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-NRC[2] 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

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 individuals. $N/2$ is the number of monozygotic twin pairs. Then the number of monozygotic pairs expected to be concordant for cancer death is $(C/N)^2(N/2)$. For the concordance analysis, causes of death were considered regardless of whether they appeared on the death certificate as underlying or associated causes. (The cohort analysis, described later, focused on only underlying cause of death.)

Monozygotic twins are virtually genetically identical, whereas dizygotic twins, as for any sibling, share on average about one-half of their genes. If monozygotic twins share environment no more than dizygotic twins share environment, then a greater similarity or concordance for a trait among monozygotic than among dizygotic twins would be evidence for effects of inherited predisposition of that trait. However, the assumption that environmental covariance does not vary by zygosity is sometimes violated in practice (8). Lacking specific knowledge of the degree to which sharing of pertinent environmental factors differs between monozygotic and dizygotic twins, greater concordance for a trait among monozygotic than

among dizygotic twins should be interpreted as indicating the possibility of effects of inherited predisposition. Conversely, concordance among monozygotic twins that is equal to that among dizygotic twins (or lower concordance among monozygotic twins) may indicate the absence of effects of inherited predisposition (14). When concordance among dizygotic twins exceeds that expected by chance alone, familial influences are considered to be present.

Cohort Analysis. This analytic approach takes time into account and also allows the calculation of absolute risk. We performed a cohort analysis that examined the mortality experience among survivors of death of a cotwin from cancer (underlying cause only). We stratified these survivors into two groups, according to whether the cotwin died of smoking-associated cancer. Cancers considered to be smoking associated were those of the lung, larynx, esophagus, kidney, bladder, pancreas, and buccal cavity/pharynx (15). The underlying cause mortality of the individuals in each of these two groups was compared to the underlying cause mortality of the United States population with the use of 5-year age-, sex-, race-, and calendar time-specific rates. The incidence of mortality of twins in the NAS-NRC Twin Registry has been about 18% below that of the general population. A favorable mortality experience has been characteristic of all World War II veterans (16), and this fact is unlikely to bias comparison of the mortality of monozygotic to dizygotic twins.

An overall rate ratio is defined as the ratio of the observed: expected ratio of cancer deaths in monozygotic twins to the observed:expected ratio in dizygotic twins. The 95% confidence limits of the overall rate ratios were computed with a log-linear model, with the use of a modified version of the GLIM computer program (Ver. 3.77; Royal Statistical Society, London, United Kingdom).

Survival Analysis. The proportion of twins (whose cotwin had died of cancer at any age) that died from cancer by age 63 years was calculated by the product-limit method (17). Age 63 years is the minimum age that all members of the cohort would have attained had they lived through 1990.

Results

Through 1990, 2,879 (25.3%) of the 11,380 monozygotic and 4,014 (27.7%) of the 14,496 dizygotic twins were reported deceased.

Concordance Analysis. More than two concordant pairs were observed within a zygosity group for all cancer mortality combined, for the subgroups smoking-associated cancer deaths and cancers deaths not related to smoking, and for only one specific site, lung cancer (Table 1). A detailed analysis of the lung cancer mortality data has been presented elsewhere (18). The observed:expected ratio of concordant pairs among dizygotic twins significantly exceeded one for death due to all cancers (1.5), smoking-associated cancers (2.4), and cancers not related to smoking (1.4), suggesting familial influences for each of these (Table 2). Because the observed:expected concordance ratio among monozygotic twins significantly exceeded the corresponding ratio among dizygotic twins, possible effects of inherited predisposition were suggested for death due to all cancers (overall rate ratio, 1.4; 95% CI, 1.0–2.0). The overall rate ratio was also 1.4 (95% CI, 0.7–3.1) for deaths from cancers not related to smoking, and for deaths from smoking-associated cancers the overall rate ratio was 1.1 (95% CI, 0.6–1.9). For none of the specific cancer sites, except lung cancer, did the frequency of concordance within a zygosity group significantly exceed the expected, nor did the frequency

Table 1   Concordance for mortality, according to zygosity[a]

Cause of death	ICD-8[b] code	Monozygotic pairs (n = 5690)		Dizygotic pairs (n = 7248)	
		One	Both	One	Both
All cancer sites	140–209	674	61[c]	988	67
Smoking-associated cancers[d]	See below	384	21	542	30
Cancers not related to smoking	See below	346	12	494	13
Selected specific cancer sites					
Buccal cavity/pharynx	140–149	24	1	41	0
Esophagus	150	34	0	32	0
Stomach	151	27	0	27	1
Colon or rectum	153–154	90	1	109	2
Liver	155–156	10	1	21	0
Pancreas	157	38	0	55	0
Larynx	161	11	0	25	0
Lung	162	259	10	352	21
Skin	172–173	18	0	28	0
Prostate	185	29	0	68	0
Bladder	188	20	0	31	0
Kidney	189	21	0	28	0
Brain or central nervous system	191–192	23	0	40	0
Non-Hodgkin's lymphoma	200, 202, 203, 208	41	0	53	0
Leukemia	204–207	17	0	45	1

[a] 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.
[b] ICD, International Classification of Diseases.
[c] For example, one twin in the pair may have died with prostate cancer and his cotwin died with colon cancer.
[d] 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.
[e] Cancer sites with fewer than 10 cancer deaths in a zygosity group are not shown.

Table 2   Concordance for mortality from all cancers, smoking-associated cancers, and cancers not related to smoking among 5690 pairs of monozygotic twins and 7248 pairs of dizygotic twins

Concordance	All cancers		Smoking-associated cancers		Cancers not related to smoking	
	Monozygotic	Dizygotic	Monozygotic	Dizygotic	Monozygotic	Dizygotic
No. observed	61.0	67.0	21.0	30.0	12.0	13.0
No. expected	27.8	43.4	8.0	12.5	6.0	9.3
Observed:expected ratio	2.2	1.5	2.6	2.4	2.0	1.4
95% confidence interval	1.7–2.8	1.2–2.0	1.6–4.0	1.6–3.4	1.0–3.5	0.7–2.4
Overall rate ratio[a]	1.4		1.1		1.4	
95% confidence interval	1.0–2.0		0.6–1.9		0.7–3.1	

[a] Overall rate ratio is the ratio of observed to expected concordance in the monozygotic twins to the ratio of observed to expected concordance in the dizygotic twins.

of concordance differ significantly between monozygotic and dizygotic twins. For death with colon cancer, one concordant pair was observed among monozygotic twins (O/E ratio, 2.7; 95% CI, 0.1–15.1). Among dizygotic twins, two such concordant pairs were observed (O/E ratio, 4.5; 95% CI, 0.5–16.4).

For the 61 monozygotic pairs in which both twins died with cancer, the specific cancer sites were cross-indexed (not shown). Of the 122 cancers in these pairs, 47 were lung, 10 colorectal, 6 stomach, and 6 buccal. Excess occurrences of patterns consistent with known cancer syndromes or possibly new complexes of cancers were not apparent.

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).

Table 3   Mortality among survivors of death of cotwin from smoking-associated cancer

Cause of death	Monozygotic (n = 294)		Dizygotic (n = 435)	
	No. of observed deaths	Ratio of observed to expected (95% CI)	No. of observed deaths	Ratio of observed to expected (95% CI)
All cancers	30	2.3 (1.5–3.2)	35	1.6 (1.1–2.2)
All smoking-associated cancer sites	19	2.5 (1.5–4.0)	24	2.0 (1.3–2.9)
All cancer sites not related to smoking	11	1.9 (0.9–3.4)	11	1.2 (0.6–2.1)
Smoking-associated cancer sites				
Buccal cavity and pharynx	3	8.8 (1.8–25.6)	1	1.8 (0.0–9.8)
Lung	11	2.1 (1.0–3.7)	19	2.2 (1.3–3.4)
Larynx	1	5.5 (0.1–30.7)	1	3.4 (0.0–18.6)
Esophagus	0	0.0 (0.0–10.0)	2	3.3 (0.4–12.1)
Kidney	0	0.0 (0.0–10.9)	0	0.0 (0.0–6.6)
Pancreas	2	3.1 (0.4–11.1)	1	1.1 (0.0–5.2)
Bladder	2	7.1 (0.8–25.8)	0	0.0 (0.0–8.0)

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 as 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.

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