

Hereditry and Prostate Cancer: A Study of World War II Veteran Twins

William F. Page,^{1*} M. Miles Braun,² Alan W. Partin,³ Neil Caporaso,⁴ and Patrick Walsh³

¹*Medical Follow-up Agency, Institute of Medicine, National Academy of Sciences, Washington, DC*

²*Division of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, Food and Drug Administration, Washington, DC*

³*James Buchanan Brady Urological Institute, The Johns Hopkins Medical Institutions, Baltimore, Maryland*

⁴*Genetic Epidemiology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland*

BACKGROUND. Increased risk of prostate cancer among men with a family history of the disease has been observed in several epidemiological studies, and family studies have identified hereditary prostate cancer characterized by early onset and autosomal dominant inheritance.

METHODS. In this study, we examine prostate cancer heritability among twins in the NAS-NRC Twin Registry, with cases ascertained from a number of sources: recent telephone interviews, Medicare and Department of Veterans Affairs hospitalizations, previous mail questionnaires, and death certificates. A total of 1,009 prostate cancer cases were identified among the cohort of 31,848 veteran twins born in the years 1917–1927.

RESULTS. Probandwise concordance for prostate cancer was substantially higher among monozygous twin pairs, 27.1%, than among dizygous twin pairs, 7.1% ($P < 0.001$).

CONCLUSIONS. These data suggest that genetic influences account for approximately 57%, and environmental influences for 43%, of the variability in twin liability for prostate cancer. *Prostate 33:240–245, 1997.* © 1997 Wiley-Liss, Inc.

KEY WORDS: genetics; twin concordance; epidemiology

INTRODUCTION

A familial and arguably genetic component to prostate cancer is consistently supported by family studies. Early studies from Utah [1] and Italy [2] identified excess prostate cancer among relatives of men with prostate cancer. More recent studies from the Utah Population Database [3–5] have confirmed and extended these findings; in all these studies there is also a suggestion that higher risk for prostate cancer is associated with earlier age at onset. Case-control studies evaluating family history as a risk factor have found that it is significant [6–10].

Recent population-based multi-center studies that have included both blacks and whites, and that have

adjusted for potential confounders such as age and geographic region, have observed excess risk associated with family history among cases consistent with earlier work [11,12]. In the former study [11], cases whose fathers had prostate cancer had an apparently lower relative risk of prostate cancer (2.5) than did cases whose brothers had prostate cancer (5.3), but this

Work performed at the Medical Follow-up Agency, Institute of Medicine, National Academy of Sciences, Washington, DC.

*Correspondence to: William F. Page, Medical Follow-up Agency, National Academy of Sciences, 2101 Constitution Avenue, N.W., Washington, DC 20418. E-mail: wpage@nas.edu

Received 19 August 1996; Accepted 13 January 1997

difference could be attributed to sampling error. In the latter study [12], there was similarly no statistically significant difference between prostate cancer risk ratios for fathers and sons (2.0) vs. brothers (2.9).

A segregation analysis demonstrated that the familial prostate cancer clustering could be explained by Mendelian inheritance of a rare autosomal gene producing prostate cancer at an early age [13]. However, the inherited form of prostate cancer (hereditary prostate cancer) represents only 9% of all prostate cancers by age 85 years.

Classic twin studies permit an estimate of the importance of genetic factors by comparing identical (monozygous: MZ) twin pairs to fraternal (dizygous: DZ) pairs. When there is a strong genetic influence, the concordance rate for MZ twin pairs (in which both members are genetically identical) is higher than the rate for DZ pairs (in which both members share approximately 50% of their genes, on the average, being related as ordinary siblings). A study of prostate cancer among members of the Swedish Twin Registry [14] found a higher concordance rate for prostate cancer among MZ than DZ twins (probandwise concordance rates of 19.2 and 4.3%, respectively), evidence of a genetic influence on prostate cancer. Moreover, the mean age at diagnosis for prostate cancer was greater than 72 years of age for cases in both concordant and discordant twin pairs.

In an earlier study of benign prostate disease among members of the NAS-NRC Twin Registry [15], evidence of a significant genetic influence was found for benign prostate disease. In this article, we report on the concordance for prostate cancer among members of the NAS-NRC Twin Registry.

MATERIALS AND METHODS

The NAS-NRC Twin Registry is a population-based twin registry composed of white male twins born in the years 1917–1927, inclusive, who served in the U.S. military [16]. The Registry was assembled from birth certificates, with some 54,000 pairs of certificates (which is thought to represent 93% of male-male twin births during the period) matched against Department of Veterans Affairs (VA) records to ascertain veteran status. A total of 15,924 veteran twins pairs was eventually identified. Zygosity has been ascertained using questionnaire, blood type and anthropometric data, eye and hair color, fingerprints, and for a subpanel, serological results. Validity studies suggest that the questionnaire data alone provide a correct diagnosis of zygosity in 95% of twin pairs [17].

One of the important features of this study is its prostate cancer ascertainment procedures. Five largely independent data sources were used to define prostate

cancer: coded responses to a mail questionnaire, computerized inpatient records of the VA and Medicare, a telephone screening interview, and mortality records. Each will be described in turn.

Two large epidemiologic surveys have been conducted in the Registry by mail questionnaire [17]. The latest of these, sent in 1985, included detailed items on health and health care and included the following item: "List any operation or illness requiring hospitalization that you have had since 1970." Approximately 10,000 questionnaires were received, and responses to this open-ended question were reviewed for evidence of prostate cancer and other prostate disease [15].

Data on all VA inpatient episodes in the years 1985–1994 were collected for all twins. There was a total of 1,504 VA inpatient episodes among the twins, including 71 with some mention of prostate cancer; these episodes occurred among 49 twins. Arrangements were also made with the Health Care Financing Administration (HCFA) to secure computerized Medicare inpatient records for 1993 for all the twins in the Registry. We chose 1993 because it contained the most recent data available when we began our discussions with HCFA, and because earlier data would have been incomplete. Nineteen hundred and ninety-two was the first (partial) year in which all twins were eligible for Medicare, this being the year in which the youngest twins in the Registry, born in 1927, would have turned 65 years of age. Out of approximately 6,000 Medicare inpatient episodes among the twins, 213 had a mention of prostate cancer. These 213 episodes corresponded to 183 twins.

Mortality data were collected primarily from the VA. In addition to the VA inpatient files, the VA maintains a computer file of beneficiaries, including those who receive veteran death benefits. Investigations of the completeness of death reporting to the VA have shown it to be quite complete; the latest investigation among twins showed it to be better than 95% complete [18]. When, however, death certificates were unobtainable through the VA, they were obtained using the National Death Index. A total of 115 deaths with mention of prostate cancer were identified in the Registry up through December 1990.

In 1993–1994, a telephone survey was conducted among 14,326 living twins whose location could be determined. Each twin was asked the following question: "Did a doctor ever tell you that you had cancer?" If an affirmative response was received, a follow-up question was asked: "What type of cancer, that is, in what part of your body did the cancer start?" There were a total of 735 responses in which the twin said that he had had prostate cancer.

TABLE I. Number of Twins Diagnosed With Prostate Cancer, by Source

Questionnaire survey	Source of diagnosis ^a				No.	%
	Medicare hospitalization	VA hospitalization	Telephone survey	Mortality files		
No	No	No	No	Yes	103	10.2
No	No	No	Yes	No	618	61.2
No	No	Yes	No	No	40	4.0
No	Yes	No	No	No	99	9.8
Yes	No	No	No	No	19	1.9
No	No	Yes	No	Yes	6	0.6
No	No	Yes	Yes	No	23	2.3
No	Yes	No	Yes	No	81	8.0
Yes	No	No	No	Yes	5	0.5
Yes	No	No	Yes	No	12	1.2
Yes	Yes	No	No	No	1	0.1
Yes	No	Yes	No	Yes	1	0.1
Yes	Yes	Yes	Yes	No	1	0.1
Total					1,009	100

^aA total of 30,839 twins were not diagnosed with prostate cancer.

All twins were assigned a value of “yes” or “no” for prostate cancer for each of the five ascertainment systems. In cases where the twin was not subject to ascertainment in a given system (for example, if he died prior to 1993 and could not appear in the Medicare inpatient database), the value “no” was assigned. Among the 30,839 twins assigned a “no” value, there were 7,099 (23.0%) who died prior to 1993 (and were thus missed by the Medicare computer linkage and telephone survey) and who had not responded to earlier mail questionnaires. These could be considered “unknown” responses, rather than “no.”

Pairwise concordance rates were compared using the two-tailed chi-square test. Concordance data were further analyzed using covariance structure analysis to estimate heritability [19]. Covariance structure analysis is based on the correlation of liability, also known as the tetrachoric correlation, calculated under the assumption that there is an underlying continuous distribution of disease, even though the diagnosis of disease is not made until the liability crosses over some threshold value. Covariance structure analysis, unlike the traditional methods of concordance analysis, makes use of the data from all the twin pairs, not just those in which one or both of the twins is affected by disease.

RESULTS

Table I shows the results of prostate cancer ascertainment by the five independent methods. Of the five methods, the telephone interview identified the most prostate cancer patients, 735 of the total of 1,009 cases

ascertained. Of these, 618 were found only by telephone interview and 117 confirmed by another ascertainment method. Next followed the Medicare hospitalization ascertainment, which found 182 cases—99 singly and 83 in combination with other methods. Next most successful was the mortality file search, which found 115 cases—103 singly and 12 in combination with other sources. VA hospitalization ascertainment found 71 cases—40 singly and 31 in combination with other sources, and the mail questionnaire screening yielded 39 cases—19 ascertained singly and 20 in combination with other sources; the mail questionnaire ascertainment was concluded nearly a decade earlier than all the others.

Table II shows a comparison of ascertainment results for MZ vs. DZ twins. For this comparison, twins of unknown zygosity are not shown, nor are ascertainment methods or combinations of methods yielding fewer than 20 cases, to avoid problems with small numbers. In general, the distribution of ascertainment results is similar for MZ and DZ twins for most methods; for example, the largest single source of prostate cancer cases, the telephone questionnaire, accounted for 61.2% of cases among MZ twins and 60.4% of the cases among DZ twins. There is, however, a statistically significant difference in ascertainment profiles for MZ vs. DZ twins (chi-square = 16.53, 6 df, $P = 0.001$). Most of this is attributable to the difference in ascertainment of prostate cancer cases found only on the mortality files (6.7% for MZ vs. 12.9% for DZ); when these prostate cancer cases are eliminated, the difference in ascertainment profiles between MZ and DZ twins is not statistically significant

TABLE II. Number of Twins Diagnosed With Prostate Cancer, by Source and Zygosity

Questionnaire survey	Source of diagnosis ^a				MZ % ^b	DZ % ^b
	Medicare hospitalization	VA hospitalization	Telephone survey	Mortality files		
No	No	No	No	Yes	6.7	12.9
No	No	No	Yes	No	61.2	60.4
No	No	Yes	No	No	4.0	4.4
No	Yes	No	No	No	10.9	8.1
No	No	Yes	Yes	No	1.7	2.9
No	Yes	No	Yes	No	9.0	7.7
All other combinations of ascertainment	—	—	—	—	6.4	3.5

^aA total of 30,839 twins were not diagnosed with prostate cancer.

^bUnknown zygosity twin pairs not shown; percentage distribution limited to categories with 20 or more total cases.

TABLE III. Concordance of Prostate Cancer Among Twin Pairs

Zygosity	No. of pairs concordant	No. of pairs discordant	No. of affected twins	Pairwise concordance rate (%)	Probandwise concordance rate (%)
MZ ^a	57	306	420	15.7 ^c	27.1 ^d
DZ ^b	17	446	480	3.7	7.1
Unknown	9	91	109	9.0	16.5

^aMonozygous.

^bDizygous.

^cMZ and DZ rates significantly different; chi-square = 36.11, 1 df, $P < 0.001$.

^dMZ and DZ rates significantly different; chi-square = 65.60, 1 df, $P < 0.001$.

(chi-square = 6.8, 5 df, $P = 0.24$). Given the significant difference between MZ and DZ ascertainment profiles, concordance data will be analyzed with and without prostate cancer cases ascertained by mortality file searches.

Table III shows the results of concordance analyses using all cases. Pairwise concordance, defined as the number of concordant pairs over the number of affected pairs, provides the most direct comparison of raw concordance rates. Pairwise concordance was 15.7% for MZ twin pairs and 3.7% for DZ twin pairs, with the pairwise concordance rate for twin pairs of unknown zygosity (9.0%) being (as expected) intermediate between the MZ and DZ rates. The difference between pairwise MZ and DZ concordance rates was highly significant (chi-square = 36.11, 1 df, $P < 0.001$).

Probandwise concordance rates, defined as the number of affected twins in concordant pairs divided by the number of affected twins, provide slightly different information. For this study, in which prostate cancer was independently ascertained for each twin, the probandwise concordance rate estimates the prob-

ability that a twin will have prostate cancer, provided his cotwin has prostate cancer. Probandwise concordance rates were 27.1% for MZ twins and 7.1% for DZ twins, with the rate for twins of unknown zygosity, 16.5%, lying between these two. The nearly fourfold higher MZ probandwise concordance means that an MZ twin whose brother has been reported as having had prostate cancer is nearly four times more likely to have prostate cancer than is a DZ twin whose brother has reported to have had prostate cancer. This difference was statistically significant (chi-square = 65.60, 1 df, $P < 0.001$).

Excluding the 115 cases of prostate cancer ascertained by mortality records changes concordance rates only slightly: pairwise concordance rates are 17.9, 3.7, and 10.0%, respectively, for MZ, DZ, and unknown zygosity pairs, while probandwise rates are 26.4, 6.8, and 16.7%, respectively (data not shown). Both MZ concordance rates remain significantly higher than the corresponding DZ concordance rates: chi-square = 30.57, 1 df, $P < 0.001$, and chi-square = 55.83, 1 df, $P < 0.001$, respectively. Thus, excluding the prostate cancer cases ascertained by mortality records (which

account for only about 10% of the total) does not substantially affect the study's results.

A covariance structure analysis of the complete data (i.e., including cases ascertained by mortality records) estimated that 57% of the variability in liability to prostate cancer between twins was due to genetic influences and that the remaining 43% was due to (unique) environmental influences. As is the case in all "classic" twin studies, a greater environmental similarity among MZ twins as compared to DZ twins—for example, a tendency for MZ twins more than DZ pairs both to undergo prostate cancer screening—is a potential confounding factor when estimating the genetic effect. There was no significant common environmental (i.e., non-genetic) influence in the best fitting covariance structure model, but the power to detect such an effect is typically low, even when samples are quite large [20].

DISCUSSION

The most important finding from the study was that there was significantly increased concordance for prostate cancer among MZ twin pairs, compared to DZ twin pairs. Probandwise concordance rates, which estimate the risk of one twin having prostate cancer given that his cotwin has prostate cancer, were roughly four times higher among identical (MZ) than among fraternal (DZ) twins: 27.1 vs. 7.1% (risk ratio = 3.83; 95% confidence interval = 3.04–4.84). This increased MZ concordance suggests that the heritability of prostate cancer is high, and the structural covariance analysis showed that roughly half of the covariance in liability to prostate cancer could be attributed to genetics. These results agree with those of earlier studies showing the importance of genetic influences in the development of prostate cancer.

Concordance rates are obviously dependent on ascertainment rates, and the large number of prostate cancer cases detected in this study comes from a complicated, multiple-source ascertainment process. Although certain methodological constraints hinder a detailed comparison of ascertainment rates, some remarks on the subject can be made. For example, it is not surprising that the largest number of cases were identified by telephone survey, for response rates to telephone surveys are generally high. However, the responses of the twins to the telephone survey were not independently verified, and indeed, the proportion (16%) of telephone-identified cases appearing in any other sources (if that is taken as a measure of verification) was next to lowest for this method of ascertainment. However, only known living subjects were included in the telephone survey, so that independent mortality data were, by definition, unavail-

able and furthermore, not all subjects responded to the earlier mail questionnaire. Similarly, only 83 of the 182 cases identified through Medicare records were validated (45.6%), 82 of these by the telephone survey (45.1%). Once again, however, mortality data and earlier questionnaire data were largely collected too early to expect much overlap. In addition, it should be noted that the Medicare data were limited to inpatient episodes, so that patients opting for expectant management or radiation therapy may well have been missed. Among the subjects labeled as not having prostate cancer, there are some unknowns (see Materials and Methods). Although we have no definitive data on the effect of including unknowns in the "no" category, it is known that the general effect of misclassification is to attenuate risk estimates.

Aside from the incomplete validation data, one can make an estimate of the number of expected prostate cancer cases using independent data. Applying annual prostate cancer incidence rates from the SEER program [21] to the surviving twins, it can be estimated that there would be roughly 65 incidence prostate cancer cases per year from 1985 to 1989 and 130 cases per year from 1990 to 1994, numbers in general agreement with the number of cases ascertained in this study. It should also be noted that prostate cancer rates have been increasing, a fact thought to be associated with an increasing rate of transurethral resections of the prostate (TURP) [22], and enhanced screening methods, such as the PSA assay [23].

Notwithstanding the above, a comparison of prostate cancer cases' ascertainment methods for MZ vs. DZ twins was made. There was a significant difference when mortality records ascertainment was included and no difference when it was excluded. Given this significant MZ vs. DZ difference, concordance analyses were repeated after excluding the 115 prostate cancer cases ascertained by mortality records. Because the results were virtually identical to those for the entire series of prostate cancer cases, the difference in MZ and DZ ascertainment rates does not appear to have substantially changed the study's results.

There are a number of other recent studies with pertinent findings. First, an investigation of prostate cancer in the Swedish Twin Registry found probandwise concordance rates of 19.2 and 4.3% for MZ and DZ twin pairs, respectively—not very much different from our rates of 27.1 and 7.1% [14]. The rate of prostate cancer in their study (458 cancers among 9,680 twins) is substantially larger than the rate among these American twins, but this is as expected because the Swedish twins are markedly older, having been born between 1886 and 1925 (cf. 1917–1927).

An earlier study of benign prostate disease among these same American twins found similar results [15].

Concordance rates for benign prostate disease were roughly three times higher among MZ than DZ twins, and the genetic factors were estimated to account for 49% of the variance in liability for benign prostate disease.

It is important to note that the finding of a genetic influence on prostate cancer in this twin population is not solely the result of the presence of early-onset prostate cancer cases (as suggested by segregation analyses). Specifically, the earlier mail questionnaire, undertaken when the twins were aged 58–68, identified only 39 cases, while the telephone survey, undertaken when the twins were aged 67–77, identified 735 cases. While the ascertainment methods used here do not provide a means of assigning a definitive diagnosis date, the indirect evidence provided by these data suggest that genetic influences play a significant part in other than early onset prostate cancer. This is in line with the findings from the Swedish Cancer Registry study, in which prostate cancer cases, identified using the Swedish National Cancer Registry, averaged roughly 72 years of age at time of diagnosis.

CONCLUSIONS

In summary, we have found a significantly higher concordance of prostate cancer among MZ twins, compared to DZ twins, suggesting that genetic influences are operating in this disease. We estimate that roughly 50% of the variability in liability to prostate cancer in the cohort of World War II white male veteran twins is due to genetics. Further, based on the ages of these twins when their prostate cancers were detected, it appears that early onset cases alone do not explain this increased MZ concordance rate for prostate cancer.

REFERENCES

1. Woolf CM: An investigation of the familial aspects of carcinoma of the prostate. *Cancer* 1960;13:739–744.
2. Morganti G, Gianferrari L, Cresseri A, Arrigoni G, Lovati G: Recherches clinico-statistiques et genetiques sur les neoplasies de la prostate. *Acta Genet Statist Med* 1956;6:304–305.
3. Miekle AW, Stanish WM: Familial prostatic cancer risk and low testosterone. *J Clin Endocrinol Metab* 1982;54:1104–1108.
4. Cannon L, Bishop DT, Skolnick M, Hunt S, Lyon JL, Smart CR: Genetic epidemiology of prostate cancer in the Utah Mormon genealogy. *Cancer Surv* 1982;1:47–69.
5. Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH: Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. *J Natl Cancer Inst* 1994; 86:1600–1608.
6. Steele R, Lees REM, Kraus AS, Rao C: Sexual factors in the epidemiology of the prostate. *J Chron Dis* 1971;24:29–37.
7. Krain LS: Some epidemiologic variables in prostatic carcinoma in California. *Prev Med* 1974;3:154–159.
8. Steinberg GS, Carter BS, Beaty TH, Childs B, Walsh PC: Family history and the risk of prostate cancer. *Prostate* 1990;17:337–347.
9. Ghadirian P, Cadotte M, Lacroix A, Perret C: Family aggregation of cancer of the prostate in Quebec: the tip of the iceberg. *Prostate* 1991;19:43–52.
10. Spitz MR, Currier RD, Fueger JJ, Babaian RJ, Newel GR: Familial patterns of prostate cancer: A case-control analysis. *J Urol* 1991; 146:1305–1307.
11. Hayes RB, Liff JM, Pottern LM, Greenberg RS, Schoenberg JB, Schwartz AG, Swanson GM, Silverman DT, Brown LM, Hoover RN, Fraumeni JP: Prostate cancer risk in U.S. blacks and whites with a family history of cancer. *Int J Cancer* 1995;60:361–364.
12. Whittemore AS, Wu AH, Kolonel LN, John EM, Gallagher RP, Howe GP, West DW, Teh C, Stamey T: Family history and prostate cancer risk in black, white, and Asian men in the United States and Canada. *Am J Epidemiol* 1995;141:732–740.
13. Carter BS, Beaty TH, Steinberg GD, Childs B, Walsh PC: Mendelian inheritance of familial prostate cancer. *Proc Natl Acad Sci USA* 1992;89:3367–3371.
14. Gronberg H, Damber L, Damber J: Studies of genetic factors in prostate cancer in a twin population. *J Urol* 1994;152:1484–1489.
15. Partin AW, Page WF, Lee BR, Sanda MG, Miller RN, Walsh PC: Concordance rates for benign prostatic disease among twins suggest hereditary influence. *Urology* 1994;44:646–650.
16. Jablon S, Neel JV, Gershowitz H, Atkinson GF: The NAS-NRC Twin Panel: methods of construction of the panel, zygosity diagnosis, and proposed use. *Am J Hum Genet* 1967;19:133–161.
17. Braun MM, Haupt R, Caporaso NE: The National Academy of Sciences—National Research Council Veteran Twin Registry. *Acta Genet Med Gemellol* 1994;43:89–94.
18. Page WF, Braun MM, Caporaso NE: Ascertainment of mortality in the U.S. veteran population: World War II veteran twins. *Milit Med* 1995;160:351–355.
19. Neale MC, Cardon LR: "Methodology for Genetic Studies of Twins and Families." Dordrecht: Kluwer Academic Publishers, 1992.
20. Neale MC, Eaves LJ, Kendler KS: The power of the classical twin study to resolve variation in threshold traits. *Behav Genet* 1994; 24:239–258.
21. Ries LA, Miller BA, Hankey BF, Kosary CL, Harras A, Edwards BK (eds): "SEER Cancer Statistics Review, 1973–1991: Tables and Graphs." Bethesda, MD: National Cancer Institute (NIH Pub. No. 94-2789), 1994.
22. Potosky AL, Kessler L, Gridley G, Brown CC, Horm JW: Rise in prostatic cancer incidence associated with increased use of transurethral resection. *J Natl Cancer Inst* 1990;82:1624–1628.
23. Partin AW, Oesterling JE: Clinical usefulness of prostate specific antigen: Update 1994. *J Urol* 1994;152:1358–1368.