validation of these results (7, 9) and the work of other investigators (10–12) suggest that the questionnaire data alone allow correct zygosity determination of approximately 95% of the pairs.

Deaths of the twins were identified with use of either the BIRLS computerized file of the VA or the analogous manual file that BIRLS replaced in 1972. For individual twins who BIRLS indicated were deceased, death certificates were requested subsequently from the VA to determine cause of death. Death certificates are filed with the VA as a prerequisite for the disbursement of death benefits.

Assessment of the completeness of mortality ascertainment utilized the computerized vital status data of the Social Security Administration. These data, when used in conjunction with BIRLS, permit nearly complete mortality ascertainment (13). The BIRLS computerized file of the VA indicated that through 1990, 9,364 of the 31,848 twin individuals in the NAS-NRC Twin Registry had died. The vital status data of the Social Security Administration indicated that of the 20,823 twins whose Social Security numbers were recorded in the NAS-NRC Twin Registry, the BIRLS file had ascertained 98.1%. For 8902 (95.1%) of the 9364 deaths ascertained through BIRLS, cause of death was determined from death certificates submitted to the VA.

The 886 twin pairs in which at least 1 twin died prior to 1946 were excluded from analysis. Almost all of these deaths were due to trauma during World War II. In addition, 2100 twin pairs were excluded from analysis because of unknown zygosity; the vast majority could not be classified according to zygosity because they did not respond to the questionnaire for zygosity determination. Concordance rates for cancer mortality among twin pairs of unknown zygosity were intermediate to the rates among monozygotic and dizygotic twins, as would be expected among an unbiased group of twins composed of both monozygotic and dizygotic twin pairs.

Concordance Analysis. With the use of the frequency of a cause of death among the twins in each zygosity group, the number of randomly concordant pairs that were expected in that zygosity group was calculated. For example, assume C is the number of monozygotic twin individuals dying with cancer and N is the number of monozygotic twin pairs. Then the number of monozygotic pairs expected to be concordant for cancer death is \((C/N)(N/2)\). Concordance rates for cancer mortality among twin pairs of unknown zygosity were intermediate to the rates among monozygotic and dizygotic twins, as would be expected among an unbiased group of twins composed of both monozygotic and dizygotic twin pairs.

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Cohort analysis. The mortality experience of the 294 monozygotic and 435 dizygotic survivors of a smoking-associated cancer death of a cotwin is summarized in Table 3. Statistically significant elevations above expected values were observed for all cancer mortality among monozygotic twins (O/E ratio, 2.3; 95% CI, 1.5–3.2) and dizygotic twins (O/E ratio, 1.6; 95% CI, 1.1–2.2). Similar to the concordance analysis the overall rate ratio, the ratio of the O/E ratio among monozygotic twins to the O/E ratio among dizygotic twins was 1.4 (95% CI, 0.9–2.3; not shown in Table 3).

Statistically significant elevations above expected values are shown in Table 3 for deaths from all smoking-associated cancer sites among monozygotic (O/E ratio, 2.5; 95% CI, 1.5–4.0) and dizygotic (O/E ratio, 2.0; 95% CI, 1.3–2.9) twins; the overall rate ratio was 1.3 (95% CI, 0.7–2.4).

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Table 1  Concordance for mortality, according to zygosity *

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>ICD-8th code</th>
<th>Monozygotic pairs (n = 5690)</th>
<th>Dizygotic pairs (n = 7248)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>One</td>
<td>Both</td>
</tr>
<tr>
<td>All cancer sites</td>
<td>140-209</td>
<td>674</td>
<td>61'</td>
</tr>
<tr>
<td>Smoking-associated cancers</td>
<td>See below</td>
<td>384</td>
<td>21</td>
</tr>
<tr>
<td>Cancers not related to smoking</td>
<td>See below</td>
<td>346</td>
<td>12</td>
</tr>
</tbody>
</table>

Selected specific cancer sites:
- Buccal cavity/pharynx: 140-149
- Esophagus: 150
- Stomach: 151
- Colon or rectum: 153-154
- Liver: 155-156
- Pancreas: 157
- Larynx: 161
- Lung: 162
- Skin: 172-173
- Prostate: 185
- Bladder: 188
- Kidney: 189
- Brain or central nervous system: 191-192
- Non-Hodgkin's lymphoma: 200, 202, 203, 208
- Leukemia: 204-207

<table>
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</tr>
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* For none of the specific cancer sites, except lung cancer, was the frequency of concordance significantly elevated above that expected by chance, nor did the frequency of concordance differ significantly between monozygotic and dizygotic twins.
* ICD, International Classification of Diseases.
* For example, one twin in the pair may have died with prostate cancer and his cotwin died with colon cancer.
* A twin pair in which one twin died with prostate cancer and the other with lung cancer would be considered concordant for cancer but not concordant for smoking-associated cancer or for cancer not related to smoking.
* Cancer sites with fewer than 10 cancer deaths in a zygosity group are not shown.
Mortality among survivors of death of cotwin from smoking-associated cancer

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Monozygotic (n = 294)</th>
<th>Dizygotic (n = 435)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of observed deaths</td>
<td>Ratio of observed to expected (95% CI)</td>
</tr>
<tr>
<td>All cancers</td>
<td>30 2.3 (1.5–3.2)</td>
<td>35 1.6 (1.1–2.2)</td>
</tr>
<tr>
<td>All smoking-associated cancer sites</td>
<td>19 2.5 (1.5–4.0)</td>
<td>24 2.0 (1.3–2.9)</td>
</tr>
<tr>
<td>All cancer sites not related to smoking</td>
<td>11 1.9 (0.9–3.4)</td>
<td>11 1.2 (0.6–2.1)</td>
</tr>
<tr>
<td>Smoking-associated cancer sites</td>
<td>3 8.8 (1.8–25.6)</td>
<td>1 1.8 (0.0–9.8)</td>
</tr>
<tr>
<td>Buccal cavity and pharynx</td>
<td>11 1.4 (1.0–5.7)</td>
<td>19 2.2 (1.3–3.4)</td>
</tr>
<tr>
<td>Lung</td>
<td>11 5.5 (0.1–30.7)</td>
<td>1 3.4 (0.0–18.6)</td>
</tr>
<tr>
<td>Larynx</td>
<td>0 0.0 (0.0–10.0)</td>
<td>2 3.3 (0.4–12.1)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>0 0.0 (0.0–10.0)</td>
<td>0 0.0 (0.0–6.6)</td>
</tr>
<tr>
<td>Kidney</td>
<td>2 3.1 (0.4–11.1)</td>
<td>1 1.1 (0.0–5.2)</td>
</tr>
<tr>
<td>Bladder</td>
<td>2 7.1 (0.6–25.8)</td>
<td>0 0.0 (0.0–8.0)</td>
</tr>
</tbody>
</table>

Statistically significant elevations were observed among monozygotic twins for death from cancer of the pharynx/buccal cavity (O/E ratio, 8.8; 95% CI, 1.8–25.6) and cancer of the lung (O/E ratio, 2.1; 95% CI, 1.0–3.7). Among dizygotic twins, significant elevations in risk were observed only for death from lung cancer (O/E ratio, 2.2; 95% CI, 1.3–3.4).

For the 285 monozygotic and 397 dizygotic survivors of death of a cotwin from cancers not related to smoking, the differences in cancer mortality incidence between the zygosity groups were more pronounced. Among monozygotic twin survivors, the observed:expected mortality ratio from cancer was 1.6 (95% CI, 1.0–2.4); among dizygotic twins the ratio was 0.9 (95% CI, 0.5–1.3), for an overall rate ratio of 1.9 (95% CI, 1.0–3.5). The only specific cancer site for which there was a statistically significant excess of mortality was esophageal cancer among monozygotic twins. The observed number of deaths was 3, whereas 0.4 was expected (O/E, 7.7; 95% CI, 1.6–22.6).

Survival Analysis. With the use of the product-limit method, follow-up of the monozygotic twins whose cotwin died from smoking-associated cancer found the proportion dying of cancer before age 63 years to be 14.0%; among the monozygotic twins whose cotwins died from cancers not associated with smoking, 9.4% died of cancer before age 63 years. The corresponding proportions among dizygotic twins were 10.1 and 6.4%, respectively. Among all twins in the cohort, 4.9% died of cancer before age 63 years.

Discussion

Our study found a moderate, statistically significant difference in concordance between monozygotic and dizygotic twins for deaths from all cancers combined (overall rate ratio, 1.4), suggesting a possible role for inherited predisposition in the etiology of cancer mortality in the general population. The difference in risk between the zygosity groups was greater among survivors of the death of a cotwin not associated with smoking. In addition, there was a nonsignificant excess concordance among monozygotic twins compared to dizygotic twins for smoking-related cancer deaths, and this is attributable at least in part to the greater concordance for smoking among monozygotic twins compared with dizygotic twins (19). Overall, our findings are consistent with prior studies among twins performed in northern Europe and the United States that have suggested that inherited predisposition does not explain a large proportion of all cancers or of all cancer mortality (4–7). The explanation for the difference in the findings for smoking-related cancer mortality and death from cancers not related to smoking may be that in smokers, a relatively small genetic contribution to cancer mortality may be overwhelmed by the risk associated with smoking. Moreover, genetic effects for cancer deaths may be more prominent among younger persons (e.g., <50 years of age); however, the small number of such deaths precluded detailed study of this issue in our cohort.

It is useful to put in perspective the magnitude of the differences between the zygosity groups in concordance rates for all cancer mortality (overall rate ratio, 1.4) by comparison with other chronic diseases. A previous study performed in the NAS-NRC Twin Registry examined concordance for several chronic diseases. The overall rate ratio for schizophrenia was 5.4; hypertension, 2.4; diabetes, 2.4; peptic ulcer disease, 1.7; ischemic heart disease, 1.6; and chronic obstructive pulmonary disease, 1.5 (20).

Although a greater degree of concordance for death from cancer was observed among monozygotic compared with dizygotic twins, death from cancer in a specific monozygotic cotwin did not indicate that his brother was likely to die soon of cancer. Indeed, fewer than 1 of 8 monozygotic twins whose cotwin died of cancer could be expected to die of cancer if they lived until age 63 years. Of the deaths that did occur, noncancer causes exceeded cancer causes; of the pairs concordant for cancer death, fewer than 25% were concordant for death from cancer of the same site.

Statistical power was limited for the detection of effects of inherited predisposition through comparison of site-specific concordance for cancer mortality among monozygotic twins to that among dizygotic twins. However, some conclusions can be drawn. For lung cancer mortality, we found greater concordance among dizygotic than monozygotic twins (Table 1). These findings have been analyzed in greater detail in a study dealing exclusively with death from lung cancer, and they suggest that the effect of inherited predisposition on lung cancer mortality in white men older than age 50 years is negligible at the population level (21).

Estimates of the proportion of colon cancers attributable to hereditary nonpolyposis colorectal cancer have often been in the range of 4–6%, with some estimates as low as 1% and others as high as 13% (22–24). In our study, of the 91 monozygotic twin pairs with a colon cancer death, only 1 pair was concordant; of the 111 dizygotic twin pairs with a colon cancer death, 2 pairs were concordant. If the estimate that 13% of colon cancers are attributable to inherited predisposition was correct, the cotwins of 12 of the monozygotic twins who died of colon cancer would be expected to be at very high risk of colon cancer; however, only one such death was observed.

Several caveats for interpretation of our data should be stated: (a) survivors of twins dying with cancer, particularly cancers that can be treated effectively, may be more likely to have early signs of cancer detected and, consequently, to have death from the disease prevented. As a result, an excess of concordance for cancer morbidity might not translate into an excess of concordance for cancer mortality. (b) about three-fourths of the brothers of affected twins were still alive through 1990 when the ages of the twins ranged from 63 to 73 years.
Therefore, they are still at risk for death from cancer. However, it is a general rule that the effect of inherited predisposition tends to wane with age (25). Therefore, we would be surprised if the O/E ratios for concordance for death with cancer increase as the age of the cohort increases. (c) the study population was restricted to white male veterans, and potential effects of this restriction should be kept in mind when generalizing the results. (d) Hereditary forms of cancer (e.g., colon cancer) may be less aggressive than other forms and, therefore, less likely to be reported in a mortality study such as ours (26).

The accuracy of death certificates for the ascertainment of cancer has been evaluated in a study that compared hospital diagnoses of cancer with the underlying cause (only) on the death certificate (27). The study found 82.7% detection and confirmation rates, and there was considerable variation in these rates according to site of cancer. However, for the two most common cancer causes of death in our cohort, lung cancer and colon cancer, these rates were above 92%.

In conclusion, the moderate excess concordance of cancer mortality that we observed among monozygotic compared with dizygotic twins probably reflects not only greater environmental similarity (e.g., smoking behavior) within monozygotic twin pairs than within dizygotic twin pairs but also the effect of inherited predisposition. Identifying the etiological genes may be useful to predict and prevent development of cancer in defined small groups of people. However, our results for monozygotic twins may have relevance to widespread screening for inherited predisposition to cancer because they demonstrate that knowledge of the cancer mortality experience of an individual will not commonly have strong predictive value for the experience of another individual who has identical genes.

References
A cohort study of twins and cancer.

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