Aetiology of testicular cancer: association with congenital abnormalities, age at puberty, infertility, and exercise

United Kingdom Testicular Cancer Study Group

Abstract

***Objective*—To determine the risk of testicular cancer associated with undescended testis, inguinal hernia, age at puberty, marital status, infertility, vasectomy, and amount of exercise.**

***Design*—A population based case-control study with a questionnaire administered by an interviewer and with relevant supplementary data extracted from general practitioners' notes.**

***Setting*—Nine health regions within England and Wales.**

***Subjects*—794 men, aged 15-49 years, with a testicular germ cell tumour diagnosed between 1 January 1984 and 1 January 1987; each had an age matched (within one year) control selected from the list of their general practitioner.**

***Results*—There was a significant association of testicular cancer with undescended testis (odds ratio 3·82; 95% confidence interval 2·24 to 6·52) and inguinal hernia (1·91; 1·12 to 3·23). The excess risk associated with undescended testis was eliminated in men who had had an orchidopexy before the age of 10 years. There were positive associations with early age at voice breaking, early age at starting to shave, and infertility. There was a significant association with a sedentary lifestyle and a moderate protective effect of exercise. There was no association with vasectomy.**

***Conclusion*—This study confirms previous reports that developmental urogenital abnormalities result in an increased risk of testicular cancer. The trend to perform orchidopexy at younger ages may reduce the risk associated with undescended testis. The increased risks associated with early age at puberty and low amounts of exercise may be related to effects of exposure to endogenous hormones. Changes in both of these factors may partly contribute to the increasing rates of testicular cancer observed in the past few decades.**

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Introduction

In the past few decades there has been a continuous rise in the incidence of testicular cancer in the United Kingdom,[1,2] United States,[3] and in most other white populations.[4,5] In England and Wales testicular cancer is now the most common form of cancer in men aged 15 to 44 years,[6] and apart from a history of undescended testis and infantile inguinal hernia no risk factors have been identified with certainty.[7]

There have been 11 published case-control studies of testicular cancer based on interview,[8-21] the largest of which included 333 cases and 729 controls.[19,20] All but one of these studies[16,17] were conducted in North America. There are also six record based case-control studies.[22-27] In general, positive results from these studies have not been found consistently, and the relative risks have been small.

In an attempt to increase understanding of the aetiology of testicular cancer we carried out a large population based case-control study within England and Wales. We report the first detailed analysis of our results and examine the associations of risk with urogenital abnormalities, age at puberty, marital status, infertility, and amount of exercise.

Subjects and methods

The study was carried out in nine health regions: South West, Wessex, South East Thames, South West Thames, North Thames, Oxford, South Wales, North West, and Yorkshire. Within each region a geographical area was defined and cases and controls resident only in this study area, covering a total population of 19·5 million, were eligible for inclusion. The study was approved by the central ethics committee of the BMA and by local ethics committees in each region.

SELECTION OF CASES AND CONTROLS

All men aged 15 to 49 years diagnosed as having a testicular germ cell tumour between January 1984 and January 1987 (dates subject to some regional variation) and who were resident in one of the defined study areas were included. The date of diagnosis was taken to be the date of the first biopsy specimen that yielded positive results. The main sources of cases were major treatment centres for oncology or radiotherapy, or both, and regional cancer registries. For every case two controls were chosen from the list of the general practitioner with whom the case was registered. The controls' dates of birth were matched to within one year, and controls had to have been registered with the general practitioner at the time of diagnosis of the case. Only one control was interviewed, the second name being kept as a reserve if the first could not be interviewed. In some instances it was necessary to choose further controls.

The study was restricted to white men with no previous malignancy. Men with a severe mental handicap or psychiatric condition (as determined by a consultant or general practitioner) which would make an interview impossible were also excluded, as were cases diagnosed abroad and controls whose names were still on the general practitioner's list but who had moved out of the study area before control selection. Cases and controls were first contacted by letter from the consultant or general practitioner, respectively, and informed of the purpose of the study. The letter was followed by a telephone call or a visit from interviewing staff within three weeks if no reply had been received. Strenuous efforts were made to maximise response rates. Failure was accepted only if a man was untraceable, had moved outside the study area, or returned the reply form stating that he did not wish to take part.

INTERVIEWING

Interviewing took place between June 1984 and April 1988. The median time between case diagnosis and interview was 10 months (range 0-50 months). Each case-control pair was seen by the same female interviewer, and interviews took place at general practitioners' surgeries, at the man's home, at his place of work, or in a hospital.

DATA

The interview included questions on personal history, sexual development and behaviour, medical history, marital history and children, lifestyle including sport and exercise, occupational history and exposures, and family history. Every control was given a pseudodiagnosis date, the date on which he was exactly the same age as his matched case was at diagnosis. A reference age was defined as the age of the case and control one year before the diagnosis or pseudodiagnosis date. Most data collected referred to events happening before the reference age. As controls were always interviewed after their matched case they had a slightly longer time interval between their reference and interview dates (median three months longer).

After interview, and with the interviewees' consent, data on medical history, particularly with respect to undescended testis, inguinal hernia, and testicular trauma, were abstracted from general practitioners' notes by the interviewers with a structured form. For cases details of their testicular tumours were abstracted from their hospital notes and a copy of their pathology reports obtained. Hospital notes were used only to confirm the diagnosis. Abstracts from general practitioners' notes and mothers' questionnaires were used to confirm the history of undescended testis, hernia, and trauma.

A diagnosis of undescended testis was regarded as definite only if there was evidence of successful orchidopexy or of surgical investigation at which a testis was found to be missing or impossible to correct. Otherwise, the testis had to be still undescended at reference age. Testes that were retractile in either childhood or adulthood or that descended spontaneously were not regarded as undescended. There was also a third category of "possible undescended testis" in which there seemed to be a genuine undescended testis but there was insufficient evidence for a definite diagnosis. Included in this category were any apparent undescended testes which were successfully treated with hormonal treatment. All the possible undescended testes were included in the category of no undescended testis for the analyses.

STATISTICAL METHODS

The EGRET package was used for statistical analysis using multivariate conditional logistic regression methods for individually matched case-control studies.[28] Relative risks were estimated by odds ratios with 95% confidence intervals. A case-control pair was excluded from the odds ratio estimation if the information for either the case or the control was not known for the variable in question. The numbers of pairs on which each analysis was based are given in the tables.

Significance tests (P values) quoted are two sided. Tests for trend were calculated either across categories or by using recorded levels for continuous variables as appropriate (see footnotes on tables). Odds ratios are presented both unadjusted and adjusted for a history of undescended testis and inguinal hernia (the latter diagnosed at ages less than 15 years).

TABLE I—*Numbers of cases of testicular cancer by age group and by region of residence at diagnosis*

Variable	No of cases (n=794)
Age (years):	
15-19	41
20-24	124
25-29	161
30-34	175
35-39	154
40-44	89
45-49	50
Region of residence:	
South West	47
Wessex	96
South West Thames	101
South East Thames	120
North Thames	15
Oxford	142
South Wales	66
North West	102
Yorkshire	105

Results

Within the predefined geographical areas of the study 863 eligible cases were identified. Interviews were completed with 794 (92·0%) of these men. Fourteen of the 863 eligible patients (1·6%) refused to participate, 12 (1·4%) were too ill to participate, 27 (3·1%) died before an interview could be arranged, and 16 (1·9%) had moved outside the study area. Of the 794 first selected individually matched controls, 609 (76·7%) were interviewed. Eighty four (10·6%) refused to participate, 26 (3·3%) could not be contacted, and 14 (1·8%) were not approached on the advice of the general practitioner. Sixty one controls (7·7%) had moved from their registered addresses and should not have been included in the sampling frame. The control response rate was therefore 83·1% (609/(794−61)). To replace the 185 controls who did not participate 142 second selected controls and 43 third or subsequent controls were interviewed.

Table I shows the distribution of cases by age and by region of residence at diagnosis. Most diagnoses occurred between the ages of 20 and 39 years. There were 446 right sided and 345 left sided cancers. Two men had bilateral disease at diagnosis and for one man the side was unknown. There were 400 tumours described as pure seminoma and 394 tumours of other (including combined) germ cell histological types. Differences in risk by histological type will be presented elsewhere.

Table II shows the risk of testicular cancer associated with undescended testis and inguinal hernia. Both were significant risk factors for testicular cancer. The overall odds ratio for a history of undescended testis was 3·82 (95% confidence interval 2·24 to 6·52). Nineteen cases and no control men had bilateral undescended testis (odds ratio ∞ (5·86 to ∞)), whereas 46 cases and 17 controls had unilateral undescended testis (2·71 (1·55 to 4·72)). Twelve of the 46 cases with unilateral undescended testis had cancer in the contralateral testis to that which was maldescended (odds ratio 1·42 compared with 4·02 for the risk to the ipsilateral testis). Confirmation of undescended testis from the general practitioners' notes was present for 57 of the 65 cases (87·7%) and 16 of the 17 controls (94·1%). The remaining eight cases and one control provided sufficient information themselves to allow a classification of the undescended testis as definite. Four cases and five controls had a possible undescended testis, of whom two cases and one control had hormonal treatment.

TABLE II—*Numbers (percentages)* of cases and controls and odds ratios (95% confidence intervals) for diagnosis of undescended testis and inguinal hernia*

Diagnosis	No (%) of cases	No (%) of controls	Odds ratio (95% confidence interval)
Undescended testis (794 matched pairs):			
No	729 (91·8)	777 (97·9)	1·00
Yes	65 (8·2)	17 (2·1)	3·82 (2·24 to 6·52)
Bilateral	19 (2·4)	0	∞ (5·86 to ∞)
Unilateral	46 (5·8)	17 (2·1)	2·71 (1·55 to 4·72)
Age at correction (unilateral only) (years):			
<10	6 (0·8)	10 (1·3)	0·60 (0·22 to 1·65)
10-14	23 (2·9)	3 (0·4)	7·67 (2·30 to 25·53)
>14	5 (0·6)	0	∞ (1·22 to ∞)
Test for trend†			χ^2=5·53;P=0·019
Uncorrected (unilateral only)	12 (1·5)	4 (0·5)	3·00 (0·97 to 9·30)
Inguinal hernia‡ (712 matched pairs):			
No	686 (94·1)	752 (96·8)	1·00
Yes	43 (5·9)	25 (3·2)	1·91 (1·12 to 3·23)
Age at diagnosis (years):			
<15	29 (4·0)	11 (1·4)	2·64 (1·32 to 5·28)
≥15	14 (1·9)	14 (1·8)	1·10 (0·47 to 2·59)

*Percentages exclude missing values.
†Trend test fitting age at correction as continuous variable considering only cases and controls with unilateral undescended testis and successful correction. Because of non-convergence in a fully matched model stratification for this test was in five year age groups.
‡All men with undescended testis (65 cases and 17 controls) were excluded from analysis.

A split of our study group at the median age (31 years) shows that in controls the prevalence of undescended testis was 3·3% (13/395) in those younger than the median and 1·0% (4/399) in those at or older than the median. Comparable figures for cases were 8·1% (32/395) and 8·3% (33/399), respectively, producing odds ratios of 2·46 (1·29 to 4·69) and 8·25 (2·92 to 23·29) for younger and older men, respectively. There was therefore a considerably reduced relative risk in the younger men, although the proportion of cases who had a history of undescended testis remained similar.

Age at correction in men with unilateral undescended testis had a strong effect on the risk of cancer. Men who were successfully operated on before the age of 10 years did not have an increased risk (0·60 (0·22 to 1·65)) whereas those corrected at or after the age of 10 years or who had an uncorrected testis had a significantly increased risk (7·67 (2·30 to 25·53) for correction at 10-14 years; ∞ (1·22 to ∞) for correction at ages older than 14 years, and 3·00 (0·97 to 9·30) if uncorrected). The odds ratio for men who had an undescended testis corrected at or after the age of 10 was significantly increased in comparison with men who had an undescended testis corrected before 10 years (6·75 (1·55 to 29·48)). Among men who had a successful correction the trend of association between age at orchidopexy (as a continuous variable) and risk of cancer (χ^2=5·53; P=0·019) was significant. Apart from one case with unilateral undescended testis who had a correction at the age of 3 years no orchidopexies were carried out below the age of 5 years. Fifteen of the 19 cases with bilateral undescended testes had successful corrections on both sides, four before the age of 10 years, 10 at 10-14 years, and one over 14 years. Because there were no controls with bilateral undescended testes the odds ratios for these categories could not be calculated.

There were 16 cases (12 unilateral, four bilateral) and four controls (all unilateral) with uncorrected undescended testis. We confirmed that of these, nine cases and one control had never had an orchidopexy whereas seven cases and three controls had had an operation but the testes either could not be found or could not be put into the scrotum.

Although a history of inguinal hernia in the absence of undescended testis was significantly associated with testicular cancer (1·91 (1·12 to 3·23)), this risk was confined to men who had a hernia diagnosed before the age of 15 years (2·64 (1·32 to 5·28)).

Table III shows results from questions relating to age at onset of puberty. There were significant trends of decreased risk of cancer with increasing age at voice breaking (P=0·010), increasing age at which shaving started (P=0·007), and age at first recalled nocturnal emissions (P=0·031). There was no significant trend with age at first masturbation (P=0·099).

Table IV shows that there was no association between risk of cancer and marital status (0·98 (0·74 to 1·30) for ever versus never married), although there was a significant relation among men who had been married of decreased risk with later age at first marriage (P=0·016). Fourteen cases and 10 controls reported having experienced homosexual intercourse (1·35 (0·56 to 3·28)); 48 cases and 42 controls refused to answer this question.

Table IV also shows the relation between infertility and risk of testicular cancer. After all cases with bilateral undescended testes were excluded 13 cases and five controls reported that they had been diagnosed with either low fertility or sterility (2·66 (0·94 to 7·54)). Confirmation of this diagnosis was available from the general practitioners' notes for nine cases and three controls (2·95 (0·79 to 10·99)).

There was no overall association between testicular cancer and having had a vasectomy (1·09 (0·77 to 1·52)).

The risk of testicular cancer decreased with increased amount of exercise and increased with increased sedentary time (table V). The trends at age 20 years and at reference age were significant for exercise (P=0·010 at 20 years; P=0·018 at reference age) and for time spent seated (P=0·024 at 20 years; P=0·006 at reference age). Those who engaged in 15 or more hours a week of exercise had a substantially reduced risk (0·62 (0·42 to 0·91) at 20 years; 0·54 (0·32 to 0·90) at reference age). At reference age there was a 71% increase in risk in men who spent 10 or more hours

TABLE III—*Numbers (percentages)* of cases and controls and odds ratios (95% confidence intervals) by variables relating to age at puberty*

Variable	No (%) of cases	No (%) of controls	Unadjusted odds ratio	Adjusted odds ratio† (95% confidence interval)
Age voice broke (years) (403 matched pairs):				
<13	99 (17·9)	80 (14·5)	1·00	1·00
13	162 (29·3)	137 (24·9)	0·81	0·80 (0·51 to 1·25)
14	175 (31·7)	177 (32·2)	0·76	0·77 (0·50 to 1·20)
15	75 (13·6)	85 (15·5)	0·70	0·71 (0·41 to 1·21)
≥16 or net yet	41 (7·4)	71 (12·9)	0·45	0·45 (0·25 to 0·80)
Not known	238	240		
Younger than age 16	4	4		
Test for trend‡				χ^2=6·68; P=0·010
Age started shaving (years) (740 matched pairs):				
<14	25 (3·3)	19 (2·5)	1·07	1·04 (0·53 to 2·04)
14	45 (6·0)	41 (5·4)	0·87	0·88 (0·52 to 1·06)
15	112 (15·0)	89 (11·8)	1·00	1·00
16	183 (24·4)	175 (23·1)	0·85	0·84 (0·59 to 1·20)
17	173 (23·1)	184 (24·3)	0·74	0·74 (0·52 to 1·06)
≥18 or not yet	211 (28·2)	249 (32·9)	0·66	0·65 (0·46 to 0·92)
Not known	18	10		
Younger than age 18	27	27		
Test for trend‡				χ^2=7·23; P=0·007
Age at first nocturnal emissions (years) (524 matched pairs):				
≤12	99 (15·2)	85 (13·5)	1·00	1·00
13	118 (18·1)	103 (16·4)	1·01	1·06 (0·67 to 1·67)
14	152 (23·3)	130 (20·7)	0·90	0·91 (0·60 to 1·40)
15	82 (12·6)	100 (15·9)	0·62	0·67 (0·42 to 1·10)
≥16 or never	201 (30·8)	210 (33·4)	0·71	0·75 (0·50 to 1·12)
Not known	138	162		
Younger than age 16	4	4		
Test for trend‡				χ^2=4·63; P=0·031
Age when first masturbated to orgasm (years) (602 matched pairs):				
≤12	108 (16·2)	97 (13·9)	1·00	1·00
13	139 (20·9)	130 (18·7)	1·01	1·03 (0·70 to 1·51)
14	173 (26·0)	193 (27·7)	0·81	0·84 (0·59 to 1·22)
15	115 (17·3)	132 (19·0)	0·78	0·81 (0·54 to 1·21)
≥16 or never	130 (19·5)	144 (20·7)	0·76	0·79 (0·54 to 1·17)
Not known	125	94		
Younger than age 16	4	4		
Test for trend‡				χ^2=2·72; P=0·099

*Percentages exclude missing values; subjects younger at reference age than oldest age category for given variable excluded from analysis.
†Adjusted for undescended testis and inguinal hernia diagnosed <15 years.
‡Trend test fitting variable as categories in table, excluding "not known" and subjects too young for analysis.

TABLE IV—*Numbers (percentages)* of cases and controls and odds ratios (95% confidence intervals) by reported marital status, sexual preference, low fertility, and vasectomy*

Variable	No (%) of cases	No (%) of controls	Unadjusted odds ratio	Adjusted odds ratio† (95% confidence interval)
Marital status (794 matched pairs):				
Never married	281 (35·4)	282 (35·5)	1·00	1·00
Ever married	513 (64·6)	512 (64·5)	1·01	0·98 (0·74 to 1·30)
Age first married‡				
16-19	42 (11·1)	31 (8·1)	1·00	1·00
20-24	237 (62·7)	225 (58·6)	0·84	0·79 (0·44 to 1·41)
25-29	84 (22·2)	96 (25·0)	0·74	0·70 (0·37 to 1·33)
≥30	15 (4·0)	32 (8·3)	0·37	0·33 (0·14 to 0·78)
Test for trend§				χ^2=5·82; P=0·016
Any homosexual intercourse (708 matched pairs):				
No	732 (98·1)	742 (98·7)	1·00	1·00
Yes	14 (1·9)	10 (1·3)	1·33	1·35 (0·56 to 3·28)
Not answered	48	42		
Reported problems with low fertility causing difficulty in conceiving‖ (775 matched pairs):				
No	474 (61·2)	508 (64·0)	1·00	1·00
Yes	13 (1·7)	5 (0·6)	2·76	2·66 (0·94 to 7·54)
Never tried to conceive	288 (37·2)	281 (35·4)	1·14	1·15 (0·90 to 1·48)
Ever had a vasectomy (794 matched pairs):				
No	713 (89·8)	719 (90·6)	1·00	1·00
Yes	81 (10·2)	75 (9·4)	1·10	1·09 (0·77 to 1·52)

*Percentages exclude missing values.
†Adjusted for undescended testis and inguinal hernia diagnosed <15 years.
‡Men who had never married and all men <30 years excluded from analysis (number of matched pairs included=332).
§Trend test fitting variable as categories in table.
‖Six pairs in which the case had bilateral undescended testis excluded from analysis.

TABLE V—*Numbers (percentages) of cases and controls and odds ratios (95% confidence intervals) by hours of exercise a week and hours spent seated a day at age 20 years and at reference age*

Variable	No (%) of cases	No (%) of controls	Unadjusted odds ratio	Adjusted odds ratio† (95% confidence interval)
Hours of exercise a week at age 20 (735 matched pairs):				
None	248 (33·6)	217 (29·5)	1·00	1·00
1-2	94 (12·8)	94 (12·8)	0·86	0·91 (0·65 to 1·29)
3-4	101 (13·7)	100 (13·6)	0·87	0·91 (0·64 to 1·29)
5-9	154 (20·9)	157 (21·4)	0·85	0·84 (0·62 to 1·14)
10-14	75 (10·2)	81 (11·0)	0·78	0·79 (0·53 to 1·17)
⩾15	65 (8·8)	86 (11·7)	0·65	0·62 (0·42 to 0·91)
Not known	0	2		
Younger than age 20	57	57		
Test for trend‡				χ^2=6·57, P=0·010
Hours of exercise a week at reference age (793 matched pairs):				
None	331 (41·7)	309 (39·0)	1·00	1·00
1-2	135 (17·0)	131 (16·5)	0·95	1·00 (0·73 to 1·36)
3-4	115 (14·5)	109 (13·7)	0·94	0·94 (0·69 to 1·29)
5-9	136 (17·1)	144 (18·2)	0·84	0·86 (0·64 to 1·16)
10-14	49 (6·2)	50 (6·3)	0·87	0·85 (0·54 to 1·35)
⩾15	28 (3·5)	50 (6·3)	0·50	0·54 (0·32 to 0·90)
Not known	0	1		
Test for trend‡				χ^2=5·63; P=0·018
Hours spent sitting down a day at age 20 (731 matched pairs):				
0-2	114 (15·6)	104 (14·1)	1·00	1·00
3-4	188 (25·7)	231 (31·4)	0·76	0·77 (0·55 to 1·08)
5-6	166 (22·7)	176 (23·9)	0·89	0·90 (0·63 to 1·30)
7-9	147 (20·1)	134 (18·2)	1·05	1·03 (0·70 to 1·52)
⩾10	117 (16·0)	91 (12·4)	1·25	1·35 (0·88 to 2·06);
Not known	5	1		
Younger than age 20	57	57		
Test for trend‡				χ^2=5·11; P=0·024
Hours spent sitting down a day at reference age (793 matched pairs):				
0-2	52 (6·6)	62 (7·8)	1·00	1·00
3-4	159 (20·1)	175 (22·0)	1·12	1·20 (0·77 to 1·87)
5-6	192 (24·2)	205 (25·8)	1·18	1·19 (0·76 to 1·86)
7-9	163 (20·6)	168 (21·2)	1·25	1·28 (0·81 to 2·02)
⩾10	227 (28·6)	184 (23·2)	1·59	1·71 (1·08 to 2·72)
Not known	1	0		
Test for trend‡				χ^2=7·63; P=0·006

*Percentages exclude missing values.
†Adjusted for undescended testis and inguinal hernia diagnosed < 15 years.
‡Trend test after excluding "not known" and "younger than 20" if appropriate and fitting variables as midpoints of categories presented and median of top group (for exercise 0, 1·5, 3·5, 7, 12, 20; for sitting 1, 3·5, 5·5, 8, 11).

a day seated compared with men who spent less than three hours a day seated. Mutual adjustment, controlling exercise time for time spent seated and vice versa, had no material effect on these results.

Discussion

This is the largest interview based case-control study of testicular cancer carried out to date. Other strengths of the study derive from our high response rate, use of population based controls, and supplementation of information obtained at inteview with that from general practitioners' notes and from the mothers of cases and controls. We believe therefore that our results are particularly reliable, although they will not be free of the reporting bias between cases and controls which may be present in retrospective studies. Some of the questions relating to sexual behaviour might be particularly sensitive to this bias. There is also a potential problem of control selection bias for two reasons. Firstly, although a high proportion of the population is registered with a general practitioner, men aged 15-49 are particularly likely to be unregistered, especially if single, healthy, and mobile, and would not be included in our sampling frame. Secondly, even though the response rate of controls of 83·1% can be regarded as good for a study of young and middle aged men, the non-responders may be systematically different in terms of their history and behaviour. It will therefore be important to consider whether our results may be due to reporting or selection biases. Because cases and controls were selected from the same general practitioners' lists, there is also a possibility of overmatching—that is, both groups having similar geographical and socioeconomic backgrounds. We do not believe that this effect is likely to be strong and, if present, would bias any risks towards unity.

CONGENITAL ABNORMALITIES

Risks associated with undescended testis and inguinal hernia were as expected from previous studies[29 30]—that is, bilateral undescended testes carry a substantial risk of cancer whereas unilateral undescended testis or an inguinal hernia early in life carry more moderate risks (both about threefold in this study). Our overall risk estimate of 3·82 associated with undescended testis is somewhat lower than that reported previously. Chilvers and Pike reported a summary estimate of 5·8 from an overview of nine studies published since 1979.[30] There are two explanations for this reduction. Previous estimates have been based largely on recall of the diagnosis by cases and controls. Men may recall retractile or late descending testes as undescended testis and cases, who may know of the association between undescended testis and cancer, may be more likely to misclassify their condition in this way. This could result in an overestimate of the relative risk. Misclassification of undescended testis has been reduced in our study by seeking verification of the diagnosis in the general practitioners' notes. We report that 8·2% of cases and 2·1% of controls had a definite undescended testis; if we had relied on the responses to the questionnaire alone, the proportions would have been 11·6% and 3·0%, respectively. There was therefore a tendency for cases to overreport a history of undescended testis relative to controls.

A second reason for a reduced risk estimate may arise from the increasing incidence of undescended testis over time.[31 32] If the population prevalence of undescended testis has increased since earlier studies took place while the proportion of cases with undescended testis has remained constant, this will produce a reduced relative risk[32] as we have shown by splitting our study group at the median age.

Our results suggest that men who had a unilateral undescended testis which was successfully corrected before the age of 10 years were no longer at increased risk of developing a cancer. This is consistent with the results of some[13 19] but not all[33 34] studies which have addressed this issue, although there are few data on men with an age at correction below 10 years. If our findings are confirmed the recent trend to reduce the age at which correction is carried out should be encouraged and the effect on rates of testicular cancer closely monitored. As all but one of the corrections under 10 years were carried out above the age of 5, it would seem from these data that orchidopexy at particularly young ages (less than 5 years) is not necessary to remove the increased risk.

Inguinal hernia is often associated with undescended testis, and to examine the risk associated with hernia alone we carried out the analysis after excluding cases and controls with a definite undescended testis. In keeping with the results of most other studies[29] we found a small increased risk associated with having had a hernia, and, consistent with results of several[11 16 23] but not all[13] studies, the risk increased for hernias diagnosed in childhood. Comparison between studies is complicated by the fact that not all analyses clearly distinguish between undescended testis and hernia and because there are misclassification problems for both conditions when self reporting is relied on.

AGE AT PUBERTY

Our results give some support to the hypothesis that early age at puberty may be a risk factor for testicular cancer. Three variables associated with age at puberty —age at starting shaving, age at voice breaking, and age at first having nocturnal emissions—were all related to risk of cancer with significant trends suggesting that the later in life these events occurred the lower was the risk of cancer. The trend in adjusted

odds ratios for reported age at first masturbation was in the same direction (table III), although the trend test was not significant. None of these trends were materially altered by excluding the "not yet" or "never" responders from the upper category. It is therefore plausible to speculate that some aspect of endocrine function may be associated with risk and that boys undergoing earlier onset of puberty, having a higher net exposure to postpubertal hormones, will be at increased risk.

Moss *et al* previously reported a twofold increased risk in men who underwent puberty (as assessed by reported age at appearance of pubic hair) at ages less than 14 years,[15] whereas Depue *et al* reported no significant effect on risk of two of the variables used here, age at voice breaking and age at starting shaving.[12] In a study in the United Kingdom Swerdlow *et al* asked directly about age at puberty and whether it was earlier, the same as, or later than that of classmates and found no effect.[17] He also reported, as here, no association with frequency of shaving or age at first sexual intercourse (our data not shown). Assessment of age at puberty by recall is particularly difficult in men. There is, however, no reason for there to be systematic differences between cases and controls in recall, and the consequence of inaccuracy would be to reduce the observed magnitude of any real effect. This may partly account for the discrepancies between the studies. It should also be noted that the average age at puberty in boys is declining,[35] an effect consistent with the increase in incidence of cancer.

There was no association of risk of cancer with sexual preference or with marital status (table IV). There have been several studies showing an effect of marital status, although not always in the same direction[25 26 36 37] but other recent case-control studies agree with our finding of no overall effect.[14 17] Among men who have been married there was a significant trend of decreased risk with later age at first marriage.

INFERTILITY

When considering infertility it is necessary to exclude subjects with bilateral undescended testes, all of whom are likely to be subfertile or infertile.[38] Men with infertility are known to have an increased prevalence of testicular carcinoma in situ,[39 40] and it has been suggested that cancer and subfertility are both associated with a common underlying defect in spermatogenesis.[41] If this is correct some association between infertility and increased risk may be anticipated. Although we observed such an association, of borderline significance, the small proportion of cases with reported low fertility (1·7%) suggests that this condition is not a major determinant of risk. Clinical data indicate, however, that a reduced sperm count is a common finding in men with testicular cancer.[42] This might be because tumour development directly leads to impaired spermatogenesis. Alternatively, impaired fertility might precede and be associated with testicular cancer but rarely be brought to clinical attention and thus would not be reported in retrospective studies such as this. One other case-control study reported risks of 6·0 and 10·0 associated with low sperm count and reported infertility, respectively,[21] whereas two other studies have failed to find an association with fertility.[14 17] Two studies found no association with paternity,[12 43] but this is a poor surrogate for fertility; of the 13 cases and five controls with confirmed low fertility in this study, six cases and four controls had fathered children.

Sharpe and Skakkebæk have proposed that a common factor, exposure to environmental oestrogens in utero, may be responsible for both a reported decreased sperm count and increased risk of testicular cancer in developed countries.[41] Tarone *et al* have reported an excess of both fertility problems and testicular cancer in American servicemen who were in Vietnam, and they suggest that this might be due to exposure to toxic pesticides or defoliants.[44]

The idea that vasectomy should be an important risk factor for testicular cancer has always been unlikely given that this cancer often occurs before the age at which men usually undergo the operation. Nevertheless, there have been concerns about such an association[45 46] and our results add to several other negative reports on this issue.[47]

EXERCISE

This is the first report that a lack of exercise and sedentary lifestyle may increase the risk of testicular cancer, although several studies have found higher rates in men with professional, non-manual occupations.[48 49 50] Our observed effects were not large, with no more than a doubling of risk comparing the groups at the highest and lowest extremes for the relevant variables (table V). For active exercise there was no major effect except a significant protection in those who reported very high amounts of exercise (15 or more hours each week). For hours spent seated each day there was a graded response with highly significant trends; these trends were virtually unchanged after adjustment for social class, indicating that this was not a social class effect. Clearly these results need to be confirmed in other studies and as yet should not be regarded as indicative of a causal relation. Changing patterns of manual work and exercise, however, together with the earlier onset of puberty could, in part, offer an explanation for the secular increase in incidence rates of testicular cancer seen in most Western countries.

GENERAL MODEL

Our results are in accord with a model of development of testicular cancer based on increased exposure to pituitary gonadotrophin. These hormones may increase rates of germ cell mitosis and thereby influence tumour development. When testes become atrophic, a state that occurs with both undescended testis and infertility, reduced synthesis of gonadal hormone may result in feedback inhibition of pituitary function and thus an excess production of gonadotrophins.[51]

Patients with Down's syndrome, which is associated with both testicular cancer[52] and undescended testis,[53] have increased concentrations of gonadotrophin[54 55] whereas patients with Kallmann's syndrome, who have insufficient gonadotrophin secretion, never develop testicular cancer.[56] Cumulative exposure of the testis to gonadotrophin will also be associated with age at puberty and may be associated with the amount of physical exercise.[57] In women it is known that regular exercise can induce luteal phase dysfunction[58] and, at extremes, may delay menarche and induce amenorrhoea.[59] There is also evidence that circulating concentrations of one specific gonadotrophin, follicle stimulating hormone, are higher in men with stage I testicular cancer,[42] especially in those who later develop second primary cancers.[60]

This model is clearly speculative and the relevant epidemiological observations in our study are for the most part weak and unconfirmed. The hypothesis does, however, suggest several important priorities for future research—notably, on the hormonal profiles of men with and without testicular cancer, the role of factors such as exercise which may influence such profiles, and the control that hormones exert over rates of mitosis of germ cells. Our data on the protective effect of early correction of unilateral undescended testis would also indicate that the deleterious effects of the position of an ectopic testis can be overcome. In

Clinical implications

- Testicular cancer is increasing in incidence and is the most common form of cancer in men aged 15 to 44
- This study confirms previously established risks associated with undescended testis and infantile inguinal hernia, which in this population were fourfold and twofold, respectively
- The excess risk associated with undescended testis was eliminated in men who had had an orchidopexy before the age of 10 years
- An early age at puberty, as assessed by age at starting to shave, age at voice breaking, and age at first nocturnal emissions, was a risk factor for testicular cancer
- There were associations between testicular cancer and a sedentary lifestyle and lack of exercise

contrast, the presence of bilateral undescended testes seems to have an irreversible harmful effect. This would suggest the benefit of examining and comparing hormonal concentrations in men with different types of undescended testis and with different ages of correction.

The regional collaborators in the study group were R A Cartwright (Leukaemia Research Fund Centre, University of Leeds); P C Elwood (MRC Epidemiology Unit, Cardiff); J Birch (Department of Epidemiology and Social Oncology, University of Manchester, Manchester); and C Tyrell (Plymouth Oncology Unit, Freedom Fields Hospital, Plymouth). The interviewing staff were R Brett (Oxford); T Bush, V Isbell (Wessex); A Cornwell, R Steer, S Thistlethwaite (Yorkshire); H Gellman (North West), J Hughes, M Llewellyn (Wales); A Ardern-Jones, A Allen, E Hilton, B Lloyd, S McVeigh, M Thorne, P Trowbridge (Thames); and S Reid (South West).

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1 Doll R. Are we winning the war against cancer? A review in memory of Keith Durrant. *Clinical Oncology* 1992;4:257-66.
2 Boyle P, Kaye SB, Robertson AG. Changes in testicular cancer in Scotland. *European Journal of Cancer and Clinical Oncology* 1987;23:827-30.
3 Brown LM, Pottern LM, Hoover RN, Devesa SS, Aselton P, Flannery JT. Testicular cancer in the United States: trends in incidence and mortality. *Int J Epidemiol* 1986;15:164-70.
4 Forman D, Møller H. Testicular cancer. *Cancer Surv* (in press).
5 Stone JM, Cruickshank DG, Sandeman TF, Matthews JP. Trebling of the incidence of testicular cancer in Victoria, Australia (1950-1985). *Cancer* 1991;68:211-9.
6 Office of Population Censuses and Surveys (OPCS). *Cancer statistics—registrations, 1987, England and Wales.* London: HMSO, 1993. (Series MB1 No 20.)
7 Forman D, Gallagher R, Møller H, Swerdlow AJ. Aetiology and epidemiology of testicular cancer: report of consensus group. In: Newling DWW, Jones WG, eds. *Prostate cancer and testicular cancer. Progress in clinical and biological research.* Vol 357. New York: Wiley-Liss, 1990:245-53. (EORTC genitourinary group monograph 7.)
8 Graham S, Gibson RW. Social epidemiology of cancer of the testis. *Cancer* 1972;29:1242-9.
9 Henderson BE, Benton B, Jing J, Yu MC, Pike MC. Risk factors for cancer of the testis in young men. *Int J Cancer* 1979;23:598-602.
10 Schottenfeld D, Warshauer ME, Sherlock S, Zauber AG, Leder M, Payne R. The epidemiology of testicular cancer in young adults. *Am J Epidemiol* 1980;112:232-46.
11 Coldman AJ, Elwood JM, Gallagher RP. Sports activities and risk of testicular cancer. *Br J Cancer* 1982;46:749-56.
12 Depue RH, Pike MC, Henderson BE. Estrogen exposure during gestation and risk of testicular cancer. *J Natl Cancer Inst* 1983;71:1151-5.
13 Pottern LM, Brown LM, Hoover RN, Javadpour N, O'Connell KJ, Stutzman RE, *et al.* Testicular cancer risk among young men: role of cryptorchidism and inguinal hernia. *J Natl Cancer Inst* 1985;74:377-81.
14 Brown LM, Pottern LM, Hoover RN. Prenatal and perinatal risk factors for testicular cancer. *Cancer Res* 1986;46:4812-6.
15 Moss AR, Osmond D, Bacchetti P, Torti FM, Gurgin V. Hormonal risk factors in testicular cancer. *Am J Epidemiol* 1986;124:39-52.
16 Swerdlow AJ, Huttly SRA, Smith PG. Testicular cancer and antecedent diseases. *Br J Cancer* 1987;55:97-103.
17 Swerdlow AJ, Huttly SRA, Smith PG. Testis cancer: post-natal hormonal factors, sexual behaviour and fertility. *Int J Cancer* 1989;43:549-53.
18 Gershman ST, Stolley PD. A case-control study of testicular cancer using Connecticut tumour registry data. *Int J Epidemiol* 1988;17:738-42.
19 Strader CH, Weiss NS, Daling JR. Vasectomy and the incidence of testicular cancer. *Am J Epidemiol* 1988;128:56-63.
20 Strader CH, Weiss NS, Daling JR, Karagas MR, McKnight B. Cryptorchidism, orchiopexy, and the risk of testicular cancer. *Am J Epidemiol* 1988;127:1013-8.
21 Haughey BP, Graham S, Brasure J, Zielezny M, Sufrin G, Burnett WS. The epidemiology of testicular cancer in upstate New York. *Am J Epidemiol* 1989;130:25-36.
22 Mustacchi P, Millmore D. Racial and occupational variations in cancer of the testis: San Francisco, 1956-65. *J Natl Cancer Inst* 1976;56:717-20.
23 Morrison AS. Cryptorchidism, hernia, and cancer of the testis. *J Natl Cancer Inst* 1976;56:731-3.
24 Graham S, Gibson R, West D, Swanson M, Burnett W, Dayal H. Epidemiology of cancer of the testis in upstate New York. *J Natl Cancer Inst* 1977;58:1225-61.
25 Mills PK, Newell GR, Johnson DE. Testicular cancer associated with employment in agriculture and oil and natural gas extraction. *Lancet* 1984;i:207-10.
26 Newell GR, Spitz MR, Sider JG, Pollack ES. Incidence of testicular cancer in the United States related to marital status, histology and ethnicity. *J Natl Cancer Inst* 1987;78:881-5.
27 Pearce N, Sheppard RA, Howard JK, Fraser J, Lilley BM. Time trends and occupational differences in cancer of the testis in New Zealand. *Cancer* 1987;59:1677-82.
28 Breslow NE, Day NE. *Statistical methods in cancer research.* Vol 1. *The analysis of case-control studies.* Lyon: International Agency for Reseach on Cancer, 1980. (Scientific publication No 32.)
29 Forman D. Epidemiology of testis cancer. In: Oliver RTD, Blandy JP, Hope-Stone HF, eds. *Urological and genital cancer.* Oxford: Blackwell Scientific Publications, 1989:289-305.
30 Chilvers C, Pike MC. Cancer risk in the undescended testicle. *European Urology Update Series* 1992;1:74-9.
31 John Radcliffe Hospital Cryptorchidism Study Group. Cryptorchidism: an apparent substantial increase since 1960. *BMJ* 1986;293:1401-4.
32 Chilvers C, Pike MC. Epidemiology of undescended testiss. In: Oliver RTD, Blandy JP, Hope-Stone HF, eds. *Urological and genital cancer.* Oxford: Blackwell Scientific Publications, 1989:306-21.
33 Pike MC, Chilvers C, Peckham MJ. Effect of age at orchidopexy on risk of testicular cancer. *Lancet* 1986;i:1246-8.
34 Depue RH, Pike MC, Henderson BE. Cryptorchidism and testicular cancer. *J Natl Cancer Inst* 1986;77:830-2.
35 Tanner J. Secular trends for puberty between 1860-1970. In: *Foetus into man.* London: Open Books, 1978.
36 Ross RK, McCurtis JW, Henderson BE, Menck HR, Mack TM, Martin SP. Descriptive epidemiology of testicular and prostatic cancer in Los Angeles. *Br J Cancer* 1979;39:284-92.
37 Davies JM. Is testicular cancer incidence related to marital status? *Int J Cancer* 1981;28:721-4.
38 Chilvers CED, Dudley NE, Gough MH, Jackson MB, Pike MC. Undescended testis: the effect of treatment on subsequent risk of sub-fertility and malignancy. *J Pediatr Surg* 1986;21:691-6.
39 Skakkebæk NE. Carcinoma in situ of the testis: frequency and relationship to invasive germ cell tumours in infertile men. *Histopathology* 1978;2:157-70.
40 Pryor JP, Cameron KM, Chilton CP, Ford TF, Parkinson MC, Sinokrot J, *et al.* Carcinoma in situ in testicular biopsies from men presenting with infertility. *Br J Urol* 1983;55:780-4.
41 Sharpe RM, Skakkebæk NE. Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? *Lancet* 1993;341:1392-5.
42 Hansen PV, Trykker H. Andersen J, Helkjer PE. Germ cell function and hormonal status in patients with testicular cancer. *Cancer* 1989;64:956-61.
43 Johnson DE, Fueger JJ, Alfaro PJ, Spitz MR, Newell GR. Subfertility: an etiologic factor in development of testicular cancer? *Urology* 1987;30:199-200.
44 Tarone RE, Hayes HM, Hoover R, Rosenthal JF, Brown LM, Pottern LM, *et al.* Service in Vietnam and risk of testicular cancer. *J Natl Cancer Inst* 1991;83:1497-9.
45 Cale ARC, Farouk M, Prescott RJ. Does vasectomy accelerate testicular tumour? Importance of testicular examinations before and after vasectomy. *BMJ* 1990;300:370.
46 Thornhill JA, Buler M, Fitzpatrick JM. Could vasectomy accelerate testicular cancer? The importance of prevasectomy examination. *Br J Urol* 1987;59:367.
47 Lynge E, Knudsen LB, Møller H. Vasectomy and testicular cancer: epidemiological evidence of association. *Eur J Cancer* 1993;29A:1064-6.
48 Coggon D, Pannett B, Osmond C, Acheson ED. A survey of cancer and occupation in young and middle aged men: non-respiratory cancers. *Br J Ind Med* 1986;43:381-6.
49 McDowall ME, Balarajan R. Testicular cancer mortality in England and Wales 1971-1980: variations by occupation. *J Epidemiol Community Health* 1986;40:26-9.
50 Swerdlow AJ, Skeet RG. Occupational associations of testicular cancer in south east England. *Br J Ind Med* 1988;45:225-30.
51 Oliver RTD. Atrophy, hormones, genes and viruses in aetiology of germ cell tumours. *Cancer Surv* 1990;9:263-86.
52 Braun DL, Green MD, Rausen AR, David R, Wolman SR, Greco MA, *et al.* Down's syndrome and testicular cancer: a possible association. *Am J Pediatr Hematology Oncol* 1985;7:208-11.
53 Benson RC, Beard CM, Kelalis PP, Kurland LT. Malignant potential of the cryptorchid testis. *Mayo Clin Proc* 1991;66:372-8.

54 Hasen J, Boyar RM, Shapiro LR. Gonadal function in trisomy 21. *Horm Res* 1980;12:345-50.
55 Sasagawa I, Nakada T, Hashimoto T, Ishigooka M, Izumiya K, Kubota Y, *et al.* Hormone profiles and contralateral testicular histology in Down's syndrome with unilateral testicular tumor. *Arch Androl* 1993;30:93-8.
56 Rajpert-De Meyts E, Skakkebæk NE. The possible role of sex hormones in the development of testicular cancer. *Eur Urol* 1993;23:54-61.
57 Opstad PK. Androgenic hormones during prolonged physical stress, sleep and energy deficiency. *J Clin Endocrinol Metab* 1992;74:1176-83.
58 Beitins IZ, McArthur JW, Turnbull BA, Skrinar GS, Bullen BA. Exercise induces two types of human luteal dysfunction: confirmation by urinary free progesterone. *J Clin Endocrinol Metab* 1991;72:1350-8.
59 Frisch RE, Gotz-Welbergen AV, McArthur JW, Albright T, Witschi J, Bullen B, *et al.* Delayed menarche and amenorrhea of college athletes in relation to age of onset of training. *JAMA* 1981;246:1559-63.
60 Hoff Wanderas E, Fossa SD, Heilo A, Stenwig AE, Norman N. Serum follicle stimulating hormone—predictor of cancer in the remaining testis in patients with unilateral testicular cancer. *Br J Urol* 1990;66:315-7.

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Management of women with mild and moderate cervical dyskaryosis

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Abstract

***Objective*—To compare the outcomes in women with mild and moderate dyskaryosis after increasing periods of surveillance and thereby to define a rational protocol for managing such women.**

***Design*—Prospective study with randomisation of women to one of four treatment groups, each with a different period of surveillance; one group in which the women were given immediate treatment and three other groups in which the women were under surveillance for six, 12, and 24 months.**

***Setting*—A dedicated colposcopy clinic in Aberdeen, Scotland.**

***Subjects*—902 women who presented with a mildly or moderately dyskaryotic smear for the first time.**

***Interventions*—Cytological and colposcopic examinations at intervals of six months until the allocated period of surveillance was completed, at which time biopsy was performed. Women with severe dyskaryosis were withdrawn from surveillance and a biopsy was performed.**

***Main outcome measures*—The histological findings after punch biopsy or large loop excision of the transformation zone, and the trends in cytological appearances of serial cervical smears.**

***Results*—793 women completed the study. In all, 769 women had an adequate final smear, of which 197 were normal cytologically, 328 were still mildly or moderately dyskaryotic, and 244 were severely dyskaryotic. Seventeen of the 67 (25%) women with one repeat smear showing non-dyskaryosis had cervical intraepithelial neoplasia grade III compared with only one of the 31 (3%) women with no dyskaryosis in four repeat cervical smears ($P < 0{\cdot}0001$). None of the women had invasive cancer. Of 158 women whose index smear showed mild dyskaryosis and who were allocated to the group under surveillance for two years, only 40 had not defaulted or still had dyskaryotic smears by the end of the two years.**

***Conclusion*—Cytological surveillance, although safe, is not an efficient strategy for managing women with mildly abnormal smears. Women with any degree of dyskaryosis in a smear should be referred for colposcopy.**

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Introduction

The purpose of a cervical cytology screening programme is to reduce both the mortality from and the incidence of carcinoma of the cervix by detecting and eradicating the preinvasive lesion, cervical intraepithelial neoplasia grade III. These aims can be fully realised only if women with cervical cytological abnormalities are managed in the most appropriate way. Although it is widely accepted that women with severe cytological abnormalities (severe dyskaryosis) should be referred for colposcopic assessment and biopsy, uncertainty exists about the best way to manage women with milder cytological abnormalities (mild or moderate dyskaryosis), who accounted for 3·2% of 1·7 million smears taken in England and Wales in 1991 (M Weston, national coordinating network cervical screening programme, personal communication). Consequently, the mangement of these abnormalities has important implications, not only for women but also for health resources.

The traditional policy of cytological surveillance, which evolved in the days before colposcopy was developed, is based on the belief that many of the milder abnormalities will spontaneously revert to normal over time[1] and reserves referral for colposcopy for women with severe dyskaryosis or persistent mild or moderate dyskaryosis. The realisation that cervical intraepithelial neoplasia grade III is present in up to one third of women with mild or moderate dyskaryosis[2-4] led to the suggestion that all women with any degree of dyskaryosis should be referred for colposcopic assessment. The advantages of this approach are that it enables a prompt histological diagnosis and avoids the possibility of the patient defaulting on a further smear test. These benefits may be achieved, however, at the risk of both overtreatment and increased anxiety for some women.[5] Of 210 health districts investigated in a survey by the British Society of Colposcopy and Cervical Pathology, 37% had a policy of immediate colposcopic referral for a single mildly dyskaryotic smear and 45% for a single moderately dyskaryotic smear. Recent guidelines on the management of women with such smears suggest immediate referral for colposcopy for women with a single moderately dyskaryotic smear and referral after two consecutive dyskaryotic smears for women with mild dyskaryosis.[7] In addition, the report recommended that women should re-enter the routine screening programme only after two further smear tests, six months apart, have yielded negative results.

The lack of reliable information on the natural course of these disorders lies at the centre of this debate about management. Previous studies[1 8-11] had methodological problems, which makes interpreting their results difficult.[12] The methodological problems included inconsistent criteria for entry, unrepresentative populations, a lack of baseline histological data, inadequate follow up, and the potential interference of a biopsy in the natural course of the disease. Four retrospective studies of outcome in women with mild cytological abnormalities showed reversion to normal in 24-60% of cases.[1 10 11 13] These studies reported that up to 25% of women defaulted from surveillance and that the incidence of cervical cancer increased even in women who did not default. The need for large randomised prospective studies of colposcopy to resolve this important problem has been emphasised.[14]

In August 1989 we began to investigate the cyto-