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Dying for love: Perimenopausal degeneration of vaginal microbiome drives the chronic inflammation-malignant transformation of benign prostatic hyperplasia to prostatic adenocarcinoma

Albert Stuart Reece *

School of Psychiatry and Clinical Neurosciences, University of Western Australia, Crawley, WA 6009, Australia

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ABSTRACT

Prostatic carcinoma is the second commonest cancer in males and is so common as to become almost holoendemic with advancing age. The recent demonstration that far from being benign, "benign" prostatic hypertrophy is a likely a reaction of the prostate to chronic untreated lower genital tract infection, and that this chronic inflammation is likely the usual precursor to the frequent occurrence of prostatic carcinoma has far reaching implications. The obvious source for the chronic inflammatory stimulus in the prostate is the documented dramatically altered lower female genital microbiota associated with the menopause. Hence the major hypothesis is that prostatic cancer may arise due to chronic infection and inflammation in the prostate gland consequent upon the altered microbiome of the menopausal female genital tract. This has implications for testing and diagnosis, treatment, population health and personal hygiene practices. It suggests that male dyspareunia, although almost never encountered in clinical practice may in fact be relatively common in older males, and in particular if diagnosed, represents a critical opportunity for therapeutic intervention to interrupt the chronic inflammation – cancer transformation and progression which has been well documented in other tissues. It implies that the coordinated application of next generation sequencing to the microbiome of the lower genital tracts of male and female couples, including seminal fluid, will have both research applications to further explore this sequence, as well as finding application as a potential population level screening procedure as is presently done for the "Thin Prep" cervical screening for human papillomavirus in females. Moreover this insight opens up new opportunities for chemointervention and chemoprevention for this important clinicopathological progression. These considerations give rise to the exciting possibility that prostatic malignancy may be preventable by various methods of local hygiene in the female partner or some antibacterial method in males. Since the long term application of oral antibiotics is likely to be of limited efficacy this indicates the need for new antimicrobial solutions.

Introduction

The prostate gland normally provides fluid to the seminal ejaculate which capacitates and potentiates the sperm at the time of ejaculation. It likely has a limited range of physiological responses to pathophysiological insults. The prostate is part of the male lower genital tract (LGT) and can become implicated in lower genital infective conditions, often in combination with seminal vesiculitis or epididymitis.

Epidemiology

Prostate cancer is a major malignant condition which occurs in increasing numbers of men up to 100% by the age of 100 years [1]. It is the second most common malignancy in males in the USA [2]. 176,450 American men were diagnosed in 2013 with this condition and it was responsible for 27,681 deaths in 2013 in that country [2]. The incidence rate is 129.4/100,000 men and the death rate is 20.7/100,000 men [2]. The median age of incidence is 66 years and the median age of death is 80 years. In 1993 there was a major spike in the national US incidence rate up to twice the usual rate to 250/100,000 annually. Significant variations in incidence occur based on racial background. Both the annual incidence and death rates related to prostate cancer are twice as high in

* Address: 39 Gladstone Rd., Highgate Hill, Brisbane, Queensland, Australia.
E-mail address: sreece@bigpond.net.au

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African-Americans, being 203.5/100,000 and 44.2/100,000 respectively [3]. These curious and unexplained epidemiological features imply environmental and/or genetic factors significantly impacting incidence rates. It should perhaps be noted here that BPH is rare in alcoholics and hypogonadal males, likely related to the relatively hyperestrogenic milieu [1,4].

Key trial

Recent re-analysis of the control arm of a classical US Prostate Cancer Prevention Trial (PCPT) trial made three seminal and pivotal observations in relation to prostatic disease in otherwise normal prostate glands [5]: firstly that chronic inflammation within the prostate gland was associated with prostatic carcinoma (O.R. (Odds ratio) = 1.78, 95% C.I. 1.04–3.06), an association which was stronger for high grade malignancy (O.R. 2.24, 95% C.I. 1.06–4.71). The situation persisted in men in whom the PSA (prostate specific antigen) was completely normal, <2. Secondly it was noted that chronic inflammation was common in the group biopsied. The third observation was that chronic prostatic inflammation and hypertrophy was not normal. Since prostate cancer seemed to have a chronic inflammatory and likely infective basis it was felt that anti-inflammatory and/or antibacterial treatment may offer an avenue for the prevention of prostate cancer [5].

These observations clearly establish that benign prostatic hypertrophy (BPH), whilst holoendemic in older males is in fact not normal, and is indeed a premalignant condition.

Pathobiology

There are many tissues where chronic inflammation leads to malignant transformation and in some respects it should come as no surprise that this progression is observed in the prostate gland also. This progression from chronic inflammation to malignancy occurs in skin (where it is called Marjolin's ulcer [6]), upper aerodigestive tract [1], oesophagus, stomach, bronchus, lung, colon, liver, bile duct, bladder, renal pelvis, and cervix uteri [1,4]. It has also been shown that fibroadenosis, a common inflammatory condition of the breast which is common in women in their forties, is also premalignant and has recently been linked with cancer [1].

There are many reasons why chronic inflammation should be linked with carcinogenesis. Obesity, interleukin (IL)-1, IL-6 and IGF1 are all known to be pro-carcinogenic and to stimulate prostate cancer [7]. Cytokines have a well demonstrated link to oncogenic processes both in liver [8] and prostate [9] and likely in many tissues. TGFβ is likely particularly involved in chronic inflammation with its repeated cycles of active inflammation and frustrated attempted healing and fibrosis induction. TGFβ is anti-oncogenic in early stages of chronic inflammation but becomes strongly pro-carcinogenic at later stages, mediated in part by epigenetic mechanisms [10–13]. TGFβ is particularly involved in the epithelial-mesenchymal transition and many steps to carcinogenesis.

Benign prostatic hypertrophy is known to be common in men in their 50s to the point of being holoendemic. However it is quite rare in men in their forties. This observation is itself a very odd scenario indeed – and indeed exists nowhere else in medicine. Possibly the closest parallel would be the emergence of fibroadenosis in the female breast commonly in their forties which is thought to be related to the hormonal dysregulation of the premenopause. However this condition in females whilst common, is far from holoendemic. Moreover the lifetime incidence of female breast cancer is much less at 12.4% [14].

However it is extraordinary that a premalignant condition (BPH) suddenly appears in one decade of life *as a holoendemic condition across the whole male population* but is almost unknown in the prior decades! It is also extraordinary that the condition goes from being almost unknown in the 50′s to having *a median age of onset at 66 years* only 16 years later!

The findings from the ground-breaking Gurel study [5] would clearly carry several major aetiopathological implications:

1) BPH, far from being benign as its name implies, is actually a premalignant condition;
2) BPH is likely a reaction of the prostate to chronic inflammation
3) BPH is not normal.

As suggested by the authors the most likely cause of the chronic prostatic inflammation is chronic lower urinary tract infection. However the likely site of origin is not immediately apparent.

Blockage of the prostatic ducts [15], blockage of the urethra [16] and viral [17] and bacterial infection [18] have been previously suggested as likely important pathogenic pathways.

It is well known that the prostate is commonly co-infected in seminal vesiculitis, and sometimes also in epididymitis [1]. Moreover it is likely involved in sexually transmissible infections including gonococcal and chlamydia infections [4]. So ascending infection is clearly a possible route of infection and secondary inflammation.

Microbiome of the postmenopausal female genital tract

Since the advent of techniques for screening of microbial populations particularly in the gut, the vaginal microbiome has also received significant research attention in recent years. It has been shown to correlate closely with female vestibular microbial populations [19], and to be highly dependent on women's hormonal status as relates to pregnancy [20], childbirth [21], cervical intraepithelial neoplasia [22], the placement of hormone loaded intrauterine devices [23] and in relation to infections seen in premature delivery [24–26]. It has been particularly studied in the female genital disorders of atrophic vaginitis [27] bacterial vaginosis [28–31] and in relation to metabolic re-programming of offspring [21]. The vaginal microbiota has also been shown to change dramatically across the menopausal period [32,33].

This is theoretically very important as it is likely that just as venereal pathological organisms can be introduced into the lower male genital tract so too can otherwise commensal organisms of the lower female genital tract.

Hypothesis

This makes it likely that the change in the female genital microbiota experienced in the perimenopausal period is the likely source and origin of the chronic inflammatory and chronic infective condition which becomes the stimulus first to chronic inflammation in the prostate which becomes manifest as BPH, and secondly with chronicity and establishment of a chronic disorder, malignant transformation.

Formal testing

This hypothesis could be readily tested in cross-sectional and longitudinal studies with paired samples from male and female sexual partners over the transitional period as the woman transitions through the fifth and sixth decades of life. Next generation genomic screening of genital samples including seminal fluid and prostatic biopsy samples would be required. It would be of particular interest to study age discordant couples which would separate the effect of age from that of the alteration of the genital microflora.