The Influence of Obesity on Prostate Cancer Diagnosis and Treatment

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1. Introduction

To date there were only a few risk factors for developing prostate cancer (Pca) like advanced age, skin color and family history (Crawford, 2003). For the long time obesity was considered a negative feature which may contribute to chronic diseases like hypertension or diabetes, but its relationship with cancers was unknown. Last years revealed the obvious truth that such relationship exists and may be very strong. The problem seems to be very important given that obesity is very common, especially in western countries.

Over the past 25 years, the number of obese men has increased from 15% to 30% in USA. In 2000 66% of adults in U.S were classified as overweight or obese (Flegal et al., 2002). Nowadays no one denies that overweight and obesity is an independent risk factor for developing colon cancer or post-menopausal breast cancer.

Relationship with other cancers is still discussed especially in case of Pca. While the connection between obesity and chronic internal diseases is simple to explain, its relation to cancers is not so unequivocal. Most theories indicate the permanent chronic inflammation in obese which may contribute to oncogenesis.

Dis Hormonose observed in obese consists of high levels of insulin, insulin growth factor – 1 (IGF-1) (Chan et al., 1998, 2002), leptin, estrogens, and low levels of androgens. Insulin and IGF -1 are strong mitosis activators which may explain such “oncopotential”. On the other hand low levels of testosterone and high of estrogen should protect men from developing Pca. It is only a simple example why the relation between obesity and prostate cancer may be very complex.

2. Nutrition

Several products are thought to be associated with increased risk for developing prostate cancer, others are known to act protectively. To the first group we may include saturated fats, red meat and dairy products (Kondo et al., 1994; Shirai, et al., 1997; Torniainen et al., 2007). In the second group we will find vitamin A, D and E, selenium, lycopene, fitoestrogens and isoflavones (Clark et al., 1998; Heinonen et al., 1998; Imaida et al., 2001; Kato et al., 2000; Schwartz et al., 1990). Vitamin A, D, E, selenium, lycopene and fitoestrogens are the compounds of fruits, vegetables, soya and tea. Vitamin A is known to improve cell apoptosis (Pienta et al., 1993; Young et al., 1994). Vitamin D facilitates cell differentiation (Hedlund et al., 1997). It was hypothesized that it may increase PSA
doubling time (PSA DT) (Beer et al., 2003). Selenium is a known antioxidant (Clark et al., 1996). In Asia, where soya and tea consumption (fitoestrogens) is higher in comparison to western countries, the prevalence of prostate cancer is lower (Adlercreutz et al., 1993; Fotsis et al., 1993). Several studies tried to prove the favorable impact of vitamin E in Pca prevention (Knekt et al., 1990; The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group, 1994). However, it has to be stressed that such influences are still rather hypothesis than evidence based facts. SELECT (Selenium and Vitamin E Comparison Trial) trial failed to demonstrate the favorable impact of selenium and vitamin E on Pca morbidity (Ledesma et al., 2011).

3. Obesity

It is of paramount significance to distinguish between high-risk and low-risk patients depending on extent of obesity. There are many ways to determine the range of overweight and obesity. The most prevalent is body mass index developed by World Health Organization. However, it does not differentiate fat mass from muscle mass. That is why waist - hip ratio (WHR) is more commonly applied while assessing the central adiposity, and correlates much stronger with hormonal alterations (the importance of that finding is emphasized later in the text) than BMI.

There are various theories concerning the influence of obesity on the natural development, diagnostics or progression after radical treatment of Pca. The Health Professional Follow-Up Study was based on 47757 men who were observed for 14 years and showed that relative risk for developing prostate cancer was 0.52 in obese compared to non-obese men (Giovannucci et al., 2003).

The 5 times increased percentage of biochemical recurrence after radical prostatectomy observed in Afro-Americans, compared to Euro-Americans, is sometimes explained by 3 times more frequent presence of overweight or obesity among the former. It also may result from the polymorphism of the androgen receptor which causes higher PSA concentration in Afro-Americans. On the other hand two large studies failed to demonstrate disastrous impact of obesity on prostate cancer morbidity (Andersson et al., 1997; Rapp et al., 2005).

Not only the absolute value of BMI seems to be important when assessing the patient’s risk. It was shown that also gaining weight at the greatest rate of ≥ 1.5 kg/year between 25 years of age and time of Pca diagnosis will result in more rapid biochemical failure after radical treatment (Strom et al., 2005).

The influence of obesity on Pca is definitely negative, including the following:
1. dishormonose – abnormal hormone concentrations, which induces the intensification of diagnostics and at the same time postpones proper treatment
2. comorbidities, which pushes the prostate diagnostics into the background and consequently patients suffer from more advanced forms of prostate cancer
3. difficulties in per rectum examination in obese patients,
4. difficulties during transrectal ultrasound (TRUS) of the prostate and prostate biopsy (due to larger prostates in obese patients) (Freedland et al., 2006).
5. difficulties during radical prostatectomy and radical radiotherapy due to:
   a. technical problems (larger hooks, smaller operational field)
   b. larger prostates observed in obese patients (much problem while conducting nerve-sparing technique)
6. Unfavorable postoperative features especially higher rate of:
   a. high grade disease
   b. positive surgical margins
   c. extraprostatic extension (pT3a)
   d. lymph node metastases (N+)
   e. biochemical recurrence
   f. fatal disease

7. Hemodilution (explained later)
Lastly it was proved that the unfavorable impact of obesity on Pca may be explained by genetic examinations. It was hypothesized that the AA genotype of rs9939609, which is associated with an increase in BMI, would protect against non-aggressive prostate tumors whilst increasing the risk of aggressive prostate tumors (Lewis et al., 2010). The abovementioned study gave us only weak proof of such correlation.

4. Prostate cancer cells and adipocytes
Skeletal metastases are most common in advanced Pca. Metastases are known to be osteoblastic ones. Prostate cancer cells are absorbing lipids directly to develop and progress, that is why bone marrow is so common place of metastases.

It was also experimentally shown that bone marrow without adipocytes is less attractive for prostate cancer cells to reside (Brown et al., 2006). It was even suggested that lowering lipid levels with statins will impact the progression of prostate cancer, but this assumption turned out not to be true (Platz et al., 2006).

5. Sex hormones
As stated in the introduction in obese levels of sex hormones are different from that observed in normal weight people. Prostate is hormone-sensitive gland and therefore androgens are needed for its development.

Also prostate cancer is hormone-sensitive and testosterone is known to accelerate its progression to advanced and metastatic form while estrogens inhibit such progress. This finding led us to application of castration (surgical or pharmacological) in the treatment of advanced or metastatic prostate cancer.

However, the relation between dishormones and prostate cancer is not so unequivocal. Testosterone also influences the differentiation of prostate cells (but not prostate cancer cells) to mature forms, while estrogens have contrary impact and therefore may lead to poorly differentiated Pca (Massengill et al. 2003; Schatzl et al., 2001).

6. Aggressive prostate cancer
It is also assumed that PCa in overweight people is more aggressive. Usually it was stated that Pca with Gleason score > 7 was significantly more frequent in obese patients. Not all authors agree with that hypothesis (Chyou et al., 1994; Major et al., 2011; Nilsen et al., 1999; Rodriguez et al., 2007; Schuurman et al., 2000; Snowdon et al., 1984).

Authors emphasize that central obesity as the outcome of excessive fat accumulation results in glucose intolerance, high blood pressure, atherosclerosis, cardiovascular disease, insulin resistance, altered metabolic profile, metabolic syndrome, and obesity-related lipid
disorders (Hsing et al., 2007). Especially insulin resistance, higher IGF-1 and leptin levels are recognized responsible for such aggressiveness (Hedlund et al., 1994; Prabhat et al., 2010). IGF-1 is involved in angiogenesis, responsible for bone metastases and developing androgen-independent progression of Pca. Leptin is responsible for cell migration and growth factor expression in hormone-resistant cells of Pca.

It is not proven that worse treatment outcomes in obese patients are due to unfavorable features of prostate cancer itself. In one of the studies it was reported that obesity was positively correlated with clinical progression independently of prostate cancer grade, stage and primary treatment (Gong et al., 2007). Higher rate of cancer progression is also due to unfavorable features of obese men after radical prostatectomy. It was proven that increased BMI is associated with high grade disease, positive surgical margins, extraprostatic extension of the disease and lymph node metastases. Biochemical recurrence after radical prostatectomy is also more frequent in obese patients compared to non-obese men (Freedland et al., 2005).

7. Androgen deprivation therapy (ADT)

Pharmacological castration with GnRH agonists is the standard treatment for patients with locally advanced or metastatic Pca. However, it is burdened with several adverse effects like osteoporosis, loss of libido, erectile dysfunction and finally metabolic syndrome. Increased levels of total cholesterol, LDL and decreased HDL, diabetes and hypertension contribute to higher risk of acute coronary syndrome (ACS).

Obese patients receiving ADT are at highest risk for developing ACS as ADT therapy and obesity shares the cardiovascular risk through the metabolic syndrome. They should be constantly monitored and treated accordingly (Cleffi et al., 2011). Osteoporosis in Pca is not only the result of cancer itself. Osteoblastic metastases of prostate cancer contribute to pathologic spine fractures which may be fatal eventually. Immediate spine decompression in orthopedics department is indicated in such condition.

The situation may be worse when patient is given ADT. I was proven that hypogonadism leads to osteopenia and finally to osteoporosis. As obese patients have lower levels of testosterone, abovementioned unfavorable factors may contribute to pathologic fractures.

To prevent such mournful course patients are advised to take bisphosphonates (alendronic, zoledronic, clodronic acid, etc.) or denosumab (RANK ligand inhibitor) which inhibit osteoclasts and slow down progression of the disease.

8. Hemodilution

Undoubtedly, a negative feature of PSA concentration is the fact that it is subject to hemodilution. Some authors claim that in overweight and obese patients PSA concentration is lower, which is, in the first place, caused by the aforementioned phenomenon. This phenomenon is supposed to consist in the dissolution of PSA mass in a large amount of plasma, finally resulting in lower PSA concentration. PSA is a protease which physiological function consists in liquefying semen.

Every man is characterized by a quite invariable amount (mass) of this secreted into the blood protein, depending on age, the size of prostate, the presence of cancer or other prostate diseases. However, standard PSA determination means that PSA mass is dissolved
in plasma volume which is mainly dependant on the obesity extent. This led some authors to explore new markers independent of hemodilution (Bryniarski et al., 2011). PSA mass meets these criteria, but further studies are needed to demonstrate its superiority over standard PSA concentration.

9. Author's contribution

Hereby we present our work on hemodilution (Bryniarski et al., 2011). The aim of our study was to prove the superiority of PSA mass over standard PSA concentration in predicting biochemical recurrence after radical prostatectomy.

9.1 Material and methods

From 1994 until the end of 2007 206 radical retropubic prostatectomies in Caucasian men suffering from prostate cancer were carried out in the Department of Urology in Zabrze, Medical University of Silesia in Katowice. The patients who underwent preoperative anti-androgen therapy, chemotherapy or radiotherapy were excluded from the research (29 patients).

177 patients were qualified for the research. In our group two types of data were subject to analysis. Preoperative data, such as: age, height, weight, BMI, PSA concentration (immunoenzymatic Elecsys test; Cobas 6000 Hitachi) and postoperative data: the extent of histopathologic differentiation of prostate tissue in Gleason score, extracapsular extension (pT3), the presence of lymph nodes metastases and the presence of positive surgical margins.

Patients are under constant control in the Hospital Outpatient Clinic, thanks to which data concerning progression (biochemical recurrence, local recurrence, death) were also collected and the cancer-specific survival time was determined. The total volume of plasma and the PSA mass were calculated on the basis of the formulas (Table 1) (Boer, 1984; Du Bois & Du Bois, 1916).

<table>
<thead>
<tr>
<th>Estimated Body Surface (EBS)</th>
<th>Plasma volume [liters] (PV)</th>
<th>PSA mass [µg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>(weight)$^{0.425}$ x (height)$^{0.72}$ x 0.007184</td>
<td>EBS x 1,670</td>
<td>PV x PSA concentration</td>
</tr>
</tbody>
</table>

Table 1. The formulas to estimate plasma volume and PSA mass.

The group of 177 patients was divided according to:

3. Preoperative PSA mass – into 3 groups: I – 71 patients with PSA < 40 µg, II – 78 patients with PSA 40 – 69.9 µg and III – 28 patients with PSA ≥ 70 µg.

The characteristics of each group is shown in tables 2 and 3.
Table 2. Characteristics of patients in groups of BMI, PSA concentration and PSA mass.

All constant variables distributions were analyzed with regard to normality by means of Kolmogorov-Smirnov and Lilliefors tests. By means of descriptive statistics the following characteristics have been determined: mean or median, standard deviation as well as maximal and minimal value.

In order to determine differences between the groups, where variables are of categorical character, Chi-square test has been used. In order to determine differences between a number of independent groups, where continuous variables have distribution other than normal, Kruskal-Wallis test has been used.

In order to eliminate the influence of factors disrupting the correlation between BMI and PSA concentration, such as: age, the extent of prostate cancer differentiation in Gleason score, extracapsular extension (pT3) or positive surgical margins, multiple regression has been used to create a model which would describe the aforesaid relationship. The aforementioned disrupting factors have been incorporated into the model.

<table>
<thead>
<tr>
<th></th>
<th>BMI (kg/m²)</th>
<th>PSA (ng/ml)</th>
<th>PSA mass (µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>Age (years)</td>
<td>mean</td>
<td>62,8</td>
<td>62,2</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>6,7</td>
<td>5,9</td>
</tr>
<tr>
<td></td>
<td>range</td>
<td>50-76</td>
<td>48-74</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>mean</td>
<td>23,4</td>
<td>27,4</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>1,4</td>
<td>1,3</td>
</tr>
<tr>
<td></td>
<td>range</td>
<td>17,9-24,9</td>
<td>25-29,9</td>
</tr>
<tr>
<td>Plasma volume (liters)</td>
<td>mean</td>
<td>3,1</td>
<td>3,2</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0,13</td>
<td>0,2</td>
</tr>
<tr>
<td></td>
<td>range</td>
<td>2,9-3,4</td>
<td>2,8-3,9</td>
</tr>
<tr>
<td>PSA concentration (ng/ml)</td>
<td>mean</td>
<td>12,8</td>
<td>14,1</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>8,9</td>
<td>11,9</td>
</tr>
<tr>
<td></td>
<td>range</td>
<td>2,8-51,8</td>
<td>1,8-61,7</td>
</tr>
<tr>
<td>Gleason score</td>
<td>median</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>PSA mass (µg)</td>
<td>mean</td>
<td>56,6</td>
<td>46,2</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>27,4</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>range</td>
<td>31,9-156,6</td>
<td>6,5-196,6</td>
</tr>
</tbody>
</table>
Table 3. Characteristics of patients in groups of BMI, PSA concentration and PSA mass.

In order to evaluate and compare the odds ratio of biochemical recurrence together with the elevated concentration and mass of the PSA, the model of logistic regression has been used. The model has been adjusted to Gleason score (<8 and ≥ 8) in postoperative specimen. As both the concentration and the PSA mass did not show normal distribution, the logarithmic (decimal) transformation of data has been performed. 10 patients who have been diagnosed with metastases in the surrounding lymph nodes have been removed from the model because the presence of metastases would distort the results of the observation.

Cancer-specific survival of patients has been evaluated by means of Kaplan-Meier analysis, while the significance of differences between them has been evaluated by means of Gehan’s Wilcoxon test.

Receiver operating characteristic (ROC) curves compared predictive variables.

For all statistical tests the critical level of significance has been adopted at p<0,05. The statistical analysis has been calculated by means of StatSoft Statistica 8.0.
9.2 Results
The values PSA mass in the research has a statistically significant influence on extracapsular extension (p<0.001), the presence of metastases in the surrounding lymph nodes (p<0.001), the frequency of positive surgical margins (p<0.001), the presence of biochemical (p<0.0001) and local recurrence (p<0.001) and the rate of death (p<0.001).

The research has shown that BMI does not influence preoperative PSA concentration and PSA mass (Fig. 1 and 2). Differences in preoperative PSA concentration between the 3 groups of patients are statistically insignificant (p = 0.28). The total plasma volume is higher in obese patients (p<0.001).

Fig. 1. Comparison of preoperative PSA concentration (ng/ml) in BMI groups.

Fig. 2. Comparison of preoperative PSA mass in BMI groups.
The model of multiple regression has proved the lack of statistically significant correlation between preoperative PSA concentration and BMI ($p = 0.99$). The research has proved that the elevated preoperative value of PSA mass ($p = 0.02$) is the factor which influences the cancer-specific survival of patients with prostate cancer after RP (Fig. 3).

Fig. 3. Comparison of overall survival time (days) in patients with prostate cancer depending on the PSA mass.

Fig. 4. Three-dimensional model of logistic regression with two independent variables (Gleason score and decimal logarithm from the value of PSA mass) and dependent dychotomic variable (biochemical recurrence).
The odds ratio of biochemical recurrence, with the PSA mass increased 10 times, is equal to 8.64 (95% CI: 2.54 – 29.3; p<0.001) (Fig. 4). The odds ratio of biochemical recurrence, with the PSA concentration increased 10 times, is equal to 7.66 (95% CI: 2.25 – 26; p<0.001).

ROC curves for preoperative PSA mass and PSA concentration showed an area under curve (AUC) of 0.72 and 0.65 respectively for biochemical recurrence after RP (Fig. 5). The difference between these two predictors (AUC) was statistically significant (p=0.04).

Fig. 5. ROC curves for PSA mass as a preoperative predictor of biochemical recurrence after RP (Area Under Curve - 0.72).

9.3 Discussion
There are various theories concerning the influence of obesity on the natural development, diagnostics or progression after radical treatment of prostate cancer. The 5 times increased percentage of biochemical recurrence observed in Afro-Americans, compared to Euro-Americans, is sometimes explained by 3 times more frequent presence of overweight or obesity among the former (Spangler et al., 2007).

Its influence is definitely negative, including the following:
1. difficulties in per rectum examination in obese patients (Bray, 2006),
2. dishormonose (Hsing et al., 2002; Kaaks et al., 2000) – abnormal hormone concentrations, which induces the intensification of diagnostics and at the same time postpones proper treatment,
3. comorbidities, which pushes the prostate diagnostics into the background and consequently patients suffer from more advanced forms of prostate cancer.
Some authors suggest another factor, namely, lower PSA concentration in obese patients (Baillargeon et al., 2005). The consequence of the aforesaid correlation may impact on prostate cancer diagnosis and evaluation of progression after its radical treatment. Other authors disclaim the abovementioned connection (Freedland et al., 2006).

The authors who prove that obese patients are characterized by lower PSA concentration, refer to the phenomenon of hemodilution. The supporters of that theory claim that obesity is characterized by a larger amount of circulating blood, so theoretically the constant PSA mass circulating in the organism would be dissolved in a large amount of plasma, resulting in a lower PSA concentration.

However, our research has not proved that the elevated BMI has a significant influence on the preoperative PSA concentration. In order to explain the inconsistency we will call upon racial differences between the analyzed groups. The following research has been done on a group of patients of Caucasian race, while the aforesaid research has been frequently based on ethnically heterogeneous groups. The cause of differences between the outcomes can result from the polymorphism of the androgen receptor which causes higher PSA concentration in Afro-Americans, as well as statistically significant bigger obesity of this group (Xu et al., 2002). The influence of ethnic differences can, of course, be dismissed by appropriate statistical manipulations, nevertheless, it seems that research done on homogenous groups is characterized by greater statistical power.

In order to exclude the potential influence of hemodilution on the PSA concentration, the PSA mass in each patient has been calculated. Thanks to mathematical formulas used to estimate the total amount of circulating blood, its amount can be quite precisely determined. It has to be underlined that the phenomenon of hemodilution in obese patients had no statistically significant influence on PSA concentration. Also, having excluded other factors influencing PSA concentration, such as: cancer differentiation in Gleason score, the extracapsular extension (pT3), positive surgical margins or the patient’s age, no significant correlation between BMI and the preoperative PSA concentration has been found.

However, comparing both parameters (PSA concentration and the PSA mass) it has to be stressed that the probability of biochemical recurrence after RP is better predicted by PSA mass, which surely results from the fact that the PSA mass includes the element eliminating the phenomenon of hemodilution. Despite the fact that both preoperative parameters “equally well” evaluate the progression after RP, the PSA mass seems to be a little more sensitive parameter (which is indicated by the difference in the odds ratio and AUC).

9.4 Conclusions
1. Increased preoperative value of the PSA mass is connected with:
   a. more frequent cancer diagnosis of pT3 prostate cancer,
   b. more frequent diagnosis of metastases in the surrounding lymph nodes,
   c. more frequent recognition of the positive surgical margin,
   d. shorter cancer-specific survival time,
   e. higher percentage of progression.
2. The preoperative PSA mass is a better predictor of biochemical recurrence after RP than PSA concentration.
3. The total plasma volume is higher in obese patients, however, it does not influence the preoperative PSA concentration significantly.
10. References


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In this book entitled "Prostate Cancer - Diagnostic and Therapeutic Advances", we highlight many of the significant advances made in our treatment armamentarium of prostate cancer. The book is subdivided into four sections termed: 1) novel diagnostic approaches, 2) surgical treatments options, 3) radiation therapy and its potential sequelae, and 4) medical management and its treatment complications. After reading the present book, readers will be very familiar with the major clinical advances made in our multifaceted treatment approach to prostate cancer over the past decade. This book is a tribute to our pioneering urologists and allied healthcare professionals who have continually pushed forward our traditional therapeutic envelope.

How to reference
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