The value of various prostate cancer tumor markers in early detection, diagnosis, follow up and monitoring of the treatment.

Essay

Submitted for the partial fulfillment of

M.Sc. Degree

In

CLINICAL & CHEMICAL PATHOLOGY

By

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Abstract

Prostate cancer is one of the most important cancers in men worldwide. Its incidence can be influenced by several risk factors including genetic susceptibility, environmental exposure in its largest sense and differences in health care and cancer registration (or a combination of these).

The marked increase in detection of prostate cancer occurred due to the development of tumor markers of prostate mainly prostate specific antigen (PSA).

The sensitivity of PSA is impressive but low specificity result in increase the number of unnecessary biopsies. The rise in the number of potential prostate markers may overcome the weakness in the use of PSA alone as a marker for cancer prostate.

KEY WORDS:

Prostate; Cancer; Tumor marker; PSA.

سرطان البروستاتِا أحد أهم أمراضِ السرطان في الرجالِ على مستوى العالم.

معدل حدوث سرطان البروستاتا يمكن ان يتأثر بعدة عوامل منها سهولةِ التأثر الوراثيةِ، البيئة المحيطة، الإختلاف فى الرعاية الصحية و تسجيل الحالات أو (مجموعة من العوامل معاً).

الزيادة الملحوظة في كشفِ سرطانِ البروستاتِا حدثت نتيجة التطور فى دلالات أورام البروستاتا و خاصة (PSA).

حساسية (PSA) رائعة إلا إن إنخفاض تخصصيته يؤدي إلى زيادة عينات البروستاتا الغير ضرورية. الأرتفاع فى عدد دلالات الأورام المحتملة لسرطان البروستاتا قد يتغلب فى النهاية على الضعف الموجود فى إستخدام PSA بمفرده فى سرطان البروستاتا.

ACKNOWLEDGEMENT

First and foremost thanks to "God" the source of all goods.

Then I would like to express my deep thanks and appreciation to ***PROF. Dr. SARAH EL KATTEB*** *Professor of clinical and chemical pathology, Faculty of medicine, Cairo University, for giving me a lot of her precious time and support and for her constructive guidance and valuable observations.*

I am also grateful for to ***PROF. Dr. SAMIA YAHIYA AKL*** *Professor of clinical pathology, Faculty of medicine, National cancer institute, Cairo University, for her great help, continuous supervision and effort with me throughout this study. She supplied me with valuable information which was the cornerstone in the completion of this study.*

My sincere appreciation to ***Dr. IMAN ATTIA*** *lecturer of clinical pathology, Faculty of medicine, National cancer institute, Cairo University, she kindly guided my steps and was always provided me with valuable suggestions, advice, experience which were important pillars in my assay.*

Finally, whatever I say will never be enough to thank my wife, I am greatly appreciating her moral help, and she was always supplying me with the feeling of hope, love and encouragement.

This assay is dedicated to a great and special mother, sisters and aunt. It is also dedicated to a cooperative kind wife and to my beloved family.

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A2M	α2-macroglobulin
ACT	α1-antichymotrypsin
AJCC	American Joint Committee for Cancer Staging
API	α1-antitrypsin
ASRR	Age specific reference ranges
Bcl-2	B-cell lymphoma 2
BCR	Biochemical recurrence
bFGF	Basic fibroblast Growth Factor
BPH	Benign prostate hypertrophy
BPSA	BPH-associated PSA
COX-2	Cyclooxygenase-2
*c*PSA	Complexed PSA
DRE	Digital Rectal Examination
ECE	Extracapsular extension
EDRN	Early Detection Research Network
FDA	Food and Drug Administration
FGFs	Fibroblast Growth Factors
GSTP1	Glutathione-*S*-transferase p1
hK11	Human kallikrein 11
hK2	Human kallikrein 2
HRPC	Hormone-refractory prostate cancer
IGF	Insulin-like growth factor
IGFBP-3	Insulin-like growth factor (IGF)-binding protein-3
IL	Iinterleukin
MAbs	Monoclonal antibodies
MIC1	Macrophage Inhibitory Cytokine 1
MIF	Migration inhibitory factor
NMPs	Nuclear matrix proteins

PCI	Protein C inhibitor
PI6	Protease inhibitor-6
PIA	Proliferative inflammatory atrophy
PIN	Prostatic intraepithelial neoplasia
PPBC	Percentage of positive biopsy core
PPV	Positive predictive value
PSA	Prostate-specific antigen
PSAD	Prostate-specific antigen density
PSA-I	Intact single-chain fPSA
PSA-N	Nicked PSA
PSAV	Prostate-specific antigen velocity
PZ	Pregnancy zone protein
SDS	Sodium dodecyl sulfate
SNPs	Single nucleotide polymorphisms
SVI	Seminal vesicle invasion
TGF-β	Transforming growth factor-β
TNF-α	Tumor necrosis factor-α
TNM	Tumor, Node, Metastasis
*t*PSA	Total PSA
TRUS	Transrectal ultrasonography

INTRODUCTION

Cancer prostate continue to be a major health problem all over the world, in fact the rates of this disease in US African American and Caucasian men are the highest in the world. Prostate cancer is now of the leading cause of cancer death in men, exceeded only by lung cancer. It accounts for 29% of all male cancer and 11% of male cancer related death (Parkin et al., 2005).

The marked increase in detection of prostate cancer occurred due to the development of tumor markers of prostate mainly prostate–specific antigen (PSA). It has both diagnostic and prognostic significance both before and after definitive therapy for prostate cancer. Although the sensitivity is impressive, low specificity result in a lack of cancer detection in a significant proportion of patients. Several studies as measuring complexed PSA and free/total PSA ratio and the rise in the number of potential new prostate markers as human kallikrein 2(hk2), vascular endothelial growth factor (VEGF), basic Fibroblast growth factor (bFGF), (**Vogelzong et al., 2008**), human kallikrein 11(hk11), macrophage inhibitory cytokine1 (MIC-1), **(Stephan et al., 2005**) as well as early prostate cancer antigen (EPCA), may eventually overcome the weakness in the use of PSA alone as a marker for cancer prostate. This considerable progress in the diagnosis of prostate cancer will be translated into better patient care and decrease in the mortality from prostate cancer.

Aim of the work

In this review we will discuss the markers routinely used for diagnosis and follow up of prostate cancer as prostate-specific antigen (PSA) either total PSA, free PSA or complexed PSA, Prostatic acid phosphatase (PAP) and other non routinely used markers as human kallikrein 2(hk2), vascular endothelial growth factor(VEGF),basic Fibroblast growth factor (bFGF), macrophage inhibitory cytokine1(MIC-1), human kallikrein 11(hk11), early prostate cancer antigen (EPCA) and other markers, which will lead to better understanding of the benefit of these markers in early detection, diagnosis, monitoring of the treatment in prostate cancer to decrease mortality incidence from this disease.

Epidemiology of Prostate Cancer

Incidence

Prostate cancer is one of the most important cancers in men with a worldwide incidence of 25.3 per 100,000. This makes prostate cancer the fifth most common cancer and the second most common cancer in, with large differences between countries men **(Parkin et al., 2005)**.

In Europe 238,000 men developed prostate cancer in 2004, that was 15.5% of newly diagnosed cancer cases in men in that year. Prostate cancer is the second most frequent cancer in European men, after lung cancer. It is, however, the most common cancer in men living in the European Union, comprising 18.1% of all incident cases. The lifetime risk (0–74 years) of developing prostate cancer in the European Union was 5.9% in 2004 (**Boyle and Ferlay, 2005**).

In the United States prostate cancer has become the most common cancer diagnosed in men, with an incidence of 124.8 per 100,000 and presents 33% of all diagnosed malignancies in men. The lifetime risk for a man to develop prostate cancer in the United States is 1 out of 6 (**Parkin et al., 2005; Quinn and Babb 2002**).

In Egypt the **GLOBOCAN 2002 database** compiled by (**Ferlay et al., 2002**) for the International Agency for Research on Cancer) estimated the number of new cases per year to be 867 cases. In the period 2002-03 the Egyptian National Cancer Institute at Cairo University reported seeing 238 new cases of prostate cancer out of a total of 9,340 new cancer cases in males (2.6 %).

Chances of developing cancer in men and women are increasing with age. In Egypt aged population represents about 6% of overall population (age 60 years and more) in 2006, it is expected that this percent will be about 9% and 15% in 2015 and

2030 respectively. In spite of the low incidence of prostate cancer in Egypt the increase of the aging population, makes that prostate cancer will become ever more an enormous challenge (**Ibrahim et al., 2011)**.

Very few cases of prostate cancer are found in men under 50 years. Three-quarters of all cases are found in men aged 65 or more, and rates increase steeply with age. It is therefore more common in populations with higher proportions of elderly men. Prostate cancer amounts to 19% of new cases in developed countries and only 5.3% in developing countries **(Quinn and Babb, 2002).**

Some of the differences between countries might be due to interethnic differences in risk. African Americans have a markedly higher incidence than whites (82.5 versus 49.6 per 100,000). African Americans have a 9.8% lifetime risk of developing prostate cancer compared to 8% in whites. Similarly in Brazil the risk for black males was 1.8 times that of whites (**Parkin et al., 2005**). Incidence can be influenced by several risk factors including genetic susceptibility, environmental exposure in its largest sense and differences in health care and cancer registration (or a combination of these) **(Schroder et al., 2003).**

Mortality

Mortality rates for prostate cancer increased until the 1980s, but less marked than incidence, averaging 2%–8% every 5 years (**Stanford et al., 1999**). Especially in countries with the highest incidence increases, mortality rates did not follow the same pattern. Since the 1990s mortality declined in several developed countries as a consequence of decreased diagnosis of distant-stage disease and improved treatment **(Parkin et al. 2005; Hsing et al. 1999; Newcomer et al. 1997; Mettlin 2000; Schroder et al. 2003b**).

Predictions for age-standardized rates mention a continuing 11% decrease by 2015, although timing and the extent of the decreases vary widely among countries. The number of cancer deaths in the European Union, however, will increase in the future when the older age groups—where incidence and mortality rates are the highest—will become proportionally larger. By the year 2015 there will be a 20% increase of people aged 65 years and older and 50% more people will be 80 years and over. This demographic shift alone results in a 25% increase in predicted cancer deaths. The effect of the demographic shifts towards the elderly outweighs that of decreasing trends in mortality rates in the predictions of mortality towards 2015 (**Quinn et al., 2003**).For prostate cancer, which mainly involves the elderly, these trends will be important.

Mortality rates are based on incidence and fatality (the inverse of survival) of a cancer and reflect prognosis. Prognosis for prostate cancer is relatively good. With 221,000 deaths worldwide in 2002 it is a less prominent cause of mortality than might be expected considering the incidence. Mortality per year is 8.1 per 100,000 (age standardized according to the world population). Mortality rates for cancer in general differ less between developing and developed countries than incidence rates. For men, total cumulative mortality for all cancers before age 65 is 18% higher in developed countries. Differences in incidence are much larger. There are several reasons for this. A large group of cancers that frequently occur in developed countries and are associated with a Western lifestyle have a good prognosis: colon, rectum, breast and prostate cancer. Cancers of liver, stomach and oesophagus are more common in developing countries and have a poor prognosis. Prognosis in general is poorer in developing countries and the ratio of deaths to cases is less favorable, especially for