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Possible Biological Mechanisms for a Relationship Between Vasectomy and Prostatic Cancer

S.S. Howards

INTRODUCTION

THERE IS no obvious logical biological mechanism for a relationship between vasectomy and prostatic cancer. There are four categories of physiological alterations after vasectomy which theoretically could increase the incidence or accelerate the growth of prostate cancer. They are (1) a change in endocrine status; (2) an alteration in systemic or local immunity; (3) a variation in exposure of the prostate to cancer enhancing growth factors and/or inhibitors of these factors; and (4) a decrease in undefined factors which inhibit malignant growth or enhance growth of non-malignant prostatic tissue. These theoretically possible relationships will be discussed in the order listed above. It is well documented that vasectomy does cause alterations in the testis, particularly in spermatogenesis, both in experimental animals [1–10] and men [11–14]. In addition, changes occur in the epididymis [15–17]. Vasectomy also results in immunological effects particularly the generation of antisperm antibodies in the majority of individuals in many species including man [18–22]. Prospective carefully conducted epidemiological studies (too extensive to review here) have not documented any increases in immunological disease states or atherosclerosis in men after vasectomy. Indeed, the prospective studies designed to investigate possible relationships between vasectomy and any disease states have all shown no correlation between vasectomy and disease. However, recent retrospective analyses have suggested a relationship between vasectomy and testis cancer [23, 24] as well as prostate cancer [25, 26].

THE ENDOCRINE HYPOTHESIS

There is extensive literature on the endocrinological effects of vasectomy in experimental animals and man. The majority of studies in man have shown no change in endocrine parameters after vasectomy [27–36]. Several studies in rats suggested that vasectomy might decrease serum testosterone levels [7, 37, 38]. However, the validity of these animal investigations has been questioned because of the possibility that the observed alterations were due to injury to testicular blood supply during the vasectomy. A few studies in man have suggested an increase in circulating androgen levels after vasectomy. Purvis *et al.* [39] found an elevation in plasma oestrogen and dihydrotestosterone but not leuteinising hormone (LH) or testosterone after vasectomy. Smith *et al.* [40] found an increase in LH and testosterone and a decrease in oestradiol levels after vasectomy. It should be emphasised that although the alterations were statistically significant all values were in the normal range. The same group [41] found an obliteration of the annual rhythm of testosterone and LH after vasectomy. In summary, the majority of evidence suggests that vasectomy does not cause significant alterations in endocrine function in man; however, there is some evidence of small increases in circulating androgen levels and one study showed a decrease in circulating oestradiol concentration. If these latter investigations are correct, one could postulate that the observed shifts in endocrine parameters favour the development of prostate cancer.

THE IMMUNOLOGICAL HYPOTHESIS

As stated above, there is no doubt that vasectomy has immunological consequences in many individuals. The most obvious of these is the generation of antisperm antibodies. It is possible, but unlikely that these antibodies by an as yet undetermined mechanism accelerate the development of prostatic cancer. It is also possible that vasectomy by eliminating the flow of testicular and epididymal fluids to the prostate decreases local immune factors, for example lymphocyte activated killer cells (LAK cells), which prevent the initiation of growth of prostate cancer. It has been recently demonstrated that LAK cells can inhibit the growth of prostate cancer in rats [42]. In summary, there is no hard evidence for a relationship between vasectomy and prostate cancer which is immunologically generated; however there are theoretically possible mechanisms such as those discussed above.

THE GROWTH FACTOR-INHIBITOR HYPOTHESIS

Recent studies from two laboratories indicate that androgen independent human prostate cancer cell lines proliferate by secreting growth factors, such as epidermal growth factor and transforming growth factor alpha, which work via receptor mediated autocrine mechanisms [43, 44] to enhance tumour cell growth. Indeed, suramin a new antineoplastic agent which works by inhibiting the binding of growth factors to cancer cells has been promoted as a possible agent for the treatment of

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prostate cancer [45, 46]. It is possible that vasectomy prevents inhibitors of these or similar cancer enhancing growth factors from reaching the prostate, or, in an undefined way, vasectomy augments the local production of growth factors which favour the development and/or progression of prostate cancer. There is no concrete evidence that vasectomy results in the alteration of any specific cancer promoting growth factors or inhibitors of such growth factors. Thus, this proposed biological mechanism linking vasectomy to prostate cancer is purely hypothetical.

THE DIRECT CANCER INHIBITOR AND/OR NORMAL PROSTATE ENHANCER FACTOR HYPOTHESIS

It is known that vasectomy alters the seminal fluid in several ways. For example, spermatozoa are eliminated and the concentrations of carnitine, glycerolphosphocholine, neutral alpha-glucosidase, zinc, and magnesium are all reduced and many other compounds are altered. Pierrepoint *et al.*[47] found that the prostate in castrated rats treated with testosterone grew more rapidly when the epididymis was present, than when it was absent. Furthermore, Grayhack *et al.* [48] demonstrated that irradiation of the testicles of dogs with benign prostatic hyperplasia resulted in a reduction of prostatic weight in spite of the fact that serum testosterone did not change. Finally, Darras *et al.* [49] have shown that in androgen replaced rats, the ventral prostate is larger if testes and epididymides are present than when they are absent. These studies suggest that there is a non-androgen factor from the testis and/or epididymis which promotes the growth of non-malignant prostate tissue. Therefore, it is theoretically possible that the alterations in seminal fluid caused by vasectomy favour the growth of prostate cancer either because of the elimination of direct inhibitors of prostate cancer from the seminal fluid or by reduced promotion of benign growth which might in turn favour malignant growth. Again, it should be emphasised there is no direct evidence for these possible mechanisms of enhanced growth of prostate cancer after vasectomy.

Summary

Four hypotheses have been reviewed, each of which might serve as a hypothetical biological explanation for a relationship between vasectomy and prostate cancer. The endocrine hypothesis is the only one of these with any firm data to support it, although the majority of the available data does not lend credibility to that theory. The other hypotheses are purely speculative with no hard data to support them. In conclusion, it seems highly unlikely, but not impossible, that there is a biological mechanism supporting a relationship between vasectomy and prostate cancer.

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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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