Multiple pathogens and prostate cancer

James S. Lawson* and Wendy K. Glenn

Abstract
Background: The aim of this review is to consider whether multiple pathogens have roles in prostate cancer.
Methods: We have reviewed case control studies in which infectious pathogens in prostate cancer were compared to normal and benign prostate tissues. We also reviewed additional evidence from relevant published articles.
Results: We confirmed that high risk human papilloma viruses are a probable cause of prostate cancer. We judged Escherichia coli, Cutibacterium acnes, Neisseria gonorrhoea, Herpes simplex, Epstein Barr virus and Mycoplasmas as each having possible but unproven roles in chronic prostatic inflammation and prostate cancer. We judged Cytomegalovirus, Chlamydia trachomatis, Trichomonas vaginalis and the Polyoma viruses as possible but unlikely to have a role in prostate cancer.
Conclusions and actions: The most influential cause of prostate cancer appears to be infection induced chronic inflammation. Given the high prevalence of prostate cancer it is important for action to be taken without waiting for additional conclusive evidence. These include:

1. Encouragement of all boys (as well as girls) to have HPV vaccines
2. The vigorous use of antibiotics to treat all bacterial pathogens identified in the urogenital tract
3. The use of antiviral medications to control herpes infections
4. Education about safe sexual practices

Keywords: Prostate cancer, Infections, Causation, Human papilloma virus, Pathogens

Introduction
The aim of this review is to consider whether multiple pathogens have roles in prostate cancer. Multiple pathogens have long been hypothesised as an underlying cause of prostate cancer. However, apart from high-risk for cancer human papilloma viruses (HPVs), no specific pathogens have confirmed causal roles.

We have previously shown that high risk for cancer human papilloma viruses have a probable, but not conclusive, causal role in prostate cancer [1]. This is important because of the availability of safe and effective vaccines against HPV infections. In this review we have updated the evidence which may implicate other infectious pathogens.

We consider it is unlikely that any acute infectious pathogens cause prostate cancer. On the other hand, infectious pathogens that cause long term chronic inflammation are likely to have roles in prostate cancer.

Epidemiology
Prostate cancer develops in 1 in 8 Western men [2]. About 60% of cases occurs in men aged 65 years or older. It is rare in men under the age of 40 years. About 30% of men have undiagnosed prostate cancer at the time of their death, hence the saying “many men die with, rather than from, prostate cancer”. Prostate cancer occurs more frequently in Western than Asian men [2]. When Asian
men migrate from low to high risk countries the risk of developing prostate cancer increases [3]. The reason is not known. However, the number of immigrants developing prostate cancer is still lower than that of men in Western countries [4]. This phenomena is also present in breast cancer for Asian women who migrate from low to high risk countries, the risk of breast cancer rapidly increases within two generations to almost equal that of the host country [5].

Methods
We have conducted a review of selected English language publications listed in PubMed from 1960 to 2021 relevant to infectious pathogens and prostate cancer. Only studies which included controls were reviewed. Any form of selection introduces bias. For this reason the two authors independently selected the studies that were considered. Any differences in the selection were discussed and joint decisions were made. Additional problems in the assessment of the role of specific pathogens in prostate cancer include (1) the variations in outcomes of studies using similar methods in the same populations, (2) contamination of the prostate specimens and (4) the absence of benign or normal prostate controls.

The selection of pathogens for this review was based on the many previous studies of infections and prostate cancer. These pathogens included Human papilloma viruses, Cetabacterium acnes, Herpes viruses including Epstein Barr virus, Neisseria gonorrhoea, Herpes simplex, Epstein Barr virus, Cytomegalovirus, Chlamydia bacteria, Trichomonas bacteria, Mycoplasmas and Polymyx viruses. Case control studies were available for each of these pathogens. Other pathogens, for which no case controls have been conducted, may also have roles in prostate cancer, for example Escherichia coli, fungal prostatitis, mouse mammary tumour virus and human immunodeficiency virus [6, 7].

The use of case control studies for the study of infections and prostate cancer can be misleading. This is because in most studies the non-cancer controls were benign prostate tissues. Chronic infections are common in the prostate and this can negate the comparisons between cancer and controls.

The Bradford Hill criteria have been frequently used for assessing causal roles of pathogens and other agents [8]. These criteria have been immensely influential. They have largely replaced the famous Koch postulates. Over the last 50 years, it has been estimated that over 100,000 published articles have used the Hill criteria [9]. Hill developed nine criteria in the context of his research into the links between tobacco smoking and lung cancer [10]. At that time the role of viruses in various human cancers was not known. In addition, since 1965 there have been major developments in knowledge and technology. It has also been realised that the relevance of the individual criteria vary according to the nature of the pathogen or harmful agent. Accordingly, there has been a need to add and modify the classic Hill criteria. The list of the Hill and extended criteria in some order of importance include:

(1) Identification and history of the candidate pathogen. (2) Epidemiology. (3) Strength of the association between the pathogen and prostate cancer. (4) Temporality (timing) of the association which includes evidence of infection by a pathogen in normal tissues before the development of the cancer. (5). Does exposure to the pathogen lead to infection, oncogenesis and cancer? (6) Experimental evidence, for example, capacity of the pathogen to cause cancer in experimental animals, capacity to infect human cells, ability to transform normal human cells into malignant cells, evidence that a vaccine or therapy can inhibit the pathogen from infecting or transforming cells. (7) Coherence, analogy, biological plausibility. (8) Transmission including identification of the source and means of transmission of the pathogen. (9) Oncogenic mechanisms. (10) Multiple viral and causal factors. (11) Specificity- this criteria was in Hill’s original list but is rarely helpful as many viruses and other pathogens can lead to cancer in different organs.

Hill [8] strongly cautioned against dogmatism. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non (meaning an essential requirement).

In this current review these criteria could only be fully used with respect to human papilloma viruses because of the limited evidence available for the other pathogens listed above.

Human papilloma viruses (HPV)
We have recently reviewed the evidence and concluded that it is highly likely that high risk for cancer HPVs have a causal role in prostate cancer [1]. The most important evidence is the demonstration that the prevalence of high-risk HPVs is consistently higher in prostate cancer than in benign prostate controls. This is shown in Table 1 [11–36]. In brief the evidence is as follows:

1. High risk for cancer HPVs have been identified in many countries by a range of methods in normal, benign and malignant prostate tissues [37].
2. In 10 of 27 case control studies conducted with PCR techniques, the prevalence of high-risk HPV DNA was significantly higher in prostate cancers as compared to normal and benign prostate controls (studies in which HPVs were not identified have not been included in Table 1). In these 27 studies there were
399 HPV positive of 1678 prostate cancers (24%) and 129 HPV positive of 1331 benign prostate controls (10%) (p = 0.001).

3. High risk HPV types 16 and 18 have the capacity to immortalise and transform normal prostate cells into malignant cells [38, 39].

4. HPVs are mainly transmitted by sexual activity [40]. HPVs can be transmitted throughout the body via circulating extra-cellular vesicles and blood [41].

5. High risk HPVs are associated with inflammatory prostatitis which can lead to benign prostate hyperplasia and later prostate cancer [42, 43].

6. High risk HPVs of the same type have been identified in benign prostate tissues 1–11 years before the development of HPV positive prostate cancer in the same patients [44].

Table 1 Identification of high risk human papilloma viruses in prostate cancer

| Study                  | Methods            | Prostate cancer | Prostate non cancer control | P value |
|------------------------|--------------------|-----------------|-----------------------------|---------|
| McNichol 1991 [11]     | PCR                | 14/27 52%       | 1/5 20%                     | 0.391 ns|
| Anwar 1992 [12] Japan  | PCR                | 28/68 41%       | 0/10 0%                     | 0.002 s |
| Ibrahim 1992 [13] US   | PCR                | 6/48 13%        | 2/16 13%                    | 1.00 ns |
| Rotola 1992 [14] Italy | PCR                | 6/8 75%         | 14/17 82%                   | 0.885 ns|
| Dodd 1993 [15] Canada  | PCR                | 3/7 43%         | 5/10 50%                    | 0.861 ns|
| Moyret-Lalle 1995 [16] | PCR hybridisation  | 9/17 53%        | 7/22 32%                    | 0.393 ns|
| Wideroff 1996 [17] US  | PCR                | 7/56 13%        | 4/42 10%                    | 0.679 ns|
| Terris 1997 [18] US    | PCR                | 10/53 19%       | 5/37 14%                    | 0.569 ns|
| Serth 1999 [19] Germany| PCR                | 10/47 21%       | 1/37 3%                     | 0.026 s |
| Carozzi 2004 [20] Italy| PCR                | 14/26 54%       | 5/25 20%                    | 0.117 ns|
| Leiros 2005 [21] Argentina| PCR              | 17/41 42%       | 0/30 0%                     | 0.002 s |
| Silvestre 2009 [22] Brazil| HPV genotyping   | 2/65 3%         | 0/6 0%                      |         |
| Martinez-Fierro 2010 [23] Mexico| PCR          | 11/55 20%       | 4/75 5%                     | 0.022 s |
| Aghakhani 2011 [24] Iran| PCR              | 13/104 13%      | 8/104 8%                    | 0.298 ns|
| Chen 2011 [25] Australia| PCR             | 7/51 14%        | 3/11 27%                    | 0.715 ns|
| Tachezy 2012 [26] Czech| PCR              | 2/95 2%         | 1/51 2%                     |         |
| Whitaker 2013 [37] Australia| In situ, standard PCR | 29/50 58%       | 8/50 16%                    | 0.003 s |
| Ghasemian 2013 [27] Iran| PCR               | 5/29 17%        | 8/167 5%                    | 0.025 s |
| Mokhtani 2013 [28] Iran| IHC               | 3/30 10%        | 1/90 1%                     |         |
| Michopoulos 2014 [29] Greece| PCR            | 8/50 16%        | 1/30 3%                     | 0.115 ns|
| Singh 2015 [30] India  | PCR                | 39/95 41%       | 11/55 20%                   | 0.056 s |
| Huang 2016 [31] China | PCR                | 30/75 40%       | 9/73 12%                    | 0.003 s |
| Davila Rodriguez 2016 [32] Mexico| HPV genotyping | 12/62 19%       | 1/25 4%                     | 0.107 ns|
| Atashafroz 2016 [33] Iran| PCR              | 32/200 16%      | 2/100 2%                    | 0.001 s |
| Medel Flores 2018 [34] Mexico| PCR          | 37/189 20%      | 16/167 10%                  | 0.022 s |
| Nahand 2020 [35] Iran  | PCR                | 19/58 33%       | 5/32 16%                    | 0.171 ns|
| Fatemipour 2021 [36] Iran| PCR             | 26/72 36%       | 7/44 16%                    | 0.074 ns|

Case control studies with benign prostate tissues as controls. Significant difference between HPV identification in prostate cancer and benign prostate controls p = <0.05

s, significant; ns, not significant; IHC, immunohistochemistry; PCR, polymerase chain reaction

While the highest prevalence of HPV genital infections occurs in younger people there is an increased prevalence in older age groups (over 55 years) [45, 46]. This increase in older people is unlikely to be due to increased sexual activity. Prostate cancer is much more prevalent in older men. Accordingly there may be an association between older age HPV reactivation and prostate cancer.

The reason for the reactivation of HPVs is not known. An explanation may be the concept of “trained immunity” [47]. This concept involves the long-term reprogramming of innate immune cells, which can be reactivated by stimuli such as infections or chemicals. While this response can be protective against a harmful stimulus, over- reactions such as inflammation can develop. In turn, chronic inflammation can be oncogenic. While there is no direct evidence available with respect to prostate cancer, HPVs can remain dormant
The oncogenic mechanisms for HPV oncogenesis in prostate cancer are not clear and may differ from HPV oncogenesis in cervical cancer. There is evidence that HPV E7 oncogenic proteins may be directly involved early in prostate oncogenesis [17]. HPV infections may have an indirect role by inhibiting the protective function of APOBEC3B enzymes against other virus infections [49, 50].

Effective and safe vaccines are available for the prevention of a wide range of different types of HPV infections [51].

With respect to Silvestre et al. [22], Tachezy et al. [26] and Mokhtari et al. [28] the numbers of positive cases are too few to justify statistical analysis.

Cutibacterium (Propionbacterium) acnes

Cutibacterium acnes (C. acnes) are part of the commensal flora of the skin where they colonize hair follicles and sebaceous glands [52]. Different types of C. acnes can also cause serious post-operative infections. Cutibacterium acnes may also be present in the urogenital tract including the prostate. Cutibacterium acnes can damage blood cells, cause host tissue degradation and disrupt cell surface components.

Cutibacterium acnes has been identified in prostate cancer tissues. In 2 of 6 case control studies C. acnes was significantly more prevalent in prostate cancer than in control benign prostate tissues (Table 2) [53–58]. Most C. acnes from prostate cancer tissues differ genetically from common skin C. acnes [59]. Alexeyev et al. [53] have identified C. acnes in benign prostate tissues taken up to 6 years apart from individual subjects. This indicates that C. acnes infection can be chronic and a cause of chronic inflammation. Cutibacterium acnes infections induce upregulation of inflammatory genes and cytokine secretion in prostate epithelial cells [60].

Accordingly C. acnes is a candidate pathogen in prostatitis and prostate cancer. The evidence that antibiotics can control C. acnes infections is based on skin infections [61]. Resistance to antibiotics is an increasing problem.

Escherichia coli

Escherichia coli have been consistently identified by PCR and Next Generation Sequencing in prostate cancer and benign prostate tissues [54, 62]. Unfortunately, good controls have not been used in these studies and no case control studies have been identified. A problem in studying E. coli and prostate cancer is that biopsies are usually conducted by gaining access to the prostate via the rectum. This can cause contamination of the prostate tissues by rectal located E. coli.

Escherichia coli is usually a harmless commensal bacterium that colonizes the human gut. However, many different types and strains exist, some of them have virulence properties that can result in inflammation and damage of the prostate. Jain et al. [63] have isolated E. coli from benign prostate tissues and demonstrated that this pathogen activated NF-kB and induced damage to normal cultured prostate epithelial cells. NF-kB proteins are activated by carcinogens and are known to be involved in oncogenesis [64]. Hemolysin and necrotizing factor type 1 occur significantly more frequently among C. coli isolates causing prostatitis than among those causing cystitis or pyelonephritis [65].

It is considered likely that some types of E. coli have causal roles in colon cancer [66]. Accordingly it is possible that E. coli can also cause prostate cancer.

Neisseria gonorrhoea (N. gonorrhoea)

Neisseria gonorrhoeae is the well known cause of the sexually transmitted disease gonorrhea [67]. The organism can manipulate the immune response which leads to a lack of protective immunity. Therefore individuals can become repeatedly infected. Gonorrhoea is generally

| Study          | Country   | Method          | Prostate cancer | Prostate non cancer | P value |
|----------------|-----------|-----------------|-----------------|--------------------|---------|
| Alexeyev 2006  | Sweden    | PCR             | 13/159 8%       | 6/159 4%           | 0.119 ns|
| Stafos 2007    | US        | Bacterial cultures | 5/8 63%       | 3/8 38%           | 0.562 ns|
| Severi 2010    | Australia | Serology        | 407/808 50%     | 332/584 57%       | 0.001 s |
| Bae 2014       | Japan     | IHC             | 27/28 96%       | 14/18 78%         | 0.630 ns|
| Davidsson 2016 | Sweden    | Bacterial cultures | 60/100 60%     | 13/50 26%         | 0.001 s |
| Kakegawa 2017  | Japan     | IHC             | 7/44 15%        | 2/36 5%           | 0.218 ns|

PCR, polymerase chain reaction; IHC, immunohistochemistry; s, significant, ns, not significant
a mucosal infection of the urethra with a pustular discharge. More severe sequelae include salpingitis and pelvic inflammatory disease which may lead to sterility and/or ectopic pregnancy. *Neisseria gonorrhoeae* can cause chronic inflammation of the prostate which in turn can be oncogenic [68]. Gonorrhoea is susceptible to an array of antibiotics. Antibiotic resistance is becoming a major problem.

There have been 22 case control studies in which the prevalence of *N. gonorrhoea* in prostate cancer has been compared to controls (Table 3) [69–90]. In six of these studies it was shown that *N. gonorrhoea* was significantly more prevalent in the prostate cancer cases. In 16 of these studies there was no significant difference between the cases and controls.

There is a possible explanation for these conflicting data, namely that sexually transmitted diseases are frequently due to multiple pathogens. In the meta-analysis by Taylor et al. [91] there were significant correlations between both *N. gonorrhoea* and HPVs and increased prevalence of prostate cancer (odds ratios gonorrhoea 1.35, HPV 1.39). It is possible that high risk HPVs were the cause of prostate cancer in these studies and that *N. gonorrhoea* was also present but not oncogenic.

### Table 3 Neisseria gonorrhoea infections and prostate cancer

| Study          | Country | Method for gonorrhoea | Prostate cancer | Prostate non cancer controls | P value |
|----------------|---------|-----------------------|-----------------|-------------------------------|---------|
| Heshmat 1975 [69] | US      | Self report           | 35/75 47%       | 29/75 39%                     | 0.486 ns |
| Baker 1981 [70]  | US      | Self report           | 20/44 45%       | 14/90 16%                     | 0.005 s  |
| Lees 1985 [71]   | Canada  | Clinical records      | 13/83 16%       | 30/166 18%                    | 0.689 ns |
| Mishina 1985 [72] | Japan   | Self report           | 26/100 26%      | 21/100 21%                    | 0.512 ns |
| Checkoway 1987 [73]| US      | Self report           | 6/40 15%        | 8/64 13%                      | 0.752 ns |
| Honda 1988 [74]  | US      | Self report           | 33/216 15%      | 25/216 12%                    | 0.324 ns |
| Oishi 1989 [75]  | Japan   | Self report           | 9/100 9%        | 35/200 18%                    | 0.086 ns |
| La Vecchia 1993 [76] | Italy   | Self report           | 3/271 1%       | 14/685 2%                     | 0.837 ns |
| Hiatt 1994 [77]  | US      | Medical record        | 9/238 4%        | 6/238 3%                      | 0.446 ns |
| Ilic 1996 [78]   | Serbia  | Self report           | 4/101 4%        | 0/202 0%                      | 0.016 s  |
| Hsieh 1999 [79]  | Greece  | Self report           | 39/320 12%      | 22/246 9%                     | 0.267 ns |
| Hayes 2000 [80]  | US blacks | Self report           | 115/477 24%    | 103/588 18%                   | 0.032 s  |
|                  | US Whites | Self report           | 15/501 3%      | 18/711 3%                     | 0.623 ns |
| Rosenblatt 2001 [81] | US     | Self report           | 85/753 11%     | 67/703 10%                    | 0.623 ns |
| Sanderson 2004 [82]| US      | Self report           | 43/401 11%     | 33/389 8%                     | 0.332 ns |
| Patel 2005 [83]  | US blacks | Self report           | 139/353 40%    | 94/257 37%                    | 0.449 ns |
|                  | US whites | Self report           | 16/357 5%      | 18/347 5%                     | 0.738 ns |
| Pelucci 2006 [84] | Italy   | Self report           | 4/280 1%       | 17/689 3%                     | 0.611 ns |
| Sarma 2006 [85]  | US blacks | Self report           | 84/129 66%     | 369/703 53%                   | 0.001 s  |
| Sutcliffe 2006 [86] | US      | Self report           | 55/8770 1%     | 1999/291,519 1%               | 0.853 ns |
| Huang 2008 [87]  | US blacks | Self report           | 30/98 31%      | 115/353 33%                   | 0.753 ns |
|                  | US whites | Self report           | 30/762 4%      | 26/907 3%                     | 0.832 ns |
| Hrbacek 2011 [88]| Czech Republic | Serology         | 20/328 6%      | 6/105 6%                      | 0.917 ns |
| Vazquez-Salas 2015 [89]| Mexico   | Self report           | 81/402 20%     | 46/805 6%                     | 0.001 s  |
| Wang 2017 [90]   | Taiwan  | Laboratory            | 6/355 2%       | 5/1420 0.4%                   | 0.001 s  |

s, significant; ns, non-significant

Herpes viruses

**Herpes simplex**

Herpes simplex virus 1 (HSV-1) commonly causes infections of the mouth (cold sores).

HSV-2 is associated with anogenital infections and is a sexually transmitted infection.

Both virus types can cause both kinds of infection. Infections due to herpes simplex do not usually confer immunity. No vaccines are currently available.

In four of 12 studies Herpes simplex 1 or 2 were significantly more prevalent in the prostate cancer cases (Table 4) [70, 87, 88, 92–98]. Dennis et al. demonstrated that herpes simplex 2 could be identified in prostate cancer tissues over a period of 8 years [98]. These findings suggest that if herpes simplex has an oncogenic capacity there may be a long latency period for prostate cancer development after HSV-2 infection.

Acyclovir has been successfully used to treat genital herpes simplex infections [99].
Epstein Barr virus (EBV) (Herpes virus 4)
Cancers including breast and prostate cancer [1, 100].

There have been four case control studies of EBV and prostate cancer. In one study by Sfanos et al. [54], EBV was significantly more prevalent in prostate cancer compared to controls (Table 5) [54, 97, 100, 101].

The effectiveness of antiviral agents (acyclovir, valovariclovir and valacyclovir) in acute infectious mononucleosis is uncertain [99, 102].

Cytomegalovirus (CMV) (herpes virus 5)
Human CMV is present in over 80% of most populations. Transmission can occur during foetal life, via breast milk, saliva and during sexual activities. Human CMV infections in healthy people are mostly mild or without symptoms. In contrast, CMV can cause serious defects during foetal life and life threatening illness among immunocompromised patients such as transplant recipients and patients with AIDS [103].

As shown in Table 6 [23, 87, 93, 104, 105] in four of five case control studies there were no significant differences between the prevalence of CMV in prostate cancers and controls. In one study CMV was identified in the controls but not in prostate cancers [23].

Chlamydia trachomatis (C. trachomatis)
Chlamydia trachomatis is a common, sexually transmitted bacteria. Chlamydia trachomatis initiates and can maintain inflammation and persistent infection including prostatitis [105]. Human prostate cancer epithelial cells are susceptible to C. trachomatis infection and initiate inflammation [106, 107]. As inflammation is associated with prostate cancer it has been hypothesized that C. trachomatis could have a causal role.

However, as shown in Table 7 [81, 87, 88, 98, 106, 108–110] in eight case control studies there were no positive associations between C. trachomatis infections and prostate cancer. On the other hand, all these studies are based on serology, and it is possible that these case control studies are misleading as C. trachomatis may be causing chronic infection in the prostate leading to prostate cancer. This would lead to positive antibodies in both benign prostate controls and prostate cancer.

### Table 4 Herpes simplex virus infections and prostate cancer

| Study          | Country | Method                        | Prostate cancer | Prostate non cancer | P value |
|----------------|---------|-------------------------------|----------------|--------------------|---------|
| Baker 1981 HSV 2 [70] | US      | Immunofluorescent Tissues     | 34/50 68%       | 81/159 51%         | 0.001 s |
| Luleci 1981 HSV 2 [92]   | Turkey  | Serology                      | 14/16 88%       | 22/35 63%          | 0.064 ns|
| Boldogh 1983 [93]       | US      | ISH                           | 2/10 20%        | 1/22 5%            | 0.012 s |
| Haid 1984 HSV 2 [94]    | US      | Immunofluorescent tissues     | 7/27 26%        | 8/33 24%           | 0.668 ns|
| Leskinen 2003           | Finland | PCR tissues                   | 0/10            | 0/10               |         |
| Korodi 2005 HSV 2 [96]  | Finland | Serology                      | 11/163 7%       | 20/288 7%          | 0.721 ns|
| Bergh 2007 HSV 1,2 [97] | Sweden  | PCR tissues                   | 0/201           | 0/201              |         |
| Huang 2008 HSV 2 [87]   | US whites | Serology                      | 70/765 9%       | 89/915 10%         | 0.729 ns|
|                         | US blacks| Serology                      | 55/103 53%      | 180/367 49%        | 0.342 ns|
| Dennis 2009 HSV 2 [98]  | US      | Serology latent period tests 1 year, 8 year | 26/55 47% | 47/139 34% | 0.002 s |
|                         |         | Serology latent period tests 1 year, 8 year | 20/56 36% | 35/156 22% | 0.050 s |
| Hrbacek 2011 HSV 2 [88] | Czech   | Serology                      | 313/329 95%     | 99/105 94%         | 0.955 ns|

s, significant; ns, non significant

### Table 5 Epstein Barr virus (herpes virus 4) infections and prostate cancer

| Study          | Country | Method                        | Prostate cancer | Prostate non cancer | P value |
|----------------|---------|-------------------------------|----------------|--------------------|---------|
| Grinstein 2002 [101] | Argentina | IHC                           | 7/19 37%        | 0/10 0%            | 0.089 ns|
| Bergh 2007 [97] | Sweden  | PCR tissues                   | 15/115 9%       | 14/115 9%          | 0.861 ns|
| Sfanos 2008 [54] | US      | PCR tissues                   | 16/200 8%       | 5/200 10%          | 0.019 s |
| Nahand 2021 [100]| Iran    | PCR tissues                   | 10/67 15%       | 3/40 8%            | 0.310 ns|

s, significant; ns, non significant
Azithromycin and Doxycycline antibiotics appear to be effective in the treatment of sexually transmitted *C. trachomatis* [111].

**Trichomonas vaginalis** (*T. vaginalis*)

*Trichomonas vaginalis* is a common protozoan infection frequently transmitted during sexual activities [112]. *Trichomonas vaginalis* in men is usually asymptomatic but may cause urethritis, prostatitis, epididymitis and infertility [113].

As shown in Table 8 [86, 114–121] in eight of nine case control studies there is no increase in risk of prostate cancer in association with *T. vaginalis* infections. In two studies positive antibodies were higher in the controls than the cancer. These nine studies were all based on serology and involved a high number of subjects.

In a large serology based study by Tsang et al. [122] there was no increase in prostate cancer deaths associated with *T. vaginalis*. This finding makes it unlikely that *T. vaginalis* is associated with prostate cancer.

The 5-nitroimidazoles (metronidazole, tinidazole, secnidazole) are the only class of antimicrobials effective against *T. vaginalis* [113]. Unfortunately, there is growing concern over drug resistance with metronidazole.

**Mycoplasma**

Mycoplasma bacteria frequently infect prostate tissues and prostate cancer. The most common are *M. hominus*, *M. ureaplasma* and *M. hyorhinus* [123]. A recent meta-analysis showed that Mycoplasma bacterial infections were 2.24 times more frequent in patients with prostate cancer as compared to benign prostate hyperplasia [124]. These data are shown in Table 9 [88, 123, 125–129].

Of particular interest are the studies based on PCR analyses of tissues as compared to studies based on serology. Three of the PCR studies with positive results were significant, and two showed a trend that Mycoplasma infections were more frequent in prostate cancers than benign prostate controls. Accordingly, it is possible that Mycoplasma bacteria may have a role in prostate cancer. However additional evidence is required.

Antibiotics can be effective in treating Mycoplasma bacterial infections. Unfortunately, resistance to antibiotic treatment is emerging [130].
Polyoma viruses (hPy)
The two human polyomaviruses (hPy), BK virus (BKV), and JC virus (JCV), are commonly present in human populations. Infections usually occur in childhood but rarely cause clinical symptoms. In immunocompromised patients JCV can cause serious neurodegenerative conditions. There is no direct evidence that hPy viruses are oncogenic [131].

We have identified 11 case control studies of BKV and JCV and their associations with prostate cancer in which polyoma viruses were identified (Table 10) [97, 132–139]. In two small studies based on PCR there was a significant association with prostate cancer. There were no significant associations in 9 studies.

Accordingly it is unlikely that these polyomaviruses have causal roles in prostate cancer.

Fungal prostatitis
Infections of the prostate by several fungi are the usual cause of prostatitis. These fungi include Blastomyces, Candida albicans and Cryptococcus [140]. There is no evidence that these fungi are associated with prostate cancer. However, there must be suspicions about any pathogen which leads to chronic inflammation.

Mouse mammary tumour virus (MMTV)
MMTV is the proven cause of breast cancer in mice. There is compelling evidence that MMTV—like viruses are also causal in human breast cancer [7]. MMTV has been identified in prostate glands of mice [141]. MMTV—like viruses have been identified in human prostate cancers [6]. However, no studies have been

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Table 8  Trichomonas vaginalis infections and prostate cancer

| Study       | Country | Method    | Prostate cancer | Prostate non cancer controls | P value |
|-------------|---------|-----------|-----------------|-------------------------------|---------|
| Sutcliffe 2006 [86] | US      | Serology  | 87/691 13%      | 65/691 9%                     | 0.090 ns |
| Sutcliffe 2009 [114] | US      | Serology  | 132/616 22%     | 153/616 25%                   | 0.262 ns |
| Stark 2009 [115] | US      | Serology  | 165/673 25%     | 144/673 21%                   | 0.402 ns |
| Chen 2013 [116] | US      | Serology  | 87/603 14%      | 65/627 10%                    | 0.056 ns |
| Shui 2016 [117] | US      | Serology  | 24/122 20%      | 42/139 30%                    | 0.130 ns |
| Fowke 2016 [118] | US      | Serology  | 69/296 23%      | 124/585 21%                   | 0.567 ns |
| Marous 2017 [119] | US whites | Serology  | 84/777 11%      | 33/405 8%                     | 0.127 ns |
| Kim 2019 [120] | Korea   | Serology  | 9/44 20%        | 1/58 2%                       | 0.001 s  |
| Saleh 2021 [121] | Egypt   | Serology  | 24/126 19%      | 10/120 8%                     | 0.015 s  |

s, significant; ns, non significant

Table 9  Mycoplasma infections and prostate cancer

| Study                  | Country     | Methods    | Prostate cancer | Prostate non cancer controls | P value |
|------------------------|-------------|------------|-----------------|-------------------------------|---------|
| Hrbacek 2011 M. hominis [88] | Czech Republic | Serology   | 60/330 18%      | 16/107 14%                    | 0.518 ns |
| Hrbacek 2011 M. urealyticum [88] | Czech Republic | Serology   | 64/328 20%      | 11/105 11%                    | 0.068 ns |
| Barykova 2011 M. hominis [123] | Russia US | Serology PCR | 28/125 22%      | 0/27 0%                       | 0.023 s  |
| Urbanek 2011 M. hyorhinus [125] | US | Serology   | 59/114 52%      | 38/105 36%                    | 0.279 ns |
| Erturhan 2013 [126]    | Turkey      | PCR        | 11/31 35%       | 0/31 0%                       | 0.004 s  |
| Yow 2014 M. genitalium [127] | Australia | PCR        | 9/115 8%        | 1/51 2%                       | 0.163 ns |
| Miyake 2019 M. genitalium [128] | Japan | PCR        | 18/45 40%       | 6/33 18%                      | 0.127 ns |
| Saadat 2020 M. Hominis [129] | Iran       | PCR        | 8/61 13%        | 0/70 0%                       | 0.003 s  |

s, significant; ns, non significant
conducted to determine if MMTV is causal in human prostate cancer.

**Human immunodeficiency virus (HIV)**

Compared to the general population, people living with HIV have a lower prevalence of prostate cancer [142, 143]. This is probably due to the suppression of immune related B and T cells associated with both HIV and MMTV infections.

**The gut microbiome and prostate cancer**

The gut microbiome may also play an indirect role in various cancers [144]. In a study which compared the gut microbiota in men with prostate cancer and benign controls there was a significant difference in gut microbiol composition [145]. The meaning of these observations is not known.

**Discussion**

High risk human papilloma viruses are the only pathogens considered in this review which have a proven oncogenic capacity. However, in its acute stage it is unlikely that an HPV infection leads to prostate cancer as HPV infections are common in young men and prostate cancer occurs mainly in older men. On the other hand, as considered above, the influence of HPV may be reactivated and lead to prostate oncogenesis via long-term reprogramming of innate immune cells.

While the oncogenic mechanisms probably differ between these pathogens, of particular relevance is the potential role of inflammation in prostate cancer. Different pathogens may each cause chronic inflammation. Multiple pathogens are frequently present in prostate tissues and chronic exposure can lead to chronic inflammation and ultimately to prostate cancer. The relevant evidence has been reviewed in detail by De Bono et al. [147] and Gobel et al. [148].

A precise mechanism linking inflammation to cancer is the nuclear transcription factor “kappa-light-chain-enhancer” of B-cells known as NF-kB. This is a protein activated by many carcinogens. It controls genes commonly associated with oncogenesis [64]. Almost all infectious agents linked with cancer activate NF-kB. This has been confirmed experimentally in mice by the inactivation of NF-kB which reduced inflammation initiated cancer formation [149]. Infectious pathogens can activate inflammatory pathways which lead to genomic instability in tissue cells which in turn lead to malignant transformation. HPV, human herpes virus, and EBV, have been specifically shown to activate NF-kB. Confirmation of this evidence has been provided by the reduction in risk

| Study          | Country | Method | Prostate cancer | Prostate non cancer controls | P value         |
|----------------|---------|--------|-----------------|------------------------------|----------------|
| Monini 1995 BKV [132] | Italy   | PCR    | 4/7 57%         | 11/19 58%                    | 0.986 ns       |
| Zambrano 2002 BKV [133] | US      | PCR    | 2/8 25%         | 1/11 9%                      | 0.427 ns       |
| Zambrano 2002 JCV [133] | US      | PCR    | 3/8 38%         | 4/11 36%                     | 0.973 ns       |
| Bergh 2007 JCV [97]   | Sweden  | PCR    | 3/159 2%        | 6/159 4%                     | 0.324 ns       |
| Lau 2007 BKV [134]    | US      | ISH    | 2/30 7%         | 4/30 13%                     | 0.481 ns       |
| Das 2008 BKV [135]    | US      | ISH    | 11/14 79%       | 4/15 27%                     | 0.090 ns       |
| Russo 2008 BKV [136]  | Italy   | IHC    | 20/26 77%       | 0/12 0%                      | 0.004 s        |
| Delbue 2013 BKV [137] | Italy   | PCR    | 18/56 32%       | 15/68 22%                    | 0.318 ns       |
| Delbue 2013 JCV [137] | Italy   | PCR    | 16/56 28%       | 16/68 24%                    | 0.624 ns       |
| Taghavi 2015 BKV [138]  | Iran    | PCR    | 17/60 28%       | 9/60 15%                     | 0.154 ns       |
| Gorish 2019 BKV [139] | Sudan   | IHC    | 17/55 30%       | 4/55 7%                     | 0.009 s        |

IHC, immunohistochemistry; ISH, in situ hybridisation; s, significant; ns, non significant

HPVs are the only pathogen considered in this review which have a proven oncogenic capacity. However, in its acute stage it is unlikely that an HPV infection leads to prostate cancer as HPV infections are common in young men and prostate cancer occurs mainly in older men. On the other hand, as considered above, the influence of HPV may be reactivated and lead to prostate oncogenesis via long-term reprogramming of innate immune cells.

While the oncogenic mechanisms probably differ between these pathogens, of particular relevance is the potential role of inflammation in prostate cancer. Different pathogens may each cause chronic inflammation. Multiple pathogens are frequently present in prostate tissues and chronic exposure can lead to chronic inflammation and ultimately to prostate cancer. The relevant evidence has been reviewed in detail by De Bono et al. [147] and Gobel et al. [148].

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of cancer by anti-inflammatory agents such as aspirin [150].

Conclusions and actions
The most influential cause of prostate cancer appears to be infection induced chronic inflammation.

Given the high prevalence of prostate cancer it is important for action to be taken without waiting for additional conclusive evidence. These include:

1. Encouragement of all boys (as well as girls) to have HPV vaccines
2. The vigorous use of antibiotics to treat all bacterial pathogens identified in the urogenital tract
3. The use of antiviral medications to control herpetic infections
4. Education about safe sexual practices

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References
1. Lawson JS, Glenn WK. Evidence for a causal role by human papillomaviruses in prostate cancer: a systematic review. Infect Agent Cancer. 2020;15:41.
2. Ferlay J, Colombo M, Soejomotaram I, Parkin DM, Piñeros M, Znaor A, Bray F. Cancer statistics for the year 2020: an overview. Int J Cancer. 2021. https://doi.org/10.1002/ijc.35588.
3. Muir CS, Nectoux J, Staszewski J. The epidemiology of prostate cancer: Geographical distribution and time-trends. Acta Oncol. 1991;30:133–40.
4. Kumar S, Singh R, Malik S, Manne U, Mishra M. Prostate cancer health disparities: an immunobiological perspective. Cancer Lett. 2018;414:153–65.
5. Stanford JL, Herrington LJ, Schwartz SM, Weiss NS. Breast cancer incidence in Asian migrants to the US and their descendants. Epidemiol. 1995;6:181–3.
6. Johal H, Faedo M, Faltas J, Lau A, Mousina R, Cozzi P, Defazio A, Rawlin-son WD. DNA of mouse mammary tumor virus-like virus is present in human tumors influenced by hormones. J Med Virol. 2010;82:1044–50.
7. Lawson JS, Glenn WK. Evidence for a causal role by mouse mammary tumour-like virus in human breast cancer. NPJ Breast Cancer. 2019;5:40.
8. Hill AB. The environment and disease: association or causation? Proc R Soc Med. 1965;58:295–330.
9. Kleinberg S. On the use and abuse of Hill’s viewpoints on causality. Obs Stud. 2020;6:17–9.
10. Doll R, Hill AB. Smoking and carcinoma of the lung: preliminary report. Br Med J. 1950;2(4682):739–48.
11. McNicol PJ, Dodd JG. High prevalence of human papillomavirus in prostate tissues. Urol J. 1991;145:850–3.
12. Anwar K, Nakakuki K, Shiraishi T, Naiki H, Yatani R, Inuzuka M. Presence of ras oncogene mutations and human papillomavirus DNA in human prostate carcinomas. Cancer Res. 1992;52:5991–9.
13. Ibrahim GK, Gravitt PE, Dittrich KL, Ibrahim SN, Melhus O, Anderson SM, et al. Detection of human papillomavirus in the prostate by polymerase chain reaction and in situ hybridization. J Urol. 1992;148:1822–6.
14. Rotola A, Monini P, Di Luca D, Savoli A, Simone R, Secchiero P, et al. Presence and physical state of HPV DNA in prostate and urinary-tract tissues. Int J Cancer. 1992;52:359–65.
15. Dodd JG, Paraskewas M, McNicol PJ. Detection of human papillomavirus 16 transcription in human prostate tissue. J Urol. 1993;149:400–2.
16. Moyet-Lalle C, Marçais C, Jaccquier M, Moles JF, Daver A, Soret JF, et al. Ras, p53 and HPV status in benign and malignant prostate tumors. Int J Cancer. 1995;61:124–9.
17. Wideroff L, Schottenfeld D, Carey TE, Beals T, Fu G, Sakr W, et al. Human papillomavirus DNA in malignant and hyperplastic prostate tissue of black and white males. Prostate. 1996;28:117–23.
18. Ternis MK, Peehl DN. Human papillomavirus detection by polymerase chain reaction in benign and malignant prostate tissue is dependent on the primer set utilized. Urology. 1997;50:150–6.
19. Serth J, Panitz F, Paeslack U, Kuczky MA, Jonas U. Increased levels of human papillomavirus type 16 DNA in a subset of prostate cancers. Cancer Res. 1999;59:823–5.
20. Carozzi F, Lombardi FC, Zendron P, Confortini M, Sani C, Bisanzi S, et al. Association of human papillomavirus with prostate cancer: analysis of a consecutive series of prostate biopsies. Int J Biol Markers. 2004;19:257–61.
21. Leiros GJ, Galliano SR, Sembler ME, Kahn T, Schwarz E, Eiguchi K. Detection of human papillomavirus DNA and p53 codon 72 polymorphism in prostate carcinomas of patients from Argentina. BMC Epidemiol Health. 2015;3:e2015005.
22. Silvestre RV, Leal MF, Demachki S, Nahum MC, Bernardes JG, Rabenhorst SH, et al. Low frequency of human papillomavirus detection in prostate tissue from individuals from northern Brazil. Mem Inst Oswaldo Cruz. 2009;104:665–7.
23. Martinez-Fierro ML, Leach RJ, Gomez-Guerra LS, Garza-Guajardo R, Johnson-Pais T, Beuten J, et al. Identification of viral infections in the prostate and evaluation of their association with cancer. BMC Cancer. 2010;10:326.
24. Aghakhani A, Hamak R, Parvin M, Ghavami N, Nadir M, Pakparast A, et al. The role of human papillomavirus infection in prostate carcinoma. Scand J Infect Dis. 2011;43:64–9.
25. Chen AC, Waterboer T, Keleher A, Morrison B, Jindal S, McMillan D, et al. Human papillomavirus in benign prostate hyperplasia and prostatic adenocarcinoma patients. Pathol Oncol Res. 2011;17:613–7.
26. Tachezy R, Hrbacek J, Heracek J, Salakova M, Smahelova J, Ludvikova V, et al. HPV persistence and its oncogenic role in prostate tumors. J Med Virol. 2012;84:1636–45.
27. Ghasemian E, Monavari SH, Iraqijan GR, Jalali Nodoshan MR, Roudsari RV, Yahyapour Y. Evaluation of human papillomavirus infections in prostatic disease: a cross-sectional study in Iran. Asian Pac J Cancer Prev. 2013;14:3305–8.
28. Mokhtari M, Taghizadeh F, Hani M. Is prostatic adenocarcinoma in a Greek group of patients. Tumour Biol. 2014;35:12765–73.
29. Singh N, Hussain S, Kakkar N, Singh SK, Sobti RC, Bharadwaj M. Implication of high risk human papillomavirus HR-HPV infection in prostate cancer in Indian population: a pioneering case-control analysis. Sci Rep. 2015;5:7822.
30. Huang L, Wu MG, He J, Wei ZS, Lü WX, Song XJ, et al. Correlation of human papillomavirus and p53 codon 72 (Arg72Pro) polymorphism in prostate cancer in a Greek group of patients. Tumour Biol. 2014;35:12765–73.
31. Huang L, Wu MG, He J, Wei ZS, Lü WX, Song XJ, et al. Correlation of highrisk HPV 16/18 infections with prostate cancer. Zhonghua Nan Ke Xue. 2016;22:501–5.
32. Dávila-Rodríguez MI, Ignacio Morales CV, Aragón Tovar AR, Olache Jimenez D, Castañón Maldonado E, Lara Miranda S, et al. Human papillomavirus detection by INNOLUX HPV in prostate tissue from men of Northeast Mexico. Asian Pac J Cancer Prev. 2016;17:4863–5.
33. Atashafrooz F, Rokkhbakhsh-Zamini F. Frequency and type distribution of human papilloma virus in patients with prostate Cancer, Kerman, southeast of Iran. Asian Pac J Cancer Prev. 2016;17:4953–9.
34. Medel-Flores O, Valenzuela-Rodríguez VA, Ocáziz-Delgado R, Castro-Muñoz LJ, Hernández-Leyva S, Lara-Hernández G, et al. Association between HPV infection and prostatic cancer in a Mexican population. Genet Mol Biol. 2018;41:781–9.
35. Nahand JS, Eshghai M, Hamidreza Monavari S, Moghoofei M, Jalal Kiani S. Human papillomavirus and Epstein Barr virus in prostate cancer in Indian population: a pioneering case-control analysis. Sci Rep. 2015;5:7822.
36. Whitaker NJ, Glenn WK, Sahrudin A, Orde MM, Delprado W, Lawson JS. High risk human papillomavirus E6 triggers upregulation of the antiviral and cancer suppressor p53 in prostate cancer. Int Immunopharmacol. 2020;88:106913.
37. Rhim JS, Webber MM, Bello D, Lee MS, Arnstein P, Chen LS, et al. Human papillomavirus infection and high-grade squamous intraepithelial lesions in 29 900 men according to HPV status, sexuality, and age: a collaborative pooled analysis of 64 studies. Lancet HIV. 2021;8:e531–43.
38. Netea MG, Domínguez-Andrés J, Baneiro LB, Chavalik T, Divangahi M, Fuchs E, Joosten LAB, van der Meer JW, Mhlanga MM, Mulder WIM, Riksen NP, Schütte A, Schultze JL, Stabell Benn C, Sun JC, Xavier RJ, Latz E. Defining trained immunity and its role in health and disease. Nat Rev Immunol. 2020;20:375–88.
39. Korostil IA, Regan DG. The potential impact of HPV-16 reactivation on prevalence in older Australians. BMC Infect Dis. 2014;14:312.
40. Ohashi K, Ichiyama K, Yajima M, Gemma N, Nkaido M, Wu Q, et al. in vivo and in vitro studies suggest a possible involvement of HPV infection in the early stage of breast carcinogenesis via APOBEC3B induction. PLoS ONE. 2014;9:e97787.
41. Vieira VC, Leonard B, White EA, Starrett GJ, Temiz NA, Lorenz L, et al. Human papillomavirus E6 triggers upregulation of the antiviral and cancer suppressor p53 in prostate cancer. Int J Cancer. 2007;121:1712–9.
42. Alexeyev O, Bergh J, Marklund I, Thellenborg-Karlsön C, Wiklund F, Grönberg H, Bergh A, Elgh F. Association between the presence of bacterial 16S RNA in prostate specimens taken during transurethral resection of prostate and subsequent risk of prostate cancer (Sweden). Cancer Causes Control. 2006;17:1127–33.
43. Sfanos KS, Sauvageot J, Fedor HL, Dick JD, De Marzo AM, Isaaci WA. A molecular analysis of pyroaryatic and viral DNA sequences in prostate tissue from patients with prostate cancer indicates the presence of multiple and diverse microorganisms. Prostate. 2008;68:306–20.
44. Severi G, Shannon BA, Hoang HA, Baglietto L, English DR, Hopper JL, Pedersen J, Southey MC, Sinclair R, Cohen RJ, Giles GG. Plasma concentration of Propionibacterium acnes antibodies and prostate cancer risk: results from an Australian population-based case-control study. Br J Cancer. 2010;103:411–5.
45. Bae Y, Ito T, Iida T, Uchida K, Sekine M, Nakajima Y, Kumagai J, Yokoyama T, Kawachii H, Akashi T, Eishi Y. Intracellular Propionibacterium acnes infection in glandular epithelium and stromal macrophages of the prostate with or without cancer. PLoS ONE. 2014;9:e90034.
46. Davidson S, Molling P, Rider JR, Uenomo M, Karlsson MG, Carlsson J, Andersson SO, Elgh F, Soderquvis B, Andre O. Frequency and typing of Propionibacterium acnes in prostate tissue obtained from men with and without prostate cancer. Infect Agent Cancer. 2016;11:26.
47. Nakagawa T, Bae Y, Ito T, Uchida K, Sekine M, Nakajima Y, Furukawa A, Suzuki Y, Kumagai J, Akashi T, Eishi Y. Infiltration of Propionibacterium acnes in prostate with or without cancer. PLoS ONE. 2017;12:e0169894.
48. Cohen RJ, Shannon BA, McNeal JE, Shannon T, Garrett KL. Propionibacterium acnes associated with inflammation in radical prostatectomy specimens: a possible link to cancer evolution? J Urol. 2005;173:1969–74.
49. Drott JB, Alexeyev O, Bergström P, Elgh F, Olsson J. Propionibacterium acnes infection induces upregulation of inflammatory genes and cytokine secretion in prostate epithelial cells. BMC Microbiol. 2010;10:126.
50. Dessinioti C, Dreno B. Acne treatments: future trajectories. Clin Exp Dermatol. 2020;45:955–61.
51. Bruggemann H, Al-Zeer MA. Bacterial signatures and their inflammatory role in prostate cancer. Curr Opin Pharmacol. 2020;52:80–91.
52. Jain S, Samal AG, Das B, Pradhan B, Sahu N, Mohapatra D, Behera PK, Satpathi PS, Mohanty AK, Satpathi S, Senapati S, Escherichia coli, a common constituent of benign prostate hyperplasia-associated microbiota.
induces inflammation and DNA damage in prostate epithelial cells. Prostate. 2020;80:1341–52.

64. Aggarwal BB, Vijayalekshmi RV, Sung B. Targeting inflammatory pathways for prevention and therapy of cancer: short-term friend, long-term foe. Clin Cancer Res. 2009;15:425–30.

65. Ruiz J, Simon K, Horcajada JP, Velasco M, Barranco M, Roig G, Moreno-Martínez A, Martínez JA, Jiménez de Anta T, Mensa J, Vila J. Differences in virulence factors among clinical isolates of Escherichia coli causing cystitis and pyelonephritis in women and prostatitis in men. J Clin Microbiol. 2002;40:4445–9.

66. Alhina EA, Walton GE, Commane DM. The role of the gut microbiota in colorectal cancer causation. Int J Mol Sci. 2019;20:5295.

67. Hill SA, Masters TL, Wachter J. Gonorrhea: an evolving disease of the new millennium. Microb Cell. 2016;3:371–89.

68. Sfanos KS, Yegnasub Bramanian S, Nelson WG, De Marzo AM. The inflammatory microenvironment and microbiome in prostate cancer development. Nat Rev Urol. 2018;15:11–24.

69. Heshmat MY, Kovi J, Herson J, Jones GW, Jackson MA. Epidemiologic development. Nat Rev Urol. 2018;15:11–24.

70. Baker LH, Mebust WK, Chin TD, Chapman AL, Hinthorn D, Towle D. The relationship of herpesvirus to carcinoma of the prostate. J Urol. 1981;125:370–4.

71. Lees RE, Steele R, Wardle D. Arsenic, syphilis, and cancer of the prostate. J Epidemiol Community Health. 1985;39:227–30.

72. Mishina T, Watanabe H, Araki H, Nakao M. Epidemiological study of prostate cancer by matched-pair analysis. Prostate. 1985;6:423–36.

73. Checkoway H, D’Erdinardo G, Hulka BS, McLickey D. Medical, life-style, and occupational risk factors for prostate cancer. Prostate. 1987;10:79–88.

74. Honda GD, Bernstein L, Ross RK, Greenland S, Gerkins V, Henderson BE. Vasectomy, cigarette smoking, and age at first sexual intercourse as risk factors for prostate cancer in middle-aged men. Br J Cancer. 1988;57:326–31.

75. Oishi K, Okada K, Yoshida O, Yamabe H, Ohno Y, Hayes RB, Schroeder FH. The relationship of herpesvirus to carcinoma of the prostate. J Urol. 1981;125:370–4.

76. Honda GD, Bernstein L, Ross RK, Greenland S, Gerkins V, Henderson BE. Vasectomy, cigarette smoking, and age at first sexual intercourse as risk factors for prostate cancer in middle-aged men. Br J Cancer. 1988;57:326–31.

77. Lees RE, Steele R, Wardle D. Arsenic, syphilis, and cancer of the prostate. J Epidemiol Community Health. 1985;39:227–30.

78. Ilić M, Vlajinac H, Marinković J. Case-control study of risk factors for prostate cancer. Cancer. 1975;6:457–60.

79. The relationship of herpesvirus to carcinoma of the prostate. J Urol. 1981;125:370–4.

80. Mishina T, Watanabe H, Araki H, Nakao M. Epidemiological study of prostate cancer by matched-pair analysis. Prostate. 1985;6:423–36.

81. Checkoway H, D’Erdinardo G, Hulka BS, McLickey D. Medical, life-style, and occupational risk factors for prostate cancer. Prostate. 1987;10:79–88.

82. Honda GD, Bernstein L, Ross RK, Greenland S, Gerkins V, Henderson BE. Vasectomy, cigarette smoking, and age at first sexual intercourse as risk factors for prostate cancer in middle-aged men. Br J Cancer. 1988;57:326–31.

83. Oishi K, Okada K, Yoshida O, Yamabe H, Ohno Y, Hayes RB, Schroeder FH. The relationship of herpesvirus to carcinoma of the prostate. J Urol. 1981;125:370–4.

84. Honda GD, Bernstein L, Ross RK, Greenland S, Gerkins V, Henderson BE. Vasectomy, cigarette smoking, and age at first sexual intercourse as risk factors for prostate cancer in middle-aged men. Br J Cancer. 1988;57:326–31.

85. Ilić M, Vlajinac H, Marinković J. Case-control study of risk factors for prostate cancer. Cancer. 1975;6:457–60.

86. Sutcliffe S, Giovanniucci E, De Marzo AM, Leitzmann MF, Willett WC, Platz EA. Gonorrhea, syphilis, clinical prostatitis, and the risk of prostate cancer. Cancer Epidemiol Biomark Prev. 2006;15:2160–6.

87. Huang WY, Hayes R, Pfeiffer R, Viscoli RP, Lee FK, Wang YF, Reding D, Whitby D, Papp JR, Rabkin CS. Sexually transmissible infections and prostate cancer risk. Cancer Epidemiol Biomark Prev. 2008;17:2374–81.

88. Hrbacek J, Urban M, Hamsikova E, Tachezy R, Eriš V, Brabec M, Heracek J. Serum antibodies against genitourinary infectious agents in prostate cancer and benign prostate hyperplasia patients: a case-control study. BMC Cancer. 2011;11:53.

89. Vázquez-Salas RA, Torres-Sánchez L, López-Carrillo L, Romero-Martínez M, Manzanilla-García HA, Cruz-Ortiz CH, Mendoza-Peña F, Jiménez-Ríos MA, Rodríguez-Covarrubias F, Hernández-Toríz N, Moreno-Alcázar O. History of gonorrhea and prostate cancer in a population-based case-control study in Mexico. Cancer Epidemiol. 2016;40:95–101.

90. Wang YC, Chung CH, Chen JH, Chang MH, Yi-Yin CH, Tsao CH, Lin FH, Chien WC, Wang ST, Chang FY. Gonorrhea infection increases the risk of prostate cancer in Asian population: a nationwide population-based cohort study. Eur J Clin Microbiol Infect Dis. 2017;36:813–21.

91. Taylor ML, Mainous AG 3rd, Wells BJ. Prostate cancer and sexually transmitted diseases: a meta-analysis. Fam Med. 2005;37:506–12.

92. Luleci G, Sakolži M, Gunapal A, Erišk V, Remzi D. Herpes simplex type 2 neutralization antibodies in patients with cancers of urinary bladder, prostate, and cervix. J Sex Med. 1981;6:457–60.

93. Boldogh I, Baskar JF, Mar EC, Huang ES. Human cytomegalovirus and herpes simplex type 2 virus in normal and adenocarcinomatous prostate glands. J Natl Cancer Inst. 1983;70:199–26.

94. Haid M, Sharon N. Immunofluorescence evidence of prior herpes simplex virus type-2 infection in prostate carcinoma. Urology. 1984;24:623–5.

95. Leskjen MJ, Vainionp R, Sjärinen S, Leppilähti M,Marttila T, Kylm T, Tammela TL. Herpes simplex virus, cytomegalovirus, and papillomavirus DNA are not found in patients with chronic pelvic pain syndrome undergoing radical prostatectomy for localized prostate cancer. Urol. 2003;61:39–41.

96. Korodi Z, Wang X, Tedesci R, Knekt P, Dillner J. No serological evidence of association between prostate cancer and infection with herpes simplex virus type 2 or human herpesvirus type 2 & a nested case-control study. J Infect Dis. 2005;191:2008–11.

97. Bergh J, Marklund C, Gustavsson C, Wulkid F, Grönb erg H, Allard A, Alexeyev O, Elgh F. No link between viral findings in the prostate and subsequent cancer development. Br J Cancer. 2007;96:137–9.

98. Dennis LK, Coughlin JA, McKinnon BC, Wells TS, Gaydos CA, Hamdy CM, Trichopoulos D. Risk factors for prostate cancer: a case-control study in southern California. Cancer Causes Control. 2004;15:647–55.

99. South Carolina. Cancer Causes Control. 2004;15:647–55.

100. Nahand JS, Khanaliha K, Mirzaei H, Moghoofei M, Baghi HB, Esghaei M, Rostami M, Khatami AR, Fatemipour M, Bokharaei-Salim F, Esghaei M, Haymnin A. Possible role of HPV/EBV infection in anikosis resistance and development in prostate cancer. BMC Cancer. 2012;11:926.

101. Grinstein S, Preciado MV, Gattuso P, Chabay PA, Warren WH, De Matteo E, Gould VE. Demonstration of Epstein-Barr virus in carcinomas of various sites. Cancer Res. 2002;62:4786–8.

102. De Paor M, O’Brien K, Fahey T, Smith SM. Antiviral agents for infectious mononucleosis (glandular fever). Cochrane Database Syst Rev. 2016;12:CD011487.

103. Griffiths P, Reeves M. Pathogenesis of human cytomegalovirus in the immunocompromised host. Nat Rev Microbiol. 2001;19:759.

104. Ezuru Y, Hyman RW, Nahhas WA, Rapp F. Herpesvirus RNA in human urogenital tumors. Proc Soc Exp Biol Med. 1983;174:296–301.

105. Samanta M, Hanks L, Klemm K, Britt WJ, Cobbs CS. High prevalence of human cytomegalovirus in prostatic intraepithelial neoplasia and prostatic carcinoma. J Urol. 2003;170:998–1002.

106. Dillner J, Knekt P, Boman J, Lehtinen M, Af Geijersstam V, Reding D, Whitby D, Papp JR, Rabkin CS. Sexually transmissible infections and prostate cancer risk. Cancer Epidemiol Biomark Prev. 2008;17:2374–81.

107. Sellami H, Said-Sadier N, Znazen A, Gdoura R, Ojcius DM, Hamy M, A. Chlamydia trachomatis infection increases the expression of inflammatory tumorigenic cytokines and chemokines as well as components of
the Toll-like receptor and NF-κB pathways in human prostate epithelial cells. Mol Cell Probes. 2014;28:147–54.

108. Anttila T, Tenkanen L, Lanne M, Leinonen M, Gislerfoss RE, Hallmans G, Thoresen S, Hakulinen T, Luostarinen T, Statin P, Saikku P, Dillner J, Lehtinen M, Hakama M. Chlamydial antibodies and risk of prostate cancer. Cancer Epidemiol Biomark Prev. 2005;14:385–9.

109. Sutcliffe S, Giovannucci E, Gaydos CA, Viscardi RP, Jenkins FJ, Zenilman JM, et al. Plasma antibodies against chlamydia trachomatis, human papillomavirus, and human herpesvirus type 8 in relation to prostate cancer: a prospective study. Cancer Epidemiol Biomark Prev. 2007;16:1573–80.

110. Lanne M, Tenkanen L, Langseth H, Gislerfoss R, Hakama M, Statin P, Hallmans G, Adlercreutz H, Saikku P, Stenman UH, Tuohimaa P, Luostarinen T, Dillner J. Longitudinal biobanks-based study on the joint effects of infections, nutrition and hormones on risk of prostate cancer. Acta Oncol. 2016;55:839–45.

111. Blanco JL, Fuertes I, Bosch J, Lazari D, Cordoñón A, Vergara A, Johnston VJ, Mabey DC. Global epidemiology and control of Trichomonas vaginalis. Lancet Infect Dis. 2011;11:1198–208.

112. Chen YC, Huang YL, Platz EA, Alderete JF, Zheng L, Rider JR, Kraft P, Shui IM, Kolb S, Hanson C, Sutcliffe S, Stanford JL. Trichomonas vaginalis in men. Clin Infect Dis. 2021;73:1119–24.

113. Saleh NE, Alhusseiny SM, El-Zayady WM, Aboelnaga EM, El-Beshbishi NA, Rakovskaya IV, Baker PS, Shyshynova I, Stephenson AJ, Klein EA, O'Malley P, Lewicki P, Ayangbesan A, O'Malley P, Barbieri RL. Mycoplasma genome with prostate cancer. Med Microbiol Immunol. 2019;202:425–30.

114. Wise GJ, Shteynshlyuger A. How to diagnose and treat fungal infections in chronic prostatitis. Curr Urol Rep. 2006;7:320–8.

115. Fogh-Anderson M, Raskin A, Furst P, Givens LA, Davidson HB, Sutcliffe S. Association between Trichomonas vaginalis infection and risk of advanced prostate cancer. Prostate. 2009;69:2046–51.

116. Russo G, Anzivino E, Fiorini D, Mischitelli M, Bellizzi A, Giordano A, Autran-Gomez A, Di Monaco F, Di Silvino F, Sale P, Di Prospero L, Pietropaolo V. β3 gene mutational rate, Gleason score, and BK virus infection in prostate adenocarcinoma. Is there a correlation? J Med Virol. 2008;80:2100–7.

117. Taghavi A, Mohammadi-Torbati P, Kashi AH, Rezaee H, Vaeejali M. Poliovirus hominis 1 (BK virus) Infection in prostatic tissues: cancer versus hyperplasia. Urol J. 2013;20:425–30.

118. Tawfik SS, Samir M, Amin MM, El-Kashif A, El-Naggar S. Comparative study of BK virus infection in prostate adenocarcinoma and benign prostatic hyperplasia. J Pathol. 2008;214:365–71.

119. Urbanek C, Goodison S, Chang M, Porvaski S, Sakamoto N, Li CZ, Boehein SK, Rosser CJ. Detection of antibodies directed at M. hyorhinis p37 in the serum of men with newly diagnosed prostate cancer. BMC Cancer. 2011;11:233.
147. de Bono JS, Guo C, Gurel B, De Marzo AM, Sfanos KS, Mani RS, Gil J, Drake CG, Allmont A. Prostate carcinogenesis: inflammatory storms. Nat Rev Cancer. 2020;20:455–69.

148. Göbel A, Dell’Endice S, Jaschke N, Pählig S, Shahid A, Hofbauer LC, Rachner TD. The role of inflammation in breast and prostate cancer metastasis to bone. Int J Mol Sci. 2021;22:5078.

149. Greten FR, Eckmann L, Greten TF, Park JM, Li ZW, Egan LJ, Kagnoff MF, Karin M. IKKbeta links inflammation and tumorigenesis in a mouse model of colitis-associated cancer. Cell. 2004;118:285–96.

150. Qiao Y, Yang T, Gan Y, Li W, Wang C, Gong Y, Lu Z. Associations between aspirin use and the risk of cancers: a meta-analysis of observational studies. BMC Cancer. 2018;18:288.

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