

## Review Article

# Prostate Cancer and the Filipino: An Updated Review of Publications

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**Abstract**

Filipinos as part of the Asian race have mostly, if not always, been classified under the low risk category of developing and dying from prostate cancer (CaP). This was based on previous publications which demonstrated a large variation in incidence between racial groups. More recent data showed increasing incidence rates of CaP in the Filipino population largely mirroring that seen in Caucasians. In order to present an updated review of recently published data on CaP in Filipino men and its comparison to other ethnicities, a literature search was performed using Medline, SUMSearch, CancerLit, NLM Gateway, Herdin, and Cochrane databases from January 1985 to April 2014. Four more internationally published articles by non-Filipino authors have been added to the thirty-nine articles included in the previous publication of Raymundo. Three local articles were also considered. No related publication was retrieved from The Cochrane database. Recent publications restate the lower incidence and mortality rates of CaP among Asians when compared to Caucasians. Current evidence, however, indicates that Filipino men with CaP present with more aggressive disease, almost similar to that of the Caucasians. It was notable that the survival of Filipino males was more comparable to other Asian groups in early stage disease and yet they have the worst prognosis among other Asian ethnicities when detected late.

**ABBREVIATIONS**

CaP: Prostate Cancer; IR: Incidence Rate; MR: Mortality Rate, ASR: Age-Standardized Rate

**INTRODUCTION**

Filipinos as part of the Asian race have mostly, if not always, been classified under the low risk category of developing and dying from Prostate Cancer (CaP). This was based on previous publications which determined a large variation in incidence between racial groups. In the period 1988-1992, the highest age-standardized rate (ASR) recorded was among the Black males in Atlanta, Georgia at 142.3 per 100,000 [1]. The lowest rate was seen in Qidong, China at 0.5, while that of Filipinos ranged from 117.2-131 [1]. According to US data, Black males had a higher ASR compared to non-Hispanic Whites, who in turn had higher rates than Hispanic Whites. Asian ethnicities such as Chinese, Japanese and Philippine migrants had the lowest rates [1]. It has been repeatedly shown that the incidence rate (IR) of CaP in Filipinos, both those living in Western countries and those still residing in their homeland is significantly lower than the IR in Caucasians

[2-13]. Age-standardized rates from 1988-1992 among Filipino migrants to Hawaii (49.5 per 100,000), San Francisco (53.0 per 100,000) and Los Angeles (46.1 per 100,000) were almost three times higher than the rate in Filipino men residing in their home country (17.6 per 100,000) [1]. These, however, were still only half of that seen among the white population (95.9-108.2 per 100,000) [1].

Recent evidence showed changing trends in the disease, both worldwide and in Asia. In all studies included in the previous review that segregated data collection into the various Asian subpopulations, Filipinos have been noted to have the highest IR and also the highest or second highest IR among Asian immigrants [14]. An increasing trend was consistently found in IR of CaP for all subpopulations, with the Philippines experiencing a fast rise in IR [14]. Hence the notion that Filipinos have a low risk for developing and dying from it has been put into question. This is relevant with the on-going diaspora of millions of Filipino migrant workers all over the world that belong to various socioeconomic and hence educational background [15].

The objective of this study is to present an updated narrative

review of recently published data on the incidence, risk factor, prognostic factor, and mortality of CaP in Filipino men and its comparison to other ethnicities. This study aims to update the review published in 2011 by Raymundo [16] by including recent articles, from 2009 to Jan 2014, as well as articles included in the Cochrane and local databases, i.e. Herdin.

## METHODOLOGY

A literature search was performed using Medline, SUMsearch (Department of Medicine, The University of Texas Health Science Center at San Antonio), CancerLit (International Cancer Research Data Bank Branch of the US National Cancer Institute, US National Institutes of Health), NLM Gateway (National Library of Medicine, US National Institutes of Health), Herdin (Health Research and Development Information Network), and Cochrane databases from January 1985 to April 2014.

## RESULTS

A search was done in each database using the keywords “prostate cancer”, “Filipino”, “prognosis”, and “Asians”. Four more foreign publications were added to the thirty-nine articles included in the previous publication of Raymundo [16]. The Herdin literature search yielded twelve local articles. After perusing the abstracts, publications that did not discuss the incidence, risk factor, mortality rate, prognosis or prognostic factors of CaP in Filipino men were eliminated, leaving three local articles. The Cochrane database was also searched but did not yield any related publication.

### PSA Screening, Incidence and Mortality Rates

Table 1 summarizes the publications that discussed the incidence rates of CaP in Filipinos in comparison to that of other Asians and Caucasians. The term migrant Filipinos refers to Philippine men residing in countries other than the Philippines,

while local Filipinos are CaP patients residing in the country. The study by Gomez et al. [14] provides a more recent estimate on the IR of CaP in migrant Filipinos.

In the study by Gomez [14], cancer incidence data between January 1, 1990, and December 31, 2008 were obtained from 13 US population-based Surveillance, Epidemiology, End Results (SEER) Program cancer registries which cover 54% of the US Asian American population. Various regions in the US with sufficiently sized Asian American populations were included in the analysis. Cancer incidence rates and 95% confidence intervals (CIs) were calculated as cases per 100,000 persons and age-adjusted to the 2000 US standard population using SEER Stat software. It was noted that CaP was the most common malignancy among most Asian American groups. Table 2 shows the incidence rates of CaP in Asian-American groups in over three time periods.

As shown in Figure 1, Filipinos have the highest IR among the Asian ethnic groups studied, second only to non-Hispanic whites followed by the Japanese. It is also noted that there is a decreasing trend in all of the groups studied save for the Koreans, which had slightly increasing numbers.

Annual percentage change (APC) statistics used to characterize the magnitude and direction of trend showed that Filipino men experienced a statistically significant 19% (95% CI = 4.5% to 35.4%) annual increase in CaP rates during the time period of 1990 to 1993 [14]. Nevertheless, that figure declined in the succeeding time periods as shown in the graph.

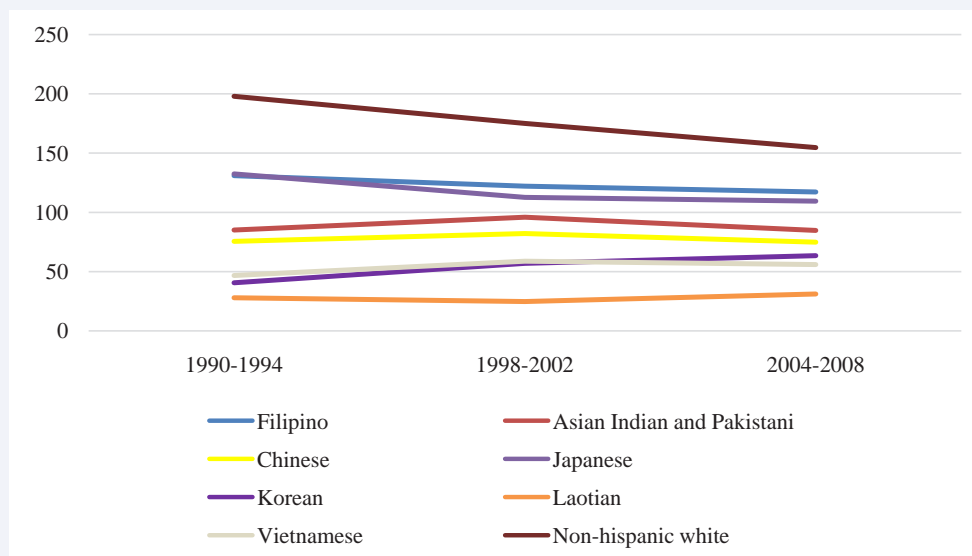
There is still limited local data on the prostate cancer antigen or prostate-specific antigen (PSA) screening rate in Filipinos residing within the Philippines, but data from the Philippine Urological Association website indicated that 2,066 and 4,348 men were screened in 2013 and 2014 respectively in their annual National Digital Rectal Examination (DRE) Day. Data

**Table 1:** Age-adjusted incidence rates of prostate cancer per 100,000 persons.

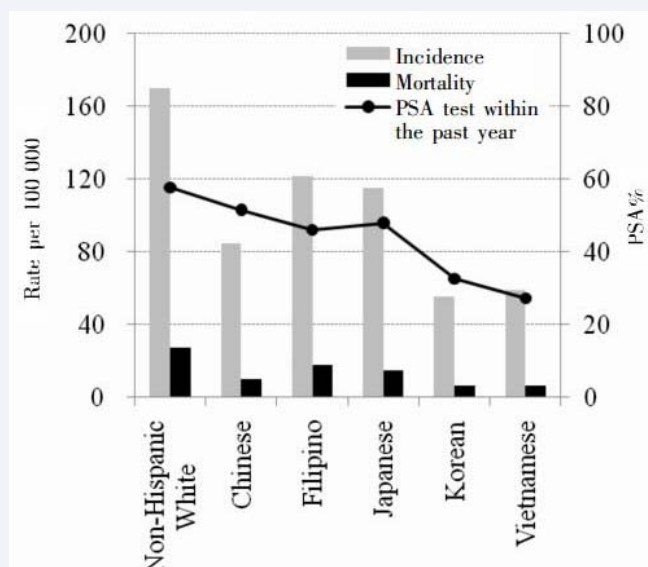
Age-adjusted Incidence Rate per 100,000 persons	Migrant Filipinos			Other Asians	Caucasians	Local Filipinos
	General	Born in Phil.	Born Abroad			
Delfino <i>et al.</i> 1998 [2]	116.5 -175.1				284.6 - 325.2	
Cook <i>et al.</i> 1999 [3]	111.3	123.4	141.1	70.1 - 120.7	106.5	
Nguyen 2003 [4]	225.34			50.4-249.45	326.55	
Pu <i>et al.</i> 2004 [5]				2.31 - 15.83	104.3	18.8
Sim <i>et al.</i> 2005 [6]				1978-82: 1.8 - 8.2 1993-97: 3.0 - 14.4		1978-82: 11.1 1993-97: 16.6
Miller <i>et al.</i> 2006 [7]	103.62			62.27-123.72	188.54	
McCracken <i>et al.</i> 2007 [8]	113.3			51.0-103.7	159.9	18.6
Miller <i>et al.</i> 2008 [9]	121.9			30.9 - 131.5	170.0	
Cheng <i>et al.</i> 2009 [10]	234.3 - 306.5				399.8 - 545.4	
Jemal <i>et al.</i> 2010 [11]				3.9 - 22.0	112.3	25.3
Laudico <i>et al.</i> 2010 [12]						21.9
Zhang <i>et al.</i> 2011 [13]	7.2				85.7	Not Available
Gomez <i>et al.</i> 2013 [14]	1990-94: 131.0 1998-2002: 122.1 2004-08: 117.2				1990-94: 198.0 1998-2002:175.1 2004-08: 154.7	

**Table 2:** Age-adjusted incidence rates of prostate cancer per 100,000 persons in three time periods Data obtained from Gomez et al. *Cancer Incidence Trends Among Asian American Populations in the United States, 1990–2008*. *J Natl CancerInst*;2013 [14].

Asian-American ethnic groups	Age-adjusted Incidence Rate of CaP per 100,000 persons		
	1990-1994	1998-2002	2004-2008
Asian Indian and Pakistani	85.1	95.9	84.8
Chinese	75.6	82.2	74.9
<b>Filipino</b>	131.0	122.1	117.2
Japanese	132.5	112.7	109.5
Korean	40.6	57.0	63.5
Laotian	27.9	24.8	31.1
Vietnamese	46.7	58.8	56.0
Non-hispanic white	198.0	175.1	154.7



**Figure 1** Age-adjusted Incidence Rate of CaP in Asian american ethnic groups and non-hispanic whites.



**Figure 2** Age-standardized incidence and mortality of prostate cancer and PSA screening rates in Asians in the United States (Based on the Surveillance, Epidemiology, and End Results Data from 1998-2002 and the California Health Interview Survey of 2003) – Reprinted with permission - Kimura, T. *East meets West: ethnic differences in prostate cancer epidemiology between East Asians and Caucasians*. *Chin J Cancer*; 2012 [18].

was collected from 64 DRE screening centers nationwide [17]. However recent publications showed that, in Asian-Americans living in the United States, the screening rate in Filipinos (46.1%) is not too different from the Chinese (51.6%) and the Japanese (48%), which were slightly lower than in non-Hispanic white men (57.7%) [18]. The incidence and mortality of CaP in these Asian groups were one-half to three-fourths compared to that in non-Hispanic whites as shown in figure 2. This reaffirmed the finding that even with comparable screening rate, Asian populations in Western countries still had a lower incidence and mortality compared to non-Hispanic white men. It can also be noted that among the Asian groups studied, Filipinos have the highest incidence and mortality rates.

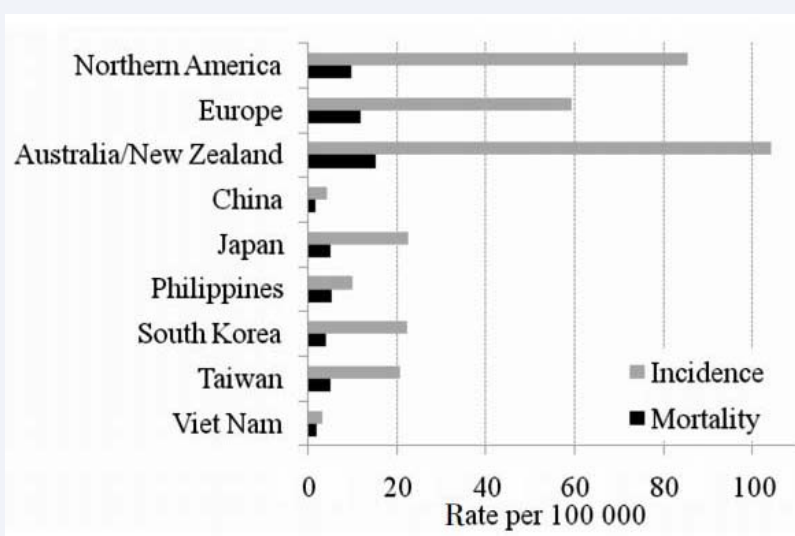
As stated in Raymundo 2011 [16], multiple studies had shown that the incidence of CaP in Asian Immigrants living in North America and European countries was much higher than in their countries of birth. The idea that this was solely attributed to the presence of a systematic PSA screening in western countries was also put into question by studies done in Europe where PSA is not offered as a routine screening. The incidence rates in European countries, however, were still much higher than that in Asian nations [18]. In the United Kingdom, for example, men aged 45 to 89 are enabled to make an informed choice about PSA screening. In 2007, screening rate in that age-group was estimated only at 6.2% [18] which is far less than the estimated average in Asian Americans (30-50%) and yet the incidence rate was estimated at 100.5 per 100,000. If populationbased PSA screening were introduced, it is estimated that CaP diagnosis rates in men aged 50 to 69 years would increase more than 20fold [18]. Figure 3 presents the comparison of incidence and mortality of CaP in selected countries. As seen in the figure, despite the relatively lower screening rate in European countries, the incidence still almost triples that of the cases of CaP in Asians. The figure shows that the reported incidence and mortality are much lower in Asian countries compared to the countries in North America, Europe, and Oceania.

## Diet and Lifestyle

It has been postulated repeatedly that aside from the disparity in access to medical systems, diet could also be attributable to an increased risk of CaP. Western diet, usually described as one with high fat and protein content, has been computed to contribute 13% increased risk of developing CaP among Asians residing in Hawaii [19]. It has been theorized that the longer a population is exposed to a westernized diet, the higher is the risk that they will develop CaP [16]. As seen in Figure 1 which compared the incidence rates of CaP in Asian-American ethnicities, Filipinos and Japanese, who began migrating to the US in the 1920s, have almost identical trends which are much higher compared to the Vietnamese and Koreans, who migrated after the 1960's [16]. The latter two also have almost similar incidence rates as seen in Figure 1. Soy foods, especially non-fermented soy products, which are popular in traditional Asian cuisine, have been consistently reported to be associated with a 25% 30% reduced risk of CaP [20-22]. The use of tofu, however, is not as popular in the Philippines as it is in many of its neighbours, and its protective properties might not be lending itself to Filipino men; thus, we almost consistently observe the highest rate of CaP in the Filipino subpopulation in researches that studied the disease in Asians [16].

## Familial and Genetic Studies

An individual with a positive family history of CaP has a 23 times higher risk of having the disease [23-25], and 10%20% of CaP cases are estimated to be such nonsporadic CaP [18]. Genetic variations were discussed in Raymundo 2011 [16] and appeared to provide protective mechanisms to Asians that are not available to other races such as the androgen receptor (AR) gene, located on Xq11.2-q12, as well as variations in the SRD5A2 gene, which encodes 5-alpha reductase II. Genetic studies to explore the familial nature of the disease have been conducted by the International Consortium for Prostate Cancer Genetics in the



**Figure 3** Age-standardized Incidence and Mortality of Prostate Cancer in Selected Countries. (Data were obtained from GLOBOCAN 2008. Incidence and mortality in all ages (0-75 years) were standardized using the world population. Reprinted with permission -Kimura, T. East meets West: ethnic differences in prostate cancer epidemiology between East Asians and Caucasians. *Chin J Cancer*; 2012[18].

**Table 3:** Genetic studies in Asians and Caucasians in relation to Prostate cancer risk – Data obtained from Kimura 2012 [18] and Medina 2003 [37].

Author	Genetic study	Prostate cancer risk
Li et al. 2006, [28]	Glu allele for the Asp541Glu polymorphism	Increased risk in Caucasians
Nakazato et al. 2003 [29]	Gln/Gln genotype	Decreased risk in Japanese
Xu et al. 2010 [30]	elaC homolog2 (ELAC2) gene/HPC2 at 17p11 (Ser allele of Ser217Leu and the Ala allele of the Ala541Thr polymorphisms)	Increased risk in Asians; Marginal impact in Caucasians
Wei et al. 2011 [31], Geng et al. 2009 [32]	Gln allele of the Arg399Gln polymorphism of the Xray repair cross-complementing group 1 (XRCC1)	Increased risk in Asians but not in Caucasians
Ntais et al. 2003 [33], Wang et al. 2010 [34], Li et al. 2010 [35], Collin et al. 2009 [36]	Vitamin D receptor (VDR) gene polymorphisms, steroid 5α reductase type 2 (SRD5A2) gene and genes on folate pathway (e.g.MTHFR)	Not significantly associated with prostate cancer risk in metaanalyses in Caucasians or in Asians
Medina et al. 2003 [37]	Bsm1 polymorphism of the Vitamin D receptor gene	29.57 times more likely to have prostate cancer if Bsm1 polymorphism is present in Filipino men

form of combined linkage analyses on a large number of families (mainly white men) with CaP. These studies showed a significant linkage at 22q12 and several other regions with “suggestive” linkage [18]. On the other hand, in the study of Matsui [26], Japanese CaP patients had minimal linkage at chromosome 8p23 and 1p36 in. Casecontrol studies on candidate genes have also been done and were found to have greater power compared to linkage analysis, but the results have been largely controversial [27]. One candidate gene studied widely was 2’ 5’ oligoadenylate-dependent RNase L (RNASEL), which is located in the hereditary CaP (HPC) 1 region (1q2425). Table 3 summarizes the gene studies done specifically on RNASEL gene in correlation to risk profiles of Asians and Caucasians in acquiring Prostate cancer, as well as one article published in the Philippines.

## DISCUSSION

The recent publications included in this updated review restate the lower incidence and mortality rates of CaP among Asians when compared to Caucasians. Recent available data on multiple factors such as diet, lifestyle choices, and genetics, have been cited and discussed above as the plausible causes of this difference in incidence rates, aside from those previously discussed in Raymundo 2011 [16].

Because of the associated harms of over diagnosis and overtreatment, screening is one of the most controversial topics in urology. The most up-to-date summary of literature regarding the topic is provided by a Cochrane review published in 2013 [38] which was based on randomized controlled trials (RCT) done in North America and Europe representing more than 341,000 randomized men. The review had the following summary of findings: (1) screening was associated with an increased diagnosis of CaP (2) screening was associated with more localized disease and less advanced CaP (T3-4, N1, M1) (3) from the results of the five RCTs, no CaP-specific survival benefit was observed. (4) From the results of four of the five RCTs, no overall survival benefit was observed. Meta-analysis of the only two studies that were assessed to have low risk of bias (ERSPC; PLCO) showed that there is no significant difference in prostate cancer-specific mortality. Hence, both the updated AUA and EAU guidelines practically veered away from screening and embraced individualized case finding. Both the EAU and AUA panel did

recognize an evidence of moderate benefit of screening derived from the ERSPC with a 21% reduction in CaP-specific mortality and a 29% reduction after adjustment for non-compliance at 11 years of median follow-up [39,40]

It has become part of clinical practice for most Filipino Urologists to apply these guidelines to manage the Filipino patient as part of the low risk population for debilitating progression and death from CaP. This has been affirmed by multiple publications as previously stated that Asians appear to have an advantage in terms of lower risk of occurrence compared to other races, say Americans of African descent. But the robustness of current evidence indicating that Filipino men with CaP were present with aggressive disease, almost similar to that of the Caucasians, cannot be denied. As presented in Raymundo [16], the percentage of CaP patients who had extra-capsular or metastatic disease was found to be equal between Filipino immigrants and Caucasians by three publications [2,10,41]. Four publications, on the other hand, which included Filipinos as part of the Asian immigrant population, all found extra-capsular or metastatic CaP in a higher percentage of Asians compared to Caucasians [42-45]. In a study done by Lichtensztajn et al published in April 2014 [46], which compared CaP risk profiles among six Asian-American groups in California (United States-born Chinese, foreign-born Chinese, United States-born Japanese, foreign-born Japanese, foreign-born Filipino and foreign-born Vietnamese), it was noted that the Asian groups studied were most likely to have an unfavorable risk profile compared to non-Hispanic white men. It was also noted that while US-born Filipino men did not differ from non-Hispanic white men in any risk category, foreign-born Filipino men had the highest odds of any group, even higher than the non-Hispanic black men, of being diagnosed with high vs intermediate risk disease (Odds ratio 1.45, 95% CI 1.31-1.60). FB Filipino men were also more likely to have high vs intermediate Gleason Score (OR 1.27, 95% CI 1.12-1.43) and high vs intermediate PSA (OR 1.35, 95% CI 1.17-1.56), and less likely to have low vs intermediate PSA (OR 0.72, 95% CI 0.65-0.81). Although the outcomes of these CaP patients were not discussed in the said article, the study by Lin [42] showed that Filipino males have the poorest 5-year cause-specific survival (85.8, 95% CI: 83.8-87.9) compared to other Asian groups such as the Japanese (91.1, 95% CI: 89.6-92.5) and the Chinese (91.4, 95% CI: 89.3-93.4),



and even worse than the Caucasians (89.3, 95% CI: 89.1-89.6). Stage-specific 5-year survival was also poorer among Filipinos with distant stage disease compared to other Asians, although remained poorest among whites. The finding that the survival of Filipino males was more comparable to other Asian groups in early stage disease compelled the said author to recommend more enhanced efforts in targeting screening in the Filipino male population. While differences in screening behavior and prevalence may account for higher incidence and higher PSA at diagnosis, the association with high grade disease and the lack of association with advanced stage at diagnosis suggest that the differences observed in the risk profile and prognosis cannot be fully explained by screening behavior or delayed access to health care alone, but rather may be attributable as well to an underlying, intrinsic biological mechanism [46].

In the face of risking overtreatment, would it be more prudent to err on the side of caution, considering that Filipino men have better survival in early stage disease and have the worst prognosis when detected late? No locally instituted randomized control trial based on this premise has been found by the author on careful search of national and international databases. A systematically conducted nationwide epidemiologic study should be foremost on the agenda of local researchers and health leaders, in order to determine the actual size of the "screenable population" for CaP in Filipino men.

The EAU Guidelines on Prostate Cancer 2014 [40] recommended a risk-adapted strategy for early detection which consisted of individual case finding initiated by the patient being screened with at least 10-15 years of life expectancy and/or his physician. The guideline recommended early PSA testing in men at elevated risk of having CaP such as men over 50 years of age; men over 45 years of age and a family history of CaP, or African-Americans. In the 2013 AUA updated statement [39] however, an earlier age of 40 years was recommended in patients with a strong family history of CaP or of African-American descent. Both guidelines consider PSA as the cornerstone of early CaP detection. Despite the demonstrated differences in CaP behavior and prognosis in different parts of the world, a study done by Madanay et al in 1995 has shown that there is no direct correlation between serum PSA and ethnicity [47]. Perhaps in the near future, it is possible that men at increased risk of developing an aggressive CaP phenotype, such as in Filipinos, may be identified earlier through genetic testing, as presented in this review, and/or new biomarkers so that these individuals could benefit from more intense screening even at a young age. In a recent publication, the use of an ERG monoclonal antibody in a Filipino population demonstrated its ability to detect intermediate and high-risk tumors through immunohistochemical staining of prostate biopsy specimen [48], but less invasive biomarkers for use in blood or urine would be most ideal for screening purposes.

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