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Representativeness of a roster of volunteer North American twins with chronic disease

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To identify large numbers of twins affected by chronic disease as potential subjects for studies of environmental and genetic chronic disease determinants, we advertised for affected twins over the period 1980–91 in newspapers across North America. Responses were received from 17 245 twin pairs in which cases of cancer or other chronic disease had occurred. To assess the representativeness of affected twins identified by advertising, we evaluated the pattern of reporting, compared the cases identified to the number of cases estimated to be prevalent among all North American twins, compared the cases to population-based singleton case series, compared the healthy co-twins to population-based samples of healthy persons, assessed the impact on ascertainment of opinions about disease causation, compared the pattern of prospective to retrospective ascertainment of disease in the originally unaffected co-twins of cases, and compared the results of the prospective ascertainment of disease in co-twins to comparable published estimates. Youth, gender, zygosity, education, and disease concordance were found to be overall determinants of ascertainment. Disease-discordant DZ twins appeared to be modestly underascertained. While somewhat better educated, both concordant and discordant pairs were judged to be reasonably representative of affected non-Hispanic white North American twin pairs of comparable status, ie of comparable age, sex, race, and zygosity. If interpreted with caution, the concordance patterns of such twins can be used to generate genetic hypotheses, but should not be the basis of definitive heritability analyses. We conclude that advertising offers a method of identifying pairs of twins that can serve as subjects for studies designed to identify disease determinants. Twin Research (2000) 3, 33–42.

Keywords: cancer, breast cancer, epidemiology, multiple sclerosis, concordance, familiality

Introduction

As subjects for scientific study of the distinct roles of inheritance and the environment in the causation of specific diseases, twins offer many advantages.[1,2] Maximal advantage of this opportunity has not generally been taken, however, largely because of the limited availability of affected twins. Even though roughly 1 in 50 Americans is a twin,[3] the fact of twinship is neither routinely requested nor routinely volunteered, and systematic ascertainment of twins with disease has been limited to a few restricted and limited circumstances. In order to identify a large number of twin pairs discordantly affected by cancer and other chronic diseases, primarily for the purpose of comparing cases with their co-twins and other healthy persons, we placed newspaper advertisements calling for affected twin pairs to volunteer for participation as research subjects in the North American component of a project called the International Twin Study. Because twin volunteers are presumed to be unrepresentative of twins in general,[4] the degree to which twin volunteers with chronic disease are representative of all such twins is of interest, especially with respect to the possible under-ascertainment of relatively unmotivated DZ twins discordant for disease. Whilst most known or presumed biases (age, gender, zygosity, concordance, education) would not interfere with the validity of multivariate intra-pair comparisons, strongly held opinions about causation in the presence of a recognized intra-pair exposure pattern might provide an extra incentive to respond and introduce bias. This report will describe the results of these solicitations and will document our best effort at comparing the set of cases and healthy twins so identified with twins and with persons considered representative of the source population.

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Materials and methods

From 1980 to 1991, advertisements seeking 'twins with cancer' or 'with (another chronic disease)' were

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placed periodically in North American magazines and newspapers. These advertisements, usually about 2 × 3 inches in size, with the words 'twins' and 'cancer' in bold type, mostly ran in the main sections of ordinary newspapers. Whilst advertisements usually appeared in two disparate markets somewhere in North America almost every week, no single publication was used more frequently than annually. More than 300 periodicals with a combined circulation of roughly 68 million were employed; the average annual circulation for a single publication was about 33 million. Respondents were requested to contact us by telephone or mail, and did so over the course of weeks to months following each advert. Direct responses from the members of affected pairs in the community served by the publication with the advert accounted for 79% of the responses, and pairs outside the area to whom the message was forwarded constituted about 4%. The remaining respondents were referred by friends or family members inside (7%) or outside (10%) the circulation area. When the latter responded, they were requested to ask a member of the pair to contact us, or to give us permission to contact members of the pair with specific reference to the identity of the respondent; otherwise no pair was included. A member of each reported pair was subsequently interviewed by telephone and asked to provide information about the case's birth date, sex, perceived zygosity, the date and place of diagnosis, and about the co-twin's vital status and chronic disease history. Our initial major focus was the study of malignancy and of multiple sclerosis. For these conditions, signed permission to access validating medical records was routinely sought (successfully in more than 70%) and, in the case of neoplastic conditions, the diagnoses were coded according to international rules[5] as if for tumor registration. Tumor specimens were requested for review of the histologic cancer diagnosis on a site-specific priority basis, as resources permitted. After an initial experience, common solid epithelial malignancies (breast, lung, colon, etc) specimens were given lower priority for review than those from cases of lymphoma, melanoma, and genital malignancy, for which review was implemented routinely.

Ordinary perceptions of zygosity by adult twins in the United States are now usually unambiguous and consistent; when the members of a pair agree, their perceptions are accurate in over 90% of pairs.[6] In the course of this project, we used molecular methods to assess the accuracy of self-assessed zygosity in more than 50 pairs of these adult twins affected by chronic disease.[7,8] Among those pairs in agreement about their zygosity, all laboratory findings to date have verified the self assessments of zygosity, and the latter have been accepted unless there was evidence of uncertainty or disagreement.

Follow-up on all pairs to identify deaths and new diagnoses was conducted by periodic mailings, roughly biannually, with up-date response requests (new address, new diagnosis) to all participants. Person-years of follow up have been counted from the date of initial diagnosis to the date of first ascertainment (retrospective), or from the latter through the date of last contact with the pair, in all instances prior to 1 February 1993 (prospective). For many conditions, including breast cancer and multiple sclerosis, detailed postal questionnaires were forwarded for completion in the context of case co-twin studies, and for the two conditions mentioned, the proportion of affected pairs from which members completed and returned the instruments was 74% and 73%, respectively. Included in each questionnaire were requests for information on absolute and comparative growth, physical characteristics, reproductive history, lifestyle, measures of social class, and opinions about the causation of the respective conditions.

To assess the representativeness of affected twins identified by means of this method of ascertainment, we constructed an estimate of the prevalence of white adult twins in North America in 1980, according to birth cohort, region of birth, zygosity (using the Weinberg rule[9]), sex, and survival–concordance status. We based this on region, race, and cohort-specific rates of twin birth,[3,10–12] singleton perinatal and infant mortality,[13] the few available estimates of cohort-specific relative twin mortality[14] (using, when possible, race, sex and zygosity-specific information), and life tables.[15] The cohorts at risk of cancer during this period were born before any measurable increase in multiple births attributable to the use of fertility agents. From available age-specific cancer incidence from US[16] and Canadian[17] population-based cancer registries and site/year-specific survival estimates[18] we estimated the number of twin pairs in which at least one member would have been diagnosed with cancer at any time between 1 January 1970, and 31 December 1990, and in which at least one member of each pair would have been alive on 1 January 1980. Among the cases estimated to have been diagnosed before 1980, we distinguished between those who would have survived at least until 1 January 1980 and those who would have died before that date.

Multiple sclerosis (MS) is the most common non-malignant disease systematically ascertained. MS is not comprehensively registered in North America, and the age-specific incidence is unavailable, so the rough prevalence of multiple sclerosis has been measured by physician survey.[19] Although MS prevalence is much less accurate than estimates of cancer

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incidence, we estimated the number of prevalent cases in twins by applying these age-specific rates to the estimates of twin prevalence described above, recognizing the crudeness of the estimate and the disparity between all perceived diagnoses and those in persons with access to a specialist.

Population age-specific incidence rates are only available in North America for neoplasms. To quantify the magnitude of subsequent risk of cancer to the healthy twins of affected individuals, age, sex, race (white) and anatomic site-specific incidence rates for the period of ascertainment available from the national SEER system of population-based registries[16] were applied to the appropriate age-specific person-years of follow-up in order to estimate the number of cases expected to appear among the healthy (ie those living and not previously so diagnosed) twins of the proband cases. The age-specific person-years of retrospective and prospective follow-up were separately enumerated. The standardized incidence ratio (SIR), ie the ratio of observed to expected cases, was calculated separately for the age-specific years between the original diagnosis and the second diagnosis or ascertainment, whichever came first (retrospective follow-up), and to obtain a measure of unaffected by ascertainment bias, for the years between the date of ascertainment and the second diagnosis or 23 February 1993, whichever came first (prospective follow-up). Because such ratios can be compared, based as they are upon the same standard of comparison, we have employed them when available in preference to the conventional concordance parameters (ie twin pairwise concordance estimator of the casewise concordance ratio[20]), which has been computed for other chronic diseases.

Results

Over the period of 11 years, 17 245 twin pairs affected by a chronic disease, including 12 134 affected by cancer, were reported in this fashion. More than 95% of the respondent pairs were non-Latino and white, and about three-quarters of the cases had been diagnosed since 1975. Among these were 3219 pairs and 1293 pairs in which breast cancer and multiple sclerosis had occurred, respectively. After receiving signed permission, validating medical records were routinely sought (successfully in 71.4%) and coded. Tumor specimens were requested for review of the histologic cancer diagnosis (successfully in 65%) according to site-specific priority as resources permitted. With respect to the fact of malignancy and the anatomic site of origin, fewer than 2% with a discrepancy between the original and review diagnoses (the discrepant cases were excluded or reclassified) were found for the common solid epithelial malignancies, including breast cancer (of which 805 were reviewed). At least 94% of the breast cancer diagnoses were of invasive disease. With reference to the more difficult histological diagnoses, two of the 133 reviewed cases of malignant melanoma were judged not to be melanoma, and two of the 159 reviewed cases of Hodgkin's disease were judged not to be Hodgkin's disease. Soon after the initial wave of ascertainment, nationally recognized MS neurologists reviewed records from a sample of 146 of the most questionable (ie followed neither at an MS clinic nor by a neurologist) or most pertinent (second diagnosis in a pair) cases using the standard (Schumacher) criteria used at the time. Among these, 96 (66%) were deemed to be definite MS, 28 (19%) probable MS, 20 (14%) possible MS, and two (1.4%) not MS. Members of the last group are not included in what follows.

Table 1 summarizes the number of breast cancer cases in twins estimated to have been prevalent over the period, and the number of those identified with known address at the time of diagnosis, according to region and, for recently diagnosed cases, the size of the residential community. By means of advertising we identified at least 6.9% of the estimated number of cancers at all sites in twins prevalent at any time over the entire period in North America and 7.9% of those diagnosed in the years 1980–1990. The equivalent figures for the ascertainment of cancer of the female breast are 11.4% of those prevalent at any time over the period and 17.2% of those diagnosed in 1980–90. The ascertainment fraction was only slightly lower for all cases diagnosed before 1980 than those diagnosed in or after 1980, even though, among the former, it was twice as great for survivors as for those who died before 1980. Only minor differences in the fraction ascertained could be attributed to region or the size of the residential community.

In a subset of large city newspapers, adverts were repeated in the same newspapers after 1 year (271 newspapers) and again after 2 (185), 3 (140), 4 (92), 5 (66), 6 (42), 7 (29), and up to 12 years (1). The mean responses from cancer-affected pairs (based on a total of more than 11 000 pairs) after the first up to the sixth adverts were 4.9, 4.9, 4.2, 3.5, 2.8 and 1.9 respondents per 100 000 circulation, respectively.

Table 2 describes the relative efficiency of ascertainment of breast cancer cases according to age at diagnosis and perceived zygosity. Middle-aged cases were ascertained four times as frequently as cases diagnosed at 60 or older. The rate of ascertainment with diagnoses before age 30 was four times as great as that for the middle-aged, and the number of such

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Table 1 Estimated fraction of identified North American twin cancer cases with known address at time of diagnosis by region and nature of the residential community

Region	Diagnosis and Death <1980			Diagnosis <1980, alive 1980			Diagnosis 1980–1990		
	Prevalent twin cases	Twin cases found	% found	Prevalent twin cases	Twin cases found	% found	Prevalent twin cases	Twin cases found	% found
New England	235	10	4.3	662	41	6.2	1108	78	7.0
Middle Atlantic	635	13	2.1	1792	100	5.6	2903	222	7.7
South Atlantic	570	17	3.0	1612	105	6.5	3098	201	6.5
East North Central	719	27	3.8	2038	120	5.9	3313	278	8.4
East South Central	257	6	2.3	730	50	6.9	1231	75	6.1
West North Central	369	12	3.3	1034	61	5.9	1681	120	7.1
West South Central	350	8	2.3	987	49	5.0	1820	141	7.8
Mountain	130	7	5.4	370	37	10.0	745	97	13.0
Pacific	427	23	5.4	1207	128	10.6	2278	287	12.6
United States, Total	3691	123	3.3	10431	691	6.6	18178	1499	8.3
Canada	306	8	2.6	874	28	3.2	1641	63	3.8
North America	3998	131	3.3	11305	719	6.6	19819	1582	7.9
Large city (>1 million)							6164	510	8.3
Area surrounding large city[a]							1030	93	9.0
Medium-sized city (>250 000)							4119	385	9.3
Area surrounding medium-sized city[a]							890	68	7.6
Small city (>50 000)							2042	153	7.5
Area surrounding small city[a]							279	28	10.0
Rural area							5149	325	6.3

[a]Same metropolitan statistical areas or Canadian equivalents.

Table 2 Estimated ascertainment fraction of 1980–1990 incident North American twin breast cancer cases[a] with known address at time of diagnosis by zygosity

Zygosity/gender	Prevalent twin cases	Twin cases found	% found	95% confidence interval
Diagnosed at age 20–29				
Identical twins	50	66	132.4	102.1–168.0
Like-sex fraternal twins	43	49	114.1	84.3–150.7
Unlike-sex fraternal twins	42	24	56.6	36.6–85.1
Diagnosed at age 30–59				
Identical twins	1975	566	28.7	26.3–31.1
Like-sex fraternal twins	1910	410	21.5	19.4–23.6
Unlike-sex fraternal twins	1844	169	9.2	7.8–10.7
Diagnosed at 60+				
Identical twins	1548	98	6.3	5.1–7.7
Like-sex fraternal twins	1552	81	5.2	4.1–6.5
Unlike-sex fraternal twins	1167	46	3.9	2.9–5.3

[a]Excluding 73 cases of unknown precise age or zygosity.

cases seemed to exceed the number thought to be present. The accuracy of self-reports of breast cancer was very high, especially in young women. Therefore the apparent excess could be due to chance (the concordance limit is just above 100%), the incidence of breast cancer in young women could be high in both MZ and DZ twins (not consistent with some current hypotheses[21,22]), or the absolute prevalence in the population of younger twins may have been underestimated, since our estimates of recent twin survival are necessarily crude.

Table 3 compares the number of ascertained cases of multiple sclerosis to the estimated true number according to gender, zygosity, and age. About a quarter of the estimated number of male cases was identified by advertising, and the effectiveness of ascertainment seems to have been nearly twice as great for females as for males. Fewer unlike-sex pairs containing female cases responded than those containing male cases, which were ascertained as effectively as other male pairs, probably because healthy females reported cases in their male co-twins more readily than healthy males reported cases in their female co-twins. Since age at onset or even diagnosis of multiple sclerosis requires an individualized detailed analysis, and since no reliable age-specific incidence figures are available for North American populations, we have provided a distribution of the age of cases reported and yet to be reported as of 1 July 1985. Only for those aged 50–59 in that year was there some modest underascertainment, presumably by chance.

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Table 3 Estimated ascertainment fraction of 1980–1990 incident North American twin multiple sclerosis cases[a,b] with known address at time of diagnosis by zygosity and age

Zygosity/gender	Estimated no. of prevalent twin cases 1980–1990[a]	Twin cases found	% found	95% confidence interval
Males				
Identical twins	412	84	20.4	16.3–25.3
Like-sex fraternal twins	362	92	25.4	20.5–31.2
Unlike-sex fraternal twins	388	91	23.5	18.9–28.8
Females				
Identical twins	669	300	44.8	39.9–50.2
Like-sex fraternal twins	600	257	42.8	37.8–48.4
Unlike-sex fraternal twins	636	215	33.8	29.4–38.6
Males and females				
Identical twins	1081	384	35.5	32.1–39.3
Like-sex fraternal twins	962	349	36.3	32.6–40.3
Unlike-sex fraternal twins	1024	306	29.9	26.6–33.4
Males and females by age in 1985[c]				
<20 years	15	6	40.0	14.4–87.6
20–29 years	242	104	43.0	35.1–52.1
30–39 years	715	392	54.8	49.5–60.5
40–49 years	810	325	40.1	35.9–44.7
50–59 years	951	240	25.2	22.1–28.6
60+ years	337	176	52.2	44.8–60.5

[a]Prevalent cases 1980 plus incident cases 1980–1990; [b]Excluding 254 cases of unknown zygosity; [c]Estimated number of twin cases identified at any time by age on 1 July, 1985.

Table 4 compares the characteristics of the unaffected (largely white) twins of ascertained breast cancer cases who returned questionnaires with those of unaffected white women from the general population, by means of a representative national survey,[23] as well as by means of the responses to questions put to women chosen as age-matched neighborhood controls in concurrent Los Angeles breast cancer case-control studies.[24,25] The healthy twins of breast cancer cases were somewhat better educated than those chosen as neighborhood controls of breast cancer cases in Los Angeles. Otherwise, while there was a tendency for premenopausal twins to use oral contraceptives slightly less often and postmenopausal twins to use them more often, the unaffected twins of cases were generally similar to other unaffected women.

Beliefs about the cause of breast cancer included, in order of frequency, 'stress' (23%), 'genetics' (19%), general diet (15%), pollution (7%), hormones (7%), trauma (6%), viruses (2%), immune abnormalities (2%), and radiation (2%); 34% of those who gave a family history of breast cancer mentioned 'genetics', whereas only 16% of the others did so. A report of breast cancer in a first-degree relative was provided by 16% of the cases and also by 16% of the healthy co-twins, even though 21% of the paired respondents disagreed on the presence or absence of such a family history. The bias attributable to prevailing hypotheses appeared to be minor. Whenever the control had used exogenous estrogens, one or both respondents in 14.9% of the pairs mentioned hormones, whereas whenever the case had used them, such a mention came from 22.0% of the pairs a marginally significant difference of 7.1 (confidence interval: 0.01–13.7).

Among the co-twins of cancer cases, subsequent cancer was documented in 850 MZ co-twins, 482 like-sex DZ co-twins, and 269 unlike-sex co-twins. Of these 698 were of the same type as the cancer in a like-sex proband. Table 5 provides the standard incidence ratios (SIR) for cancers diagnosed in the like-sex co-twins of proband cancer cases, according to cancer combination, gender, zygosity, and type of ascertainment. For each method of ascertainment, the ratio of SIRs for MZ to DZ pairs is provided, as is, for each zygosity, the ratio of prospectively to retrospectively observed SIRs. In addition to any cancer in the twins of cases of any cancer, Table 5 shows combinations of unlike cancers, the twin combinations of breast and any other cancer, and the pairs in which breast cancer occurred in both twins. Only for breast cancer in the MZ co-twins of breast cancer cases were the observed number of cases in co-twins as high as twice that expected. Whilst the SIRs themselves will vary with the age distribution of the person-years at risk (younger person-years being more likely to be at preferentially higher risk for MZ co-twins), as well as with the prevalence of high risk genes in the population, the ratio of MZ to DZ SIRs measured prospectively without bias ought to be roughly comparable with those found in other populations. However, prospective surveillance invariably yielded SIR estimates lower than those from retrospective surveillance, and with the inexplicable

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Table 4 Characteristics of healthy twin respondents in comparison with healthy US non-twins

	Healthy twins of breast cancer cases	Healthy US white females
Mean height in inches at age 20	64.2	64.4[a], 64.6[b]
Mean Quetelet's index, age 20	20.3	22.5[a], 22.5[b]
Mean Quetelet's index, age 40	22.3	24.9[a]
% with college degree		
Age <42	36.2	37.2[b]
Age 51+	18.3	20.3[c]
% menarche <age 12		
Age 40–54	19.4	21.8[a]
Age 65–74	15.5	15.8[a]
% ever married		
Age <42	89.2	91.3[b]
Age 51+	94.0	97.1[c]
% ever used oral contraceptives		
Age 40–54	67.2	60.5[a]
Age 65–74	7.5	4.3[a]
Mean age at first full-term pregnancy		
Age <42	23.7	23.6[b]
Age 51+	24.6	23.9[c]
Mean no. full-term pregnancies		
Age <42	2.1	2.2[b]
Age 51+	3.1	4.0[c]
% ever smoked cigarettes	48.0	49.4[a]
% smoked 25+ cigarettes daily	24.4	22.4[a]
'Heavy' alcohol drinkers		
Age 40–54	4.4	4.2[a]
Age 65–74	5.6	3.8[a]

[a]National sample of healthy women.[23]
[b,c]Population-based (neighbourhood) controls from case-control studies, each with >500 controls, conducted in Los Angeles County.[24,25]

exception of any cancer combination in males, this disparity was greater for DZ twins than for MZ twins, suggesting a generally lower level of ascertainment for DZ discordant cases.

Among the co-twins of non breast cancer cases diagnosed before age 30, based on three, two, and two cases, the SIRs were 1.7 (0.3–4.9), 1.5 (0.1–5.7), and 3.3 (0.3–12.3) for MZ, like-sex DZ and unlike-sex DZ female co-twins respectively. Among the co-twins of non-breast cancer cases diagnosed at 30–39, based on two, four, and two cases, the SIRs were 0.6 (0.1–2.3), 1.7 (0.5–4.5), and 2.2 (0.2–8.2) for the same three groups. In all groups the mean number of person-years of follow-up was less than 5, indicating that the risks to co-twins are for the years at age 30–34 and 35–44, respectively.

Prospective ascertainment after recognition of prevalent cases of multiple sclerosis yielded few cases. Based on all ascertainment, the probandwise estimators for 104 male MZ, 107 male like-sex DZ, 350 female MZ, 302 female like-sex DZ, and 359 unlike sex DZ pairs were respectively 0.22, 0.09, 0.11, and 0.08.

Discussion

Advertising enabled us to identify a very large number of affected twin pairs as possible study subjects. Assuming that the average newspaper is actually read by 1.5 persons, well under half the target population of North America was never covered, and no more than a quarter was covered annually. Given that, our ascertainment, especially of younger female cases and cases of long-duration chronic disease such as multiple sclerosis, was substantial, probably amounting to the majority of those aware of the ads. After about three advertisements in the same periodical, the rate of response began to drop, suggesting that the pool of potential respondents was being depleted. Except for the pronounced relative underascertainment of older cases, recruitment of affected twins by newspaper advertisement appears to have identified a population of female twin breast cancer cases that is reasonably representative of those of comparable age and race in the US population, and the characteristics of the healthy members of the ascertained pairs seem to correspond well to the characteristics of the population at risk. As expected, MZ pairs and females in general preferentially respond to advertising, and there was the expected moderate underascertainment of unlike-sex pairs, especially those with affected females. After comparing the retrospective ascertainment to those ascertained prospectively without bias, moderate underascertainment of DZ discordant pairs can be recognized. It cannot therefore be assumed that estimates of the relative magnitude of MZ to DZ concordance are inevitably overestimates, although the bias introduced by these losses was always less than twofold, and is partly compensated by overascertainment of MZ concordant pairs. Assuming the prospective ascertainment to be unbiased and the retrospectively ascertained MZ cases to be representative, the magnitude of the relative loss of DZ pairs discordant for any cancer is below 20%, but may be as high as 70% in the case of those discordant for breast cancer. These estimates are compatible with the differences in ascertainment fraction seen in Table 2. When using such cases to compare cases and unaffected co-twins in case-control fashion, the degree to which any risk estimate is modified by zygosity should be interpreted with caution.

Our principal concern about ascertainment bias, given our goals, was the possibility that the incomplete response from disease-discordant twins would partly be based on whether the pattern of exposure

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Table 5 Occurrence of cancer in twins of North American cancer cases: comparison of ascertainment methods

Method of ascertainment	Pairs[c]	Exp[d]	Obs	SIR[e]	Pairs[c]	Exp[d]	Obs	SIR[e]	SIRmz/ SIRdz[f]
Any cancer in the second twin following any cancer in the first twin									
	Male MZ[b]					Male DZ[b]			
Prospective[a]	1310	55.1	73	1.3 (1.0–1.7)	836	37.2	42	1.1 (0.8–1.5)	1.2
Retrospective[a]	1505	62.4	178	2.9 (2.4–3.3)	936	42.9	87	1.3 (1.6–2.5)	2.2
Pro/retro				0.45				0.85	0.5
	Female MZ[b]					Female DZ[b]			
Prospective[a]	2918	103.2	170	1.6 (1.4–1.9)	2101	77.3	80	1.0 (0.8–1.3)	1.6
Retrospective[a]	3369	139.5	429	3.1 (2.8–3.4)	2386	108.6	273	2.5 (2.2–2.8)	1.2
Pro/retro				0.52				0.40	1.3
Any other cancer in the second twin following any specific cancer in the first twin									
	Male MZ[b]					Male DZ[b]			
Prospective	1557	61.8	65	1.1 (0.8–1.3)	928	39.1	40	1.0 (0.7–1.4)	1.1
Retrospective	1694	64.7	90	1.4 (1.1–1.7)	1025	43.2	64	1.5 (1.1–1.9)	0.9
Pro/retro				0.79				0.67	1.2
	Female MZ[b]					Female DZ[b]			
Prospective	3490	107.7	128	1.2 (1.0–1.4)	2457	77.7	76	1.0 (0.8–1.2)	1.2
Retrospective	3829	137.9	248	1.8 (1.6–2.0)	2700	100.3	205	2.0 (1.8–2.3)	0.9
Pro/retro				0.67				0.50	1.3
Breast cancer in one twin with any non-breast cancer in the other twin									
	Female MZ					Female DZ			
Prospective	3559	65.6	81	1.2 (1.0–1.5)	2487	46.4	44	0.9 (0.7–1.3)	1.3
Retrospective	3806	81.7	105	1.3 (1.1–1.6)	2689	59.7	111	1.9 (1.5–2.2)	0.7
Pro/retro				0.92				0.47	1.9
Breast cancer in the second twin following breast cancer in the first twin									
	Female MZ					Female DZ			
Prospective	1340	17.2	77	4.5 (3.5–5.6)	970	13.1	22	1.7 (1.1–2.5)	2.6
Retrospective	1555	22.2	180	8.1 (7.0–9.4)	1097	18.4	97	5.3 (4.3–6.4)	1.5
Pro/retro				0.56				0.32	1.7

[a]Prospective ascertainment: follow-up between first notification and 31 January, 1993; retrospective ascertainment: follow-up between diagnosis of first twin and first notification. [b]Zygosity: MZ=monozygotic, DZ=dizygotic like-sex.[c]Excluding pairs: imprecise age or date of diagnosis, death or outcome diagnosis before entry, non-validated diagnosis. [d]Based on SEER age, sex and site-specific incidence rates applied to person-years of follow-up. [e]Standard Incidence Ratio. [f]Prospective SIR or ratio/retrospective SIR or ratio.

in the pair corresponded to their perception of etiology. We were reassured to observe that most etiologic speculation was exceedingly vague. Still, it was apparent that the issue could not be completely ignored, since we could demonstrate, for example, that there was a marginal relationship between etiologic concern about 'hormones' and preferential use of exogeneous hormones by the case. In the case of breast cancer, this small proportion of pairs can easily be excluded when evaluating the role of hormones, but similar considerations might well be more important in the examination of other hypotheses.

Using the same study design in Sweden, with an identical instrument (in translation), it was observed that unaffected co-twins were as likely as the cases themselves to indicate the presence of other cases of breast cancer in first-degree relatives.[26] That was also the case in North America, even though the Swedish cases are often less well informed about the nature of their illness, were older, and were interviewed in person, rather than by mail.

The higher SIRs for co-twins of a cancer case contracting any cancer can be explained on the basis of the known specific genetic determinants of specific cancers. Based only on prospectively obtained information, the ratio of MZ to DZ SIRs for males and females were estimated at 1.2 and 1.6 respectively. For males, estimates from Sweden,[27] Finland,[28] and US World War II veterans[29] were 1.4, 1.6, and 1.4, and for females, estimates from Sweden,[27] Finland,[28] and Denmark[30] were 1.1, 1.2, and 0.9. Thus our

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estimates are slightly lower for males, and slightly higher for females, although all the estimates from the literature are within the estimated limits of confidence. Real differences might be expected, however. The estimates from the literature are based on cases with a substantially older age distribution, and generally occurred in earlier decades. Thus smoking-related cancers were more prominent among the male cases, and concordance for smoking is more common among MZ twins.[31] As for females, breast cancer is the single most common entity, and youthful diagnosis is associated with heritable disease.[32]

We have no means of directly estimating the risk to MZ or DZ twins per se, but the absolute risk of a cancer in the co-twin of a case with a different cancer should be only a slight overestimate, since the genes which determine cancer at any of several sites are relatively rare. Our estimates from prospective ascertainment in males were 1.1 and 1.0 for MZ and DZ co-twins respectively, and for females the estimates were 1.2 and 1.2. As expected, these are only marginally higher than the estimates, essentially of unity, from Sweden[33] and Finland.[28] These results provide additional reassurance that the cancer risk for twins overall is identical to that for singletons, and that heritable risk from cancer is largely site-specific.

Similarly, our estimates of the breast cancer risk to the twins of cases with other cancers should be slightly higher than direct estimates of the breast cancer risk to individual twins. Here we estimate MZ and DZ risks at 1.2 and 1.3, with confidence limits which include the estimates from Sweden,[33] Finland,[22] and Britain[34] of 0.9, 0.8, and 0.9 respectively. Because of the known prevalence of genetically determined multiple cancer syndromes including breast cancer, it is not surprising that the disparity is somewhat larger than for all cancers. Considering the estimated breast cancer risk for the co-twins of young cancer cases as a surrogate for the risk to young twins, we found elevated risk for all co-twins in the youngest category, and highest in the female DZ co-twins of male cases. Considering the width of the confidence intervals and the complex genetics of multiple cancer syndromes, these result provide no support for either the hypothesis of increased risk in DZ twins[21] or that of decreased risk in MZ twins;[22] only the hypothesis of increased female breast cancer risk to women from unlike-sex pairs[35] is weakly supported.

There are three studies of twin concordance for multiple sclerosis which are based on ascertainment from defined populations, and from which more than two-thirds of the pairs identified were judged to be eligible based on known zygosity and disease status.[36–38] In the aggregate, 52 MZ and 77 DZ pairs were assessed in those studies, and the summary probandwise estimates can be calculated at 0.42 and 0.08 respectively, compared with 0.24 and 0.10 among the 454 MZ and 409 like-sex DZ pairs upon which this report is based. The reason for the disparity is not obvious, since the DZ concordance estimates are nearly identical, and our estimate of MZ concordance is lower, not higher, than that from the population-based sets. Thus neither loss of DZ discordant pairs nor overascertainment of MZ concordant pairs could explain the difference. It is also notable that in one of the population-based sets (Heltberg[36]), the MZ concordance was 0.35, and that our estimates are nearly identical in males, females, and even unlike-sex pairs. It is true that about 20% of our pairs were under age 40 at the time of last follow-up, and it is possible that additional concordant pairs will be found. Alternatively, it is not impossible that population-based ascertainment, which is necessarily based on medical visitation, underascertains those cases in discordant pairs who have pathognomonic physical signs but no obvious symptoms and who need minimal or no medical care.

In summary, the ascertainment of affected twin pairs by advertising can produce very large numbers of affected pairs. However, reliance solely upon retrospective ascertainment does alter the ratio of concordant to discordant pairs. The degree of ascertainment bias doubtless varies in relation to the degree of identification with, and the magnitude of concern about, the specific medical condition. If a contribution to our understanding of the role of inheritance can be made, it can only be from relying exclusively on prospective ascertainment, or when results indicate an unexpectedly low concordance in MZ twins (given an appropriate length of follow-up[7]), a very substantial level of concordance in MZ pairs with negligible or no concordance in DZ pairs,[39] or notable differences in the pattern of risk in relation to the latency after the first diagnosis.[8] However, the purpose of ascertaining affected twin pairs by the means used was not definitively to assess absolute or relative disease concordance, but to identify relatively large numbers of discordant and concordant pairs as subjects for intra-pair comparisons or as a means of identifying cases more likely to represent the heritable fraction of disease. There is no reason not to consider concordant pairs unrepresentative. As long as the gender, age, zygosity, general social class and concordance of subjects is accurately reported, and as long as potential underascertainment of DZ discordant pairs is recognized, if findings within MZ pairs are to be compared with findings within DZ pairs, conclusions derived from the study of discordant pairs are as

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generalizable to other populations as are the results of other epidemiological studies.

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