Journal of Epidemiology and Community Health, 1987, **41**, 349–354

Testicular cancer in young men: the search for causes of the epidemic increase in the United States

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SUMMARY A case-control study of 271 men with testicular cancer and 259 controls was conducted in the Washington, DC area to evaluate whether suggested risk factors could be responsible for the epidemic increases in testicular cancer in young men. No substantial risks were associated with a history of groin hernia operation, the common childhood diseases, allergies, *x* rays below the waist, venereal disease, vasectomy, or external means of elevating the temperature of the testis. Excess risks were associated with a history of undescended testis (RR = 3·7, CI = 1·5-9·5), testicular trauma (RR = 2·6, CI = 1·6-4·2), and mumps orchitis (RR = 5·8, CI = 0·7-129·7). It is unlikely, however, that any of these conditions has increased sufficiently over time to markedly affect the testicular cancer incidence patterns. Therefore, while the risk factors identified in this paper are of epidemiological interest, they do not account for the increase in testicular cancer in young men.

Over the past several decades there have been dramatic increases in the incidence of testicular cancer, the most striking increases occurring among young men aged 15–44.[1] An aetiological role for undescended testis, groin hernia, testicular trauma, mumps, mumps orchitis, elevated testicular temperature, and hormonal, prenatal, and occupational factors in the development of young adult testicular cancers has been suggested by a number of studies.[2–12] However, previous researchers have in general been hampered by small study populations, which made it difficult to test those hypotheses. Therefore, we conducted a case-control study of testicular cancer in young men at three large referral centres to test the hypotheses generated by previous studies and to evaluate whether any of the suggested risk factors could be responsible for the epidemic increases in this cancer.

Methods

All testicular cancer cases aged 18–42 who had been newly diagnosed between 1 January 1976 and 30 June 1981 and referred to one of three collaborating medical centres in the Washington, DC area: National Institutes of Health Clinical Center (NIHCC), Uniformed Services University, Naval Hospital (USUNH), and Uniformed Services University, Walter Reed Army Medical Center (WRAMC) were selected for study. Cases diagnosed prior to 1979 were ascertained from tumour registry, hospital admissions, urology, and pathology records at the three centres and were interviewed over the telephone. Face-to-face interviews were conducted in the hospital for those cases seen on the oncology, surgical, and urology wards during 1979–81. Twenty-seven deceased testicular cancer patients diagnosed prior to 1979 were excluded from the study.

Controls were patients at the same hospital as the cases diagnosed with a malignancy other than cancer of the genital tract. They were similar to the cases in age (±2 years), race, vital status, and year of diagnosis. Controls diagnosed during 1976–78 were identified from computerised discharge logs at NIHCC and WRAMC and from tumour registry records at USUNH and were interviewed over the telephone. Controls diagnosed during 1979–81 were identified on the oncology, surgical and medical wards and were interviewed in the hospital in the same manner as the cases. The medical records of all patients were reviewed to confirm the diagnosis.

Interviews of the study subjects were conducted during 1979–81. A standardised questionnaire was used by trained interviewers to obtain detailed information on the study subject's medical history (eg, childhood diseases, hernia, undescended testis, trauma to the testis, venereal disease, and diagnostic *x* rays), personal history (eg, type of underwear and bathing habits), smoking history, and demographic information. Due to the young age of the study subjects, the measure of residence used in the analysis

was usual residence as a child. Subjects were asked to classify this area as being either rural (farm country or small town/community) or urban (city or suburb).

Telephone interviews were conducted with the study subjects' mothers to elicit information on the sons' in-utero exposures and childhood medical history.[2] Information was provided by the mothers on undescended testis, inguinal hernia, mumps orchitis, and childhood diseases. Information from the sons' questionnaires were used to supplement the mothers' responses when they were either unknown or unavailable.

The measure of association between testicular cancer and variables of interest was the relative risk (RR), approximated by the odds ratio.[13] Ninety-five per cent confidence intervals (CI) were calculated according to the method described by Gart.[14] Summary RR estimates adjusted for the stratifying (matching) variables hospital and age at diagnosis were calculated by the Mantel-Haenszel method.[15] Since the RR adjusted for the matching variables were similar in magnitude and direction to the unadjusted RR, the crude RR are presented in this paper unless otherwise specified. Type of patient interview, in person or telephone, did not affect the risk estimates. Fisher's exact test was used to calculate a lower bound CI when the number of controls in a cell was zero.[13] The population attributable risk associated with undescended testis was estimated assuming that prevalence of an undescended testis in the general male population is about 2·5% by age 3 years.[16–18] Chi-square tests of homogeneity were used to test for case-control differences in referral patterns.[13] Mantel's extension test[19] was used to test for trends (two-tailed) in risk related to cigarette consumption.

Results

Completed valid interviews were obtained for 271 cases (88·0%) and 259 controls (89·9%). Four per cent of the cases and 2% of the controls refused to be interviewed. The remainder were either unlocatable or unavailable for interview. One control with unreliable information was dropped from the analysis. Sixty-nine per cent of the cases and 71% of the controls were interviewed in person in the hospital, while 31% of the cases and 29% of the controls were interviewed at home over the telephone. The malignancies among the controls were Hodgkin's disease (29%), non-Hodgkin's lymphoma (18%), melanoma (17%), soft tissue sarcoma (7%), bone tumour (7%), leukaemia (7%), and other (15%). The histological types of testicular cancer were embryonal carcinoma (25%), teratocarcinoma (25%), seminoma (22%), mixed tumours with seminoma (14%), mixed tumours without seminoma (7%), teratoma (5%), and other or unknown (2%). The percentage of study subjects seen at each hospital was: NIHCC, 48%; USUNH, 22%; and WRAMC, 30%. To assess the possibility of referral bias, a chi square for homogeneity with regard to the geographic distribution (ie, Maryland, DC or Virginia; south; northeast; midwest; west; and foreign country) of the referring physicians of cases and controls was conducted. There were no significant differences in their referral patterns ($\chi^2 = 7{\cdot}4$; $p = 0{\cdot}19$).

The study population was 98% white with 70% between the ages of 16 and 30 years. The mean age at diagnosis was the same for cases and controls, 27 years. The percentage of study subjects with more than a high school education was similar for cases (51%) and controls (52%). Mean height obtained from the

Table 1 *Relative risks of testicular cancer according to demographic characteristics*

Risk factor	*No. of cases*	*No. of controls*	*RR*	*95% CI*
Childhood residence				
Rural	132	144	1·0	–
Urban	130	108	1·3	0·9–1·9
Both	9	7	1·4	0·5–4·3
Religion				
Protestant	167	173	1·0	–
Catholic	85	68	1·3	0·9–1·9
Jewish	4	10	0·4	0·1–1·5
Mormon	5	0		0·9–∞
Other	10	8	1·29	0·5–3·7
Marital status				
Ever married	141	135	1·0	–
Never married	130	124	1·0	0·7–1·4
Infertility*				
No	127	121	1·0	–
Yes (saw doctor)	8	9	0·8	0·3–2·5
Yes (no doctor)	5	5	1·0	0·2–3·9

* Includes only married study subjects.

medical records was 70·0 inches for cases and 69·5 inches for controls.

Table 1 presents the RR of testicular cancer for selected demographic characteristics. Although none of the RRs was statistically significant, there was an increased risk for usual childhood residence in a primarily urban rather than a primarily rural area. Compared to Protestant, a reduced risk was seen for Jewish and slightly elevated risks were seen for Catholic and no religion. Five cases and no controls reported being Mormon. No excess risk was seen according to marital status or infertility. The average age at marriage was 22 years for both cases and controls.

In order to evaluate the risks associated with two external means which have been speculated to elevate the temperature of the testis, study subjects were asked what type of underwear they usually wore and whether they usually took a shower or a bath when they bathed. There were no excess risks associated with wearing jockey type shorts versus boxer type shorts or with taking a bath instead of a shower (table 2).

RRs for testicular cancer according to history of specific medical conditions are presented in table 3. Undescended testis was the only medical condition that was associated with a significantly elevated risk of testicular cancer: RR = 3·7, yielding a population attributable risk estimate of 6·3%. The risks were similar for subjects who were interviewed in person (RR = 3·3, CI = 1·1-10·6) and over the telephone (RR = 4·5, CI = 0·9-31·3). The associations between testicular cancer risk and undescended testis and groin hernia have been explored in detail in another publication.[3]

No substantial differences were seen for histories of groin hernia operation uncomplicated by undescended testis, measles, chicken pox, allergies, *x* rays below the waist, venereal disease (primarily gonorrhoea), and vasectomy. Specific allergies (eg, hayfever and trees/grasses) also were not related to testicular cancer risk. A decreased risk was seen for a history of receiving acne treatments from a doctor. A history of mumps orchitis was associated with an almost six-fold risk (based on the combined positive responses from two cases and six case mothers and one control and no control mothers), whereas the RR for a history of uncomplicated mumps was nonsignificantly reduced.

Table 2 *Relative risks of testicular cancer according to external means of elevating temperature of the testis*

External means	*No. of cases*	*No. of controls*	*RR*	*95% CI*
Usual type of underwear*				
Boxer shorts	36	25	1·0	–
Jockey shorts	219	222	0·7	0·4–1·2
None	15	11	0·9	0·3–2·7
Usual bathing habits				
Shower	237	223	1·0	–
Bath	31	32	0·9	0·5–1·6
Both	3	4	0·7	0·1–3·8

* excludes 1 case and 1 control who did not report a usual type of underwear.

Table 3 *Relative risks of testicular cancer according to medical history*

*Risk factor**	*No. of cases*		*No. of controls*		*RR*	*95% CI*
	Yes	*No*	*Yes*	*No*		
Undescended testis	25	246	7	252	3·7	1·5– 9·5
Hernia operation†	18	228	15	237	1·2	0·6– 2·7
Measles	251	18	236	18	1·1	0·5– 2·2
Chicken pox	246	18	236	19	1·1	0·5– 2·3
Mumps	200	66	206	49	0·7	0·5– 1·1
Mumps orchitis	6	265	1	258	5·8	0·7–129·7
Treated for acne	24	247	33	226	0·7	0·4– 1·2
Allergy	75	196	75	184	0·9	0·6– 1·4
x rays below waist	47	224	45	214	1·0	0·6– 1·6
Venereal disease	22	249	22	237	1·0	0·5– 1·8
Vasectomy	5	266	5	254	1·0	0·3– 3·3

* Don't know responses are excluded from table.
† Excludes subjects with concommitant undescended testis and hernia.

A history of smoking at least 100 cigarettes during their lifetime was reported by 62·4% of the cases and by 53·3% of the controls (RR = 1·5, CI = 1·0-2·1). The RR for smoking was significantly elevated at NIHCC (RR = 2·1, CI = 1·2-3·6) but not at USUNH (RR = 1·2, CI = 0·5-2·6) or WRAMC (RR = 1·0, CI = 0·5-2·1). Since the RRs for the number of packs of cigarettes smoked per day were similar for USUNH and WRAMC (military hospitals), their combined results are presented in table 4. There was a significant trend with number of packs of cigarettes smoked at NIHCC (p for trend = 0·022), although the RR declined for the highest smoking category. No dose-response was seen at the two military hospitals. A similar pattern of risk was seen at NIHCC for the number of years smoked (ie, a drop in the RR for subjects smoking the greatest number of years). Results remained similar when controls with leukaemia and other cancers possibly related to smoking were removed.

The RR for study subjects reporting a history of trauma to the testis was significantly elevated, RR = 2·6 (CI = 1·6-4·2; 79 cases, 35 controls) and remained elevated, RR = 2·3 (CI = 1·3-4·1; 45 cases, 21 controls) when those reporting a trauma less than ten years before their cancer diagnosis were removed from the analysis. For this latter group, the average ages for first trauma to the testis were 11·6 years for the cases and 11·1 years for the controls. For both cases and controls, mean age at last trauma was 12·7 years. There were no differences in risk for the most frequently reported sources of trauma, being kicked (RR = 2·0, CI = 1·3-3·9), injured in an accident or fall (RR = 2·3, CI = 0·5-11·2), and injured on a bicycle (RR = 1·9, CI = 0·5-7·8).

Discussion

This case-control study was designed to investigate a number of factors potentially related to the risk of testicular cancer in young men and to evaluate whether any of these factors could be responsible for the dramatic increases in incidence over time.

A variety of sociodemographic characteristics were examined but none was significantly elevated. A slight excess risk was found for spending one's childhood in an urban rather than a rural area. This is consistent with a study reported in Denmark[20] but contrary to studies in England and Wales,[21] the Netherlands,[22] and Upstate New York.[23] No marked differences were seen according to religion in which the study subjects were raised, with the exception of the Mormon religion. There was an apparent excess of Mormons with testicular cancer (although based on small numbers). However, Lyon *et al*[24] reported no difference in the age-adjusted rates of testicular cancer in Mormons and Non-Mormons in Utah.

It has been suggested that external factors that elevate the temperature of the testis have been associated with increased risk of testicular cancer.[6-9] However, in this study there were no differences between cases and controls in the type of underwear usually worn or their typical bathing habits.

It has been well documented in the literature that individuals with undescended testis are at an increased risk for developing testicular cancer. In our case-control study, 10% of the cases and 3% of the controls reported a history of undescended testis, resulting in a significantly elevated risk of 3·7. This is consistent with the findings of other case-control studies which have reported risks ranging from 2·5 to 17·1.[3-8 11]

Inconsistent findings regarding the degree and significance of the risk of testicular cancer associated with groin hernia have been reported.[3-5 7 8 11] In our study, those men who had a history of a hernia operation but no history of undescended testis did not have a significant excess risk of testicular cancer. The reduced risk seen for acne treatments by a doctor was not significant. However, the reduction in risk was similar to that reported by Depue *et al*.[4]

Table 4 *Relative risks of testicular cancer according to number of packs of cigarettes smoked and type of hospital*

Hospital	*Packs*	*No. of cases*	*No. of controls*	*RR**	*95% CI*
NIHCC†					
	Non smoker	43	67	1·0	–
	< 1	25	22	1·8	0·8-3·7
	1	38	19	3·1	1·5-6·5
	> 1	19	20	1·5	0·7-3·3
Military					
	Non smoker	57	54	1·0	–
	< 1	24	22	1·0	0·5-2·2
	1	37	33	1·1	0·6-2·0
	> 1	25	22	1·1	0·5-2·3

* Risks relative to 1·0 for non-smokers at each hospital.
† Excludes 2 cases with unknown smoking habits.

In agreement with other studies[5 8 25] we found no significant excess risks associated with a history of measles, chicken pox, uncomplicated mumps, or venereal disease. Several clinical reports[12] and a population-based study of mumps orchitis[10] have suggested a relation between mumps orchitis and testicular cancer. In our study, mumps orchitis was reported for six cases and one control—a positive, although nonsignificant, association. However, the structure of this question, asking those subjects who reported a history of mumps whether it involved the testis, may have encouraged recall bias. Also, it is not clear whether study subjects could discriminate between mumps orchitis and other testicular conditions such as epididymitis.[26]

The relation between cigarette smoking and testicular cancer has not been well studied. In our study, there was a significantly elevated risk of 1·5 for ever smokers of cigarettes using the total study group. However, when cigarette smoking was stratified by hospital, the excess risk was restricted to those cases referred to NIHCC. Therefore, our results in conjunction with the previous negative findings reported in the literature[5,8] suggest that a causal relation between cigarette smoking and testicular cancer is unlikely.

To investigate the association between testicular trauma and testicular cancer, study subjects were asked if they had ever had any trauma or injury to the testis and the specific type of trauma. Since trauma to the testis may have caused some study subjects to seek medical care, thus bringing otherwise asymptomatic testicular tumours to the attention of a physician, only those traumas that occurred at least one year prior to diagnosis were included in the analysis. A risk of 2·6 was associated with having a trauma to the testis. Risks were elevated for injuries incurred during the following situations: riding a bicycle, playing sports, or having an accident or fall. Risks remained elevated when study subjects whose first trauma occurred less than ten years prior to diagnosis were excluded. Only one previous case-control study has addressed the issue of testicular cancer following trauma or injury to the testis.[5] That study asked specific questions on participation in sports activities and found excess risks with bicycling and horseback riding. Although testicular trauma appears to be related to the risk of testicular cancer, the positive association should be viewed cautiously because of the problem of recall bias.

As in other investigations, the associations found or the failure to find associations could be due to bias. Selection bias does not appear to be a factor in this study since response rates were high and the controls chosen had referral patterns similar to those of the cases. However, it is possible that some of the childhood exposures studied could play an aetiological role in other cancers in young adults. If this is the case, it is possible that an important association of interest could have been 'matched out' since the comparison group was composed of young men with other cancers. Nevertheless, the choice of other cancers for the comparison population was purposeful since childhood exposures may be subject to recall bias. Because cases and controls both developed a malignancy, these types of exposures should not be remembered differently by cases and controls. It is possible, however, that testicular cancer cases may have been more likely than the controls to recall a history of other urogenital conditions or injuries because of the location of the tumour.

This study did not find substantial risks associated with external means which have been speculated to elevate the temperature of the testis or with a history of groin hernia operation, the common childhood diseases, allergies, *x* rays below the waist, venereal disease, vasectomy, or cigarette smoking. It did find excess risks due to undescended testis, mumps orchitis, and testicular trauma. However, none of these conditions has increased sufficiently over time to markedly affect the testicular cancer incidence patterns.

Reasons for the increases in testicular cancer incidence, especially among young men, remain elusive. The increases do not appear to be related to improved diagnostic practices or to risk factors identified in this and other case-control studies.

We thank Dr Nasser Javadpour, NIHCC, Dr Kevin J O'Connell, USUNH, and Dr Ray E Stutzman, WRAMC, for allowing us access to their patients; Ms Jeanne Rosenthal, Ms Kathy Weber, Ms Judith Walsh, Ms Sandra Becker, and the staff of Westat Inc for data management and interviewing; and Ms Roselyn Weil, NCI, for data collection and interviewing.

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Accepted for publication June 1987