



## Management of Cryptorchism and Risk of Testicular Cancer

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Cryptorchism is an established risk factor for testicular cancer, but the role of age at surgical correction is unclear. The authors investigated this relation using information obtained from comprehensive medical records dating to childhood. They conducted a case-control study of 183 Kaiser Permanente members, who were diagnosed with testicular cancer during 1973–1996 and who were 15 years or younger when they first joined the health plan, and 551 controls. Notes pertaining to the testes were reviewed up to the case's diagnosis date or comparable date among the controls. The odds ratio for the association of a history of cryptorchism with testicular cancer risk was 4.8 (95% confidence interval (CI): 1.9, 11.8). Compared with no history of cryptorchism, men with a history who had natural descent or successful orchiopexy by the 11th birthday were not at increased risk of testicular cancer (odds ratio = 0.6, 95% CI: 0.08, 5.4). However, successful treatment of cryptorchism only after the 11th birthday, or never, was related to a 32-fold increased risk (95% CI: 4, 250). Orchiopexy was performed before the 11th birthday on three men who developed testicular cancer but, in each, the procedure failed. In contrast, all four of the early orchiopexies performed on the controls were successful. Boys with failed orchiopexy should be considered for reoperative orchiopexy or orchiectomy to prevent testicular cancer.

cryptorchidism; orchiectomy; risk factors; testicular neoplasms

Abbreviations: CI, confidence interval; OR, odds ratio.

Cryptorchism has been strongly and consistently related to risk of testicular cancer, with more than a dozen studies reporting relative risks ranging from 2.1 to 17.6 (1). Two hypotheses have been proposed to explain this association. The first posits that local temperature elevation of an ectopic testis is somehow procarcinogenic. If this hypothesis is correct, then orchiopexy, the surgical repositioning of the testis into the scrotum, could protect against cancer, if the procedure is performed before precancerous cells differentiate to a critical point such as could occur in puberty. The second hypothesis posits that an underlying hormonal condition predisposes to both cryptorchism and testicular cancer. If so, orchiopexy would not prevent testicular cancer, and orchiectomy would be required. The role of orchiopexy in reducing the risk of testicular cancer among persons with cryptorchism has been examined in four studies, but their results are somewhat equivocal, particularly with regard to the timing of the procedure in relation to puberty. Thus, the surgical treatment of cryptorchism to prevent testicular cancer remains unclear.

We sought to confirm reports that successful treatment at an early age substantially reduces the risk of testicular cancer. Our case-control study, set within the Kaiser Permanente Medical Care Program of Northern California, used medical records dating to childhood to ascertain the management of cryptorchism.

### MATERIALS AND METHODS

#### Study population

Male Kaiser Permanente members diagnosed with germ cell testicular cancer (*International Classification of Diseases* site code C62, histology codes 9060–9091) (2) during the period 1973–1996 were identified as cases. They were ascertained through the Northern California Cancer Center, which has reported incident cancer cases occurring in the seven-county Bay Area to the Surveillance, Epidemiology, and End Results Program since 1973, or the Kaiser Permanente Regional Cancer Registry, which has reported incident cases diagnosed among members of the 23-county

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northern California service area since 1988 directly to the Northern California Cancer Registry in conjunction with state reporting requirements. In addition, men with testicular cancer must have first joined Kaiser Permanente when they were 15 years of age or younger, to ensure an opportunity to ascertain early life exposures. We selected a cutoff of 15 years to obtain as many cases as possible, while expecting at least limited information about a history of cryptorchism. Of the 228 testicular cancer cases initially identified, 45 were ineligible at chart review. Of these, 41 were 16 or more years upon entry into the plan, three were diagnosed with a non-germ cell malignancy, and the chart was inaccessible for one. The final number of eligible men with testicular cancer was 183.

Male Kaiser Permanente members enrolled during the period when incident testicular cancer cases were ascertained (1973–1996) who, like the cases, first joined Kaiser Permanente when they were 15 years of age or younger were eligible as controls. Three controls were selected for each eligible man with testicular cancer, to whom they were frequency matched on the following: year of birth (1940–1949, 1950–1959, 1960–1969, 1970–1979, 1980–1992) and age at entry in Kaiser Permanente (0–3, 4–7, 8–11, 12–15 years). In addition, each control without testicular cancer was assigned a reference date, at which he was an active member of the health plan, so that the distribution of reference dates among the controls corresponded to the distribution of diagnosis dates among the cases with testicular cancer. The number of ineligible controls was 165, of whom 83 were 16 or more years at entry into the plan, 19 had lost or inaccessible charts, and three were female. In addition, 60 had not had a visit to the health plan in the 5 years prior to their reference date; these were excluded for it was unclear whether they had double coverage and received their care outside the health plan. The final number of eligible controls without testicular cancer was 551.

### Data collection

Information on demographic characteristics, prenatal and birth characteristics, congenital anomalies, childhood growth and development, injuries to the groin, hormonal disorders, and sports participation was obtained from the medical record by a single, trained medical record analyst. Every note discussing undescended (cryptorchid or ectopic) testes, retractile testes, or inguinal hernia was ascertained, including the location of the cryptorchid testis, if mentioned, as well as therapeutic options and procedures. We also ascertained testicular biopsies. The medical record was reviewed from the first chart date to the diagnosis or reference date.

### Data analysis

Histories of cryptorchism, retractile testes, inguinal hernia, and treatment were compared between men with and men without testicular cancer in contingency tables and in logistic regression analysis using SAS software (3). In addition, we examined the age at orchiopexy, using the 11th birthday as a cutpoint. This was the most commonly used cutpoint in earlier reports, which used the following: the eighth birthday

**TABLE 1. Demographic characteristics of Kaiser Permanente members with incident testicular cancer diagnosed between 1973 and 1996 and controls\***

Characteristic	Cases (%) (n = 183)	Controls (%) (n = 551)
<b>Birth year</b>		
1940–1949	8	8
1950–1959	27	27
1960–1969	47	47
1970–1995	19	19
<b>Age at entry into Kaiser Permanente (years)</b>		
0–3	41	48
4–7	20	18
8–11	19	18
12–15	20	16
<b>Age at reference date (years)</b>		
≤19	18	22
20–29	49	46
30–39	30	27
≥40	4	5
<b>Year of reference date</b>		
1973–1987	30	30
1988–1990	28	28
1991–1993	20	20
1994–1996	22	22
<b>Race/ethnicity</b>		
White	82	69
African American	1	14
Other	17	17
<b>Marital status at reference</b>		
Living alone	37	31
Living with a partner	22	18
Other and unknown	40	51
<b>Alcohol use at reference</b>		
None	15	21
Drinker	29	21
Unknown	56	58
<b>Smoking status at reference</b>		
Nonsmoker	29	31
Smoker	13	11
Unknown	58	58

\* Cases and controls were aged 15 years or younger at first entry into Kaiser Permanente. Information was ascertained from the medical record.

(4), the 10th birthday (5), the 11th birthday (6), and the 11th birthday (7). Maximum likelihood methods were used to estimate the odds ratios for the association of these conditions with testicular cancer risk, and the 95 percent confidence interval was calculated using standard errors. Potential confounding was examined through adjustment. The

**TABLE 2. Relation of cryptorchism and its management, ascertained from the medical record, with subsequent risk of testicular cancer among Kaiser Permanente members with incident testicular cancer diagnosed between 1973 and 1996 and controls, aged 15 years or younger at first membership**

	Cases (no.) (n = 183)	Controls (no.) (n = 551)	Odds ratio	95% confidence interval
No ectopic testis	171	543	1.0	Reference
Ectopic testis	12	8	4.8	1.9, 11.8
Treatment*				
Natural descent by 11th birthday	1	1		
Complete orchiopexy by 11th birthday	0	4		
Total resolved by 11th birthday	1	5	0.6	0.08, 5.4
Complete orchiopexy at 11th birthday or later	3	0		
Incomplete orchiopexy	3	0		
No treatment	2	1		
No evidence of treatment but documentation poor	2	0		
Total unresolved by 11th birthday	10	1	32	4.0, 250

\* Excludes one case whose cancerous testis was contralateral to a cryptorchid testis removed at 5 years of age, one control who underwent orchiectomy, and one control diagnosed with ectopic testis at 1 month of age whose membership was subsequently interrupted.

following were examined as potential confounding factors using logistic regression: the variables birth year and age at entry into the health plan, by which the men without testicular cancer were matched to those with testicular cancer, as well as race, marital status, smoking history, and alcohol use. With respect to the latter three variables, there were large numbers of subjects with missing information, so "missing" was treated as a separate exposure category. None of these potential confounding factors was observed to change the odds ratio to an important degree, and none was retained in the final analysis.

## RESULTS

Because of the eligibility requirements concerning age at entry and year of entry, the men were relatively young at diagnosis (table 1). Testicular cancer cases and controls without testicular cancer were nearly comparable with respect to their age at entry into Kaiser Permanente: by eighth birthday, 61 percent of cases and 66 percent of controls. Compared with men without testicular cancer, those with testicular cancer were less likely to be African American (1 percent of cases vs. 14 percent of controls), while they were more likely to have a history of ectopic testes (6.7 percent vs. 1.2 percent). They were similar with respect to marital status, alcohol use, and smoking history, although this information was missing for a large number of men.

A history of cryptorchism with or without inguinal hernia or retractile testis was associated with the risk of testicular cancer (odds ratio (OR) = 4.8, 95 percent confidence interval (CI): 1.9, 11.8) (table 2). Inguinal hernia with or without

retractile testis but without cryptorchism was not associated with risk of testicular cancer (OR = 0.9, 95 percent CI: 0.5, 1.7). Furthermore, retractile testis alone was not associated with the risk of testicular cancer (OR = 1.4, 95 percent CI: 0.3, 7.9), although the number of affected men (two cases and four controls) was too small to permit meaningful interpretation.

In one of the 12 men with both testicular cancer and a history of cryptorchism, the cancer developed in the testis contralateral to a cryptorchid testis that had been removed at 5 years of age, the cancerous testis itself not having been ectopic (table 2). In another of these 12 men, the testes descended naturally at an unrecorded time between clinic visits at 5 and 9 years of age. Of the remaining men, three had received one or two failed orchiopexies that were not followed up, three had received successful orchiopexies at age 12 or more years (12, 12, and 15 years), two had received no treatment, and two had not received treatment by 10 and 13 years of age, respectively, when their medical records were interrupted for an extended period.

Among the eight controls without testicular cancer who had a history of cryptorchism, one was diagnosed with cryptorchism at 1 month of age after a premature birth, after which his medical record was interrupted. Another was untreated. The remaining six had their cryptorchism successfully resolved by their 11th birthdays, through natural descent (at 2 years), orchiectomy (at 5 years), or a single, successful orchiopexy procedure (at 1, 6, 8, and 10 years).

In our analysis of the timing of cryptorchism, we excluded the man whose testicular cancer was contralateral to his cryptorchid testis that had been removed by orchiectomy, because orchiopexy would not be indicated or recommended

for this patient. We further excluded the control without testicular cancer who underwent orchiectomy, as his testis was not at risk of cancer. In addition, we excluded the control without testicular cancer who was born prematurely, diagnosed with bilateral cryptorchism at 1 month of age, and then lost to follow-up, as 95 percent of ectopic testes among premature births descend during the first year (8). Among the remaining men, the odds ratio for the association of complete resolution of cryptorchism by the 11th birthday with risk of testicular cancer was 0.6 (95 percent CI: 0.08, 5.4). For cryptorchism that was untreated, treated unsuccessfully, or treated after the 11th birthday, it was 32 (95 percent CI: 4, 250).

We also sought to evaluate whether testicular biopsy was associated with risk, but biopsy had been performed in only one man with and one man without testicular cancer.

## DISCUSSION

We observed no increased risk of testicular cancer among men whose cryptorchism had been successfully resolved by their 11th birthday (95 percent CI: 0.08, 5.4) but a 32-fold increased risk (95 percent CI: 4, 250) among men whose cryptorchism persisted after this age. This age cutpoint was somewhat arbitrary. Had we used the 10th birthday as the cutpoint, the odds ratio for the association of successfully treated ectopic testes would have been 0.8 (95 percent CI: 0.03, 7.5) and, for unsuccessfully treated, 15.8 (95 percent CI: 3.2, 105). On the other hand, had we used the 12th birthday as the cutpoint, the odds ratios would not have changed.

The strengths of the study included its use of comprehensive medical records dating to early childhood, as well as its population base. Its primary limitations were its size and the uncertain status of the potential controls who had not visited Kaiser Permanente during the 5 years before their reference date. It is possible that some of these patients may simply have had no health problems, in which case we may have underestimated the overall association of ectopic testes with risk of testicular cancer. We believe this potential bias to be minimal because the prevalence of ectopic testes among the controls was very low.

Our estimate of a 4.8-fold increased risk of testicular cancer among men with a history of cryptorchism is consistent with numerous earlier reports, as noted in a review of this topic (1), although there was one poorly controlled study that did not observe the relation (9). However, the range of estimates from previous studies is quite wide (relative risks = 2.5–18.0). Most of the earlier studies were based primarily on interview, and variation in their results may stem from differences in ascertainment of cryptorchism and from geographic and temporal variation in the management of cryptorchism.

The United Kingdom Testicular Cancer Study Group (6), using general practitioners' notes, observed no increased risk of testicular cancer among men who had undergone orchiectomy before 10 years of age. Similar results were obtained in a Danish study (5), where treatment was ascertained using a self-administered questionnaire. In contrast, two US interview-based studies observed increased risks of testicular

cancer among men who had undergone orchiectomy by 10 years of age, although they did observe a trend of decreasing risk with younger age at treatment (4, 7). Because the study was based on recalled, self-reported information, both the diagnosis of ectopic testis and the timing of treatment may have been underascertained by the controls, particularly if their malformation was resolved at an early age. More importantly, however, none of these four studies ascertained the success or failure of orchiectomy.

Testis retraction is well known to occur following orchiectomy and can be due to inadequate dissection or insufficient cord length (8). Reoperative orchiectomy is recommended when this occurs. In the present study, one of the three men whose initial orchiectomy failed did receive reoperative orchiectomy; however, it failed as well. The patient was not considered for orchiectomy.

Our study differs from earlier studies in that we used the comprehensive medical record to follow the management of cryptorchism over time. Considering the difficulty of conducting a larger study of this topic with similarly complete information on the outcome of orchiectomy, our study argues for the consideration of reoperative orchiectomy or orchiectomy among patients whose initial orchiectomy fails.

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