# Prostate cancer incidence, mortality, total and free prostate specific antigen

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## Abstract

The causes of prostate cancer (PC) and its progression are not yet known. Mortality and incidence from PC has increased throughout European countries until early 1990s. In Greece, PC is the second commonest cancer in men after lung cancer. The traditional Greek diet old in its origin may protect against common chronic diseases, including PC. Hormonal causes have been postulated in the aetiology of PC, mainly because androgen ablation causes regression of PC. Total and free prostate specific antigen (PSA and fPSA) screening were introduced to detect PC at an early stage, to reduce PC specific mortality, differentiate PC from hypertrophy and monitor response after hormonal treatment in advanced PC.

*Keywords:* Incidence of prostate cancer – Mortality – Total PSA – fPSA – Prostate cancer in Greece

## Introduction

The incidence and mortality of prostate cancer (PC) differ in various countries and data are not always available. In this article we present information on the incidence and mortality of PC not only in various countries but also in Greece. We describe positive and negative factors like diet and hormones for the induction and management of PC. Finally, we describe total and free prostate specific antigen (PSA and fPSA) as unique indicators of PC and of follow-up of PC treatment.

## Incidence and mortality

PC is the 6th commonest cancer worldwide and the 3rd most important for males with 543,000 new cases every year. According to the American Cancer Society, one in every six men develops PC during his life, while only 1 out of 32 will die from the disease [1].

Between the years of 1973 and 1989 the incidence of PC in the USA increased by 2.7/100000 per year and was followed by a reduction between the years of 1992-1993 and over the following years [2]. In 1997, mortality was reduced to 1.2% annually [3].

In western European countries the incidence of PC, is relatively higher as compared to the eastern and southern parts of Europe [4]. In Greece, PC is the second commonest cancer in men after lung cancer and comprises 13.2% of all cancers in men. In 2002, 2.920 new cases have been reported. It seems that Greece has one of the lowest incidences of PC in Europe and a mortality of 8.7-12 /100.000 or 0.087 to 0.120/1.000 Greek males [5, 6].

According to Geneva Cancer Registry database, PC mortality is relatively increasing to increase in Belgium, Denmark, Greece, Ireland, Bulgaria, Czech Republic, Belarus, Ukraine, Russian Federation, Romania, Poland, Argentina, Chile, Cuba, Mexico, Japan, China Hong Kong and the Republic of Korea [7].

Autopsy studies in Greece and Spain demonstrated that the incidence of PC in these Mediterranean Caucasian male populations was significantly lower than in other Caucasian males while epidemiological studies showed a significant degree of adherence to Mediterranean diet for Greek and Spanish males with a relatively lower saturated and higher monosaturated fat ratio [8].

The traditional Greek diet resembles the Paleolithic diet in terms of fibre, antioxidants, saturated and mono-unsaturated fat thus is consistent with human evolution. While many traditional diets reflect regionally available foods, Greek traditional diet can be applied in many countries, since it is based on the nutrient composition of plant and animal foods. The evidence suggests that a traditional Greek or Cretan style diet may protect against common chronic diseases, including PC [9].

## The diagnostic significance of PSA

Total human prostate specific antigen (PSA) is a 33 kD serine protease which, in human serum, is predominantly bound to alpha 1-antichymotrypsin (PSA-ACT) and alpha macroglobulin (PSA-AMG). Current methods of screening men for prostate cancer utilize the detection of major PSA-ACT form. Trace amounts of alpha 1-antitrypsin and inter-alpha trypsin inhibitor bound to PSA can also be found. Any remaining PSA is in free form (fPSA) [10-12].

PSA is measured in ng/mL of blood. In the past, most doctors considered PSA values below 4.0ng/mL as normal. However, recent research found PC in men with PSA levels below 4.0ng/mL. Many doctors are now using the following ranges, with some variations [13-15]: low levels 0-2.5ng/mL, slightly to moderately elevated levels, 2.6-10ng/mL, moderately elevated, 10-19.9ng/mL, significantly elevated, 20ng/mL or more. This new approach reflects the fact that relatively low PSA levels in blood may mask some aggressive prostate cancers [13-15]. On the other hand elevated PSA levels are not specific for PC [15].

The fall in the incidence of PC in the USA may be partly attributed to the systematic use of PSA in screening and diagnosing PC [9]. Studies in many other countries in Europe and in Asia, suggest that PSA screening may reduce mortality from PC [5].

Unfortunately, at the time of diagnosis in 75% of the patients the tumour has advanced beyond the prostatic capsule and in nearly half of them distant metastases can be detected [16]. Nowadays, with the wide use of PSA, many PC are detected at early stages and can be treated either surgically or conservatively [16]. On the other hand PC often remains undetected. It has been reported that out of 212 prostate autopsy specimens of Greeks between 30-98 years of age who died of diseases other than PC and related conditions, 40 cases had PC. In more than half of them tumour mass was less than 1cm and PC was well differentiated [17, 18].

PSA is a specific prostate marker but not a specific tumor marker, as it can also be increased in benign prostate hyperplasia, in inflammations of the urinary tract and after manipulations of the prostate as in trans-rectal ultrasound and biopsy. Cystoscopy and digital rectal examination appear to have no effect on serum PSA levels [19, 20]. After a positive diagnosis of PC, serum PSA levels are used for the follow up and are considered specific tumor marker. After radical prostatectomy serum PSA levels lower than 0.01ng/mL, indicate the absence of residual tumour in situ [21].

PSA is an effective marker to monitor patients with advanced PC. High serum PSA levels were detected in 98%-100% of the patients with advanced stage of PC [22, 23]. Several studies have also shown that serum PSA is a useful marker to monitor hormonal treatment response in advanced PC cases [24, 25].

The fPSA test is a solid phase two-site immuno-radiometric assay (IRMA). Two monoclonal antibodies are prepared against sterically remote sites on the PSA molecule. The first one is coated on the solid phase (coated tube). The second is specific for fPSA radio-labeled with iodine-125 and used as a tracer. The fPSA molecules present in the standards or the samples to be tested are sandwiched between the two antibodies. Following the formation of the coated antibody /antigen/iodinated antibody sandwich, the unbound tracer is easily removed by a washing step. The radioactivity bound to the tube is proportional to the concentration of fPSA present in the sample.

The fPSA test measures the proportion of fPSA to the bound PSA in a blood sample. It's called free because fPSA circulates in the bloodstream "unbound," without a carrier protein. Eleveted serum PSA levels have also been attributed to benign prostate hyperplasia (BPH) or prostatitis, leading to a large percentage of false positive screening results. A potential solution to this problem involves the determination of fPSA levels. Preliminary studies have suggested that the percentage of fPSA is lower in patients with PC than those with BPH. Thus, the measurement of fPSA in conjunction with total PSA, can improve specificity of PC screening in selected men with elevated PSA levels, which would subsequently reduce unnecessary prostate biopsies with minimal effects on cancer detection rates [26-28].

High PSA, above 25% usually indicates BPH. Most men with PC have a fPSA below 15%. If fPSA is below 7%, PC is most likely. According to the American Cancer Society and the National Cancer Institute, men with fPSA at 7% or lower should undergo biopsy. If biopsy is negative but fPSA remains low, repeated biopsy is indicated [28-30].

Combined with prostate volume, percent fPSA calculation helps reduce the number of biopsies based on "false positive" PSA test results. PSA velocity is an independent measure of likely prostate cancer [31].

## Hormones and PC

Entanglement of hormonal factors in inducing PC is based on: a) the finding of steroids' receptors in prostate adenocarcinoma, b) the successful treatment of PC after using androgen antagonists and c) the possibility to "cause" PC in animal experiments after extended issuing of male genital hormones [32]. Experimental studies suggest that rich in fat diets interfere with the metabolism and hormone synthesis in males and relate to PC and other forms of cancer like colon and breast carcinoma [33, 34].

It is known that prostate growth depends on maintenance of a balance between cellular proliferation and cellular apoptosis - the programmed cellular death which is regulated by androgens [35]. Changes in androgen levels produce changes to the epithelial cells. Decline in the level of androgens leads to programmed cellular death (apoptosis) of mature epithelial cells of the prostate. The effect of testosterone (T) in cellular kinetics was experimentally shown in castrated rats. One week after castration, roughly 75% of epithelial cells of the prostate will suffer apoptosis. Reinstitution of T even one year after castration will lead to minimal apoptosis and a substantial increase in cellular proliferation in the prostate [36]. Androgen withdrawal in adult men results in a decline of T to levels equivalent to those of pre-pubertal boys. Androgen deprivation will lead to apoptosis of the androgen-dependent cellular population, that is of all epithelial secretory cells, and to a dramatic shrinkage of the size of the prostate [37].

Hormones have been postulated in the aetiology of PC, mainly because testosterone suppression causes regression of prostate cancer. However, results from a large study comparing patients with prostate cancer to controls found no difference in baseline T, dihydro-testosterone, prolactin, follicular-stimulating hormone, or oestrone [38].

## Optimal testosterone suppression

It is known long ago that PC cells function depends on androgens. Therefore, the key for the management of metastatic and advanced PC is suppression of testosterone production. The deprivation of androgens by surgical castration (bilateral orchiectomy) constitutes since the last 40 years and even today the reference standard method of treatment. Issuing es-

trogens as an alternative for surgical castration has been abandoned due to their potential for serious side effects, like pulmonary embolism, deep vein thrombosis and congestive heart failure [39].

Others purified the decapeptide gonadotropin-releasing hormone, also referred as luteinizing hormone releasing hormone (LHRH), thus producing synthetic peptides having an antagonistic action to that of LHRH and offering an alternative to orchiectomy for testosterone deprivation. The introduction of LHRH analogues is a safe and effective method of medical castration sparing the psychological impact of surgical castration or the cardiovascular risks related to oestrogen treatment [40-41].

The Prostate Cancer Prevention Trial studied the prevalence of PC between a control group and a group given a 5-alpha reductase inhibitor. While the 5-alpha reductase inhibitor appeared to decrease the prevalence of tumours, those tumours that did arise appeared more aggressive by histology. Only long-term follow-up of these patients will determined whether more aggressive histology accurately reflects the underlying biology of these tumours or it was an artefact of treatment [42].

By radio-immuno-assay (RIA) and immuno-radiometric assay (IRMA) methods we have recently shown after radical prostatectomy, an increase in serum luteinizing and follicular-stimulating hormones witch may have caused an increase in serum thyroid-stimulating hormone and a decrease in serum dihydro-testosterone [43]. If these changes are due to the hypothalamic-pituitary axis, it may be that PC before radical prostatectomy may have secreted a substance that induced a negative feedback to the pituitary gonadotrophin secretion.

One can realize the importance of measuring these hormones in patients with PC. Even if prognostic significance of these hormones regarding the natural course of PC is not completely defined, it is obvious that at the time of initial diagnosis, serum T measurements are important, both as a prognostic factor and as an early indicator of treatment failure, preceding the consequent rise of PSA [44]. After hormonal treatment, increased serum PSA indicates biochemical recurrence [45-48].

## Current indications of androgen deprivation treatment (ADT)

According to the US Food and Drug Administration, ADT is indicated only for the palliation of symptomatic metastases and as neoadjuvant treatment for radiotherapy. Nevertheless, ADT is widely used to treat men with clinically localized PC, biochemical PSA relapse after radical prostatectomy, locally advanced PC (LAPC), lymph node metastases, and asymptomatic metastatic disease. The benefits of ADT for these unapproved indications have not been definitively ascertained owing to the requirement for performance of large-scale, multi-center, randomized trials with long term follow-up [49-50].

Hormone treatment for intermediate or high-risk PC and in some cases for radical prostatectomy or as a neoadjuvant to improve responses to subsequent radiotherapy is now commonly used as an adjuvant to radiotherapy [51].

Laboratory studies have demonstrated that early hormone treatment does not result in earlier resistance and also showed a benefit of early hormone treatment in patients with distant metastases [52]. This conclusion was substantiated by a Medical Research Council, UK clinical study in 938 patients with locally advanced or asymptomatic metastatic prostate PC. Patients received either immediate treatment with orchiectomy or LHRH agonists versus the same treatment deferred until symptoms occurred. Development of extraskeletal metastases, pathologic bone fractures, spinal cord compression, and ureteric obstruction were twice more in the deferred-treatment group. Overall survival was significantly prolonged in the patients who were treated early [53].

*In conclusion,* PC is the 6th commonest cancer worldwide and the 3rd most important to men tending to increase in many countries. In Greece and Spain, the incidence of PC is significantly lower than in other European countries perhaps partly due to traditional Greek or Cretan style diet. PC seems to be hormone dependent. Total and fPSA, prostate volume and digital rectal examination are effective markers to diagnose and follow-up patients with advanced PC. Androgen deprivation treatment is undoubtedly the mainstay of treatment for symptomatic metastatic PC. The LHRH-analogues are a possible treatment equivalent to surgical castration, when maintaining serum low level of T overtime.

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