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Testicular Cancer After Vasectomy : Origin from Carcinoma *in situ* of the Testis

N. Jørgensen, A. Giwercman, S.W. Hansen and N.E. Skakkebaek

Vasectomy is a commonly used male contraceptive procedure. Reports have indicated that vasectomy is associated with an increased risk of development of germinal testicular cancer. Carcinoma *in situ* of the testis (CIS) is a preinvasive lesion which preceedes germinal testicular cancer. CIS is almost always found in the tissue adjacent to a germinal testicular cancer. It is believed that CIS is a malignant gonocyte formed during embryogenesis. We have studied the testicular tissue from 5 previously vasectomised patients with testicular cancer and found CIS in the tissue adjacent to their cancer as well as changes in the epididymis of the patients. We discuss the findings and conclude that testicular cancers occurring after vasectomy is not an exception from the rule that testicular cancer originates from CIS. Thus, there is no causal relationship between vasectomy and testicular cancer, but vasectomy might precipitate the development of testicular cancer from the preinvasive CIS lesion.
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INTRODUCTION

VASECTOMY IS a commonly used procedure for male contraception throughout the world. Thus, in 1988 almost 4000 vasectomies were performed in Denmark [1]. This number corresponds to more than 15% of a male birth cohort.

Vasectomy, like other contraceptive procedures, should be safe without serious side-effects. However, some studies have recently indicated a link between vasectomy and increased incidence of testicular germinal cancer [2–5] (in the following referred to as testicular cancer). Although the question is still unresolved it is important to elucidate whether a possible biological mechanism exists between vasectomy and testicular cancer.

Recent research has shown that testicular cancer is preceeded by a preinvasive stage of carcinoma *in situ* (CIS) of the testis [6–9]. Untreated, CIS is almost invariably associated with development of cancer [10]. Furthermore, CIS cells are almost always detected in the seminiferous tubules in the macroscopically normal testicular tissue adjacent to a testicular tumour, stressing the association between CIS and testicular cancer [11, 12].

The CIS cells differ from normal spermatogonia and have several morphological and biochemical characteristics of gonocytes (primordial germ cells) [13]. Thus, it is believed that the CIS cell is a malignant gonocyte formed during embryogenesis and in most cases present at a 'resting' stage in the immature testis until puberty when the continuous endocrine stimulation subsequently results in invasive tumour growth [13]. This pathogenetical hypothesis excludes a causal association between vasectomy and cancer of the testis, as development of the latter

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Table 1. *Vasectomy and testicular cancer*

Patient no.	Vasectomy	Epididymis: Duct diameter (μm)	Epididymis: Epithelium height (μm)	Interval between vasectomy and cancer (years)	Adjacent carcinoma *in situ* testis
1	+	520	29	1.3	+
2	+	570	20	8.0	+
3	+	620	17	4.5	+
4	+	240	65	12.1	+
5	+	390	21	10.1	+
6	0	273/162	76/40		+
7	0	292/185	66/40		+
8	0	318/204	75/41		+
9	0	245/132	68/25		+
10	0	309/	88/		+
11	0	274/153	50/36		0

is dependent on factors influencing the gonad during the fetal life.

MATERIALS AND METHODS

We have studied 5 cases of testicular cancer occurring 1.3–12.1 years after vasectomy; two seminomas and three non-seminomas, including the adjacent testicular tissue and epididymis. The tissue was fixed in formaldehyde, sectioned at 4 μm and stained with haematoxylin and eosin. Light microscopy was performed including use of a framed ocular in order to determine the diameter of the epididymal ducts and the height of duct epithelium. The material from the 5 patients was compared to six control tumours (one seminoma and five non-seminomas) occurring in non-vasectomised patients.

RESULTS

In the seminiferous tubules adjacent to the tumours we found CIS in all cases except one control (Table 1). Conspicuous changes were present in epididymis of all the vasectomised patients: the diameter of the ducts was increased approximately 100% in 4 of the 5 patients (Table 1, Fig. 1). In the same 4 patients the height of the duct epithelium was significantly diminished—approximately 50%—compared to the controls (Figs 1 and 2). In one of the patients (patient no. 4 in Table 1) neither distension of the epididymal ducts nor ongoing spermatogenesis was seen and all the seminiferous tubules showed total atrophy. A sperm granuloma was present in one of the patients.

DISCUSSION

We found CIS in the tissue adjacent to the tumours of all 5 previously vasectomised patients. These findings show that testicular tumours—also in vasectomised patients—are associated with CIS, indicating an origin from this preinvasive lesion.

It is also noteworthy that we found gross changes in the epididymis from the vasectomised patients. We believe that the changes in the duct system reflect intratubular hydrostatic pressure in the epididymis. Our findings seem to be in accordance with studies of Johnson and Howards who reported increased epididymal pressure after vasectomy in the golden hamster [14]. The vasectomised patient without signs of distension of the epdidymal duct system showed total atrophy of the seminiferous tubules. Thus, the lack of production of fluid into the rete testis system might have resulted in low epididymal pressure in the patient. This might explain the fact that the duration from vasectomy to the diagnosis of cancer in this patient was 12.1 years which is the longest period in the group of studied patients.

The theory that germ cell tumours of young men originate from CIS cells derived from gonocytes during fetal life does not exclude a relationship between vasectomy and the occurrence of testicular cancer, as the vasectomy might accelerate the progression from CIS into invasive cancer. It has also been described that vasectomy might cause alterations in the seminiferous tubules including increase in the thickness of the tubular walls and an increase in the mean cross-sectional tubular area [15]. We hypothesise that an increased intratubular hydrostatic pressure occurring after vasectomy and the resulting structural changes in the tissue facilitate the spread of malignant germ cells from the seminiferous tubules to the interstitial tissue thus accelerating the time for tumour formation.

In conclusion, our study showed that testicular cancer occurring after vasectomy is not an exception from the rule that testicular cancer originates from CIS. We believe that there is no causal relationship between vasectomy and testicular cancer. However, vasectomy might precipitate the development of testicular cancer from the preinvasive CIS lesion.

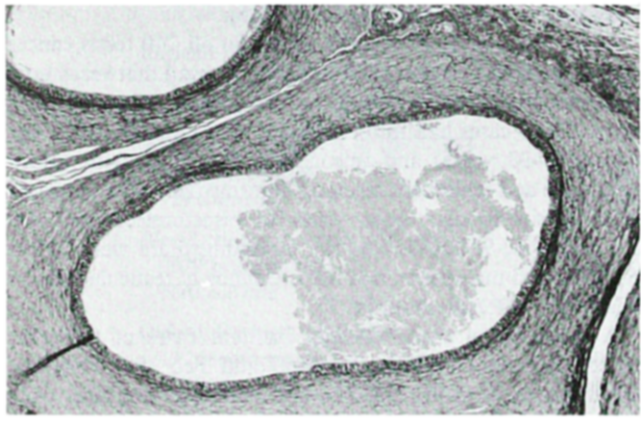

Fig. 1. Four micrometre section of epididymal duct from a previously vasectomised patient with testicular cancer. Note an increase of the diameter of the duct and a diminished height of the epithelium. Formadehyde fixed. Haematoxylin and eosin staining.

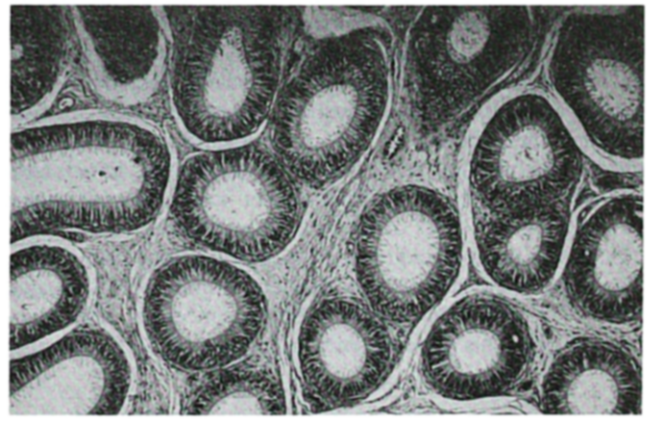

Fig. 2. Four micrometre section of epididymal duct from a non-vasectomised patient with testicular cancer. Same magnification as Fig. 1. Note the smaller diameter of the ducts and the normal morphology of the epithelium compared with Fig. 1.

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Vasectomy and Testicular Cancer: Epidemiological Evidence of Association

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INTRODUCTION

INFORMATION ON the possible relation between vasectomy and subsequent risk of testicular cancer is available from eight studies. An additional three studies provide information on the overall cancer risk following vasectomy. These eleven studies are summarised below. Some of these studies have been covered by two recent reviews [1, 2].

VASECTOMY AND TESTICULAR CANCER

The Scottish Hospital Inpatient Statistics system was used to identify all of the 1764 men aged 25–49 years who had undergone vasectomy as inpatients in Scotland between 1968 and 1974. A total of 14641 men who had undergone meniscectomy, resection for benign nasal conditions or operations on haemorrhoids were chosen as controls. All subsequent discharges from Scottish hospitals until the end of 1976 were identified for these two groups by a matching procedure based on surname, initials, sex and date of birth. 1 testicular cancer case occurred in the vasectomy group (0.12 cases per 1000 man-years), and 4 cases occurred in the control group (0.04 cases per 1000 man-years). The cancer incidence rates for Scotland during 1963–1966 and 1970–1972 show 0.06 cases of testicular cancer per 1000 man-years [3, 4]. This gives an expected number of 0.5 testicular cancer case in the vasectomy group, and the finding of 1 case is therefore not unexpected.

All testicular cancer patients reported to the California Tumour Registry between 1979 and 1981 were contacted for interview. Of 171 eligible cases, 131 were interviewed. In addition, 247 cases were contacted as clinical referrals from various hospitals primarily from 1976 to 1979, 193 were interviewed. The patients were asked to name "peer controls". The analysis was based on 273 pairs of cases and controls and their mothers. Information on vasectomy was provided only by 173 cases and 212 controls. 15 and 30 men, respectively, had had a vasectomy (RR 0.6, 95% C.I. 0.3–1.2) [5].

Review (probably of clinical notes) for all 240 testis cancer cases in Ireland between 1980 and 1985 showed that vasectomy had been performed within 2 months prior to diagnosis in 3 cases. The 3 cases had features in common including their age (range 35–38 years) and uncommon pathology with mixed seminoma and malignant teratoma intermediate. The expected number of testicular cancer cases in vasectomised men was 0.8 (SIR 3.8, 95% C.I. 0.8–11), assuming there were 23148 vasectomised man-years, and the incidence of testicular cancer was 3.52×10^5 males/year [6, 7].

A case–control study covered incident cases of testicular cancer diagnosed between Jan 1977 and Feb 1981 from the catchment areas of five radiotherapy centres in England. Only 259 out of 469 eligible patients were interviewed. One control group was 238 men treated in the same radiotherapy centers. Another control group was 251 men hospitalised with non-malignant diseases in the same towns as the radiotherapy centres.

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