Prostate Cancer in Fathers With Fewer Male Offspring: the Jerusalem Perinatal Study Cohort

Susan Harlap, Ora Paltiel, Yehiel Friedlander, Ronit Calderon-Margalit, Lisa Deutsch, Karinne R. Kleinhaus, Orly Manor, Alfred I. Neugut, Mark Opler, Mary C. Perrin, Mary B. Terry, Efrat Tiram, Rivka Yanetz

Recent studies have suggested the involvement of loci on the Y chromosome in prostate cancer. We studied the relative risk (RR) of prostate cancer in relation to sex ratio of offspring in a cohort of 38 934 Israeli men who were followed from the birth of their offspring (in 1964 through 1976) until 2005. Cox models were used to adjust for changes in incidence over time, age, the man's year of birth, and social and ethnic variables. A total of 712 men were diagnosed with prostate cancer. Compared with men who had at least one son, men with only daughters had an increased risk of prostate cancer (adjusted RR = 1.40, 95% confidence interval [CI] = 1.20 to 1.64, *P*<.0001). In men with one, two, or three or more offspring, the relative risks associated with absence of sons were 1.25 (95% CI = 1.00 to 1.56), 1.41 (95% CI = 1.04 to 1.91), and 1.60 (95% CI = 1.05 to 2.43), respectively. Men with no daughters showed no statistically significantly altered risk, compared with men who had offspring of both sexes. The relative risk of prostate cancer decreased as the number of sons increased (P_{trend}<.0001) but did not change with the number of daughters. These findings suggest that a Y chromosome locus may be involved in prostate cancer risk in this population.

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The etiology of prostate cancer is not well understood. Established risk factors from epidemiologic studies include family history and geographic or ethnic origin; associations have also been noted with diet, lifestyle, occupation, and environment (1,2). Although prostate cancer occurs with increased frequency in men carrying mutations in BRCA1, BRCA2, and other genes involved in DNA repair (3), the prevalence of such mutations is low, and only a small proportion of cases of this cancer can be attributable to them. Furthermore, for autosomal and X chromosome genes, the search for common variants that might define men at risk for prostate cancer has been frustrating (3), although some progress has been made recently (4). Some studies have suggested the involvement of loci on sex chromosomes, both X (5–9) and Y (6,10–15). Because mutations or variants in sex chromosomes might alter the probabilities of having sons or daughters, we questioned whether the risk of this malignancy could be related to sex of offspring. Previous studies of this association have yielded conflicting results (16–19).

We surveyed vital status and cancer incidence in fathers from the Jerusalem Perinatal Study, a family-based research cohort. The methods and characteristics of the population have been described (20–22). In brief, from January 1, 1964, through December 31, 1976, all 92 408 births to residents of western (i.e., Israeli) Jerusalem were recorded. Demographic information on parents and grandfathers was abstracted from birth certificates; this information was supplemented with data from medical records relating to the mother's pregnancy and the child's health, from interviews with mothers, and via data gleaned through surveillance of pediatric inpatients and the district health office. The cohort was linked with Israel's Population Registry to trace both offspring and mothers in 2000 and to trace the fathers in 2005. Tracing involved verifying identity numbers (IDs) and obtaining a current address or ascertaining date of death. The IDs of the traced fathers were linked in 2005 to Israel's Cancer Registry. The study was approved by the institutional review boards at Hadassah Medical Center, Jerusalem, and Columbia University Medical Center, New York, and was exempted from the requirement for informed consent.

We used proportional hazards models as implemented in SAS version 9.1 to estimate relative risks (RRs) and to control for covariates. Assumptions of proportionality were verified by inspecting "log-negative-log" plots (23) and by testing each variable as a time-dependent product of its coded value (0,1) with length of follow-up. Observations were timed for each man from 9 months before the birth of the first of his observed offspring until his death or the diagnosis of cancer at any site; survivors were censored on December 31, 2004. Covariates—i.e., variables altering the relative risk associated with lack of sons by at least 10% and/or independent predictors of prostate cancer at $P<.05$ or less—included the father's age at the start of follow-up (years, deviations from mean = 28); social class (a 6-point ordinal scale (21) based on the man's occupation at the most recently observed birth); and sets of mutually exclusive variables or dichotomies coded 0 (absent) or 1 (present), representing the man's year of birth (1950 or later, 1945–1949, or 1940–1944, versus earlier), his education (≥13 years versus less); rabbis/students in Talmudic academies (yes versus no); wife's job status (high versus others); and ethnic origin, based on grandfather's place of birth (North Africa versus all others). Variables that failed to meet criteria for inclusion were year of birth of the first observed offspring, categories of the man's year of birth before 1940,

Affliliations of authors: Department of Epidemiology, Mailman School of Public Health (SH, AIN, MO, MCP, MBT), and Department of Psychiatry (KRK), Columbia University, New York, NY; Epidemiology Unit, Braun School of Public Health, Hebrew University-Hadassah School of Public Health, Jerusalem, Israel (OP, YF, RCM, LD, OM, ET, RY).

Correspondence to: Susan Harlap, MB BS, Department of Epidemiology, Mailman School of Public Health, Columbia University, 722 W 168th Street, New York, NY 10032 (e-mail: sh2209@columbia.edu).

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CONTEXT AND CAVEATS

Prior knowledge

Genes on the Y chromosome have been implicated in prostate cancer. Mutations in such genes have the potential to influence the sex ratio of the offspring of men carrying them.

Study design

Men who were fathers in a family-based research cohort in Israel were followed for up to 40 years after the birth of their children.

Contribution

Men with only daughters had a 40% higher risk of prostate cancer than men with at least one son.

Implications

The findings support hypotheses that Y chromosome loci are involved in prostate cancer. Further investigation of reproductive outcomes of men might provide additional information on genes involved in prostate cancer.

Limitations

Information on sex of offspring was determined over a single 13-year period, and men who had sons before or after that period would have been misclassified in the analysis. No information on individual screening behavior was available. The study analyzed a single population, limiting generalizability.

religion (Muslim versus Jewish), wife's education (≥13, 9–12, or 5–8 years, versus others), one or more offspring with low birth weight (i.e., <2.5 kg) versus all offspring weighing more; one or more offspring with high birth weight (i.e., ≥4.0 kg) versus all offspring weighing less; and any major birth defect (versus none) or any minor defect (versus none). To test for trend, we entered the numbers of offspring into the Cox models as ordinal variables, truncated at five or more for total offspring and four or more for offspring of either sex. Two time-dependent variables were used, as dichotomies, for follow-up during calendar years 1991–1995 and 1996–2004 to control for changes in incidence that followed the introduction of testing with prostate-specific antigen (PSA) in 1991.

The 91467 live offspring in the Jerusalem Perinatal Study included 12 with unknown sex and 47037 males (51.43%). We had traced 98.5% of offspring by 2005 and through them verified 95.7% of their fathers' IDs; these 38995 IDs were then linked to Israel's Cancer Registry. We excluded 58 men with cancers diagnosed before their first offspring's estimated date of conception and three with unknown dates of death, leaving 38934 for analysis. Among these, there were 4026 men with invasive malignancies; they had sired 8526 offspring, of whom 51.70% were males. The men without cancer had 75921 offspring, with 51.5% males.

A total of 712 men were diagnosed with invasive prostate cancer at the age of 42–87 years (median = 68 years), after 7–41 years of follow-up (median = 31). Their 1445 offspring included 48.58% males (95% confidence interval [CI] = 46.00% to 51.16%). This crude sex ratio differed (P = .023) from that of the offspring of the rest of the cohort (51.57%, 95% CI = 51.23% to 51.91%) and was also lower (P = .0051) than that of the offspring sired by men who developed other malignancies (52.26%, 95% CI = 51.10% to 53.43%).

Estimates of the risk of prostate cancer in men without sons, conditional on the total numbers of offspring, are shown in Table 1. Overall, there was a 40% increase in prostate cancer in men lacking sons. In subgroup analyses (data not shown), this increase was consistently associated with lack of sons; we observed relative risks similar to 40% across different age groups, ethnic groups, and social classes, as well as in men diagnosed both before and after 1991, when PSA came into use. The data in Table 1 show that the relative risk associated with absence of sons increased as the numbers of offspring increased.

We also investigated whether risk was associated with lack of daughters (data not shown in table). In men with exactly two offspring and a reference group who sired one offspring of each sex, those lacking daughters had RR = 1.11 (95% CI = 0.79 to 1.56, based on 53 cases in 3153 men) whereas those without sons had RR = 1.47 (95% CI = 1.06 to 2.04, P = .021). Similarly, in men with three or more offspring and a reference group of men who sired at least one of each sex, those without daughters showed RR = 1.09 (95% CI = 0.68 to 1.73, based on 20 cases in 1155 men), whereas the group lacking sons showed RR = 1.60 (95% CI = 1.05 to 2.45, P = .03). The small excess risk of prostate cancer in fathers lacking daughters was likely to be due to chance and did not strengthen with increasing numbers of offspring.

Table 2 shows an analysis of the risk of prostate cancer that considers the numbers of offspring and numbers of sons and daughters as ordinal variables. There was a strong trend for a decrease in prostate cancer risk as the number of sons increased. Although there was no such trend for the number of daughters, the difference between numbers of sons and numbers of daughters is not formally statistically significant because the confidence limits for the two estimates of trend overlap.

Of the 712 fathers diagnosed with prostate cancer, 185 died during follow-up. In the whole cohort, the relative risk of mortality "with prostate cancer" associated with the lack of sons—i.e., regardless of immediate cause of death—was 1.59 (95% CI = 1.17 to 2.18, P = .0035), somewhat higher than the relative risk of prostate cancer incidence (i.e., 1.40). Regarding survival after diagnosis of prostate cancer in the 712 men, however, the relative risk of death associated with the lack of sons was 0.99 (95% CI = 0.72 to 1.34).

To assess specificity of the association of lack of sons with the incidence of prostate cancer, we analyzed the age-adjusted incidence of malignancies at specific sites other than the prostate; none was statistically significantly related to lack of sons (data not shown). The age-adjusted relative risk of cancer at all sites combined, excluding prostate cancer, was 0.95 (95% CI = 0.88 to 1.03) in men lacking a son compared with those who had at least one son. We also analyzed mortality from all causes (6324 deaths) in the cohort of 38 934 fathers; this outcome was also unrelated to the lack of sons (RR = 0.97, 95% CI = 0.91 to 1.02).

This study has several limitations. One is that we have no information about the offspring born to the same fathers before 1964 or after 1976. There is, however, no reason to suspect that the 712 men diagnosed with prostate cancer would have sired a different proportion of males outside of 1964–1976 than during that period. Furthermore, any misclassification within the group of men in which we observed no sons would have biased the relative risk toward the null. We also have no information on family history of prostate cancer, individual screening behavior, or measures

Table 1. Incidence and relative risks of prostate cancer in men with offspring in the Jerusalem Perinatal Study by numbers of total offspring and male offspring*

Total offspring, No.	Male offspring, No.	Prostate cancer		Age-adjusted	Fully adjusted†	
		No	Yes	RR (95% CI)	RR (95% CI)	*P* value‡
1	0	6951	168	1.25 (1.00 to 1.55)	1.25 (1.00 to 1.56)	.050
	1	7767	149	1 (referent)	1 (referent)	
2	0	2655	59	1.41 (1.04 to 1.91)	1.41 (1.04 to 1.91)	.027
	1 or 2	9126	145	1 (referent)	1 (referent)	
≥3	0	999	25	1.60 (1.05 to 2.43)	1.60 (1.05 to 2.43)	.029
	≥1	10724	166	1 (referent)	1 (referent)	
Total	0	10605	252	1.43 (1.22 to 1.68)	1.40 (1.20 to 1.64)	<.0001
	≥1	27616	460	1 (referent)	1 (referent)	

* RR = relative risk; CI = confidence interval.

† Adjusted for age (continuous), calendar year of follow-up (1996–2004, 1991–1995, versus earlier), man's year of birth (1950 or later, 1945–1949, 1940–1944, versus earlier), years of education (≥13 years versus less), occupational social class (continuous), wife's social class (highest group versus all others), North African origin (versus all others), and rabbis and students in Talmudic academies (versus all others).

‡ *P* value from χ^2, applies to fully adjusted estimate.

of disease progression, such as Gleason score. For example, if fathers of daughters had been screened more than fathers of sons, which might be one hypothetical explanation of our results, we should have seen risk related to the number of daughters, but we did not. Furthermore, had our results been explained by this type of differential screening, resulting in earlier diagnosis or overdiagnosis, we would have expected to see a spuriously decreased mortality (i.e., apparently better survival) in the men diagnosed with prostate cancer who lacked sons. We observed no such altered survival. The strongest evidence that our findings are unlikely to be spurious comes from the data in Table 1, which suggest that the biologic significance of lack of sons—whatever it is that leads to increased risk of prostate cancer—becomes increasingly important as family size increases.

Overall, our findings are consistent with hypotheses that tie Y chromosome loci to prostate cancer, although other explanations cannot be excluded. The Y chromosome, which is inherited from father to son, is extremely vulnerable to mutation because it undergoes minimal recombination with the X chromosome (24–26). Well-defined haplogroups in men with different geographic ancestries (24,27) have been associated with various diseases (28). Lineages of Israeli Jews, including Ashkenazim, are similar to those found in the non-Jewish populations of Eastern Turkey, Iran, and northern Iraq; they differ from those prevalent in European non-Jews (29). Thus, if the increased risk of prostate cancer that we observed in men without sons turns out to reflect an association with Y chromosome haplogroups, our findings might be more relevant to populations in West Asia than to those in Europe or the United States. In another population, a recent study has shown that Y chromosome haplogroups found only in Japanese men are related to the risk of prostate cancer (15).

Other evidence for involvement of loci on the Y chromosome comes from studies of prostate tumors. Loss of the Y chromosome is the most frequently observed cytogenetic abnormality in malignant prostate epithelium (6,12), and although the Y chromosome is frequently lost in other tissues with aging, it is generally preserved in normal prostate tissue (12), probably because some of its genes are essential for the prostate gland to function normally. The expression of some Y chromosomal genes—including TSPY, a multicopy gene implicated in gonadoblastoma, testicular,

Table 2. Incidence and relative risks of prostate cancer in men with offspring in the Jerusalem Perinatal Study by numbers of total, male, and female offspring*

No. of offspring	Prostate cancer		Age-adjusted	Further adjusted†
	No	Yes	RR (95% CI)	RR (95% CI)
Total offspring				
1	14718	317	1.60 (1.23 to 2.07)	1.46 (1.10 to 1.92)
2	11871	204	1.35 (1.04 to 1.76)	1.23 (0.93 to 1.61)
3	6512	113	1.23 (0.92 to 1.65)	1.13 (0.84 to 1.51)
≥4	5211	78	1 (referent)	1 (referent)
P_{trend}			<.0002	.0026
Male offspring				
0	10605	252	1.73 (1.26 to 2.37)	1.58 (1.15 to 2.18)
1	17089	286	1.24 (0.91 to 1.68)	1.13 (0.83 to 1.55)
2	7346	126	1.25 (0.90 to 1.74)	1.17 (0.84 to 1.63)
≥3	3182	48	1 (referent)	1 (referent)
P_{trend}			<.0001	.0005
Female offspring				
0	12002	222	1.1 (0.81 to 1.49)	0.98 (0.72 to 1.33)
1	16538	309	1.12 (0.84 to 1.50)	1.00 (0.74 to 1.34)
2	6709	127	1.14 (0.83 to 1.57)	1.04 (0.76 to 1.44)
≥3	2973	54	1 (referent)	1 (referent)
P_{trend}			.789	.659

* RR = relative risk; CI = confidence interval.

† Adjusted for age (continuous), calendar year of follow-up (1996–2004, 1991–1995, versus earlier), man's year of birth (1950 or later, 1945–1949, 1940–1944, versus earlier), years of education (≥13 years versus less), occupational social class (continuous), wife's social class (highest group versus all others), North African origin (versus all others), and rabbis and students in Talmudic academies (versus all others).

and prostate cancer (30), and SRY, the master switch for sex determination (31,32)—is reduced through hypermethylation (14) in malignant prostate tissue (10–13). SRY negatively regulates the X chromosome–linked androgen receptor (AR) gene (33); thus its loss in the prostate would likely increase the gland's sensitivity to androgens. The AR's numerous other coactivators and corepressors include DAX1, the product of an X chromosome gene that is also involved in sex determination (31,32,34), and BRCA1 (35); BRCA2 also plays a role in regulating the expression of the AR (36).

The incidence of prostate cancer is increased in some (37–40) but not all (41,42) families carrying mutations in BRCA1 or BRCA2. In such families, regardless of whether they include men with prostate cancer, male carriers have a lower percentage of male offspring than the general population (43,44). In two case–control studies, the prostate cancer patients reported fewer male siblings than control subjects (45,46). These observations and our results suggest that some men with prostate cancer may carry abnormalities involving loci on the Y and/or X chromosomes or factors interacting with them. Further investigation of reproductive outcomes of men might throw light on prostate cancer and other male-specific malignancies.

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Notes

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