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# PROSTATE CANCER WHICH AFFECTS AN ELDERLY MAN IS A FEATURE OF SENESCENCE (CELLULAR) — A BIOLOGY PHENOMENON

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**Some prostate cancers are clinically significant (i.e. life-threatening) but others are not. Small proportion of elderly men dies of prostate cancer while most of them harbor tumor lesions in their prostates. The aim of this paper was to present late-life form of the prostate cancer, which differs from its aggressive counterpart that affects men between 55–65 years old and younger. The differences can be found in carcinogenesis risk factors, cancer biology and finally patients' survival. The most important is that these two clinical (age-related) forms of the prostate cancer are still undistinguishable in clinico-pathology reports and patients bearing different diseases are offered the same treatment. Potential mechanisms leading to development of the late-life clinically indolent prostate cancer are discussed. It seems that the key abnormalities are proteins involved in control of regenerative potential and cell senescence.** ***Conclusions:*** **We postulate that late-life low-grade (clinically indolent) prostate cancer subcategory should be established. This type of «cancer» should rather be viewed as a senescence-related feature and probably not treated at all.**

***Key Words:*** **prostate cancer, late-life onset cancer, cellular senescence, stem cells, indolent cancer.**

## EPIDEMIOLOGY OF THE PROSTATE CANCER IN ELDERLY MEN

Prostate cancer is diagnosed (and often treated) in 1 of 6 men, however it is the cause of death of only 3% of men [1]. It is the most commonly diagnosed single malignancy (almost 220,000 cases in 2007) in the United States [2]. Prostate cancer more often affects elderly men and thus it is a bigger health concern in developed countries. Increasing incidence rates in these countries are likely to be a part of the widespread and still increasing prostate-specific antigen testing and as well increased life expectancy. Prostate-specific antigen screening is associated with psychological harms, and its potential benefits remain uncertain. This considerable amount of prostate cancer cases would be much higher if it would included all the cancer cases in elderly men that remain undiagnosed under normal circumstances. According to some reports the chance of finding cancer within the prostate is 29% in population of males older then forty and this percentage is rising among elderly. The probability of finding clinically significant prostate cancer obtained from biopsy in an autopsy study is only 43% among all diagnosed prostate cancers. The results of autopsy and screening studies suggest that prostate cancer may be found even in about 80% of males over the age of 80, but most of those tumors are clinically insignificant [3–5]. It is interesting why only a small proportion of elderly men die of prostate cancer while most of them harbor lesions in their prostate glands. This phenomenon occurs not because of highly effective treatment as according to some studies. Such statistical results of prostate cancer management are rather because of indolent biology of most of them. The majority of cancers are not even diagnosed in elderly. These cancers that do not influence patient's survival are referred to as 'clinically irrelevant' or 'latent'. According to Parker *et al.* [6], there is a significant difference in disease course dependent on patient's age at diagnosis — patients over 70 have much lower chance of dying from prostate cancer than those aged 55–60. The age of patient who was diagnosed cancer is too simple explanation of the observed phenomenon. This would indicate that the proportion of 'clinically irrelevant' cancers increases with age. Nevertheless, for most clinically relevant cancers curative treatment makes the difference between life and death. The management of prostate cancer includes surgery, radiation therapy, hormone therapy, chemotherapy, cryotherapy, radiofrequency and ultrasound therapy and combinations of these methods. It seems that such an armamentarium should lead to substantial improvement of treatment results. However, such a trend may not be observed. While prostate cancer in some cases follow an aggressive and fatal path, in a significant proportion of cases it behaves in an entirely different way, having no impact on patient's survival. Some authors suggest that prostate cancer may be overdiagnosed even in 30–50% of cases, especially in elderly men, and that many of these patients are treated unnecessarily [7–9].

Why some prostate cancers are clinically significant (i.e. life-threatening) but others are not? It seems that the key are proteins involved in control of regenerative potential and cell senescence. Cells from organisms with high renewable potential tissues are permanently withdrawing from the cell cycle in response to diverse stresses. This response, termed cellular senescence, is controlled by the tumor suppressor proteins and constitutes a potent anticancer mechanism. Nonetheless, senescent cells acquire

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genotypic changes that may contribute to aging and certain age-related diseases, including late-life cancer [10]. It seems that «late-life low-grade» prostate cancer is a good example.

## AGE INFLUENCES ON TUMOR BEHAVIOR

There exist other models of differences of biological/clinical behavior of particular types of tumors occurring in different age populations. These examples include soft tissue tumors, especially embryonal rhabdomyosarcoma, which typically occurs in first years of life. Use of nowadays treatment modalities give over 90% survival. Whereas the same type of tumor occurring in adult or elderly, however as a rare entity, is known as a very malignant tumor with poor prognosis [11]. Same is true for majority of so called «–blastoma» tumors, e.g. medulloblastoma, Wilm's tumor (nephroblastoma), acute lymphoblastic lymphoma. Some authors were postulating that rather good prognosis of aforementioned tumors in children population reflects a different mechanisms of tumor development. As such tumors have morphology of embryonal (early stage of differentiation and maturation) structure it was suggested that their development depends on misshaped local signaling responsible for proper cell differentiation and then maturation [12, 13].

## IS THERE A LINK BETWEEN CARCINOGENESIS AND STEM CELL SENESCENCE?

Stem cells tissue renewal ability suggests that they are protected from ageing processes. Tissue ageing can be explained as a reduction of mitotic potential of its stem cells. Apart from exhaustion of mitotic potential, the ability of stem cells to differentiate into certain other cell types is also limited, for example hematopoetic stem cells lose the lymphopoetic ability while maintaining myelopoetic [14, 15]. And this is a natural pathway of cell differentiation. However, it should be viewed according to the phenomenon that bone marrow of elderly is less cellular and less effective — keep in mind increased infection susceptibility in elderly patients. This age related change of stem cells differentiation profile has numerous consequences. Disturbance of the balance of number and type of cells in tissue increases the risk of carcinogenesis. Marrow haematopoetic cells, and probably all stem cells, are sensitive to changes in their environment — cell-cell and cell-matrix interactions. These changes may potentially induce carcinogenesis by altering cell differentiation profile and also reduce tissue regenerative potential by limiting multipotentiality of stem cells, even leading to unipotential differentiation directed into cell type other than one required for tissue renewal [14, 16]. Not only epigenetic factors, but also the ones related to internal information in DNA changes (for instance DNA methylation) influence stem cells ageing [17]. Expression of certain genes change during stem cells ageing, expression of the ones connected with cell metabolism decreases, while expression of genes encoding proteins taking part in cell adhesion is increased [14]. Genome stability, which is closely related with genome repair processes, also plays an important part in stem cells ageing. Reduced expression of proteins taking part in DNA repair processes has been observed in ageing haematopoetic stem cells. This phenomenon also increases the risk of carcinogenesis and reduces stem cells tissue regeneration potential [14, 16, 18]. Stem cells ageing processes has an impact on cell division. Differentiated diploidic cells undergo symmetrical division resulting in two daughter cells with lower proliferative potential. Cells divide until they reach replication senescence, a state discovered in vitro and described by Hayflick and Moorhead [19]. It is difficult to clearly define the role of cells senescence as the genetic mechanisms involved in organisms ageing are still not fully explained. Hayflick [20] suggests that genetic processes programmed to ensure proper organism development until the reproductive age are the basis of ageing. While in this part of organism development, biological phenomena laws appear to have a clear purpose, functioning of the organisms in the period of time between achieving reproductive maturity and death is more problematic. An important question is whether cells and organisms ageing is a result of the same genetic program that leads to reproductive maturity, inability of repairing accumulated random changes leading to the loss of proliferative and regenerative potential or a combination of both processes [20]. In case of cells and single-celled organisms replicative life span can be defined as the number of daughter cells produced by a mother cell before senescence [21]. There is a growing body of evidence that ageing processes in stem cells are similar to the ones in differentiated ones [22]. This phenomenon is more complex because stem cells must perform two opposite functions: they must multiply, which leads to cell senility, and simultaneously they must maintain replicative youth. The number of cells with numerous replication errors, including stem cells, increases in tissues of ageing organisms, which inevitably leads to death of cells and the entire organism [20, 23–25]. Cell proliferative potential depends on its age defined as number of divisions the cell has already underwent. Determination of cell age based on accumulated replication errors and DNA metylation is a reliable information about number of cell divisions [26, 27]. This method, however, has a limited reliability because of differences in stem cells division kinetic in tissues. It also does not allow to determine cell absolute age. Cell age based on number of divisions is different in tissues where stem cells divide continuously, i.e. intestine epithelium, different in tissues with periodical growth (i.e. hair) in which stem cells die with every growth cycle and finally different in tissues with low mitotic rate, for example nervous tissue. Cells' mitotic age may be significantly different in different tissues of an organism [27]. An important question is whether the absolute age of stem cells has a biological significance. Stem cells ability to proliferate and differentiate decreases with organism age [15]. Num-

ber of fetal defects increases with chronological age of gametes indicating that chronological age of cells is also a significant factor. Determination of cell mitotic age is further complicated by the fact that in case of stem cells different types of cell division occurs, some of which were only described in theoretical models [28, 29]. According to the most common concept of stem cells division, the asymmetric division theory, when a stem cell divides, one of daughter cells remains in stem cell layer and the other one differentiates. This division type can be observed in epithelia and nervous tissue of mammals. In many tissues, however, asymmetric divisions were not observed [29, 30]. It has not been proven whether asymmetric division model is an ideal one providing an inexhaustible pool of progenitor cells. Other stem cells division models perform the same functions and are equally probable. A stem cell can also undergo symmetrical division resulting in two daughter stem cells or two differentiating cells. In this case, the type of division is influenced by the stem cell's environment [31–34].

Brecher *et al.* [35] define clonal succession, a stem cells division theory originally proposed by Kay [36], as a continuous release of stem cells for differentiation. Kay in his hypothesis assumes the existence of a pool of stem cells, some of which undergo symmetrical division and differentiation.

Cells', including stem cells, ageing is connected with progressing deterioration of genes functions, which together with certain toxic factors, consecutive cells division and loss of DNA repair abilities lead to cell's death. Epigenetic factors also have a significant influence on cells ageing. All these processes reduce cells regenerative potential and increase the risk of neoplastic transformation [14, 31].

## DOES CELLULAR SENESCENCE EXPLAIN INDOLENT PROSTATE CANCERS AT ELDERLY?

Tissue aging is connected to exhaustion of mitotic potential of stem cells responsible for its renewal. Stem cells must take part in two seemingly opposite processes, in first which leads to aging and loss of replication potential of stem cells and in the second in which these cells have to preserve this potential. Normal, differentiated diploid cells undergo symmetric division resulting in two daughter cells with lower proliferative potential. Cells divide until reaching 'replication senescence', discovered almost fifty years ago. Aging processes are similar in differentiated cells and stem cells [22]. In later, apart from reduction of mitotic potential, the ability to differentiate is also reduced in these cells [14, 15]. Normal prostate epithelial stem cells and prostate cancer stem cells have a similar phenotype. These cells have a similar expression profile of certain proteins, such as CD44, CD133, CXCR4 receptor and integrin $\alpha 2\beta 1$. It should be emphasized, that immortalization of prostate epithelial cells makes their phenotype similar to stem cells. Normal epithelial prostate stem cells and prostate cancer cells have similar proliferative and regenerative abilities, the latter ones also have metastasize and invasive abilities [37]. Cancer cells are believed to originate from stem cells population. Cancer cells with luminal phenotype are unable to form tumors in animal models, which confirms the hypothesis of cancer stem cells role in tumor formation [38–40]. Stem cells are sensitive to changes in interaction between cells and between cell and extracellular matrix. These changes may, along with age, result in change of differentiation profile of stem cells, which is connected with increased risk of carcinogenesis, and reduced regeneration potential. In extreme situation it may even lead to 'unipotentiality' with cell differentiation not directed to tissue renewal or generative layer atrophy [14, 15, 38]. In prostate cancer, atrophy of generative layer of acinar epithelium can be observed. P63 protein is absent in prostate cancer cells. Apart from epigenetic, stem cells aging is influenced by DNA-related phenomena, like genome stability [17]. An age-related decrease in expression of DNA-repair proteins can be observed, which impairs genome stability and increases the risk of carcinogenesis. In aging tissues, the proportion of cells with multiple replication errors increases, also among stem cells. Some of such events were attributed to increasing levels of methylation. Such models were tested in laryngeal, hematologic, and colon neoplasms. Number of replication errors and degree of DNA methylation are correlated with number of cell divisions and also with cell age [27]. Cells aging, reduction of regenerative potential and probability of cancer transformation are also influenced by epigenetic factors [14, 31]. The function of P53 protein is an example of mentioned adaptation to mutagenic factors. This protein is inactive in young cells, which allows them to maintain high regenerative potential. Young cells have a low number of accumulated mutations and thus low P53 activity in these cells does not result in increased risk of carcinogenesis. In older cells, when DNA repair is necessary, increased P53 activity is an important factor limiting cell divisions. This allows cells to repair replication errors and decreases tissue regenerative potential — cells proliferate slower but maintain genome stability. As a result of cell aging, P53 protein may undergo mutation and lose the ability to regulate cell cycle. However, in colon cancer model P53 expression was found to be increased, but it is inactive form of mutated protein. In such circumstances cells regain the ability to proliferate but, because of accumulation of mutation and other changes in genome, their ability to regenerate proper/normal tissue is diminished. Such cells often undergo cancer transformation as a result of numerous accumulated mutations [16, 41–44]. Mechanisms that regulate regenerative potential and prevent carcinogenesis are similar. Cell aging in stem cells disturb the balance between the ability to regenerate and processes preventing oncogenesis. Carcinogenesis in an elderly is a process connected with decreased regenerative potential of tissues. Prostate cancer, with basal layer atrophy

(no P63 protein expression) and acinar neoplasia are examples of such processes. Prostate cancer in an elderly is probably a consequence of both, cellular senescence and diminished regenerative potential.

## CONCLUSIONS

Prostate cancer could be divided into two distinct clinical phenotypes with similar pathological features. One type is an aggressive prostate cancer, which is a life-threatening disease usually diagnosed in relatively young men between 55–65 years old [45]. The second one is a clinical insignificant cancer, which does not affect life expectancy. Most of these cancers are diagnosed in men around 75–80 years old. These men have usually elevated prostate specific antigen (PSA). The most difficult task is the identification and early radical treatment of all clinically significant cancers and possibly the lowest rate of positive «false» diagnoses of insignificant cancers [46]. There is no need to treat patients with insignificant cancers, because no profit from this management will be expected. The next problem is cost-effectiveness in global (population) based studies.

The main problem is that many patients with late-life low-grade prostate cancers are offered an armamentarium of treatment methods. The treatment of prostate cancer is often connected with many side effects related to extensive surgical procedures, hormonal manipulations and radiation therapies. All these treatment methods have a negative effect on the quality of life of elderly people.

Based on clinical data and experimental work a subtype of late-life low-grade prostate cancer subcategory should be established. This «cancer» should rather be viewed as a senescence-related feature and probably not treated at all.

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