Changes in prostate cancer incidence in 50–75-year-old men in Lithuania 2006–2009: effect of early diagnosis program

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Background. The Lithuanian Prostate Cancer Early Diagnosis Program (LPCEDP) was launched in 2006. Our study aimed to evaluate the PSA testing offered by general practicians for prostate cancer screening as its results may differ from those reported in randomised screening studies.

Materials and methods. In the LPCEDP, GPs offered a PSA (prostate-specific antigen) test for informed men aged 50–75 years. A PSA > 3 ng/ml was a cut-off limit for referral to urologist. The study group comprised men aged 50–75 years, diagnosed with prostate cancer in 2006–2009. The Lithuanian Cancer Registry data: age at diagnosis, date of diagnosis, clinical stage. The state Patient Fund data: dates of PSA testing in the LPCEDP. The distribution of clinical stages of prostate cancer was analysed in the following age groups: 50–54, 55–59, 60–64, 65–69, 70–75 years. The incidence rate was expressed as cases per 100000 men per year. The logistic regression model was used to assess the effect of the LPCEDP.

Results. In 2006–2009, early prostate cancer accounted for 60.9% of incidence in the study group. The LPCEDP resulted in a sharp rise of the incidence of prostate cancer in 2007, followed by a gradual decline. Major changes in stage II and III tumour incidence resulted in stage migration. The peaks of total prostate cancer incidence and stage II cancer incidence among men aged 65–75 years coincided. In all age groups except 50–54 years, the incidence of stage III prostate cancer followed a downward trend since 2006. The logistic regression model showed that using the LPCEDP significantly increased the chances of men to be diagnosed with prostate cancer at an early stage.

Conclusions. The LPCEDP has resulted in a high incidence of prostate cancer (especially of stage II) in men aged 65–75 years. A steady decline of stage III prostate cancer incidence was observed. Men aged 50–54 years cannot benefit from the LPCEDP as they seldom come to GPs. In the current situation, overdiagnosis and overtreatment in men aged over 65 years may overshadow the benefits of timely PSA testing in younger men.

Key words: prostate cancer, early diagnosis, PSA

INTRODUCTION

Prostate cancer is the most common oncological disease in men in developed industrialized countries (1). In Lithuania, before 2006, early detection measures in the early diagnosis of prostate cancer had not been applied in primary medical care in an organized way. Since 2000, the incidence of prostate cancer in Lithuania was steadily increasing (2). The disease was mostly found in an advanced stage. In recent decades, the incidence of prostate cancer has grew in many countries. This fact was attributed to the spread of organized or opportunistic testing of prostate-specific antigen (PSA) levels in the blood serum of men (3). Due to

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the intensive PSA testing, prostate cancer is more often diagnosed at an early stage, and the incidence of advanced disease decreases over time (4). Based on this knowledge, in 2006 the Lithuanian Prostate Cancer Early Diagnosis Program (LPCEDP) was launched (5). The LPCEDP provides a possibility for men to undergo PSA testing and urological examination for prostate cancer. The LPCEDP provides recommendations for patients and physicians, but does not require following a strict sequence of actions, in contrast to randomised screening trials. It is unclear whether such a program would be able to improve early diagnosis and survival in prostate cancer patients to the level reported in such studies as the European Randomised Study of Screening for Prostate Cancer (6). An increase of early-stage prostate cancer detection and a reduction of the morbidity of prostate cancer patients are mentioned among the most important objectives of the LPCEDP. Previously, in our publication, we had reported the LPCEDP inequalities of penetration and repeated PSA testing in different age groups (7). Changes in the incidence of different clinical stages of prostate cancer should be taken into account in order to assess the possibilities of the LPCEDP to achieve its objectives. Here, we analyze changes in the incidence of different stage prostate cancer adjusted for the age at the time of diagnosis, because age is an important variable predicting the possibility of achieving better results in the early detection and treatment of clinically significant prostate cancer.

MATERIALS AND METHODS

Implementing the LPCEDP information about the early diagnosis of prostate cancer, a PSA test was provided to men attending general practitioners (GPs): during 2006–2008 once a year and starting from 1 July 2009 once in two years. This service could be offered to men aged 50–75 years and from 45 years if their father or brothers had prostate cancer. A patient was referred to consult a urologist, if his PSA was 3 ng/ml or more. Patients were not obliged to go to the urologist. The urological consultation included case history, DRE, ultrasound examination and transrectal biopsy of prostate, if prostate cancer was suspected. The urologist, even at the increased level of serum PSA, was not required to perform prostate biopsy when the increase of PSA was obviously due to a pathology other than prostate cancer. Our study sampled men according to the Lithuanian Cancer Registry data, in whom prostate cancer diagnosis was established in 2006–2009 and they were 50–75 years old at the time of diagnosis. Data used for the analysis included the age at the time of diagnosis, the date of diagnosis, and the clinical stage of prostate cancer. For each person, in a selected group of men, data from the State Patient Fund Database were derived (dates of PSA testing in the LPCEDP). A person was considered to have benefited from the LPCEDP

early PSA check (hereinafter – early PSA screening service, or EPSS) if at least once EPSS had been registered prior the date of prostate cancer diagnosis. The distribution of clinical stages of prostate cancer was analysed in groups according to age at the time of diagnosis: 50–54, 55–59, 60–64, 65–69, 70–75 years. Incidence rate was expressed as cases per 100 thousand men per year. The average annual number of men in a specified group was used for calculations.

The logistic regression model was used to assess the effect of the LPCEDP on early stage prostate cancer detection. Clinical stage I and II tumours were considered as early stage prostate cancer and III and IV as an advanced disease. Only cases of prostate cancer of a known clinical stage were included into calculations. Variables in the logistic regression model: age at the time of diagnosis, the fact of EPSS prior to diagnosis. The logistic regression model was applied to the whole study group and to each age group separately. SPSS 16.0 and SAS statistical software packages were used for calculations.

RESULTS

During 2006–2009, 11 454 men aged 50–75 years were diagnosed with prostate cancer in Lithuania. The incidence by clinical stage: I – 89 (0.8%), II – 6 883 (60.1%), III – 2 921 (25.5%), IV – 414 (3.6%). The clinical stage was unknown in 1 147 cases (10.0%); 6 972 cases of early prostate cancer accounted for 60.9% of the total incidence in this group. Introduction of the LPCEDP resulted in a sharp rise of the incidence of prostate cancer, which reached its peak in 2007, i. e. in the second year of the LPCEDP (3 202 new cases). During 2008 and 2009, the incidence of prostate cancer began decreasing gradually. It should be noted that in 2008–2009 the proportion of cases of the unknown clinical stage increased: 2006 – 257 cases (10.0%), 2007 – 179 (5.6%), 2008 – 399 (13.2%), 2009 – 312 (11.8%). A considerable number of cases with the unknown stage should be kept in mind while reading the results of statistical analysis. The proportion of early-stage prostate cancer, as expected, was higher among younger prostate cancer patients, although the group of advanced disease was rather large in this early stage of LPCEDP (Fig. 1).

During 2006–2009, different trends in the incidence of all stages of prostate cancer were observed. Until 2010, the clinical classification of prostate cancer, assigning clinical stage I only to incidental carcinoma (pT1A and pT1B), had been used in the Lithuanian Cancer Registry. Stage I tumours comprised less than 1% of the total incidence: in 2006 – 38 cases, 2007 – 30, 2008 – 6, 2009 – 15. The incidence of clinical stage IV prostate cancer did not change much in the study period: 2006 – 104, 2007 – 97, 2008 – 111, 2009 – 102 cases. Major changes in the incidence of clinical stage II and III tumours were observed. Stage II tumours
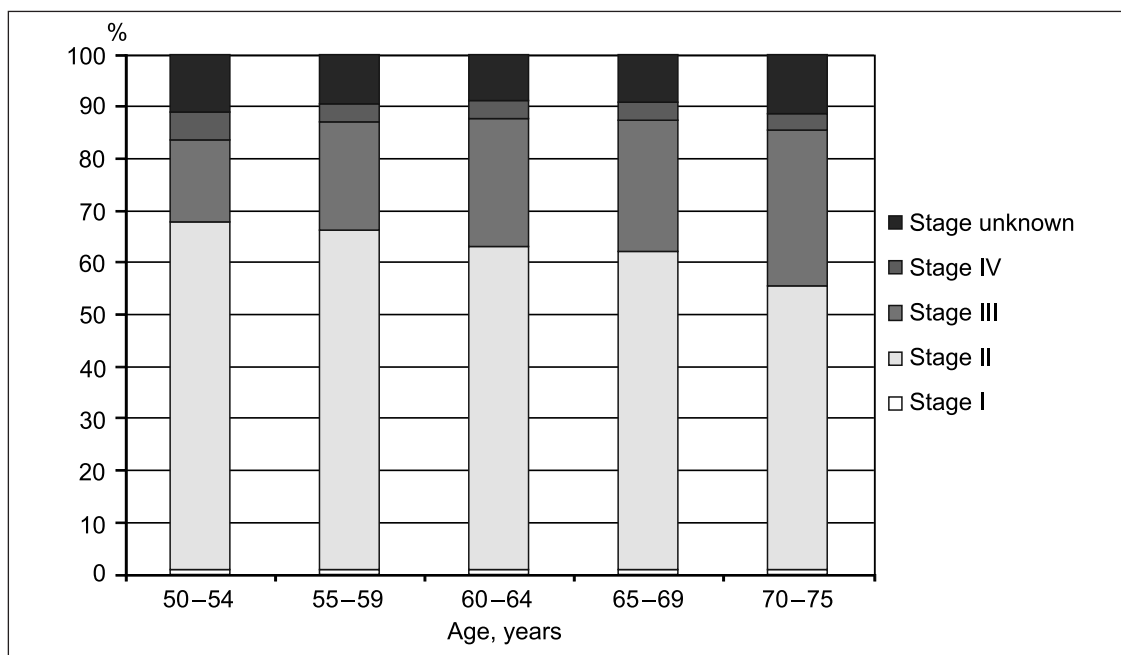
Fig. 1. Distribution (percent) of clinical stages of new prostate cancer cases according to age at the time of diagnosis (2006–2009)

accounted for 60.1% of all prostate cancer in 50–75-year-old male population: in 2006 – 1 427 cases (55.3% of total incidence), 2007 – 2 108 (65.8%), 2008 – 1 761 (58.1%), 2009 – 1 587 (60.1%). Stage III tumours accounted for 25.5% of prostate cancer cases: in 2006 – 753 (29.2% of total incidence), 2007 – 788 (24.6%), 2008 – 756 (24.9%), 2009 – 624 (23.6%). Each year the proportion of men involved in the LPCEDP increased among new prostate cancer

cases. The stage migration phenomenon was observed mainly due to the redistribution of stage II and III prostate cancer cases. In 2006–2009, most of stage II and III tumours were diagnosed for men who tested their PSA in LPCEDP (Fig. 2).

The introduction of the LPCEDP produced different effects on prostate cancer incidence in separate age groups. The prevalence of stage II and III tumours was evaluated while calculating the incidence rate for each age group
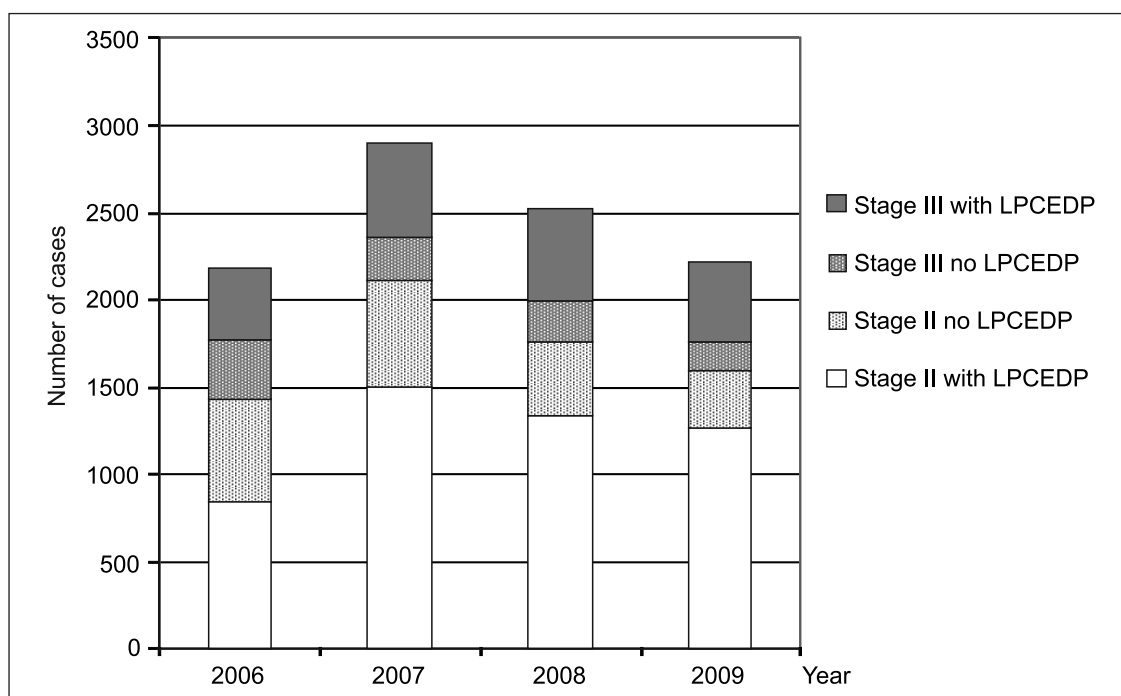

Fig. 2. The distribution of stages II and III prostate cancer according to participation in the LPCEDP (organised PSA testing)

(Figs. 3 and 4). The peak of prostate cancer incidence in 2007 was related to the rise of stage II cancer incidence among men aged 70–75 years. In all age groups except 50–54 years, the incidence of stage III prostate cancer followed a downward trend.

The application of the logistic regression model showed that the use of EPSS (PSA testing in LPCEDP) significantly increased the chances of men to be diagnosed with prostate cancer at an early stage (OR 1.406, 95% CI 1.278–1.547, p < 0.0001). A one-year delay to check PSA resulted in a reduction of the probability to detect early stage prostate cancer (OR 0.971, 95% CI 0.964–0.977, p < 0.0001).

Chances of detecting prostate cancer at an early stage by PSA testing in the LPCEDP according to our model clearly decrease with age – from 3.4 : 1 for 50-years-old men to only 1.4 : 1 for men aged 75 years. Application of the logistic regression model to separate age groups has shown that participation in the LPCEDP most evidently increases the chances of early prostate cancer detection in men aged 60–64 years (OR 1.512, CI 95% 1.228–1.863, p < 0.0001). Meanwhile, a one-year delay of PSA check most adversely affects the chances of early diagnosis in 65–69-year-old men (OR 0.918, CI 95% 0.867–0.971, p = 0.002). Men aged 50–54 years have a similar likelihood to be diagnosed with early stage prostate cancer at any time of this age period; a one-year delay of PSA check has the OR 1.133 (95% CI 0.764–1.679, p < 0.0001).
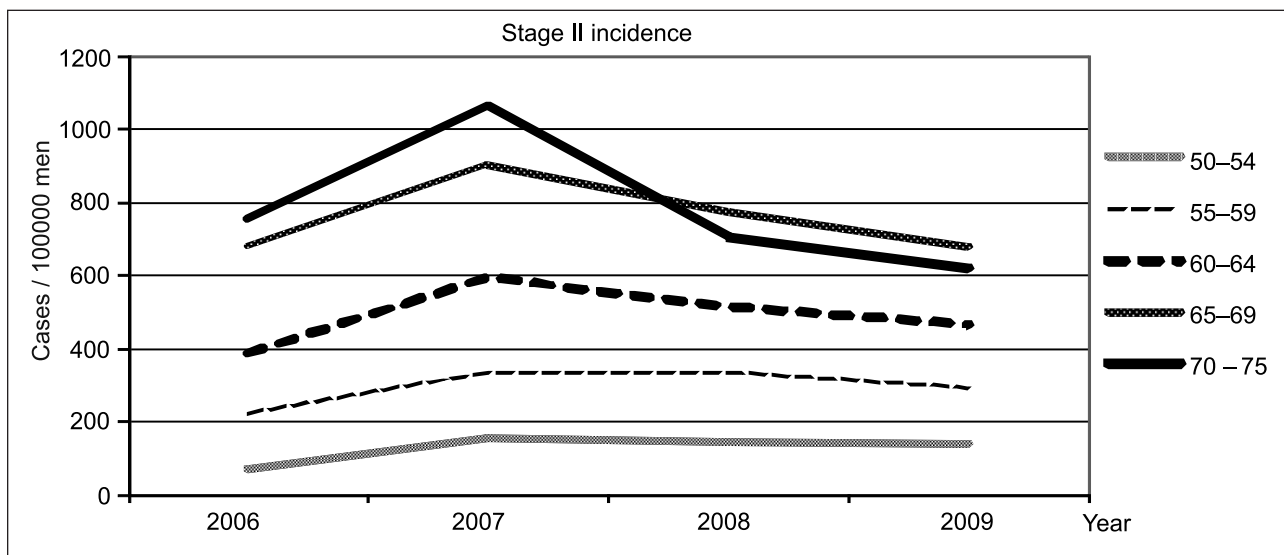

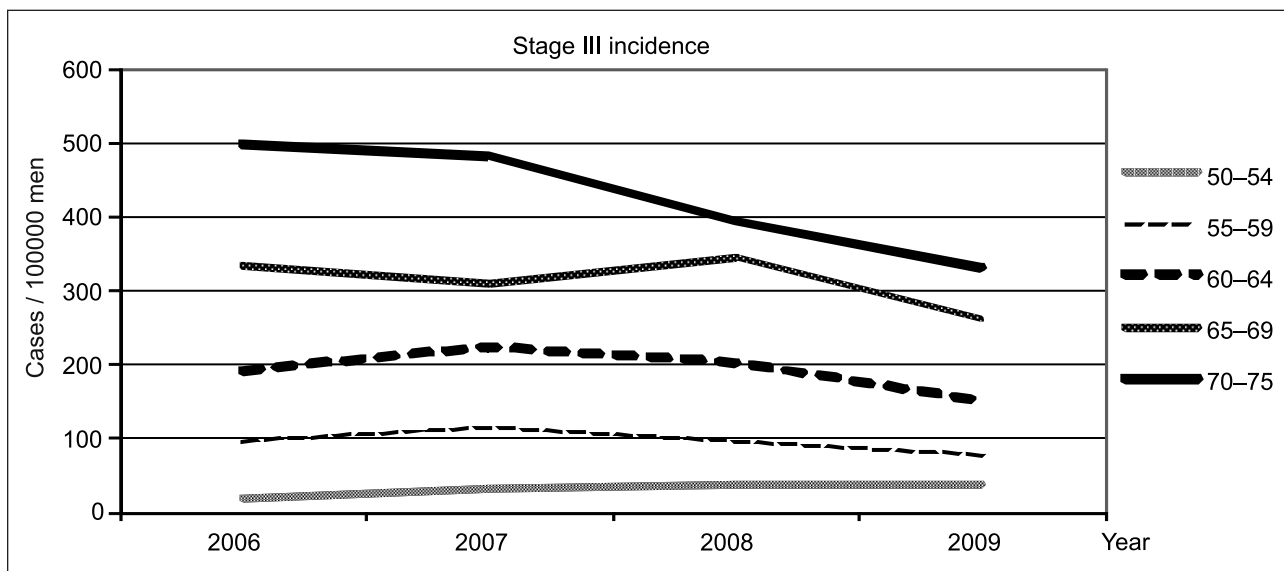**Fig. 3.** Stage II prostate cancer incidence in the LPCEDP target group

Fig. 4. Stage III prostate cancer incidence in the LPCEDP target group

DISCUSSION

In 2006–2009, the Lithuanian Cancer Registry registered 13 760 new cases of prostate cancer in Lithuania (8–11). Clinical stage I prostate cancer was registered in 106 cases (0.8% of all new cases of prostate cancer), stage II in 7 728 (56.2%), stage III in 3 712 (27%) and stage IV in 633 cases (4.6%). Clinical staging was not reported in 11.4% of cases.

A slightly larger proportion of advanced disease in the total incidence of prostate cancer in comparison with our study population is associated with a higher incidence of stage III and IV tumours in men aged over 75.

In 2006–2009, 88.9% of all early prostate cancer cases in Lithuania were reported in men aged 50–75 years, i. e. exactly in the LPCEDP target group. There is no doubt that the LPCEDP had a strong effect on prostate cancer detection in Lithuania. Results of our study show that early detection measures offered to men through GPs' services exert some limitations on the stage migration phenomenon produced by PSA screening. In our earlier publication (7), we have concluded that EPSS penetration into the LPCEDP is significantly higher among older men. This limitation results in a more evident growth of incidence among frequent GP visitors, i. e. most likely in men with concomitant diseases.

The variations of total prostate cancer incidence in recent years reflected the trends of prostate cancers detection in men aged 65–75 years. During the first four years of the LPCEDP, stage II prostate cancer was reported in 1919 cases in men aged 65–69 years and in 1896 cases in 70–75-year-old men. The leading causes of death among men older than 64 years in Lithuania are cardiovascular disorders (12). It is very likely that for many men aged 65–75 years prostate cancer will not become a disease limiting life expectancy, even if such diagnosis is established. The experience of countries in which large-scale PSA testing has already been applied for several decades (13) has shown that clinically insignificant prostate cancer is likely to become more and more prevalent in the future in Lithuania. An intensive PSA testing in older men may increase the rate of prostate cancer overdetection and overtreatment in Lithuania. On the other hand, the LPCEDP over a relatively short period of time allowed decreasing the incidence of stage III tumours. Stage III prostate cancer patients comprise a group requiring a long-term expensive treatment. The shrinkage of this group may lower treatment costs and indicate the possibility to observe a decrease of metastatic disease in the nearest future.

There is an increasing body of evidence that the effectiveness of the PSA test in prostate cancer early diagnosis and mortality prevention is higher if used for the first time at a younger age (14). The LPCEDP has made only minor changes in prostate caner incidence among 50–54-year-old men. One of the possible reasons is a poor penetration of LPCEDP services among younger men. Thus, the problem of penetration of the PSA test in Lithuania may be one of the most important factors limiting the effectiveness of the LPCEDP.

CONCLUSIONS

The implementation of the LPCEDP resulted in a temporary increase of prostate cancer incidence. A considerable proportion of stage II cases detected in men older than 64 years accounts for this increase, but it is likely to be clinically insignificant. Additional efforts are necessary to improve the LPCEDP penetration among younger men in order to increase its effects on prostate cancer mortality in the future. GPs and urologists should carefully select elderly patients for the initial and especially for a repeated PSA testing to avoid overdetection of clinically insignificant prostate cancer.

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50−75 METŲ VYRŲ SERGAMUMO PROSTATOS VĖŽIU KAITA LIETUVOJE 2006–2009 M.: ANKSTYVOS DIAGNOSTIKOS PROGRAMOS ĮTAKA

Santrauka

Įvadas. 2006 m. Lietuvoje buvo pradėta priešinės liaukos vėžio ankstyvos diagnostikos programa (LPLVADP). Organizuotai bendrosios praktikos gydytojų (BPG) siūlomos PSA patikros dėl prostatos vėžio ir atsitiktinės imties patikros rezultatai gali skirtis.

Medžiaga ir metodai. Vykdydami LPLVADP BPG informavo 50–75 metų vyrus ir atliko PSA tyrimą. Kai PSA > 3 ng/ml, pacientas buvo siunčiamas urologo konsultacijai. Tiriamąją grupę sudarė 50–75 metų vyrai, kuriems 2006–2009 m. buvo nustatytas prostatos vėžys. Lietuvos vėžio registro duomenys: amžius diagnozės metu, diagnozės data, klinikinė stadija. Valstybinės ligonių kasos duomenys: LPLVADP PSA patikros datos. Klinikinių vėžio stadijų pasiskirstymas nagrinėtas 50–54, 55–59, 60–64, 65–69, 70–75 metų grupėse. Sergamumo rodikliai apskaičiuoti 100 000 vyrų per metus. LPLVADP reikšmė vertinta taikant logistinės regresijos modelį.

Rezultatai. 2006–2009 m. ankstyvų stadijų prostatos vėžys sudarė 60,9 % tiriamosios grupės atvejų. Pradėjus LPLVADP, sergamumas prostatos vėžiu staiga išaugo 2007 m., tačiau vėliau palaipsniui mažėjo. Stadijų migracijos fenomeną nulėmė ryškūs pokyčiai II ir III stadijos navikų grupėse. Sergamumo prostatos vėžiu pikas su-tapo su išaugusiu 65–75 metų vyrų sergamumu II stadijos vėžiu. Visose amžiaus grupėse, išskyrus 50–54 metų vyrus, sergamumas III stadijos prostatos vėžiu mažėjo nuo 2006 metų. Pritaikius logistinės regresijos modelį pasitvirtino prielaida, kad dalyvavimas LPLVADP siūlomoje patikroje statistiškai reikšmingai padidino galimybę aptikti ankstyvos stadijos prostatos vėžį.

Išvados. Pradėjus įgyvendinti LPLVADP, ypač išaugo 65–75 metų vyrų sergamumas prostatos vėžiu (daugiausia II stadijos). Stabiliai mažėjo III stadijos atvejų skaičius. Penkiasdešimtmečiai vyrai retai lankosi pas BPG, todėl LPLVADP poveikis sergamumui prostatos vėžiu šioje amžiaus grupėje nėra didelis. Esant dabartinėms tendencijoms per dažna kliniškai nereikšmingo prostatos vėžio diagnostika ir gydymas pagyvenusiems vyrams gali nusverti teigiamą PSA patikros poveikį tarp jaunesnių vyrų.

Raktažodžiai: prostatos vėžys, ankstyva diagnostika, PSA