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The Microbiome and Prostate Cancer

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Abstract

There is growing evidence that the microbiome is involved in development and treatment of many human diseases, including prostate cancer. There are several potential pathways for microbiome-based mechanisms for the development of prostate cancer: direct impacts of microbes or microbial products in the prostate or the urine, and indirect impacts from microbes or microbial products in the gastrointestinal tract. Unique microbial signatures have been identified within the stool, oral cavity, tissue, urine and blood of prostate cancer patients, but studies vary in their findings. Recent studies describe potential diagnostic and therapeutic applications of the microbiome, but further clinical investigation is needed. In this review, we explore the existing literature on the discovery of the human microbiome and its relationship to prostate cancer.

Keywords

Prostate Cancer; Microbiome; Microbiota

Introduction:

In the human body, over thirty-eight trillion microbial organisms co-exist, predominantly in the aerodigestive tract, with smaller populations on other body sites [1][2]. These microbes, which include bacteria, viruses, archaea, protists, and fungi[3] are the microbiota[4] while the *microbiome* describes the sum of these organisms and genetic information. Multiple human microbiomes can be said to fill complex, organ-specific environmental niches and underlie interactions between endogenous microbes and the human body, frequently through the immune system[5], as well as mediating interactions with pathogens[6]

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Although studies of the human microbiome as an extension of the field of microbial ecology have been around for decades, only recently has appreciation of the impact of the microbiome and its potential associations with human diseases come to the forefront of medicine[7]. Microbiome-focused disease models have emerged to describe obesity, inflammatory bowel disease, psoriasis, reflux esophagitis, and colorectal carcinoma amongst others[4]. Similar data are appearing linking microbiomes with prostate cancer diagnosis and its treatment[7]. Interactions of various microbiomes with the prostate, which may associated with prostate cancer, may broadly be characterized using two distinct categories: direct and indirect[3]. The direct pathways involve the prostate tissue and urinary microbiomes; the indirect pathways involve the gastrointestinal tract, including the oral and fecal microbiomes[8], though evidence of prostate cancer-associated microbial signatures in blood may link indirect effects to other sites in the future[3].

In this review, we summarize published data on potential direct and indirect microbiome-based mechanisms of prostate cancer pathogenesis, diagnosis and implications for therapeutic targeting. The vast majority of this early work on the microbiome and prostate cancer focuses on surveying bacterial and viral species within the genitourinary tract with the goal of identifying natural and diseased microbiomes. Recent technological advances have enabled sequencing and data analysis of tissue biospecimens and blood.

In theory, alterations of the natural microbiome may lead to the development of prostate cancer. Chronic infections, viral genetic incorporation, and microbial metabolites could potentially influence prostate carcinogenesis[9], and the identification of relevant microbial genetic or metabolic signatures may lead to improved diagnostic capabilities and further influence treatment paradigms. While much of this data has not matured, this review will focus on the literature to date in this domain.

Methods

Literature search

The current literature review was performed with the aim to examine original research and reviews on the topic of the microbiome and prostate cancer. We performed a systematic search of PubMed. The search included only articles published from 01/01/1998 to 10/1/2020 in the English language. We searched for the following keywords: (prostate OR prostate cancer OR prostate neoplasm OR prostatic tumor OR prostatic carcinoma) AND (microbiome OR microbiota). We then performed a review of the titles and abstracts of the retrieved studies, and we further evaluated the full texts of studies that met our study selection criteria.

Study selection criteria

The articles were considered eligible if they met all of the following inclusion criteria: the study population included patients with suspected prostate cancer, a diagnosis of prostate cancer, and/or a diagnosis of benign prostatic hyperplasia with available microbiome data. See Figure 1 for further details on the number of studies included and excluded.

Prostate and Urinary Microbiome (Direct)

Prostate cancer remains amongst the most prevalent diseases in males, with a variety of treatment strategies and an unclear cause[10 11]. Over the last two decades, several studies have attempted to elucidate the microbiome of the prostate as well as its role in prostate cancer development. Advances in analytical and contamination control techniques have identified a potential natural tissue microbiome, and its dysbiosis may indicate a cause for prostate cancer. While much is still unclear, the following studies illustrate attempts to define species that make up the microbiome in patients with or without prostate cancer.

Bacteria

In an early prostate microbiome study from 2000[12], prostate tissue was collected from 27 patients and included: organ donors who were otherwise healthy men (n = 18 patients), radical prostatectomy specimens taken in the context of prostate cancer (n = 7 patients), and simple prostatectomy specimens in the context of benign prostatic hyperplasia (n = 2 patients). The authors performed 16S rRNA gene PCR on all of the specimens to identify the presence/absence of bacteria, and found no bacterial DNA in the organ donor controls further revealed a PCR detection sensitivity as little as six bacteria per 25 milligrams of prostate tissue. In contrast, there were bacteria in the radical and simple prostatectomy specimens, but the study did not perform sequencing to identify the species[12]. While this study had its limitations, this was an early identification of a potential prostatic microbiome in the setting of prostate pathology.

Several other studies have since evaluated the presence of a prostate microbiome and highlighted that the prostate is not a sterile organ. One study evaluated bacterial DNA in tumor tissue, peri-tumor tissue, and non-tumor tissue in 16 patients who underwent radical prostatectomy for prostate cancer[13]. Overall the authors noted that *Propionibacterium acnes*, now classified as *Cutibacterium acnes* species, was the most represented species of bacteria equally present in all tissues. *C. acnes* has a known role in pro-inflammatory pathways within prostate tissue in murine models[14], which some authors suggest could be associated with the development of prostate cancer[15]. However, one of the major limitations of this analysis was the use of a formalin-fixed paraffin-embedded (FFPE) medium, which has a high risk of contamination with other bacteria, and *C. acnes* is a well-known contaminant [7,16]. Amongst radical prostatectomy specimens analyzed, the authors did note differences, namely that there was a greater proportion of *Streptococcaceae* in non-tumor tissue compared to either peri-tumor tissue ($p<0.05$). They also found a greater proportion of *Staphylococcaceae* in peri-tumor or tumor tissue compared to normal tissue ($p<0.05$). It is hypothesized that the exclusive presence of *Streptococcus* in non-tumor tissue may indicate a normal microbiome of healthy prostatic tissue[13]. It is further speculated that bacteria such as *Streptococcus*, a member of the Lactobacillales order, may help maintain a beneficial ecosystem for the host environment. However, *Streptococcus* and *Staphylococcus* spp. are also among the most common bacteria on human skin and are frequent laboratory contaminants[17].

In a separate study of 65 patients who underwent radical prostatectomy, authors identified *Pseudomonas, Escherichia, Acinetobacter, and Cutibacterium* as being the most abundant

bacterial genera, however there was no difference from adjacent benign tissue[18], and as previously mentioned, these organisms are all common laboratory contaminants[17]. Sfanos *et al.* evaluated radical prostatectomy specimens and found bacterial DNA in prostate tissue, but when this was compared to core samples, the biopsies were negative. The authors hypothesized that this discrepancy could be attributed to the presence of focal microbiota or remnant bacterial DNA that has been "fossilized" in corpora amylacea[19]. Although they cite their finding as evidence that a true prostatic microbiome may not exist, other reports provide more convincing evidence for its presence.

More recent studies have examined the role of bacteria in prostate cancer not in terms of a natural flora, but rather as infectious agents. For example, sexually transmitted infections with a bacterial species such as *Chlamydia trachomatis* has been analyzed as a potential cause for prostate cancer[20]. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial found that the odds of developing prostate cancer were higher if men had any of the seven sexually transmitted infections [Chlamydia, Human Papilloma Virus (HPV)-16, HPV-18, Herpes Simplex Virus-2, Cytomegalovirus, Human Herpes Virus- 8, syphilis, or gonorrhea] compared to no infection (OR 1.3; 95% CI, 1.0–1.6, p=0.05)[21].

In another study, authors evaluated the presence of pathogens using the pan-pathogen microarray (PathoChip), which was designed from NCBI GenBank sequences, rather than prior studies that relied on assignment of putative taxonomic labels from DNA or RNA sequencing methods[22]]. In their study of 50 radical prostatectomy patients and 15 patients with BPH who underwent transurethral resection of the prostate[22], the authors identified a distinct pathogenic microbiome in prostatic cancer patients compared to normal tissue. One of the authors' major finding from this study is the detection of *Helicobacteri pylori* in greater than 90% of prostate cancer specimens. Specifically, they found integration of *H. pylori* cytotoxin-associated gene A (CagA) gene into the prostatic tumor DNA. Previous studies have shown that *H. pylori* can integrate itself within the human somatic chromosomes, and this may lead to deregulation of gene expression[23]. The CagA gene is the virulence factor of *H. pylori*[24] that has a known association with gastric cancer development[21] through the activation of proto-oncogenes and inactivation tumor suppressor genes[25]. Therefore, the authors concluded that integrating *H. pylori* DNA might play a role in prostatic cancer development. In contrast to this study, a second study found *H. pylori* in BPH specimens[26]. In a third study *H. pylori* was found in both BPH and prostate cancer specimens[27]. These studies demonstrate that significant controversy remains regarding the role of *H. pylori* and other pathogenic bacteria in prostate cancer development, but also highlight a lack of standardization in methods used for determining bacterial presence/absence, abundance and specificity. Further study with standardization of methods will be needed to define whether their role in cancerous tissue is causative, coincidental, or contamination[28].

The urinary microbiome within the context of prostate cancer is actively being explored, but data remain limited. The historical teaching is that urine is sterile, but several studies have indicated that the true urinary microbiome is underrepresented due to limitations in standard culture methods[29 30]. The origins of urine-residing microbiota also remain elusive and whether they originate in the urinary tract, such as in the kidney, bladder, or

prostate, or elsewhere[31]. In a recent study evaluating urine from men prior to prostate biopsy, the authors identified diverse bacterial populations using 16S rRNA gene amplicon sequencing, but there was no difference between benign and cancerous samples[32]. However, the authors found pro-inflammatory bacteria involved in a subset of prostate cancer patients[32], supporting an emerging hypothesis that pro-inflammatory bacteria may influence inflammation, urine reflux and prostate cancer[33]. As is the case for prostate tissue examinations, further studies are needed to clarify the involvement of urinary microbiome on prostate cancer.

Viruses

Viruses might be a component of the prostate microbiome, although they have remained an understudied component of the microbiome due to the emphasis on 16S rRNA gene amplicon sequencing and the high cost of shotgun metagenomics in the presence of high relative amounts of human DNA. However, specific viral associations have been examined. One of the original studies on this topic found cytomegalovirus in patients with prostatic intraepithelial neoplasia[34]. Several subsequent studies have identified BK Virus, polyomaviruses (JC virus), HPV, and Epstein Barr viruses in association with prostatic tumors[34–38] These findings were replicated in a subsequent study using PathoChip, described above[22]. The authors of this study detected HPV-18, Cytomegalovirus virus, Karposi Sarcoma associated herpes virus (KSH), Epstein Barr virus, BK virus, and JC virus in prostatic tumors[22]. Both HPV-18 and KSH viruses were also identified in BPH specimens within this study. Notably HPV-18 and KSH virus were determined to be the viruses that integrated the most into host chromosomes[22]. HPV-18 also has a known role in the development of squamous cell carcinoma and adenocarcinoma of the cervix, making its relationship to prostate cancer interesting[39]. However, it still remains uncertain whether or not these viruses are causative in their relationship to prostate cancer as these viruses were also found in BPH specimens and the time course of their tissue acquisition is unclear.

Combined microbial signatures of prostate cancer

In another recent publication, authors evaluated treatment naïve whole genome and whole transcriptome samples from 33 cancer types in The Cancer Genome Atlas (TCGA), including 830 samples of prostate adenocarcinoma. The authors found unique microbial compositions in tissue and blood samples amongst most cancer types, even after stringent statistical decontamination that discarded more than 90% of identified microbial reads and taxonomic information. The authors then validated these computational findings by verifying the ability to strongly discriminate between non-cancer, HIV-negative control subjects (n=69) and prostate cancer patients (n=59) solely using plasma-derived, cell-free microbial nucleic acids (area under ROC curve of 94.8%). Notably, the authors included more than 50 experimental contamination controls with positive, spike-in controls and negative blank controls in their validation study to ensure that findings in the plasma were not being driven by contamination. Such findings suggest a potential diagnostic opportunity using the microbiomes of prostate cancer patients[40].

As described above, specimen types, specimen collection techniques and analytical methods often vary between studies, but the approach of Poore *et al.* to normalize and compare data

across studies and sites shows promise for re-examining the role of multiple microbiomes in prostate cancer detection and development. Additional investigations underway will continue to provide opportunities for comparing these historic data with new datasets collected with contamination controls and standardized sample processing methods focused on microbial identification[17].

Microbiome of the Gastrointestinal Tract (Indirect)

The gastrointestinal tract microbiome impact on the development of prostate cancer has also been underexplored. In the evaluation of the fecal microbiome, a recent study evaluated rectal swabs prior to transrectal biopsy between 64 patients with prostate cancer and 41 patients without prostate cancer. The authors found mostly overlapping bacteria between the two cohorts, but a greater proportion of *Bacteroidetes* and *Streptococcal* species in prostate cancer patients[41]. These findings are supported by another study that evaluated feces in twelve patients with prostate cancer and eight patients with BPH and found that there was a higher proportion of *Bacteroidetes* in patients with prostate cancer[42]. The investigators of the first study also noted the association between carbohydrate metabolism pathways and natural B-vitamin production, specifically the production of arginine and folate were lacking in prostate cancer patients compared to non-cancer patients, although the significance of this remains unclear[41].

In contrast, another study where investigators compared 16S rRNA gene amplicon sequencing of rectal swabs before performing a biopsy and prior to antibiotic treatment found no separation of cancer from BPH patients[43]. However, this study found that the microbiome of paired urine samples did distinguish prostate cancer patients from those with BPH.

In another recent study, the authors evaluated murine prostate cancer models with a focus on elucidating the role of lipopolysaccharide (LPS). LPS, a major component of the outer membrane of Gram negative bacteria[44 45], has been studied in many human diseases for its role in promoting a non-specific, pro-inflammatory state by binding toll-like receptor 4 (TLR4), which causes upregulation of NF-κB and the release of inflammatory cytokines[45]. Increased NF-κB signaling has also been observed in prostate cancer[46], and this study found that LPS and/or LPS induced inflammation could cause an increase in prostate cancer metastasis[45].

Lastly, one study identified a potential link between oral microbiota and prostatic fluid in patients with concurrent prostatic and periodontal[8]. Specifically, twenty-four patients with chronic prostatitis or BPH underwent thorough periodontal examination and had combined subgingival plaque and prostatic fluid samples analyzed for bacterial DNA of *Prevotella intermedia*, *Prophyromonas gingivalis*, *Treoponema denticola* and *Escherichia coli* using RT-PCR. After finding that all patients had at least mild chronic periodontitis, the authors discovered that seventeen out of twenty-four patients (70.8%) had one or more oral bacteria in their prostatic fluid, with *Treoponema denticola* being found in nearly half of both subgingival and prostatic secretion samples. There are limitations of this study given its small sample size and lack of healthy controls, but it suggests potential bacterial movement

from the oral cavity to the prostate in the setting of periodontal pathology. Moreover, it remains unclear if there is a link between chronic prostatitis and prostate cancer. There have been no histological studies of these tissues nor have there been analysis of the role of prostatic secretions in prostate cancer development.

Collectively, conflicting conclusions of these studies and their limited sample sizes have made it challenging to ascertain the specific role of the gastrointestinal microbiome on prostate carcinogenesis and their time course.

Developing Therapeutic Applications

The gastrointestinal microbiota has a well-known effect on the metabolism and pharmacokinetics of drugs[47 48], but the connection between the gastrointestinal microbiota and prostate cancer therapy has not been thoroughly explored. Initial studies focused on elucidating the effects of androgen deprivation therapy (ADT) in murine models on shaping gut microbiota composition[49]. More recently, one study evaluated rectal swabs from 30 patients with BPH or prostate cancer (treated by ADT) and found significantly higher diversity in BPH controls compared to prostate cancer patients on ADT[29]. More specifically, the authors found increased relative abundance of *A. muciniphila* and *Ruminococcaceae* in men taking oral androgen targeted therapy (abiraterone acetate or enzalutamide) compared to those taking gonadotropin-releasing hormone (GNRH) agonist/antagonist without concurrent abiraterone or enzalutamide. The authors also found that the species of bacteria present were capable of steroid/hormone biosynthesis and could potentially influence treatment response. However, the study did not correlate treatment type with the patients' clinical outcomes and the therapeutic significance of their findings remain uncertain[29]. Although the authors noted the association of *A. muciniphila* in the gut and anti-PD-1 immunotherapy response[50], immunotherapy is not currently approved for use in prostate cancer.

The significance of *A. muciniphila* was further explored in later study. Authors performed 16S rRNA amplicon sequencing on fecal samples collected from 68 patients with prostate cancer who were receiving systemic ADT alone, systemic ADT and oral abiraterone acetate (AA), or no treatment[51]. The authors found that ADT alone or ADT+AA administration depleted *Corynebacterium* species that relied on androgens for growth while ADT+AA shifted the fecal microbiome toward higher populations of *A. muciniphila*. Further experiments revealed that AA alone could promote *A. muciniphila* growth in pure culture, but AA alone was not sufficient as a carbon source. Collectively, these results suggested that oral AA administration provided a useful fuel for gut-inhabiting *A. muciniphila* that selectively stimulated its growth in prostate cancer patients. Additionally, the authors determined that vitamin K2 biosynthesis related pathways were consistently increased in AA-exposed gastrointestinal samples[51]. Vitamin K2 is a prospective anti-cancer agent that has been shown to inhibit androgen-dependent and independent tumor growth in murine models[52]. These findings suggest that part of AA's efficacy in castrate-resistant prostate cancer may derive from increased vitamin K2 synthesis through a symbiotic relationship with *A. muciniphila,* although an interventional trial clinical trial showing enhancement of AA with *A. muciniphila* dosing remains to be shown. Nevertheless, this study raises interest

in further investigating the microbiome of castrate-resistant prostate cancer patients and the potential role of strain-specific probiotics in these patients.

Finally, a recent study that evaluated sera from patients on ADT and a low carbohydrate diet found that ADT use was associated with a reduction in 3-formyl indole, which is a microbiota derived metabolite from tryptophan that reduces steroid synthesis[53]. This metabolite is known to regulate mucosal reactivity and inflammation[54]. Therefore, downregulation of 3-formyl indole via restricted ketogenic diets may improve the therapeutic impact of ADT. Further study is needed to examine the role of microbiota and their metabolites on the effects of treatment.

Conclusion

The relationship of the microbiome to prostate cancer is still emerging and the studies presented here often present conflicting information, highlighting the need for additional work with standardized methods and appropriate contamination controls[17]. Nonetheless, recent work demonstrating that ~1.5% of sequencing reads were of microbial origin in normal and cancerous prostate tissue from TCGA, paired with the ability to use these reads to distinguish healthy and tumor tissue after correcting for technical variables and decontamination, strongly suggests the presence of a prostate cancer microbiome[40]. Additional work is still needed to examine the causal impact, if any, of these microbes and their potential role in carcinogenesis and treatment. The interaction between the urinary microbiome and the prostate is even more challenging to explore due to complexity of sampling bias and determining which organisms interact with the prostate, but new studies with better sampling procedures may be able to address these issues. Likewise, standardized sampling with frequent contamination controls and evaluation of multiple microbiomes (tissue, urine, blood, feces) will be needed to draw strong conclusions and resolve contradictory findings.

Future studies will be strengthened by correlating microbiome data with patient outcomes. If the microbiome does play a role in the development of prostate cancer, then alteration of the microbiome through the diet may provide a powerful way to aid prostate cancer prevention and treatment. Expanding the scope of research to microbial metabolites may also prove successful, with a recent report demonstrating how a single microbial metabolite can change the phenotype of common TP53 mutations[9]. Furthermore, a systemic approach might be necessary to identify microbiome's influence on prostate cancer as simpler methods such as Koch's postulates might not establish causality[55]

In conclusion, the microbiome may play an important role in prostate cancer diagnosis, development, and treatment, and further study will be needed to elucidate these processes.

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Key Points:

- The microbiome of the prostate has at least three contributory pathways: prostate tissue, urine (direct) and the gastrointestinal tract (indirect).
- Investigation into the makeup of these microbiomes has yielded conflicting results and an unclear role in the development of prostate cancer, possibly due to differences in methodology among studies.
- Therapeutic applications of the microbiome in the treatment of prostate cancer is understudied and being investigated.
- Advances in sampling techniques and analytic methods, and use of consistent laboratory and computational methods, offer promising opportunities to further define the microbiome and its relationship to prostate cancer.

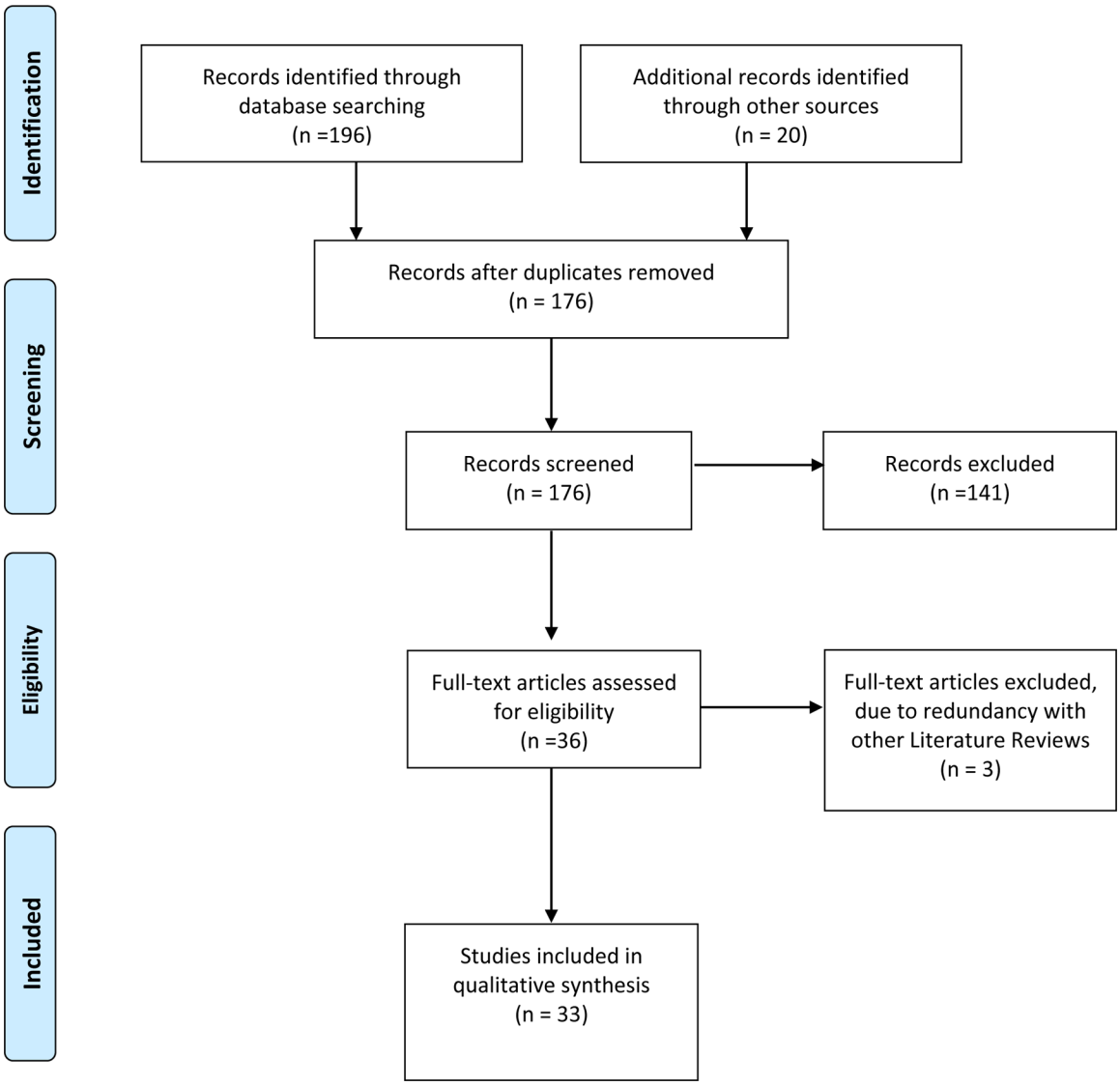

Figure 1:
Article Selection Flow Diagram