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2022 Update on Prostate Cancer Epidemiology and Risk Factors —A Systematic Review

Oskar Bergengren[a,b,*], **Kelly R. Pekala**[a], **Konstantina Matsoukas**[c], **Jonathan Fainberg**[a], **Sean F. Mungovan**[d], **Ola Bratt**[e], **Freddie Bray**[f], **Otis Brawley**[g,h], **Amy Luckenbaugh**[i], **Lorelei Mucci**[j], **Todd M. Morgan**[k], **Sigrid V. Carlsson**[a,e,l]

[a]Department of Surgery (Urology Service), Memorial Sloan Kettering Cancer Center, New York, NY, USA

[b]Department of Surgical Sciences, Uppsala University, Uppsala, Sweden

[c]Medical Library, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[d]Westmead Private Physiotherapy Services and The Clinical Research Institute, Westmead Private Hospital, Sydney, Australia

[e]Department of Urology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

[f]Cancer Surveillance Branch, International Agency for Research on Cancer, Lyon, France

[g]Department of Oncology, Johns Hopkins School of Medicine, Baltimore, MD, USA

[h]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

[i]Vanderbilt University Medical Center, Nashville, TN, USA

[*]Corresponding author. Department of Surgery (Urology Service), Memorial Sloan Kettering Cancer Center, New York, NY, USA. Tel. +1 3472589684. oskar.bergengren@surgsci.uu.se (O. Bergengren).

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Study concept and design: Bergengren, Matsoukas, Morgan, Carlsson.

Acquisition of data: Bergengren, Pekala, Matsoukas, Fainberg, Mungovan, Bratt, Bray, Brawley, Luckenbaugh, BT, Morgan, Carlsson.

Analysis and interpretation of data: Bergengren, Pekala, Matsoukas, Fainberg, Mungovan, Bratt, Bray, Brawley, Luckenbaugh, BT, Morgan, Carlsson.

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[j]Harvard T.H. Chan School of Public Health, Boston, MA, USA

[k]Department of Urology, University of Michigan, Ann Arbor, MI, USA

[l]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Abstract

Context: Prostate cancer (PCa) is one of the most common cancers worldwide. Understanding the epidemiology and risk factors of the disease is paramount to improve primary and secondary prevention strategies.

Objective: To systematically review and summarize the current evidence on the descriptive epidemiology, large screening studies, diagnostic techniques, and risk factors of PCa.

Evidence acquisition: PCa incidence and mortality rates for 2020 were obtained from the GLOBOCAN database of the International Agency for Research on Cancer. A systematic search was performed in July 2022 using PubMed/MEDLINE and EMBASE biomedical databases. The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines and was registered in PROSPERO (CRD42022359728).

Evidence synthesis: Globally, PCa is the second most common cancer, with the highest incidence in North and South America, Europe, Australia, and the Caribbean. Risk factors include age, family history, and genetic predisposition. Additional factors may include smoking, diet, physical activity, specific medications, and occupational factors. As PCa screening has become more accepted, newer approaches such as magnetic resonance imaging (MRI) and biomarkers have been implemented to identify patients who are likely to harbor significant tumors. Limitations of this review include the evidence being derived from a meta-analysis of mostly retrospective studies.

Conclusions: PCa remains the second most common cancer among men worldwide. PCa screening is gaining acceptance and will likely reduce PCa mortality at the cost of overdiagnosis and overtreatment. Increasing use of MRI and biomarkers for the detection of PCa may mitigate some of the negative consequences of screening.

Patient summary: Prostate cancer (PCa) remains the second most common cancer among men, and screening for PCa is likely to increase in the future. Improved diagnostic techniques can help reduce the number of men who need to be diagnosed and treated to save one life. Avoidable risk factors for PCa may include factors such as smoking, diet, physical activity, specific medications, and certain occupations.

Abstract

Prostate cancer remains the second most common cancer among men. Screening is gaining acceptance, likely reducing mortality at the cost of overdiagnosis and overtreatment. Increasing use of magnetic resonance imaging and biomarkers may mitigate some of the negative consequences of screening.

Keywords

Prostate cancer; Epidemiology; Screening; Risk factors

1. Introduction

Prostate cancer (PCa) is one of the most common cancers worldwide, accounting for a large proportion of all cancer-related deaths [1,2]. Understanding the epidemiology and risk factors of the disease is of paramount importance. Identifying risk factors for the development of PCa is key to targeting primary and secondary prevention.

Age, race, family history, and germline mutations are well-established nonmodifiable risk factors for PCa, and metabolic syndrome, obesity, and smoking have been identified as possible modifiable risk factors [3]. In addition, an abundance of environmental, lifestyle, infectious, and dietary risk factors may play a role in the etiology of PCa, although the supporting evidence is generally weak [3].

In this update and systematic review, we aim to present and summarize contemporary evidence on the epidemiology of PCa, including modifiable and nonmodifiable risk factors for the disease, screening recommendations, and strategies to optimize screening.

2. Evidence acquisition

The International Agency for Research on Cancer (IARC) compiles and disseminates the estimates of the number of new cases of PCa and corresponding PCa deaths for 185 countries in the year 2020 as the GLOBOCAN database [4]. These were visualized geographically as age-adjusted incidence and mortality rates, standardized to the world standard population, using graphics available on IARC's Global Cancer Observatory [5].

We conducted a systematic literature search in July 2022 using PubMed/MEDLINE and EMBASE biomedical databases to identify publications in English from the past 5 yr (Supplementary material). Published search hedges were applied to filter the search results to systematic reviews, meta-analyses, consensus statements, and guidelines. Comments, letters, editorials, meeting abstracts, and conference proceedings were excluded. Two reviewers (O.B. [Memorial Sloan Kettering Cancer Center] and K.R.P.) independently reviewed the titles and abstracts, facilitated by the software Covidence. Conflicts were discussed between reviewers, and if consensus could not be reached, it was resolved by a senior author (S.V.C.). Manuscripts then underwent full-text review to determine eligibility for inclusion and were categorized by section. One reviewer independently extracted the findings, and a second reviewer verified the extracted data. As this is an umbrella review of many publication types—most of which were already individually assessed for quality—no formal quality appraisal of the included manuscripts was performed.

The review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [6] and was registered a priori in PROSPERO (CRD42022359728).

3. Evidence synthesis

A total of 334 studies were included in the review and organized by section (Fig. 1, PRISMA flow diagram).

3.1 Epidemiology

3.1.1. PCa incidence—PCa is the most frequently diagnosed cancer among men in more than half of the countries in the world (112 of 185 countries/territories), with an estimated 1.4 million new cases in 2020. The highest age-standardized incidence rates are seen in Northern and Western Europe, the Caribbean, Australia/New Zealand, North and South America, and Southern Africa (Fig. 2).

3.1.2. PCa mortality—PCa is the leading cause of cancer death among men in a quarter of the world's countries (48 of 185 countries), with an estimated 375 000 deaths in 2020. The highest age-standardized mortality rates are seen in the Caribbean (Barbados, Jamaica, and Haiti), parts of South America, and sub-Saharan Africa (Fig. 3). Global differences in PCa incidence and mortality can be attributed to differences in screening, imaging, access to care, and healthcare infrastructure [1,7]. In addition, there are emerging data to suggest that differences in germline genetic factors as well as lifestyle factors across populations may underlie geographic differences. PCa when diagnosed and treated at localized stages has a 97% 5-yr cancer-specific survival compared with 30% in the metastatic setting.[7]

3.1.3. Racial and ethnic disparities—In the USA, Black or African American men are 1.7 times more likely to be diagnosed with PCa than White men and 2.1 times more likely to die of the disease [7]. Reasons for this observation are unclear, given that race is a social construct. Underlying factors for this could include genetics associated with ancestry/geographic origin, environmental factors, or social determinants of health [8,9].

To elucidate the underlying causes of PCa as well as existent healthcare disparities, methods of categorizing populations can be helpful. Ancestry is one way of categorizing populations, as genetic traits can be passed down from one generation to another. Area of geographic origin is another way of categorizing populations. There are some known genetic traits that correlate with the area of geographic origin [10,11]. Assessment by the area of geographic origin is also complicated by admixture.

Race is a categorization of populations that may rely on a combination of ancestry, skin color, facial traits, and area of geographic origin. Within any one race, there are hundreds of areas of geographic origin [12]. In the USA and Europe, race as used today is a complex sociopolitical construct. Contrary to popular belief, race is not a biological categorization related to inherent biological traits.

Aspects often associated with certain races such as social deprivation, culture, and diet can influence biology and risk of disease, response to treatment, and risk of poor outcome. In the USA, African-American race generally correlates with a population more likely to be socioeconomically underprivileged. Social deprivation can lead to environmental exposures

that increase the risk of some diseases including cancer. Social deprivation is closely linked to reduced access to quality health care [13–15].

The precise reasons for the higher incidence of PCa among Black and African American men are unknown, but it appears to be related more to genetic ancestry rather than race [16]. There is the suggestion of an increased risk of PCa among men with ancestry from northwestern sub-Saharan Africa, and it may be due to the higher prevalence of certain genetic factors [17]. It may also be due to environmental influences leading to inflammation and subsequent carcinogenesis [18].

Even though Black men are at a higher risk of developing the disease, there are substantial data to show that when Black and White men are diagnosed with similar grade and stage of PCa and are treated equally in equal-access healthcare systems, they have equivalent outcomes [19–21]. However, Black men are often diagnosed with more aggressive PCa. Using the National Cancer Database, a cancer registry drawing incidence and mortality data from a group of American cancer-accredited facilities, Black men with high-grade, localized PCa treated with radical prostatectomy had 50% higher mortality than White men (hazard ratio [HR] 1.51 [95% confidence interval {CI} 1.47–1.56]) [22]. Owing to social influences, the Black or African American population, in general, has a higher prevalence of comorbidities that can complicate treatment [19]. When adjusting for socioeconomic parameters and comorbidities, the disparity was reduced to 20% greater than that for White patients [22]. The coarse adjustment made here removed much of the disparity in mortality; however, it is rarely possible to fully adjust for socioeconomics and comorbidities.

3.1.4. Transgender—

Three systematic reviews evaluated the risk of PCa in the transgender population receiving gender-affirming hormones. None of the studies found an increased risk of PCa. However, evidence is limited, and more long-term studies are needed. In the absence of evidence, transgender individuals with a prostate may be offered screening similarly to cis-gender males [23–25].

3.2. Risk factors

3.2.1. Nonmodifiable risk factors

3.2.1.1. Age: Age is a well-established risk factor for PCa. Recent US cancer statistics indicate that the probability of PCa increases from 1.8% in men 60–69 yr to 9.0% in men 70 yr and older for a lifetime probability of 12.5% [7]. Autopsy studies reveal that 40% of unscreened men older than 60 yr harbor PCa; this increases to 60% in men older than 80 yr. Notably, 32% of these cancers were of International Society of Urological Pathology grade group ≥2 [26].

3.2.1.2. Family history: Family history of PCa is well established as a risk factor for PCa incidence and may also increase the risk of fatal forms of PCa. However, determining the association between reported family history and PCa risk can be challenging, given family status, recall bias, and degree of screening. The risk of PCa is influenced by the number of afflicted relatives, closeness of the relative (ie, first degree vs second degree [27]), the family member's age at diagnosis and age at death from PCa, high-grade disease, and other

cancers (eg, breast or ovarian). Brothers and sons of men with PCa have approximately a 2.5-fold increased risk of being diagnosed with PCa [28], and there is evidence that a PCa family history increases the risk of fatal disease. A family history of high-grade or metastatic disease increases the risk of a similarly severe PCa more than a family history of low-grade, nonmetastatic disease [29,30]. A recent systematic review and meta-analysis showed that having a first-degree relative with breast cancer is associated with a 1.2-fold increased risk of PCa [31]. Recent data from the UK Genetic Prostate Cancer Study showed that a stronger family history was inversely associated with PCa mortality, attributable to greater awareness of screening and PCa among those with a familial risk [32]. Other studies have suggested the opposite, and so the context of family history and what it means need to be taken into account.

3.2.1.3. Genetic predisposition/germline variants: Twin studies suggest that PCa is more genetically heritable than other common cancers, with an estimate of heritability of 58% [33,34]. As with other cancers, genetic susceptibility can be classified into genetic factors with a low prevalence but high penetrance, and those with a higher prevalence but generally lower penetrance. The two most common alleles that confer autosomal dominant susceptibility to PCa are mutations in the *HOXB13* and *BRCA2* genes [35–37]. Still, the prevalence of these mutations in the general population is around 0.3%. There is increasing evidence of mutations in several DNA repair pathway genes, such as *BRCA1*, *ATM*, *CHEK2*, *NBS1*, and genes involved in Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) are associated with PCa risk, with a higher prevalence in metastatic versus localized PCa; however, the associations with PCa incidence and disease aggressiveness are variable [35,38–40]. In a study of over 21 000 men from the UK Biobank, 1.4% carried a rare pathogenic mutation in at least one of the following three genes: *BRCA2, HOXB13*, and *CHEK2* [41]. While rare in the general population and among patients with low-risk PCa, the prevalence of germline genetic mutations in DNA repair pathways is 10–20% in patients with advanced PCa.

A larger proportion of the underlying heritability in PCa can be explained through common genetic single nucleotide polymorphisms (SNPs) [42]. In multiethnic populations, genome-wide association studies in large international consortia have now validated 269 individual SNPs, each of which is associated with a PCa risk [43]. While each SNP contributes little to a man's risk of developing PCa, the additive effects of multiple alleles are substantial when weighted and summed into polygenic risk scores (PRSs) [42–47]. Indeed, a higher PRS is associated with a substantially increased risk of incident PCa of any grade [48,49]. While the PRS is not able to differentiate between indolent and aggressive disease, that is, it is not prognostic, the PRS is associated with a higher risk of fatal PCa because it increases the overall risk [42,50]. Addition of a PRS to prostate-specific antigen (PSA) does not appear to contribute additional risk stratification [42].

3.2.1.4. Baldness: Four meta-analyses evaluated the relationship between male pattern baldness and PCa [51–54]. None of these studies found a relationship between overall male pattern baldness and the risk of PCa. However, in subgroup analyses, the meta-analyses found an association between vertex pattern baldness and an increased risk of PCa.

3.2.1.5. Height: Taller height is consistently associated with an increased risk of overall and high-grade PCa [55]. The potential mechanism underlying this association may be related to the levels of insulin-like growth factor during puberty.

3.2.2. Modifiable risk factors

3.2.2.1. Physical activity and sleep: There was no clear increased risk of PCa among those with sedentary behavior in multiple studies [56,57]. However, those with the highest versus lowest level of physical activity had a lower risk of PCa-specific mortality [58,59] and, among patients, longer cancer-free survival from PCa [60]. The inverse association is seen for both vigorous forms of physical activity as well as brisk walking. Most studies have focused on leisure time and recreational physical activity, whereas the effects of occupational physical activity are less established [58]. Long-term occupational physical activity may reduce PCa risk [59].

There does not appear to be an impact of sleep duration on the overall risk of PCa [61]. However, there are some studies that have found an association between sleep quality and risk of aggressive PCa [62].

3.2.2.2. Dietary intake

3.2.2.2.1. Specific diets—Mediterranean, vegetarian, semivegetarian, plant based: A Mediterranean diet was found to have a weak protective association for overall PCa among those with the highest adherence (relative risk [RR] 0.96, 95% CI 0.92–1.00), while another study found no association [63,64]. Vegetarians had a lower risk of PCa than meat eaters (HR 0.57, 95% CI 0.43–0.76) [65]. This was seen in other studies that demonstrated either mild protection or no association with plant-based, vegetarian, pesco-vegetarian, or semivegetarian diets [66,67]. In interventional studies, a plant-based diet showed positive results on short-term oncological outcomes among men with PCa [66].

3.2.2.2.2. Inflammatory and hyperinsulinemic diets: A proinflammatory diet defined by a high Dietary Inflammatory Index [68] is a risk factor for the development of PCa. Five studies evaluated a possible association, all of which found a positive association (ranging between odds ratio [OR] 1.31, 95% CI 1.04–1.57) and RR 1.74, 95% CI 1.24–2.43 for the highest vs lowest Dietary Inflammatory Index) [69–73]. Additionally, a hyperinsulinemic and inflammatory diet may be associated with an increased risk of aggressive PCa [74,75].

3.2.2.2.3. Macronutrients (protein, carbohydrates, and fat): There was no association between overall protein intake and PCa risk [76,77]. On further investigation of protein intake, for dairy protein, an increased PCa risk was found (for men who consumed ≥30 g/d, RR 1.08, 95% CI 1–1.16). This was dose dependent, and with every 20 g/d increase in dairy protein, there was a pooled RR of 1.1 (95% CI 1.02–1.20). No increased risk was found for animal protein or plant-based protein [77].

Several studies have evaluated carbohydrate intake as a possible risk factor for PCa. Results were mixed, with two studies evaluating sugar-sweetened beverages finding an increased

risk [78,79] ,while studies evaluating Glycemic Index or glycemic load found no or only weak associations [80–83].

Trans fatty acid intake, which are commonly found in the production of ultraprocessed food, was associated with an increased PCa risk (OR 1.49, 95% CI 1.13–1.95) [84].

3.2.2.2.4. Specific food intake (eg, meat, dairy, and tomato): No associations were found for total fruit and vegetable intake and the risk of PCa [85,86]. Several articles assessed a possible association between red meat, processed meat, and total meat consumption [65,87–91]. Almost all found a positive association between meat consumption and PCa risk. However, associations were generally weak and mainly for processed meat [86–89]. No associations were found for fish consumption and fish-derived omega-3 fatty acid intake (both dietary and supplement) [86,92–94].

There were multiple studies on dairy consumption [95–99]. An umbrella review found an increase in PCa risk for dairy milk (RR 1.11, 95% CI 1.03–1.21) and an increased risk of PCa mortality (RR 1.50, 95% CI 1.03–2.17) [95]. The risk for fermented dairy milk products and yogurt may be similar to that of dairy milk [96].

Tomato, high in lycopene, as a protective factor for PCa has been debated extensively. Results were inconclusive: one meta-analysis as well as a systematic review pointed toward a protective effect [100–102], while a recent meta-analysis including only prospective studies showed no association [103].

Phytoestrogens are found in foods such as soybeans, lentils, tofu, peanuts, chickpeas, and kidney beans. One meta-analysis examined specific phytoestrogen subclasses and found that daidzein, genistein, and glycitein were possible protective factors [104]. Another meta-analysis found that soy was associated with a decreased risk of PCa (RR 0.71, 95% CI 0.58–0.85) [105]. One meta-analysis found a decreased PCa risk in men with high consumption of legumes, also high in phytoestrogens (RR 0.85, 95% CI 0.75–0.96) and with a 3.7% reduction in the risk of PCa with each 20 g increment of legume intake per day [106]. Another study evaluated circulating isoflavones and lignans and PCa risk, and found large differences based on population (Japan vs Europe) with a significant protective effect for Japanese men with high concentrations [107].

Tea consumption was evaluated as a possible protective factor; however, results were inconsistent, and no clear association was seen [86,108,109]. An umbrella review [110] and multiple meta-analyses [111,112] confirmed that coffee consumption was a probable protective factor for the development of localized PCa (RR 0.90, 95% CI 0.85–0.95) [110]; however, there was no association with advanced or fatal disease [110,112]. The most recent well-conducted large prospective study found no evidence of an association [113], so the effect is likely weak, if present (Table 1).

3.2.2.2.5. Alcohol: Alcohol intake did not appear to increase overall or aggressive PCa risk in most studies [86,114,115].

3.2.2.2.6. Smoking: The majority of epidemiology studies have found no association between cigarette smoking and overall PCa for smokers [86] or for those who used waterpipe tobacco (OR 7.0, 95% CI 0.9–56.9) [116]. However, previous reports have shown that smoking may be associated with an increased risk of lethal PCa [117,118], including a recent meta-analysis of cohort studies that found current smokers had an RR of 1.42 (95% CI 1.20–1.68) compared with nonsmokers [119]. There was an increased risk of PCa mortality for those who used smokeless tobacco (eg, snuff; OR 2.1, 95% CI 1.1–4.1) [120].

3.2.2.3. Diseases and treatments

3.2.2.3.1. Circumcision: A systematic review and random-effect meta-analysis found that circumcised men had a decreased risk of PCa (OR 0.87, 95% CI 0.76–1) [121], possibly due to differences in sexually transmitted infections and penile microbiome. However, circumcision patterns vary widely based on geographic and cultural norms.

3.2.2.3.2. Infertility and vasectomy: Four systematic reviews evaluated infertility and subfertility as a risk for PCa [122–125]. These were limited by substantial heterogeneity in study design, definitions of infertility, and limited length of follow-up. Both meta-analyses found a significant association between infertility and subfertility, and PCa (OR 1.65, 95% CI 1.17–2.40 [122] and OR 1.48, 95% CI 1.05–2.08 [125], respectively) compared with fertile men.

Multiple meta-analyses evaluated a possible association between vasectomy and PCa with varying results [126–130]. There was a weak significant association for any or localized PCa [128,129]; however, there was no association with high-grade PCa or PCa-specific mortality in studies that controlled for bias [128–130].

3.2.2.3.3. Prostatitis and prostate size: Several studies found a possible increased risk between prostatitis and PCa [131–134]. However, there was significant heterogeneity among included studies and definitions of prostatitis. In one analysis, there was a positive association (OR 2.05, 95% CI 1.64–2.57); however, this association disappeared when including only studies that had the most rigorous analyses to limit the detection bias (OR 1.16, 95% CI 0.77–1.74) [134]. Increasing prostate size was associated with a decreased PCa risk [135].

3.2.2.3.4. Autoimmune diseases—Sjogren's syndrome and systemic lupus erythematous: Sjogren's syndrome was associated with an overall increase in PCa risk and an increased standardized incidence ratio (SIR) of PCa 1.50 (95% CI 1.02–2.22) [136]. Systemic lupus erythematous was not associated with the risk of PCa [137,138].

3.2.2.3.5. Periodontitis: A possible association between periodontal disease and PCa was evaluated in five meta-analyses, all of which found a positive association [139–143]. However, the method of diagnosis of periodontal disease varied among included studies. The authors stated potential genetic predisposition to PCa or bacterial and viral pathogens to be responsible for the increased risk.

3.2.2.3.6. Inflammatory bowel disease: Seven studies evaluated whether men with inflammatory bowel disease (Crohn's disease and ulcerative colitis) had an increased risk of PCa [144–150]. Results were mixed; three studies found a slightly increased risk, whereas two studies found no increased risk. In the subgroup of men with ulcerative colitis, results were more consistent with a clear association (SIR 1.58, 95% CI 1.08–2.30) [147].

3.2.2.3.7. Metabolic syndrome, nonalcoholic fatty liver disease and obesity, and elevated body mass index: Three meta-analyses evaluated a possible association between metabolic syndrome and PCa [151–153], and results were mixed. Two studies found a positive weak association. However, when looking specifically at men with higher-grade disease, a stronger association was found.

Similarly, seven studies evaluated a possible association between obesity and PCa [154–160]. No association was found regarding the overall risk of PCa, but several studies reported an increased risk of aggressive PCa (OR 1.06, 95% CI 1.00–1.12) [157]. One review article assessed the impact of body composition on PCa and found that a higher whole-body fat mass was associated with a lower risk of PCa [159].

Two studies evaluated a possible association between nonalcoholic fatty liver disease as the manifestation of metabolic syndrome in the liver and PCa. Results varied, and one meta-analysis that included more studies found no association [161], while a second meta-analysis found a weak positive association with the overall risk of PCa [162].

3.2.2.3.8. Type 2 diabetes, hyperglycemia, and high glycemic index: It has been suggested that type 2 diabetes is associated with a lower risk of PCa; however, results are mixed and it is unclear whether causal relationship exists [163–165]. Further, in the most updated meta-analysis, there was no association with PCa risk [166]. The studies that evaluated the impact of hyperglycemia, high glycemic index, and prediabetes were inconclusive [83,167].

3.2.2.3.9. Solid organ transplants: A meta-analysis that evaluated prospective observational studies of renal transplant recipients found an increase in the overall cancer risk but no association with PCa risk [168]. Another study evaluated the PCa risk in solid organ transplant recipients who were on immunosuppression and found no association with PCa risk [169].

3.2.2.3.10. Other medications: Multiple studies evaluated commonly used medications for patients with type 2 diabetes, and found no association between the use of metformin, thiazolidinediones, sulfonylureas, insulin, or dipeptidase-4 inhibitors and the risk of PCa [170–174].

Regarding hypertension medications, there was no association between PCa risk and the use of angiotensin converting enzyme inhibitors, angiotensin receptor blockers, diuretics, antiadrenergic agents, or beta-blockers [175,176]. Multiple studies identified an increased risk of PCa associated with calcium channel blocker use [175,177], whereas others found no association [176,178]. On subgroup analyses, some studies found an increased risk with

longer durations of use [177] or longer follow-up [178], but this was not found in all studies [179].

No association was found between allopurinol [180] or acid suppressive use [181] and overall PCa.

3.2.2.4. Environmental and occupational factors

3.2.2.4.1. Specific environmental and chemical exposures: Two reviews and meta-analyses evaluated the risk of PCa among men exposed to asbestos. Results varied, and one article found no association [182], while the other found a weak association (effect size 1.10, 95% CI 1.05–1.15) [183]. No association was found for mixtures of persistent, bioaccumulative, and toxic chemicals; permethrin (a broad-spectrum insecticide); or work stress [184–186]. There was a possible positive association with cobalt exposure and hexavalent chromium [187,188].

3.2.2.4.2. Occupational factors: An increased risk of PCa was found among firefighters (RR 1.15, 95% CI 1.05–1.27) [189] and police workers (RR 1.14, 95% CI 1.02–1.28) [190]. However, there was significant heterogeneity among included studies and a probable higher rate of PSA testing in these populations. Additionally, there was an increased risk among workers with occupational chemical and pesticide exposures such as agricultural workers (SIR 1.06, 95% CI 1.01–1.12) [191] and petroleum workers (effect size 1.13, 95% CI 1.05–1.22) [192]. Increased occupational physical activity appeared to decrease PCa risk, possibly explaining the reduced risk seen in occupations such as those of coal miners [193,194]. There was an increased risk of PCa for shift work, specifically rotating shifts and rotating night shifts, but no increased risk of PCa for night shift work alone, except for men in Asian countries [195–198]. Possible mechanisms include unnatural light/melatonin suppression, disruption in circadian rhythm, and lifestyle factors [197].

3.2.2.5. Sexual activity: Older age at first intercourse was associated with a reduced risk of PCa (OR 0.96, 95% CI 0.92–0.99), and every ten female sexual partners were associated with an increased risk of PCa (OR 1.10, 95% CI 1.01–1.21) [199]. By contrast, men with >21 ejaculations per month had a reduced risk of both overall and aggressive PCa (OR 0.78, 95% CI 0.61–1.00 and OR 0.75, 95% CI 0.57–0.99, respectively) [200] and men with moderate ejaculation frequency (two to four times per week) had a lower risk of PCa (OR 0.91, 95% CI 0.87–0.96, $p < 0.001$) [199].

3.2.2.6. Infectious agents: A positive association between human papilloma virus (HPV) and overall PCa was demonstrated in multiple studies [201–204]. The risk of PCa was highest for men with HPV-16 (OR 1.38, 95% CI 1.16–1.64, $p < 0.01$) [201,204]. There may be an association between *Neisseria gonorrhea*, herpes simplex 1 and 2, Epstein-Barr virus, and *Mycoplasma*, and PCa, but results were conflicting [205]. Meanwhile, there was no association between hepatitis C virus infection [206], *Trichomonas* [207], *Cytomegalovirus*, *Chlamydia*, polyoma viruses, human immunodeficiency virus, and fungi, and overall PCa [205].

3.2.2.7. Marital status: Single men had an increased risk of high-grade PCa compared with married men (OR 1.21, 95% CI 1.00–1.50) [208]. Men who were widowed had an increased risk of PCa compared with men who were married or had a partner (OR 1.19, 95% CI 1.03–1.35) and more often had advanced disease at the time of diagnosis [208].

3.3. Primary prevention/chemoprevention

3.3.1. 5-Alpha reductase inhibitors—There is high-level evidence including randomized trials assessing the association between 5-alpha reductase inhibitors and PCa risk. One recent systematic review and meta-analysis [209] reported an approximate 30% reduction in the risk of PCa (OR 0.70, 95% CI 0.51–0.96), but a two-fold increase in the risk of high-grade disease (OR 2.10, 95% CI 1.85–2.38) associated with finasteride. Similar effect sizes have been reported with dutasteride [210]. Overall, the majority of studies assessing these drugs have shown a lower risk of overall, low-risk, and intermediate-risk PCa, but an increased rate of detection of high-grade disease [211]. However, studies that have examined 5-alpha reductase inhibitors and lethal PCa have found no association in populations with access to care and regular screening [212,213].

3.3.2. Anti-inflammatories—Consistent aspirin use has been found to be associated with a lower risk of development of PCa [214]. Regular aspirin use significantly reduced the risk of PCa (RR 0.92, 95% CI 0.86–0.98) [215,216]. Similarly, in a meta-analysis of 43 observational studies, long-term use of nonsteroidal anti-inflammatories was found to be protective against PCa (RR 0.88, 95% CI 0.79–0.99) [217].

3.4.3. Statins—The impact of statin use on the development of PCa remains controversial, although studies suggest that statins may lower the risk of aggressive PCa and, in patients, may reduce mortality. In one meta-analysis, statins were associated with a 12% reduction in the risk of overall PCa (RR 0.88, 95% CI 0.84–0.93) [218]. Another meta-analysis found statin use to be associated with a lower risk in advanced PCa, but found no impact of statins on localized disease [219]. A recent review meta-analysis found a lower risk of PCa with higher dose and duration of statin use [220]. By contrast, other studies have found limited to no association between statin use and the overall incidence of PCa [221].

3.3.4. Vitamins and supplements—Vitamin D has been shown to have no impact on PCa incidence overall [222]. However, higher circulating 25-hydroxyvitamin D concentration was associated with an increased risk of PCa (RR 1.15, 95% CI 1.06–1.24), and there was a nonlinear dose response [223]. In the VITAL randomized trial, men randomized to vitamin D had lower PCa mortality than those randomized to placebo [222]. This finding is important given the lower vitamin D levels in Black versus White men [224].

A meta-analysis found selenium to be protective against the development of PCa (RR 0.86, 95% CI 0.78–0.94) and particularly protective against the development of advanced PCa (RR 0.67, 95% CI 0.52–0.87) [225]. In the SELECT randomized trial, however, there was no association with PCa incidence overall; SELECT did not follow participants for mortality [226].

3.3.5. Miscellaneous medications—There are many other medications that have been suggested to have a potential impact on PCa, for example, phosphodiesterase-5 inhibitors [227], spironolactone [228], Glucagon-like peptide-1 receptor agonist [229], and vitamin K antagonist [230,231]; however, data are limited and of relatively poor quality.

3.4. Secondary prevention/screening and early detection

3.4.1. Guideline recommendations regarding screening—In December 2022, the EU Council recommended their member states to evaluate the feasibility and effectiveness of the implementation of organized screening programs for PCa with PSA testing in combination with magnetic resonance imaging (MRI) scanning as a follow-up test.

In 2021, the EAU-EANM-ESTRO-ESUR-SIOG revised their PCa guidelines on screening and recommended offering PSA testing to well-informed men. However, they strongly recommend to evaluate and stop testing based on life expectancy and performance status [232].

In 2018, the U.S. Preventive Services Task Force updated their recommendations regarding PSA screening. For men aged 55–69 yr, the decision to undergo periodic PSA-based screening for PCa should be individualized [233]. Given the increased PCa incidence and mortality rates for Black men in the USA, some groups suggest annual screening starting at age 40 yr for these men, based on modeling studies [234].

In summary, screening for PCa is gaining acceptance and is expected to increase in the future.

3.4.2. Large screening studies—In the 16-yr follow-up of the European Randomized study of Screening for PCa (ERSPC), the benefits of screening became more pronounced as data had matured and the number needed to invite to screen and the number needed to diagnose to prevent one PCa death continued to decrease to 570 and 18, respectively. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial published data from 17 yr of median follow-up in 2019 and found no differences in PCa mortality between the screening and control arms [235]. However, pooling the results of ERSPC and PLCO, and taking into account contamination of the control arms showed a reduction in PCa mortality by 30% [236].

3.4.3. Magnetic resonance imaging—In the PROMIS study [237], using prebiopsy prostate multiparametric MRI (mpMRI) to triage men reduce the number of patients having a primary biopsy by 27% and may result in 5% fewer clinically insignificant cancers as compared with the standard pathway of transrectal ultrasound (TRUS) biopsy. The PRECISION study further strengthened the recommendation for mpMRI as 28% of men in the MRI arm had normal MRI and avoided biopsy. Of the men who underwent biopsy, 38% in the MRI group compared with 26% of the standard TRUS biopsy group had clinically significant PCa (csPCa) [238]. Several meta-analyses have evaluated the role of prostate mpMRI [239–242] and estimated the negative predictive value to be around 90% for the detection of grade group ≥2 disease and a positive predictive value of 40%. For example, a recent study compared TRUS alone versus prebiopsy MRI pathways [242] and found that

prebiopsy MRI with or without a biopsy was associated with a 57% improvement in the detection of csPCa, a 33% potential reduction in the number of biopsy procedures, and a 77% reduction in the number of cores taken. Two recently published randomized controlled trials have provided evidence for the use of MRI-targeted biopsy in PCa screening to reduce overdiagnosis [243,244].

3.4.4. Biomarkers—Several blood- and urine-based biomarkers can help better risk stratify before biopsy [245–248]. The 4 kallikrein panel, commercially known as the 4Kscore, or Prostate Health Index can be used to estimate the risk of csPCa on biopsy [249–251]. IsoPSA, which partitions isoforms of PSA, has also been found to predict the risk of csPCa, more so than PSA, in preliminary studies [252]. Proclarix, using plasma protein biomarkers PSA, free PSA, THBS1, and CTSD, outperformed total PSA and free PSA for men with larger prostates, ≥35 cc [253]. The Stockholm-3 test is a risk model that combines PSA, SNPs, clinical variables, as well as established and novel plasma protein biomarkers, and has been shown to outperform PSA alone in predicting csPCa [254].

Regarding urine-based biomarkers, ExoDx Prostate, a urine RNA exosome gene expression assay, and MyProstateScore predicts csPCa and can be used to aid in decision-making before biopsy [255–257]. SelectMDx is another urinary RNA biomarker, which was found in a meta-analysis to be comparable with predicting high-grade PCa, similar to mpMRI [258].

A recent systematic review did not yet recommend the use of biomarkers for reflex testing based on current evidence [259].

3.5. Limitations

The GLOBOCAN estimates assembled at IARC at the national level use the best available sources of recorded cancer incidence and mortality information within a given country. A strength of the estimates is their comprehensiveness based on routine data nationally, while an inherent weakness is that their validity is dependent on the degree of representativeness and quality of the source information [4]. At present, high-quality information on new cases of cancer from population-based cancer registries is available in only one of three countries worldwide, while the equivalent cause-of-death information from national vital registration systems is available in only one of four countries.

This systematic review performed a qualitative synthesis of the findings, with evidence mainly derived from systematic reviews and meta-analyses of retrospective studies and predominately from Europe and North America. While the strongest evidence for PCa risk factors lie in nonmodifiable risk factors, we highlight the emerging data for modest yet modifiable risk factors. Not all meta-analyses reported on clinical subtypes of PCa, such as by advanced stage, high grade, or lethal forms of PCa. PSA screening is an important confounder in epidemiology studies of PCa. Moreover, PSA screening increases the proportion of overall PCa cases that are low-grade, low-stage tumors. This review did not examine the extent to which studies accounted or did not account for PSA screening in the analyses.

4. Conclusions

PCa remains the second most common cancer among men with higher incidences and mortality in North and South America, Northern and Western Europe, Australia, and the Caribbean. Screening is gaining acceptance, which will likely reduce mortality at the cost of overdiagnosis. New techniques such as increasing use of MRI and biomarkers for the detection of PCa can help mitigate some of these issues. Herein, we have identified modifiable risk factors for PCa, which could be targeted to further reduce the incidence and mortality of PCa.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A: Search Methodology

1) Search strategy translated for **PubMed/MEDLINE (NLM)**

	Search strategy component concepts
1	Prostate cancer
	((“Prostatic Neoplasms”[Mesh] OR ((prostat*[ti] OR “Prostate”[Mesh]) AND (cancer* OR oncolog* OR “neoplasms”[MeSH Terms] OR neoplasm* OR carcinom* OR tumor* OR
	tumour* OR malignan* OR adenocarcinoma* OR adenoma*)))
2	Epidemiology/incidence/prevalence/mortality
	(“Epidemiologic Studies”[Mesh] OR “Epidemiology”[Mesh] OR “epidemiology” [Subheading] OR epidemiolog*[tiab] OR “Incidence”[Mesh] OR incidence[tiab] OR “Prevalence”[Mesh] OR prevalence[tiab] OR “Mortality”[Mesh] OR “mortality” [Subheading] OR “Morbidity”[Mesh] OR morbidit*[tiab] OR follow up studies[MeSH:noexp] OR prognos*[Text Word] OR predict*[Text Word] OR course*[Text Word] OR association*[Text Word]))
3	Risk factors/screening/socioeconomic/disparities
	((risk*[tiab] OR risk*[MeSH:noexp] OR risk adjustment[MeSH:noexp] OR risk assessment[MeSH:noexp] OR risk factors[MeSH:noexp] OR risk management[MeSH:noexp] OR risk taking[MeSH:noexp]) OR (delivery of health care[MeSH:noexp] OR health behavior[MH] OR health knowledge, attitudes, practice[MH] OR health services accessibility[MH] OR health services, indigenous[MH] OR mass screening[MH] OR mass screening[TIAB] OR mass screenings[TIAB] OR health inequality[TIAB] OR health inequalities[TIAB] OR health inequities[TIAB] OR health inequity[TIAB] OR health services needs and demand[MH] OR patient acceptance of health care[MH] OR patient selection[MH] OR quality of health care[MAJR:noexp] OR quality of life[MH] OR quality of life[TIAB] OR social disparities[TIAB] OR social disparity[TIAB] OR social inequities[TIAB] OR social inequity[TIAB] OR Socioeconomic Factors[MAJR] OR socioeconomic factor[TIAB] OR socioeconomic factors[TIAB]))
4	Limit: Study Designs – Systematic reviews/meta-analyses/guidelines

	((("Meta-Analysis as Topic"[MeSH] OR meta analy*[TIAB] OR metaanaly*[TIAB] OR "Meta-Analysis"[PT] OR "Systematic Review"[PT] OR "Systematic Reviews as Topic"[MeSH] OR systematic review*[TIAB] OR systematic overview*[TIAB] OR "Review Literature as Topic"[MeSH]) OR (cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR "science citation index"[TIAB] OR bids[TIAB] OR cancerlit[TIAB]) OR (reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR "relevant journals"[TIAB] OR manual search*[TIAB]) OR (("selection criteria"[TIAB] OR "data extraction"[TIAB]) AND "Review"[PT])) OR ((clinical[tiab] AND pathway[tiab]) OR (clinical[tiab] AND pathways[tiab]) OR (practice[tiab] AND parameter[tiab]) OR (practice[tiab] AND parameters[tiab]) OR algorithms[mesh:noexp] OR care pathway[tiab] OR care pathways[tiab] OR clinical protocols[mesh:noexp] OR Consensus[mesh:noexp] or consensus development conference[pt:noexp] OR "Consensus Development Conference, NIH"[pt:noexp] OR "Consensus Development Conferences as Topic"[Mesh:noexp] OR "Consensus Development Conferences, NIH as Topic"[Mesh:NoExp] OR critical pathway[mesh:noexp] OR guidance[tiab] OR guideline*[ti] OR guidelines as topic[mesh:noexp] or practice guidelines as topic[mesh:noexp] or Health Planning Guidelines[mesh:noexp] OR practice guideline[mesh:noexp]))
5	Limit: English, date range
	(english[Filter]) **AND** (y_5[Filter])
6	Limit: Human
	(("Animals"[MeSH]) NOT ("Animals"[MeSH] AND "Humans"[MeSH]))
7	Exclude: Publication types – Comments, letters, editorials, meeting/conference abstracts
	("Comment"[PT] OR "Letter"[PT] OR "Editorial"[PT])
8	Search strategy
	(1 AND 2 AND 3 AND 4 AND 5) NOT (6 OR 7)

2) Search strategy translated for **EMBASE (Elsevier)**

	Search strategy component concepts
1	Prostate cancer
	('prostate tumor'/exp OR 'prostate cancer'/exp OR 'prostate adenoma'/exp OR ((prostat*:ti OR 'prostate'/exp) AND (cancer* OR oncolog* OR 'neoplasm'/exp OR neoplasm* OR carcinom* OR tumor* OR tumour* OR malignan* OR adenocarcinoma* OR adenoma*)))
2	Epidemiology/incidence/prevalence/mortality
	('epidemiologic studies' OR 'epidemiology'/exp OR 'epidemiology'/lnk OR epidemiolog*:ab,ti OR 'incidence'/exp OR incidence:ab,ti OR 'prevalence'/exp OR prevalence:ab,ti OR 'mortality'/exp OR 'mortality'/lnk OR 'morbidity'/exp OR morbidit*:ab,ti OR 'follow up'/exp OR prognos* OR predict* OR course* OR association*)
3	Risk factors/screening/socioeconomic/disparities
	(risk*:ab,ti OR 'risk'/de OR 'risk assessmen'/de OR 'risk factor'/de OR 'risk managemen'/de OR 'high risk behavior'/de OR ((((((((((((('health care delivery'/de OR 'health behavior'/exp OR 'attitude to health'/exp OR 'health care access'/exp OR 'indigenous health care'/exp OR 'mass screening'/exp OR mass) AND screening:ab,ti OR mass) AND screenings:ab,ti OR health) AND inequality:ab,ti OR health) AND inequalities:ab,ti OR health) AND inequities:ab,ti OR health) AND inequity:ab,ti OR 'health service'/exp OR 'patient attitude'/exp OR 'patient selection'/exp OR 'health care quality'/mj OR 'quality of life'/exp OR quality) AND of AND life:ab,ti OR social) AND disparities:ab,ti OR social) AND disparity:ab,ti OR social) AND inequities:ab,ti OR social) AND inequity:ab,ti OR 'socioeconomics'/exp/mj OR socioeconomic) AND factor:ab,ti OR socioeconomic) AND factors:ab,ti))
4	Limit: Study Designs – Systematic reviews/meta-analyses/guidelines
	('meta analysis (topic)'/exp OR 'meta analysis'/exp OR ((meta NEXT/1 analy*):ab,ti) OR metaanaly*:ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR ((systematic NEXT/1 review*):ab,ti) OR ((systematic NEXT/1 overview*):ab,ti) OR cancerlit:ab,ti OR cochrane:ab,ti OR embase:ab,ti OR psychlit:ab,ti OR psyclit:ab,ti OR psychinfo:ab,ti OR psycinfo:ab,ti OR cinahl:ab,ti OR cinhal:ab,ti OR 'science citation index':ab,ti OR bids:ab,ti OR ((reference NEXT/1 list*):ab,ti) OR bibliograph*:ab,ti OR 'hand search*':ab,ti OR ((manual NEXT/1 search*):ab,ti) OR 'relevant journals':ab,ti OR (('data extraction':ab,ti OR 'selection criteria':ab,ti) AND review/it) OR (((clinical:ab,ti AND pathway:ab,ti OR (clinical:ab,ti AND pathways:ab,ti) OR (practice:ab,ti AND parameter:ab,ti) OR (practice:ab,ti AND parameters:ab,ti) OR 'algorithm'/de OR care) AND pathway:ab,ti OR care) AND pathways:ab,ti) OR 'clinical protocol'/de OR 'consensus'/de OR

	'consensus developmen'/de OR 'clinical pathway'/de OR guidance:ab,ti OR guideline*:ti OR 'practice guideline'/de OR 'health care planning'/de)
5	Limit: English, date range
	([english]/lim **AND** [2017–2022]/py)
6	Limit: Human
	('animal'/exp NOT ('animal'/exp AND 'human'/exp))
7	Exclude: Publication types – Comments, letters, editorials, meeting/conference abstracts
	(letter/it OR editorial/it OR 'conference abstrac'/it)
8	Search strategy
	(1 AND 2 AND 3 AND 4 AND 5) NOT (6 OR 7)

Search filters consulted/used/adapted:

PubMed's Clinical Study Categories search filters https://pubmed.ncbi.nlm.nih.gov/help/#clinical-study-category-filters

PubMed's Health Disparities search hedge (National Library of Medicine) https://www.nlm.nih.gov/services/queries/health_disparities_details.html

Systematic Reviews study design filter

Avau B, Van Remoortel H, De Buck E. Translation and validation of PubMed and Embase search filters for identification of systematic reviews, intervention studies, and observational studies in the field of first aid. J Med Libr Assoc. 2021 Oct 1;109(4):599–608. doi: 10.5195/jmla.2021.1219. PMID: 34858089; PMCID: PMC8608173. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8608173/

Consensus statements/guidelines search filter (University of Texas School of Public Health) https://libguides.sph.uth.tmc.edu/search_filters/pubmed_filters

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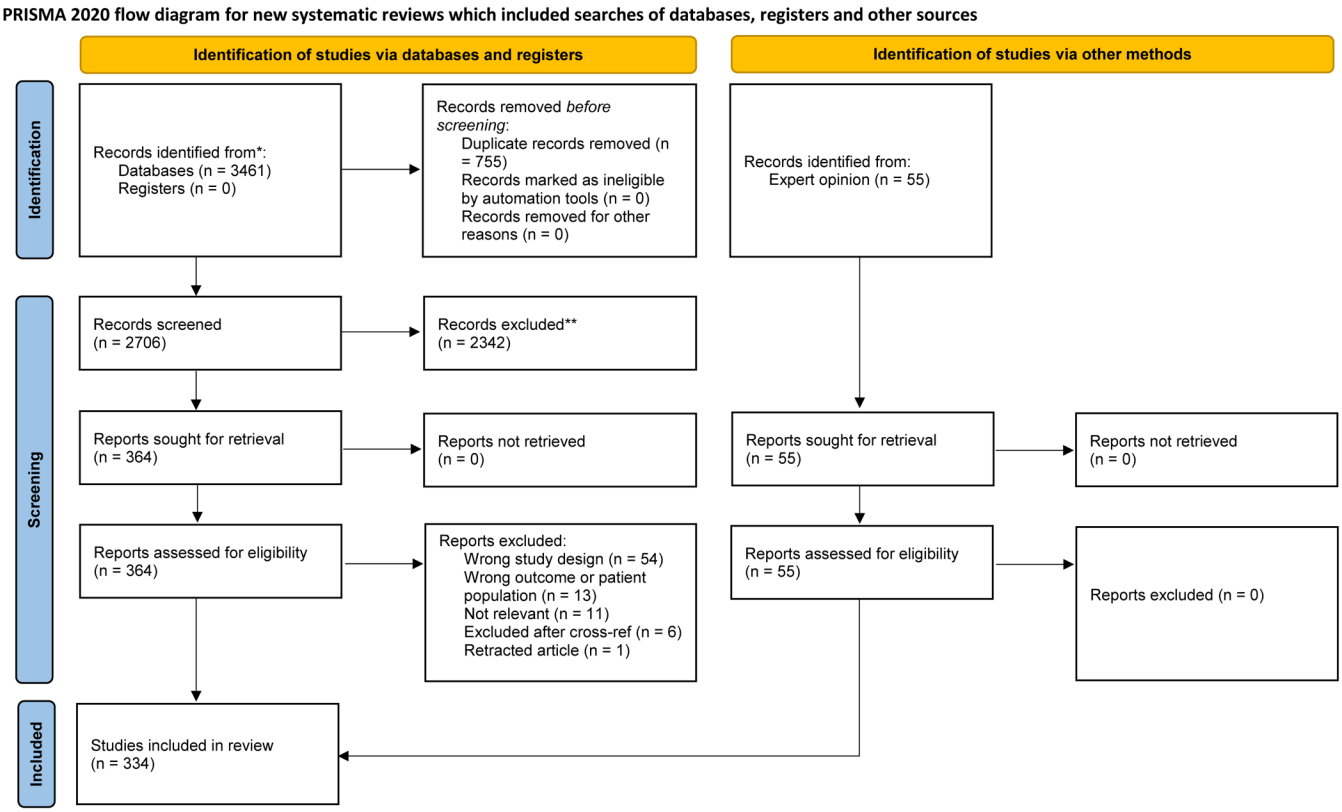

Fig. 1 –.

PRISMA flow diagram. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses.

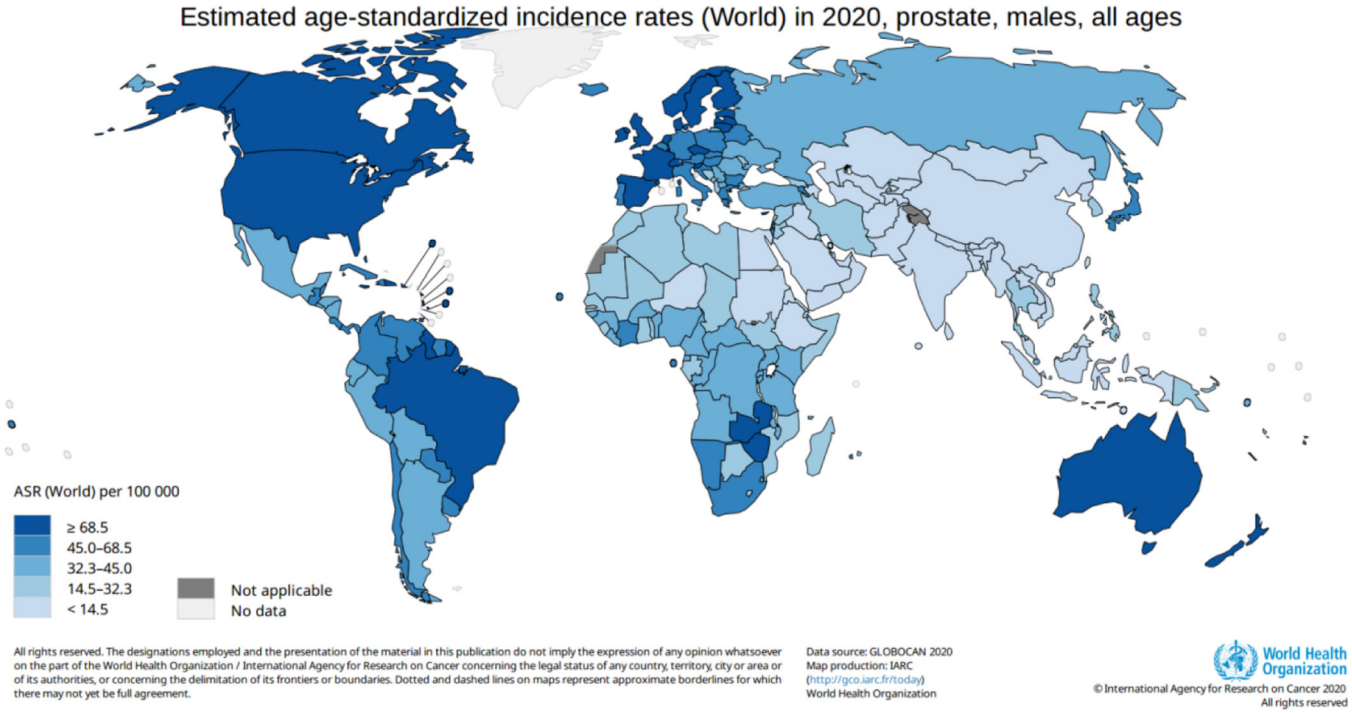

Fig. 2 –.

Estimated age-standardized prostate cancer incidence (world). ASR = age-standardized incidence rate.

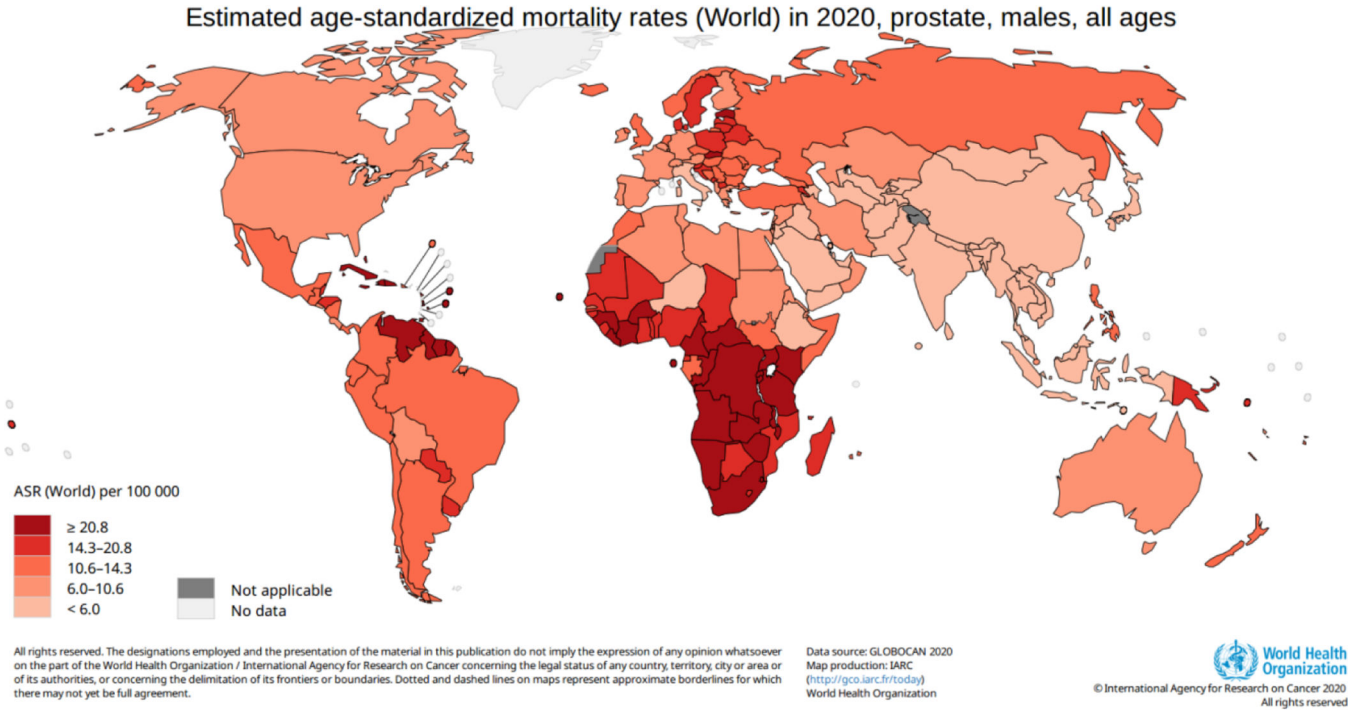

Fig. 3 –.

Estimated age-standardized prostate cancer mortality rate (world). ASR = age-standardized incidence rate.

Table 1 –

Summary of modifiable risk factors and protective factors for prostate cancer

Confirmed	Possible
Modifiable risk factors	
Dietary	Dietary
Meat consumption	Sugar-sweetened beverages
Dietary inflammatory index	Dairy consumption
Trans fatty acid intake	
Medical diseases and treatments	Medical diseases and treatments
–	Vasectomy
	Prostatitis
	Obesity and metabolic syndrome
	Periodontitis
	Human papillomavirus-16
	Calcium channel blocker use
Occupational factors	Occupational factors
–	Agricultural workers
	Petroleum workers
	Rotating night shift work
Lifestyle factors	Lifestyle factors
–	Smoking
Modifiable protective factors	Smokeless tobacco
Dietary	Dietary
–	Mediterranean diet
	Plant-based diet
	Coffee consumption
	Dietary intake of phytoestrogens
Medical diseases and treatments	Medical diseases and treatments
–	Aspirin
	Nonsteroidal anti-inflammatory drugs
	Statins
	Selenium intake
Lifestyle factors	Lifestyle factors
–	Physical activity
	Ejaculation frequency