Bulletin of the *Transilvania* University of Braşov
Series VI: Medical Sciences • Vol. 6 (55) No. 2 - 2013

EPIDEMIOLOGICAL CONSIDERATIONS, RISK FACTORS, HISTOPATHOLOGICAL FORMS AND CLINICAL ASPECTS IN THE PROSTATE CANCER

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Abstract: *The incidence and the mortality rate of prostate cancer have a high variability everywhere in the world. The risk of developing prostate cancer is associated with old age, a positive family history, the Afro-American race and can be influenced by diet and a variety of other factors. The incidence of this malignant disease has increased substantially after the introduction of the screening method for the determination in the blood of the PSA (prostate specific antigen), the beneficial effect of this test on the mortality being the significant increase of tracing the number of the cases that are in curative stage.*

Key words: *prostate, PSA, epidemiology.*

1. Introduction

Malignant disease with a very frequent diagnosis, the prostate cancer represents the second type of cancer as frequency of occurrence among the male gender, after the lung cancer. With an incidence whose occurrence is directly proportional to the age of the patient, the prostate cancer records the highest rate of occurrence in Australia and New Zeeland [6], despite of a mortality rate extremely variable depending on the country and geographical area.

As it is one of the most accessible malignant diseases, from the diagnosis point of view, the prostate cancer benefits by an easy clinical examination of the target organ, the prostate. In other words, the screening of this disease consisting of "the common" but very important rectal exam, corroborated with the elementary preclinical investigation everywhere (the blood determination of the specific prostatic antigen and the eco-guided prostatic trans-rectal puncture-biopsy), have led inevitably to the premature and increased finding of new cases of prostatic cancer.

2. Epidemiological consideration

With a value of incidence in the year 2008, of 24.5 % at the European Union level and 13.6% at the global level [9], the cancer of prostate represents a significant

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problem of public health among the male population. In the case of our country, the incidence of this disease places it in the third place as frequency (9.7%) after the lung cancer and the colorectal cancer [9]. The highest rates of the incidence of prostate cancer are encountered in Australia, New Zeeland, North America, the Western Europe countries, and the lowest values in the countries from the South Eastern Asia.

From the point of view of mortality, the prostate cancer represents the sixth cause of death by malignant diseases in the male population [9], the highest value of this indicator being encountered in the areas with many Afro-American populations (the Caribbean area – 26.3/100000, the Sub-Saharan Africa 18-19/100000), and the lowest values in Asia (2.5/100000). In the European Union, the rate of mortality is 12.1/100000 [9]. Linked to the prevalence of prostate cancer, in 2008 it was estimated that throughout the world there were 3.2 million patients suffering from this illness, diagnosed in the last 5 years [9].

3. Risk factors

Epidemiological studies have revealed the presence of numerous risk factors in close relationship to the development of prostate cancer.

3.1. Age

The incidence of the prostate cancer reaches significant values and is growing exponentially starting with the age of 50, the highest value being recorded for the age group of 70-74. The percentage of patients diagnosed with prostate cancer under the age of 50 years is less than 0.1 % of the total number of patients with this illness [3]. In more than 75% of the cases, the disease appears to the patients over 65 years old. [3]

3.2. Family and genetic factors

The risk of prostate cancer is significantly increased in patients with 1st and/or 2nd degree relatives diagnosed with this illness. In case of the existence of a single 1st degree relative with prostate cancer, the relative risk is doubled. For the cases where there are 2 or 3 relatives affected, the value of the relative risk varies between 5 and 11. [20]

It is known that approximately 90% of the prostate cancers are considered to appear sporadically, only 10% expected to be in the family. It has been found that in the latter case, the age of the appearance of the prostate cancer is rather small, as compared with the forms which are rather occasional (< 55 years). [18]

The incidence of the prostate cancer varies depending on the race as well. Thus, the incidence at the Afro-American men, as compared with the Caucasian men, it is increased by 1.6 times [16], fact explained by the level of free testosterone greater by 15% at the men in the first category, as compared with those of white skin. [3][18]

At the populations of the same race, but resident in different geographical areas, have been found statistical differences of the epidemiological data concerning the prostate cancer, fact which was explained by the existence of certain environmental factors (exposure to toxins, diet) that play an important part in starting this disease. The incidence of prostate cancer in the Japanese population in Northern America is much higher as compared to the rate of the incidence encountered at the male population in Japan.

3.3. Diet

Data showed that the diet rich in polyunsaturated fats is in close relationship to the development of prostate cancer [3]. The increased

contribution of meat and fats would raise the risk of the appearance of the disease, while the consumption of raw vegetable would have a protective role.

It is assumed that the increased addition of calcium would have a more favourable role in the prostate cancer, while vitamin E and selenium may diminish the appearance. The 2008 data show that the addition of vitamin E was associated with the decreased risk of advanced prostate cancer [15]. The izoflavones existing in the soybeans would also have a role in the decrease of the occurrence of prostate cancer.

3.4. The alcohol

Although there are no precise epidemiological data, studies have shown that men who consume daily three glasses of strong liquor have an increased risk of the appearance of prostate cancer [7]. It was not noticed an increased risk to consumers of wine or beer. In certain trials, moderate consumption of red wine (one to 3 glasses/week) has proved to be a factor of protection for the prostate cancer [7].

3.5. Smoking

It has not been proved an association between smoking and the increased risk of the appearance of the prostate cancer, although smoking involves exposure to toxic substances (such as cadmium) and leads to an increase in serum levels of androgen hormones [3].

3.6. Obesity

In the case of obesity, it has not been demonstrated the direct association between it and the prostate cancer.

3.7. Sexual activity

The exposure to infectious agents – papiloma viruses (HPV) and their role found in the occurrence of the cervical cancer have called for assumptions that there is a link between sexual behaviour and the development of prostate cancer [3]. It has not been demonstrated that the risk of its occurrence is significantly changed by this element.

3.8. Vasectomy

A meta-analysis made in 2002 showed that men that suffered a vasectomy have a relatively high risk of 1.37 for developing prostate cancer, as compared to the men that have not suffered a vasectomy [3].

The rate of the risk has an ascending tendency as time passes from the vasectomy.

4. Histopathological forms

Although there are a variety of histopathological forms, the most frequent type of malignant tumour of the prostate is the common adenocarcinoma or acinar, which is encountered in approximately 97% of the cases. [1]

On a distant place two, it is situated the prostatic primitive urotelial carcinoma, met in a percentage of approximately 0.7 -2.8 with starting point either at the urotelium of the mucus membrane of the prostatic urethra either at the periurethral structures of the prostatic ducts [18]. Both histological types were placed in the category of tumours with epithelial origin. There are other histopathological forms, but they have extremely reduced incidence [6].

The classification of histopathological prostate tumours forms:

Tumours with epithelial origin:

- Adenocarcinoma (acinar)
- Squamous tumours

- Basal cell tumours (basocelular)

Neuroendocrine tumours;
Stromal prostatic tumours;
Malignant mesenchymal tumours:

- Leimyosarcomas
- Rhabdomyosarcomas
- Chondrosarcomas
- Angiosarcomas
- Others

Hematolymphoid tumours:

- Lymphoma
- Leukaemia

Tumours with germ cells;
Nephroblastoma (Wilms Tumour);
Melanoma;
Metastatic tumours - secondary after pulmonary, skin, gastro-intestinal and testicular primary tumours or by direct extension (urinary bladder, rectum, urethra).

For the histopathological description of the prostate adenocarcinoma it is used the grading score Gleason, accepted in 1993 by the WHO. It refers to the architectural appearance encountered in the tissue specimens of the prostatic adenocarcinoma.

There are described 5 degrees, from 1 to 5, form the best differentiated, to the least differentiated /undifferentiated. Within the framework of a tumour may be encountered areas with varying degrees of differentiation. The Gleason score (which can have values from 2 to 10) shall be obtained by aggregating the degree described for the predominant histological type with that described for the secondary histological type. Tumours with Gleason score of between 8 and 10 are considered to be particularly aggressive, quick with the tendency of local development and distance (metastasis).

In the histopathological prostatic specimens have often been described cellular proliferations in the epithelium of ducts and acinas, without being affected their architecture. These cytological anomalies, brought together under the name of prostatic intraepithelial neoplasia (PIN) may vary from minimum differences to differences similar to those encountered in malignant lesions. Depending on morphological aspects, the lesions have been grouped in intraepithelial neoplasia with low grade (Low Grade PIN) or high grade (High Grade PIN). The presence of Low Grade PIN does not increase the risk of occurrence of prostate cancer in a future biopsy [7], [12]. On the other hand, the rate of detecting prostate cancer, for the patients to whom the first biopsy showed High Grade PIN, is approximately of 30%. [4], [13]. In case of detecting High Grade PIN, the rate of a future occurrence of prostate cancer is directly proportional to the number of biopsies in which High Grade PIN is present [18].

The existence of High Grade PIN was strongly associated with the adenocarcinoma slightly or vaguely differentiated [2], [8], [14].

5. Clinical aspects

The prostate cancer develops in the majority of cases in the peripheral prostatic zone, and the low urinary symptoms due to local tumour progression appear only in advanced stages. Whereas the prostate cancer frequently coexist with benign hypertrophy of the prostate, urinary symptoms may be caused by the benign disease.

Lower urinary tract symptoms or LUTS, are divided in:

- Irritating or storage symptoms: the nocturnal and daily polachiuria, then sensation of emergency urination and dysuria,
- Obstructive or draining symptoms: sensation of difficulty in initiating urinating, drop in the urinary jet pressure, cutting-off urinating. The obstructive symptomatology can evolve gradually by

incomplete retention of urine, initially without the bladder distension, complete retention of urine or false urinary incontinency. The tumour invasion of urethra and of the external urinary sphincter may determine the appearance of "real" urinary incontinency.

- Post urinating symptoms: sensation of incomplete drainage of the urinary bladder.

In the early stages of advanced local evolution (by invasion of the urinary bladder) can be encountered hematuria, collective lumbar pains (via uni/bilateral ureterohidronefrosis), nausea, vomiting, dehydrated teguments, (renal insufficiency).

Hemospermia, erectile disfunction - major erectile disorder or sexual impotence are described slowly, and appear through the invasion of the seminal vesicles, ejaculatory ducts and the periprostatic neurovascular bundles.

The pelvi-perineal pain, rectoragies, constipation or rectal obstruction symptoms are rare, due to tumoral locoregional extension.

Clinical panel met in patients diagnosed with prostate cancer is complemented by signs and symptoms caused by the presence of secondary determinations.

The bone metastasis in the toraco-lumbar column, the pelvic bone, the joints of coxo-femoral artery, are manifested through loco regional pains of increased intensity and which do not respond to the usual pain killers.

Bone-marrow invasion determines normocrome and normocitemic anemia, represented by the appearance and general whiteness of the skin. The metastasis present on the vertebral body may trigger neurological symptoms through the spine compression – paresthetis, paraparesis, paraplegia [2], [10].

Certain statistics showed that in 17% of patients, the bone pain is the first clinical manifestation of the disease.

The extended lymphatic metastasis encountered in advanced stages (groups of internal and external diagnosis, iliac wings, obstructions, para-aortical) are likely to cause significant edema of the lower limbs.

The obstructive jaundice or hepatic pain may announce the presence of hepatic secondary determinations, and dry cough, whether or not coupled dyspnoea or fever may suggest the pulmonary artery metastasis. Persistent headache, to patients in advanced stage can represent a clue for this cerebral metastasis.

In a very small percentage, the evolution of prostate cancer may become associated with the appearance malignant retroperitoneal fibrosis or with the paraneoplasic symptoms (poliglobulya, hipercalcemy, intravascular coagulation).
In the last 10 years, extensive use of the prostate-specific antigen as a method of screening for cancer of the prostate has led to an increase in the number of patients diagnose in early stages. In spite of this fact, the percentage of patients in metastatic stage when first diagnosed has not fallen significantly.

References

1. Ackerman, D.A., et al: *Analysis of risk factors associated with prostate cancer extension to the surgical margin and pelvic node metastasis at radical prostatectomy*. In: J Urol (1993), 150: 1845-1850.
2. Ambert, V.: *Prostate cancer diagnosis (Diagnosticul in cancerul de prostata)*. Bucuresti. Editura Universitara „Carol Davila", 2011.
3. *Campbell-Walsh Urology*, nineth edition. In: Wein A.J, (editor in chief). Saunders Elsevier, Philadelphia 2007.
4. Davidson, D., Bostwick, D.G., et al,: *Prostatic intraepithelial neoplasia is a risk factor for adenocarcinoma:*

predictive accuracy in needle biopsies. In: J Urol (1995) 154: 1295-1299.
5. Dennis, L.K., Dawson, D.V., et al.: *Vasectomy and the risk of prostate cancer: a meta-analysis examining vasectomy status, age at vasectomy, and time since vasectomy*. In: Prostate Cancer Prostatic Dis. (2002) ;5(3):193-203.
6. Eble, J.N., Sauter G., et al.: *Pathology and Genetics of Tumors of the Urinary System and Male Genital Organs*. World Health Organization (ed.), IARC Press, Lyon, 2004.
7. Epstein, J.I., Potter, S.R., et al.: *The pathological interpretation and significance of prostate needle biopsy findings: implications and current controversies.* In: J Urol (2001), 66: 402-410.
8. Erbersdobler, A., Gurses, N., et al: *Numerical chromosomal changes in high-grade prostatic intraepithelial neoplasia (PIN) and concomitant invasive carcinoma.* In: Pathol Res Pract (1996), 192: 418-427.
9. Ferlay, J., Shin, H.R., et al.: *GLOBOCAN 2008 v1.2, Cancer incidence and mortality worldwide: IARC CancerBase No. 10*. Lyon, France: International Agency for Research on Cancer; 2010. Available at: http://globocan.iarc.fr. Accessed: May 2011.
10. Huddart, R.A., Rajan B., et al: *Spinal cord compression in prostate cancer: treatment outcome and prognostic factors.* In: Radiother Oncol (1997) 44: 229-236.
11. Iacovou, J.W., Marks, J.C., et al: *Cord compression and carcinoma of the prostate; Is laminectomy justified?* In: B. J. Urol (1985); 57; 733-736.
12. Keetch, D.W., Catalona, W.J.: *Prostatic transition zone biopsies in men with previous negative biopsies and persistently elevated serum prostate specific antigen values.* In: J Urol (1995) 154: 1795-1797.
13. Kronz, J.D., Epstein, J.I. et al.: *Predicting cancer following a diagnosis of high-grade prostatic intraepithelial neoplasia on needle biopsy: data on men with more than one follow-up biopsy.* In: Am J Surg Pathol (2001) 25: 1079-1085.
14. Montironi, R., Thompson, D., et al: *Premalignant lesions of the prostate.* In: *Recent Advances in Histopathology* D.G. Lowe, J.C.E. Underwood (eds.). Churchill Livingstone, Edinburgh, 1999, pp. 147-172.
15. Peters, U., Littman, A.J., et al: *Vitamin E and selenium supplementation and risk of prostate cancer in the Vitamins and lifestyle (VITAL) study cohort*. In: Cancer Causes Control (2008); 19: 75–87.
16. Ries, L., Melbert, D., et al.: *SEER Cancer Statistics Review, 1975-2005*, in Prostate Cancer, Table XXXII – 4, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2005/, based on November 2007 SEER data submission, posted to the SEER web site, 2008.
17. Scott, R. Jr, Mutchnik D.L., et al: *Carcinoma of the prostate in elderly men: incidence, growth characteristics and clinical significance.* In: J Urol (1969), 101: 602-607.
18. Sinescu I., Gluck G.: *Tratat de Urologie (Urology*), 3rd volume. Bucuresti. Editura Medicala, 2008.
19. Stanford, J.L., Stephenson, R.A., et al.: *Prostate Cancer Trends 1973-1995*. In: SEER Program, National Cancer Institute, NIH Pub., No. 99-4543. Bethesda, MD, 1999.
20. Steinberg, G.D., Walsh, P.C. et al.: *Family history and the risk of prostate cancer.* In: Prostate (1990), 17: 337-347.