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Aušvydas
PATAŠIUS

PSA tyrimu paremtos ankstyvos priešinės liaukos vėžio diagnostikos programos Lietuvoje tyrimas: vykdymo eiga ir efektyvumas

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Visuomenės sveikata (M 004)

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PATAŠIUS

PSA test-based prostate cancer screening program in Lithuania: performance and effectiveness

DOCTORAL DISSERTATION

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TURINYS

SANTRUMPOS

ADP – Lietuvos priešinės liaukos vėžio ankstyvos diagnostikos programa.

DRT – digitalinis rektalinis tyrimas – tiesiosios žarnos ir priešinės liaukos apčiuopa pirštu.

ERSPC – *The European Randomized Study of Screening for Prostate Cancer* – Europos atsitiktinės atrankos daugiacentris patikros dėl priešinės liaukos vėžio efektyvumo tyrimas.

JAV – Jungtinės Amerikos Valstijos.

MPP – metinis procentinis pokytis.

PLCO – *Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial* – Jungtinių Amerikos Valstijų priešinės liaukos, plaučių, storosios žarnos ir kiaušidžių vėžio patikros tyrimas.

PSA – prostatos (priešinės liaukos) specifinis antigenas.

PSO – Pasaulio sveikatos organizacija.

SAM – Lietuvos Respublikos sveikatos apsaugos ministerija.

TLK – tarptautinė ligų klasifikacija.

TPV – teigiama prognostinė vertė.

USPSTF – *United States Preventive Service Task Force* – Jungtinių Valstijų prevencinių paslaugų tarnyba.

VMPP – vidutinis metinis procentinis pokytis.

PUBLIKACIJŲ SĄRAŠAS

Daktaro disertacija parengta šių publikacijų pagrindu:

I. Patasius A, Krilaviciute A, Smailyte G. Prostate Cancer Screening with PSA: Ten Years' Experience of Population Based Early Prostate Cancer Detection Programme in Lithuania. Journal of Clinical Medicine. 2020, 9 (12), 3826; doi: https://doi.org/10.3390/jcm9123826

II. Patasius A, Innos K, Barchuk A, Ryzhov A, Leja M, Misins J, Yaumenenka A, Smailyte G. Prostate cancer incidence and mortality in the Baltic states, Belarus, the Russian Federation and Ukraine. BMJ Open. 2019 Oct 9; 9 (10): e031856. doi: https://doi.org/10.1136/bmjopen-2019-031856.

III. Patasius A, Smailyte G. Changing Incidence and Stage Distribution of Prostate Cancer in a Lithuanian Population – Evidence from National PSA-Based Screening Program; International Journal Enviromental Research and Public Health; 16 (23): 4856. https://doi.org/10.3390/ijerph16234856

IV. Patasius A, Smailyte G. All-cause mortality risk in national prostate cancer cohort: an impact of population-based prostate cancer screening; Journal of Clinical Medicine. 2021, 10 (11), 2459; doi: https://doi.org/10.3390/jcm10112459

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- Patasius A, Kaceniene A, Ulys A, Stukas R, Smailyte G, Suicide risk among prostate cancer patients before and after the implementation of prostate-specific antigen-based prostate screening in Lithuania in 2006. Eur J Cancer Prev. 2021 Jan; 30 (1): 103–107. doi: https://doi.org/10.1097/CEJ.0000000000000573
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- Drevinskaite M, Patasius A, Kincius M, et al. Retrospective cohort study of androgen deprivation therapy and the risk of diabetes in men with prostate cancer in Lithuania BMJ Open 2021; 11: e045797. doi: 10.1136/bmjopen-2020-045797

1. ĮVADAS

Priešinės liaukos vėžys yra antra dažniausia piktybinė vyrų liga pasaulyje ir šešta pagal dažnumą jų mirties nuo piktybinių ligų priežastis. 2018 metais buvo diagnozuota maždaug 1 276 000 naujų priešinės liaukos vėžio atvejų ir šios lokalizacijos vėžys buvo atsakingas už maždaug 359 000 mirčių pasaulyje [1]. Sergamumas priešinės liaukos vėžiu pasaulyje nuolatos didėja. Ekonomiškai išsivysčiusiose šalyse dėl pagerėjusios socialinės padėties, ilgėjančios gyvenimo trukmės ir mažėjančio sergamumo kai kurių lokalizacijų piktybiniais navikais, priešinės liaukos vėžys tapo dažniausia vėžio lokalizacija tarp vyrų. Priešinės liaukos vėžio diagnostika yra neatsiejama nuo prostatos specifinio antigeno (PSA) naudojimo, todėl didėjantis sergamumas priešinės liaukos vėžiu yra tiesiogiai susijęs su dažnesniu PSA naudojimu klinikinėje praktikoje [2].

PSA yra baltymas, gaminamas epitelinėse priešinės liaukos kanalėlių ląstelėse. PSA koncentracijos kraujo plazmoje padidėjimas gali rodyti, kad yra priešinės liaukos vėžys. PSA buvo atrastas *Ablin* su kolegomis 1970 metais Jungtinėse Amerikos Valstijose (JAV), bet išgrynintas ir charakterizuotas *Wang* su kolegomis 1979 metais [3]. Mokslininkų grupė, vadovaujama *Steamey*, 1987 metais aptiko, kad padidėjęs PSA lygmuo yra susijęs su priešinės liaukos vėžio išplitimu, todėl PSA pradėtas naudoti kaip priešinės liaukos vėžio kraujo serume žymuo [4].

Pirmą kartą PSA tyrimas kaip testas diagnostikos tikslumui pagerinti buvo panaudotas 1991 metais *Catalona* ir kitų tyrėjų atliktame tyrime, kuriame nagrinėta PSA testo nauda profilaktinei patikrai. Nustatyta, kad tuo metu profilaktinei patikrai naudojamus klinikinius tyrimus, digitalinį rektalinį tyrimą (DRT) ir tyrimą ultragarsu, papildžius PSA testu, diagnozuojama 32 % daugiau priešinės liaukos vėžio atvejų nei naudojant tik DRT ir ultragarsinį tyrimą [5].

Optimali ribinė PSA koncentracija, kuri turėtų būti naudojama priešinės liaukos vėžio patikroje, nėra žinoma iki šiol. Istoriškai 4 ng/ml ir didesnės koncentracijos PSA buvo naudojamas kaip indikacija priešinės liaukos biopsijai. Tačiau buvo pastebėta, kad nemaža dalis didelio piktybiškumo priešinės liaukos vėžio atvejų aptinkama, kai PSA koncentracija yra mažesnė nei 4 ng/ml [6]. Esant PSA koncentracijos ribinei vertei 4 ng/ml, šio testo jautrumas diagnozuojant priešinės liaukos vėžį yra 78,7 %, o specifiškumas 59,2 % [7]. Didinant PSA ribinę koncentraciją iki 5 ng/ml, galima pasiekti PSA testo specifiškumą iki 95 % diagnozuojant priešinės liaukos vėžį, tačiau testo jautrumas sumažėja iki 33 % [8]. PSA koncentracija nėra tinkamas

parametras atskirti mažos ar didelės rizikos vėžį [5]. Todėl natūraliai kyla hiperdiagnostikos ir hiperterapijos grėsmė.

Remiantis anksčiau minėtais tyrimais ir nesant atsitiktinės atrankos tyrimų, devinto dešimtmečio pabaigoje PSA tyrimas JAV pradėtas naudoti profilaktinei priešinės liaukos vėžio patikrai [9].

Pradėjus PSA plačiai naudoti priešinės liaukos vėžio patikrai, buvo išanalizuotas ir jos efektyvumas atsitiktinių imčių kontroliuojamuose tyrimuose. Geriausiai žinomi priešinės liaukos vėžio patikros efektyvumo tyrimai yra Europos atsitiktinės atrankos daugiacentris patikros dėl priešinės liaukos vėžio tyrimas (*The European Randomized Study of Screening for Prostate Cancer* – ERSPC) ir Priešinės liaukos, plaučių, storosios žarnos ir kiaušidžių vėžio patikros tyrimas (*Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial* – PLCO). PLCO tyrime dalyvavo 10 JAV centrų. Tyrimas vyko nuo 1993 iki 2001 metų, pacientai stebėti iki 2015 metų. Tyrime dalyvavo 76 693 vyrai, kurie buvo atsitiktinės atrankos būdu paskirstyti į grupes: vieni įtraukti į patikros grupę (kasmetinis PSA + DRT), kitiems skiriamas standartinis stebėjimas. Esant didesnei nei 3 ng/ml PSA koncentracijai, buvo atliekama priešinės liaukos biopsija. Po septynerių stebėjimo metų nebuvo rasta mirtingumo skirtumų tarp tiriamųjų grupių; po 13 išplėstinio stebėjimo metų rezultatai parodė tą patį. ERSPC tyrime dalyvavo 182 000 50–74 metų vyrų iš septynių Europos šalių, kurie atsitiktinės atrankos būdu buvo suskirstyti į patikros ir kontrolinę grupes. Esant didesnei nei 4 ng/ml PSA koncentracijai, tiriamiesiems buvo atliekama priešinės liaukos biopsija. Patikra vyko nuo 2001 iki 2006 metų, pacientų stebėjimas tebevyksta iki šiol. Šio tyrimo duomenimis, po devynerių, vienuolikos, trylikos ir šešiolikos tyrimo vykdymo metų PSA testu paremta patikra sumažino asmenų, dalyvavusių patikroje, mirties nuo priešinės liaukos vėžio riziką 20 % [10-13].

Be minėtų tyrimų, buvo atlikta keletas mažesnių profilaktinės patikros dėl priešinės liaukos vėžio efektyvumo tyrimų. Tirolio tyrimas Austrijoje pradėtas 1993 metais. Visiems 45–74 metų amžiaus grupės vyrams buvo pasiūlyta nemokamai atlikti PSA tyrimą, tikintis, kad 75 % pasitikrins bent vieną kartą. Tai buvo stebėsenos tyrimas, kuriame Tirolio regiono vyrų mirtingumas buvo lyginamas su bendrosios Austrijos vyrų populiacijos mirtingumu. Nustatytas tyrimo dalyvių mirtingumo nuo priešinės liaukos vėžio mažėjimas [14]. Nepriklausomame Geteborgo tyrime, kuris vykdytas nuo 1994 iki 2004 metų, o vėliau įtrauktas į ERSPC tyrimą, dalyvavo 20 000 vyrų, gimusių nuo 1930 iki 1944 metų. Tyrimo metu nustatyta, kad PSA tyrimu paremta patikra sumažina mirtingumą nuo priešinės liaukos vėžio 44 % [15]. 1988–1996 metais vykdytame Kvebeko (Kanada) tyrime, į kurį buvo

įtraukti 46 193 45–80 metų vyrai, parodė, kad mirties nuo priešinės liaukos vėžio rizika gali būti sumažinta 62 % (palyginti su kontroline grupe), pasirinkus kasmetinę PSA tyrimu paremtą patikrą [16].

Nors PSA tyrimu paremta neorganizuota profilaktinė patikra dėl priešinės liaukos vėžio yra vykdoma beveik visose pasaulio šalyse, yra bandymų tokią patikrą vykdyti organizuotai populiaciniu lygmeniu. Japonija yra vienintelė Azijos šalis, kuri nuo 2010 metų rekomenduoja vykdyti profilaktinę patikrą dėl priešinės liaukos vėžio. Šioje šalyje tokia patikra veikia keliuose regionuose. Patikroje dalyvauja iki 20 % patikros populiacijai priklausančių vyrų. Priešinės liaukos vėžio nustatymo dažnis siekia 0,54–1,13 % [17]. Centrinės ir Pietų Amerikos regione tik Meksikoje profilaktinė patikra dėl priešinės liaukos vėžio yra rekomenduojama vyrams, kurie yra vyresni nei 50 metų [18]. Australijoje ir Naujojoje Zelandijoje rekomenduojama profilaktinė patikra dėl priešinės liaukos vėžio vyrams, ne vyresniems nei 70 metų. Patikroje bent kartą dalyvavo 84,9 % patikros populiacijos vyrų [19,20].

Remdamasi tuo, kad PLCO tyrime nenustatytas mirties nuo priešinės liaukos vėžio rizikos sumažėjimas, o ERSPC tyrime buvo nustatyta, kad, norint pasiekti PSA tyrimu paremtos patikros naudą, reikia didelio patikros dalyvių skaičiaus, 2012 metais Jungtinių Valstijų prevencinių paslaugų tarnyba (*United States Preventive Service Task Force* – USPSTF) išleido D lygio rekomendaciją, kuria pasisakė prieš PSA testo naudojimą profilaktinei patikrai dėl priešinės liaukos vėžio [21]. Kaip atsaką į tai, profesinės organizacijos priešinės liaukos vėžio diagnostikos ir gydymo rekomendacijose pasisakė prieš organizuotą populiacinę patikrą dėl priešinės liaukos vėžio ir nurodė, kad sprendimas dalyvauti patikroje turi būti kiekvieno paciento asmeninis, pabrėžiant bendrą paciento ir gydytojo sutarimą dėl patikros naudos ir galimos žalos [22]. USPSTF pateikus rekomendaciją, JAV gerokai sumažėjo atliekamų PSA testų skaičius akademinėse ir bendruomenės ligoninėse bei pirminės sveikatos priežiūros įstaigose. Taip pat buvo atliekama mažiau priešinės liaukos biopsijų pacientams, kurie kreipiasi pirmą kartą, o tarp diagnozuotų priešinės liaukos vėžio atvejų smarkiai sumažėjo blogos vėžio diferenciacijos (remiantis Gleasonu 7–10) atvejų [23]. Ši rekomendacija buvo atnaujinta 2018 metais. Tada minėta tarnyba rekomendavo PSA testu paremtą profilaktinę priešinės liaukos vėžio patikrą 55–59 metų vyrams, prieš tai su gydytoju gerai aptarus galimą teigiamą ir neigiamą šios patikros poveikį [24].

Šiuo metu Europos urologų asociacija priešinės liaukos vėžio diagnostikos ir gydymo gairėse PSA tyrimu paremtą priešinės liaukos vėžio patikrą rekomenduoja kaip dalį individualizuotos, pagal riziką adaptuotos

ankstyvos diagnostikos strategijos, kuri gali būti pasiūlyta gerai informuotam vyrui su 10–15 metų išgyvenimo tikimybe [25].

PSA testas ankstyvai priešinės liaukos vėžio diagnostikai ir profilaktinei patikrai naudojamas plačiai, tačiau organizuota profilaktinė patikra kitose pasaulio šalyse nevykdoma [26]. Neseniai Europos urologų asociacija, remdamasi gerais ERSPC tyrimo rezultatais, pasiūlė, kad PSA testu paremta populiacinė priešinės liaukos vėžio patikra būtų pradėta vykdyti visose Europos Sąjungos šalyse [27]

Lietuvoje 2006 metais pradėta vykdyti priešinės liaukos vėžio profilaktinė patikra – Lietuvos priešinės liaukos vėžio ankstyvos diagnostikos programa (ADP). Kaip vykdoma programa, nuolat vertina Valstybinė ligonių kasa. Programos vertinimas apsiriboja programos vykdymo kriterijais, geografine suteiktų ADP paslaugų analize ir panaudotų lėšų ataskaita [28].

Kaip bandymai įvertinti programos vykdymą yra paminėtina R. Adomaičio disertacija „Ankstyvos diagnostikos programos poveikio sergamumui priešinės liaukos vėžiu Lietuvoje vertinimas“ ir R. Šturienės disertacija „Sergamumo prostatos vėžiu ir mirtingumo nuo jo ypatumai Lietuvoje bei vyrų nuostatos, skatinančios dalyvavimą prostatos vėžio patikros programoje“. Tačiau minėti tyrimai apsiribojo pirmais penkeriais programos vykdymo metais.

Aiškių prostatos vėžio profilaktinių patikros programų eigos ir efektyvumo vertinimo rekomendacijų iki šiol nėra sukurta, tačiau modernus profilaktinės patikros dėl priešinės liaukos vėžio vertinimas pirmiausia atliekamas vertinant mirtingumo pokyčius nuo priešinės liaukos vėžio. Taip pat vertinami priešinės liaukos navikų patologinių charakteristikų pokyčiai, patikros eiga, dalyvavusių asmenų iš patikros tikslinės populiacijos dalis. Kadangi profilaktinė patikra dėl priešinės liaukos vėžio yra kompleksas sprendimų, glaudžiai susijusių su kitomis sveikatos būklėmis, vertinant priešinės liaukos programos efektyvumą kompleksiškai turi būti vertinama ir priešinės liaukos vėžiu sergančių asmenų mirties rizika dėl visų mirties priežasčių [29].

2. TYRIMO TIKSLAS

Įvertinti priešinės liaukos vėžio ADP eigą, efektyvumą bei įtaką priešinės liaukos vėžio epidemiologinės situacijos pokyčiams Lietuvoje.

3. TYRIMO UŽDAVINIAI

1. Aprašyti ADP eigą ir vykdymo rodiklius.
2. Įvertinti sergamumo priešinės liaukos vėžiu ir mirtingumo nuo jo pokyčius vykdant priešinės liaukos vėžio ADP Lietuvoje.
3. Nustatyti priešinės liaukos navikų patologinių charakteristikų pokyčius vykdant ADP.
4. Įvertinti mirtingumo nuo priešinės liaukos vėžio ir kitų priežasčių riziką ADP dalyvavusių ir nedalyvavusių vyrų grupėse.

4. TYRIMO NAUJUMAS

Lietuva yra vienintelė šalis pasaulyje, kurioje nacionaliniu mastu vykdoma organizuota profilaktinė patikra dėl priešinės liaukos vėžio. Kadangi nuo tada, kai ADP buvo pradėta vykdyti, iki šiol nebuvo vertintas jos efektyvumas, tyrimas neabejotinai yra aktualus ne tik nacionaliniu, bet ir tarptautiniu mastu. Iki šiol atlikti atsitiktinės atrankos kontroliuojami tyrimai, kuriuose nagrinėtas profilaktinės patikros dėl priešinės liaukos vėžio veiksmingumas (angl. *efficiency*). Veiksmingumas yra nustatomas idealiomis tyrimo sąlygomis ir tai daroma atliekant atsitiktinės atrankos kontroliuojamus tyrimus. Tyrimuose apsiribota tik tiriamųjų grupėmis, o organizuotos profilaktinės patikros efektyvumas bendrojoje populiacijoje lieka neaiškus. Kadangi efektyvumas yra apibrėžiamas kaip specifinės intervencijos poveikio įprastomis sąlygomis vertinimas, o Lietuvoje yra atlikta visos populiacijos patikra dėl priešinės liaukos vėžio, tyrimas leido nustatyti PSA tyrimu paremtos patikros efektyvumą.

5. METODIKA

5.1. Duomenų šaltiniai

Valstybinės ligonių kasos (VLK) „Sveidra“ duomenų bazėje kaupiama informacija apie draustuosius privalomuoju sveikatos draudimu: asmens sveikatos priežiūros įstaigose suteiktos pirminės, antrinės ir tretinės sveikatos priežiūros paslaugos, kreipimaisi dėl skubios pagalbos, hospitalizacijos. Taip pat kaupiami duomenys apie kompensuojamųjų medikamentų paskyrimus.

Tyrime naudoti duomenys iš VLK „Sveidros“ duomenų bazės apie ADP suteiktas paslaugas 2006–2016 metais 1931–1966 metais gimusiems vyrams (programos populiacija), informavimo paslaugų apie ADP ir PSA testo atlikimo data, nustatyta PSA koncentracija (< 3 ng/ml, ≥ 3 ng/ml), priešinės liaukos biopsijos data ir rezultatai, gyvybinis statusas, stebėjimo informacija, informacija apie emigraciją.

Naujų susirgimų priešinės liaukos vėžiu skaičius 1978–2016 metais Lietuvoje gautas iš Lietuvos vėžio registro (pagal tarptautinę ligų klasifikaciją (TLK) TLK-9 185, TLK-10 C61). Lietuvos vėžio registras yra populiacinis registras, kurio tikslas – užtikrinti piktybinių navikų registraciją visoje Lietuvoje. Naujų vėžio atvejų registracija vykdoma nuo 1978 metų. Vėžio registras yra Tarptautinės *(International Association of Cancer Registries*) ir Europos (*European Network of Cancer registries*) vėžio registrų asociacijų narys. Nuo 1988 metų sergamumo duomenys periodiškai pateikiami Tarptautinio vėžio tyrimų centro leidiniui „Sergamumas vėžiu penkiuose kontinentuose“, rengiant kurį yra atliekama pateikiamų duomenų kokybės analizė. Tyrimui naudoti tokie 1978–2016 metų duomenys: asmeniui nustatytos priešinės liaukos vėžio diagnozės data, amžius, stadija ir vėžio diferenciacijos laipsnis diagnozės nustatymo metu.

Mirčių nuo priešinės liaukos vėžio ir kitų priežasčių skaičius Lietuvoje buvo gautas iš Pasaulio sveikatos organizacijos (PSO) Mirtingumo duomenų bazės, penkerių metų amžiaus grupėmis nuo 1985 iki 2015 metų [30].

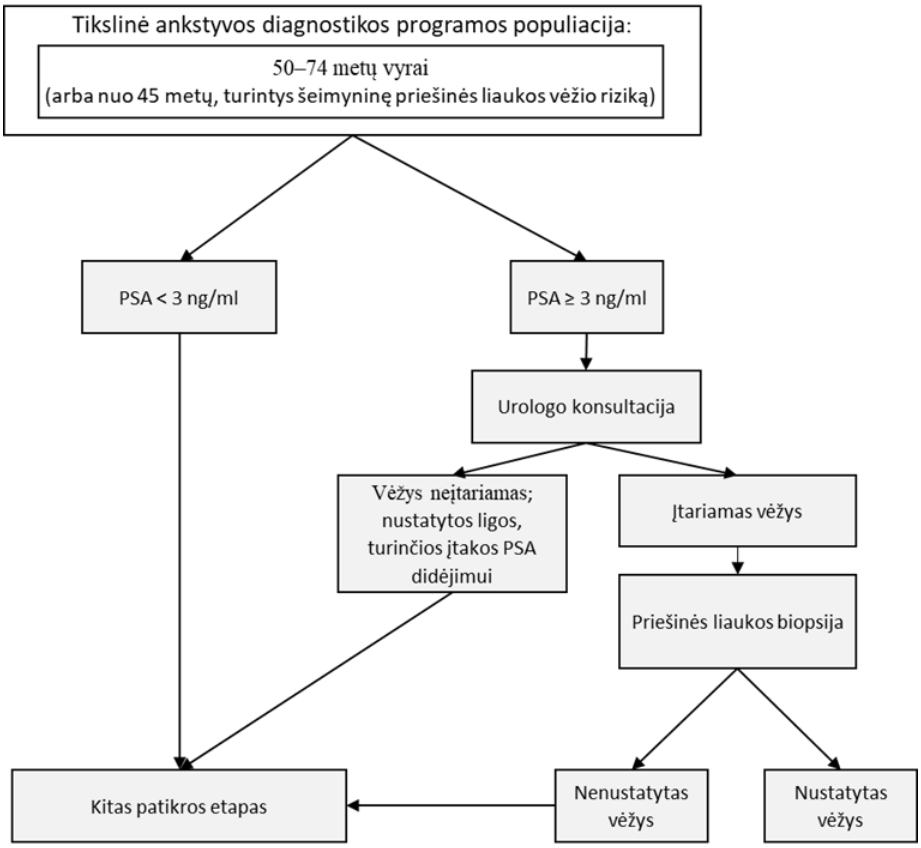
Rodiklių skaičiavimui naudoti Lietuvos statistikos departamento duomenys apie gyventojų skaičių penkerių metų amžiaus grupėmis pagal kalendorinius metus.

5.2. ADP vykdymo metodika

Lietuvoje priešinės liaukos vėžio profilaktinė patikra yra vykdoma remiantis Lietuvos Respublikos sveikatos apsaugos ministro (SAM) 2005 m. gruodžio 14 d. įsakymu Nr. V-973 „Dėl Priešinės liaukos vėžio ankstyvosios diagnostikos finansavimo programos patvirtinimo“. Programos tikslas yra pagerinti ankstyvųjų priešinės liaukos vėžio stadijų diagnostiką, taikyti radikalius priešinės liaukos vėžio gydymo metodus, siekiant pailginti sergančiųjų išgyvenamumo trukmę ir sumažinti pacientų neįgalumą ir mirtingumą dėl šios ligos. Programa pradėta vykdyti 2006 metais. Pacientas, sulaukęs 50–74 metų (arba nuo 45 metų, jei šeimoje yra priešinės liaukos vėžio anamnezė), kviečiamas dalyvauti programoje. Už asmens pakvietimą dalyvauti programoje atsakingas šeimos gydytojas. Pagal SAM įsakymą buvo numatyta pakvietimo dalyvauti programoje forma, tačiau kvietimus siunčia

tik pavienės asmens sveikatos priežiūros įstaigos. Dažniausiai dalyvauti siūloma vyrams šeimos gydytojo konsultacijos metu, kai asmuo kreipiasi į šeimos gydytoją dėl kitų priežasčių.

Iki 2016 metų dalyvauti programoje buvo siūloma 50–74 metų vyrams ir 45–49 metų vyrams, jei šeimoje yra priešinės liaukos vėžio anamnezė. Vyrai, kurių PSA koncentracija buvo didesnė nei 3 ng/ml, yra konsultuojami urologo, kuris pacientui atlieka priešinės liaukos biopsiją, jei yra nustatomi įtartini pakitimai DRT metu (1 pav.). Vyrai, kurių PSA koncentracija buvo mažesnis nei 3 ng/ml, taip pat tie, kuriems konsultacijos metu neatlikta biopsija arba kurie atsisakė priešinės liaukos biopsijos, arba biopsijos metu nenustatyti piktybiniai pakitimai, kviečiami kitai patikrai po dvejų metų. Nuo 2006 metų patikros tikslinės ADP populiacijos vyrams buvo atliekamos kasmet, o nuo 2009 metų patikros buvo vykdomos kas antrus metus. Nuo 2017 metų atsirado programos tikslinės populiacijos apribojimas pagal amžių. Pasitikrinti buvo pradėti kviesti 50–69 metų vyrai. 50–59 metų vyrai, kuriems nustatyta PSA koncentracija < 1 ng/ml, ir 60–69 metų vyrai, kuriems nustatyta PSA koncentracija < 2 ng/ml, kitą kartą pagal ADP yra tikrinami po penkerių metų.



1 pav. ADP organizavimo schema 2006–2016 metais

Remiantis SAM 2005 m. gruodžio 14 d. įsakymu Nr. V-973 „Dėl Priešinės liaukos vėžio ankstyvosios diagnostikos finansavimo programos patvirtinimo“ programos vykdymo rodiklius, rezultatus ir efektyvumą pagal nustatytus kriterijus vertina, siūlymus dėl programos vykdymo teikia Priešinės liaukos vėžio ankstyvosios diagnostikos finansavimo programos administravimo grupė. Įsakyme yra nustatyti programos vykdymo kriterijai:

- asmenų, kuriems per ataskaitinį laikotarpį pirminės sveikatos priežiūros įstaigos suteikė informaciją apie galimybę dalyvauti patikroje dėl priešinės liaukos vėžio, skaičius;
- per ataskaitinį laikotarpį pirminės sveikatos priežiūros įstaigos suteiktų informavimo apie priešinės liaukos vėžio ankstyvąją diagnostiką ir PSA nustatymo paslaugų skaičius;
- asmenų, kuriems per ataskaitinį laikotarpį nustatytas 3 ng/ml ir didesnis PSA kiekis, skaičius;

- asmenų, per ataskaitinį laikotarpį gavusių siuntimą konsultuotis pas urologą ir atlikti prostatos biopsiją, skaičius;
- asmenų, kurie per ataskaitinį laikotarpį kreipėsi į urologą dėl konsultacijos ir prostatos biopsijos, skaičius;
- per ataskaitinį laikotarpį suteiktų urologo konsultacijos ir priešinės liaukos biopsijos paslaugų skaičius.

Įsakyme taip pat numatyti programos efektyvumo kriterijai:

- asmenų, kuriems per ataskaitinį laikotarpį pirmą kartą buvo diagnozuotas priešinės liaukos vėžys, skaičius;
- asmenų, kuriems per ataskaitinį laikotarpį pirmą kartą buvo diagnozuotas T1 ir T2 stadijų priešinės liaukos vėžys, skaičius;
- programoje dalyvaujančių asmenų mirtingumo, susijusio su priešinės liaukos vėžiu, dinamika, palyginti su visos Lietuvos vyrų mirtingumu nuo šios ligos.

ADP administravimo grupė atlieka programos rezultatų vertinimą pagal jos vykdymo rodiklius ir efektyvumo kriterijus ne rečiau kaip vieną kartą per metus. Programos rezultatų ir efektyvumo ataskaitas administravimo grupė teikia Sveikatos apsaugos ministerijai ir Valstybinei ligonių kasai prie Sveikatos apsaugos ministerijos.

5.3. ADP eiga ir vykdymo rodikliai

Kad būtų galima atlikti ADP vykdymo analizę, programa buvo suskirstyta į septynis vykdymo etapus, kurie atitiko kalendorinius metus (2006–2009 metais kasmet, 2010–2015 kas dveji metai). Tokį pasirinkimą lėmė vykdant programą atsiradę patikros dažnumo pokyčiai (PSA testą iki 2009 metų tikslinės populiacijos vyrams buvo siūloma atlikti kasmet, vėliau – vieną kartą per dvejus metus). Patikros populiacija buvo apskaičiuota dienų tikslumu, t. y. asmuo įtrauktas į patikros populiacijos skaičiavimą tą dieną, kai jam sukanka 50 metų, ir pašalinamas, kai sukanka 75 metai. Kievienam patikros etapui aprašyti į tikslinę populiaciją įtraukti vyrai, kurių amžius buvo 50–74 metai. Informacija apie jų dalyvavimą programoje gauta iš VLK „Sveidra“ duomenų bazės. Programoje dalyvavusiais laikyti tie asmenys, kuriems programos vykdymo etape buvo suteikta bent viena ADP paslauga. Diagnozuoti vėžio atvejai identifikuoti iš VLK duomenų bazės „Sveidra“ (paslaugos kodas – 2038) ir vėžio registro (TLK10 kodas – C61). Kiekvienam patikros etapui buvo suskaičiuota patikrintų asmenų iš tikslinės populiacijos

(50–74 metų vyrai) dalis, santykis tarp padidėjusio PSA ir nepadidėjusio PSA rezultatų, santykis tarp biopsijų skaičiaus ir padidėjusio PSA skaičiaus, santykis tarp nustatyto priešinės liaukos vėžio atvejų ir padidėjusio PSA skaičiaus.

5.4. Sergamumo priešinės liaukos vėžiu ir mirtingumo nuo jo pokyčiai

Buvo suskaičiuoti standartizuoti pagal amžių sergamumo ir mirtingumo rodikliai (1976 metų Europos standartas). Rodikliai buvo suskaičiuoti visų amžiaus grupių, 50–74 metų amžiaus grupės ir 75 metų ir vyresnių amžiaus grupės, kiekvieniems kalendoriniams metams. Remiantis PSA atsiradimu klinikinėje praktikoje, vidutinių sergamumo ir mirtingumo rodiklių palyginimui 1995–1999 metų laikotarpis pavadintas laikotarpiu iki PSA atsiradimo, o 2011–2015 metų laikotarpis – laikotarpiu po PSA atsiradimo.

Vidutiniams procentiniams sergamumo ir mirtingumo pokyčiams ir statistiškai reikšmingų pokyčių taškų įvertinimui buvo naudota *Joinpoint* programa. Vidutinis metinis procentinis pokytis (VMPP) yra geometrinis metinių procentinių pokyčių (MPP) vidurkis. Nesant reikšmingų pokyčių per stebėjimo laikotarpį, VMPP yra lygus MPP. *Joinpoint* regresijos analizė nustato geriausiai tinkančius taškus, kur nustatomas reikšmingas tendencijos linijinio nuolydžio pokytis. Reikšmingumo testui naudotas Monte Carlo permutacijos testas. Vidutinis procentinis pokytis laikytas statistiškai reikšmingu, kai p reikšmė mažesnė nei 0,05. Atlikta visų amžiaus grupių ir atskirai 50–74 metų ir 75 metų bei vyresnių amžiaus grupės *Joinpoint* analizė. Maksimalus pokyčio taškų skaičius buvo lygus trims. Buvo naudota *Joinpoint* programinio paketo 4.3.1.0 versija.

5.5. Priešinės liaukos navikų patologinių charakteristikų pokyčiai vykdant ADP

Taikant tiesioginės standartizacijos metodą (1976 m. Europos standartas) buvo suskaičiuotas standartizuotas pagal amžių sergamumo rodiklis kiekvienai vėžio išplitimo grupei [31]. Pagal vėžio išplitimą, remiantis TNM klasifikacija, buvo nustatytos trys priešinės liaukos vėžio išplitimo grupės: lokalus (T1-T2N0M0 arba I–II stadijos), pažengęs (T3-T4N0M0 arba III stadija), išplitęs (bet kuris T, N1 arba M1 arba IV stadija). Dalies užregistruotų susirgimų stadija ir išplitimas nebuvo nurodyti. VMPP ir statistiškai reikšmingų pokyčių taškų analizei taikyta metodika, kuri aprašyta 8.3 skirsnyje.

5.6. Mirtingumo nuo priešinės liaukos vėžio ir kitų priežasčių rizikos analizė

Mirtingumo rizika analizuota dviem laikotarpiais: asmenys, kuriems priešinės liaukos vėžys diagnozuotas 1998–2006 metais, buvo priskirti grupei „Iki ADP“, o asmenys, kuriems priešinės liaukos vėžys diagnozuotas 2006–2016 metais, buvo priskirti grupei „ADP metu“. Tolesnės analizės metu asmenys, kuriems priešinės liaukos vėžys diagnozuotas nuo 2006 metų, buvo padalyti į dvi grupes: „Dalyvavę ADP“ ir „Nedalyvavę ADP“. Apribėžimas „Nedalyvavę ADP“ reiškia, kad asmeniui tiriamuoju laikotarpiu niekada nebuvo suteiktos ADP paslaugos.

Tyrimo dalyvių asmens stebėjimo metai (*person-years*) buvo skaičiuoti dienų tikslumu įvertinant kiekvieno asmens indėlį į stebėjimo metus kiekvienu tyrimo laikotarpiu. Asmens stebėjimo metai pradėti skaičiuoti nuo diagnozės nustatymo datos iki artimiausio įvykio: mirties datos, emigracijos datos arba tyrimo pabaigos (2016 m. gruodžio 31 d.).

Buvo suskaičiuotas standartizuotas mirtingumo santykis (SMS), dalijant įvykusių mirčių skaičių iš tikėtino mirčių skaičiaus. Tikėtinas mirčių skaičius tiriamojoje grupėje buvo apskaičiuojamas sudauginant asmens stebėjimo metus tiriamojoje grupėje su mirties priežasčiai specifiniais mirtingumo rodikliais bendrojoje Lietuvos vyrų populiacijoje penkerių metų amžiaus grupėse kasmet. 95 % pasikliautinieji intervalai (PI) rizikos rodikliui (SMS) skaičiuoti darant prielaidą, kad duomenų pasiskirstymas atitiko Puasono skirstinį.

6. REZULTATAI

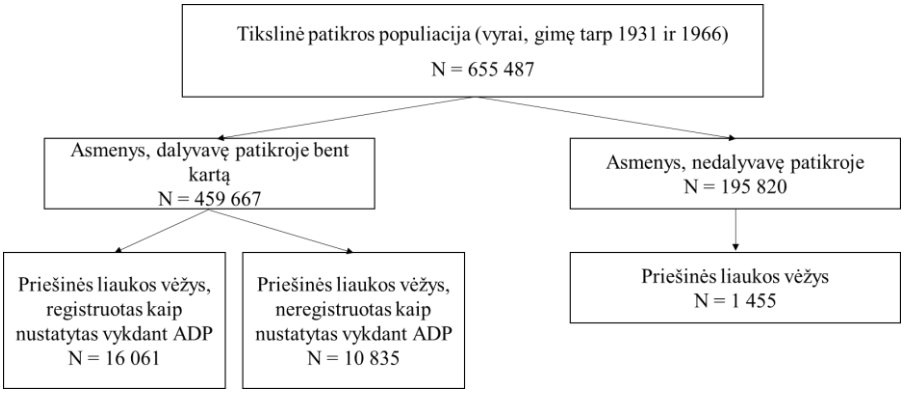
6.1. ADP programos vykdymas ir jo rodikliai

2006–2015 metais tikslinei grupei priklausė 655 487 vyrai (gimę tarp 1931 ir 1966 metų). Iš jų 459 667 (70,1 %) PSA testas vykdant ankstyvos diagnostikos programą buvo atliktas bent vieną kartą. Iš viso buvo atlikti 1 179 283 PSA testai, 1 044 448 iš jų buvo atlikti vyrams, kurie priklausė tikslinei populiacijai. Tik 1 455 priešinės liaukos vėžio atvejai iš 26 tūkstančių diagnozuoti vyrams, nedalyvavusiems ADP.

Pagrindiniai ankstyvos diagnostikos programos rodikliai yra pateikti 1 lentelėje. Dalyvavusių ADP programoje tikslinės populiacijos vyrų dalis buvo nuo 22,4 % iki 28,8 %, jie tikrinti kasmet, ir nuo 39,5 % iki 45,5 % vyrų patikra buvo atliekama kartą per dvejus metus. Dalis patikrintų vyrų, kuriems buvo padidėjusi PSA koncentracija (≥ 3 ng/ml), nuo 16,9 % pirmame patikros etape

sumažėjo iki 10,7 % septintame patikros etape. Tiems vyrams, kuriems PSA buvo padidėjęs (skirtingais programos vykdymo etapais nuo 28,4 % iki 39,2 % jų) buvo atlikta priešinės liaukos biopsija ir 35,9–42,0 % atvejų nustatytas priešinės liaukos vėžys.

16 061 (56,7 %) priešinės liaukos vėžio atvejis buvo nustatytas vykdant ADP programą, o 10 202 (38,2 %) priešinės liaukos vėžio atvejai buvo diagnozuoti tiems, kurie buvo dalyvavę ankstyvos diagnostikos programoje, tačiau vėžys neužregistruotas kaip jiems nustatytas vykdant šią programą (2 pav.).

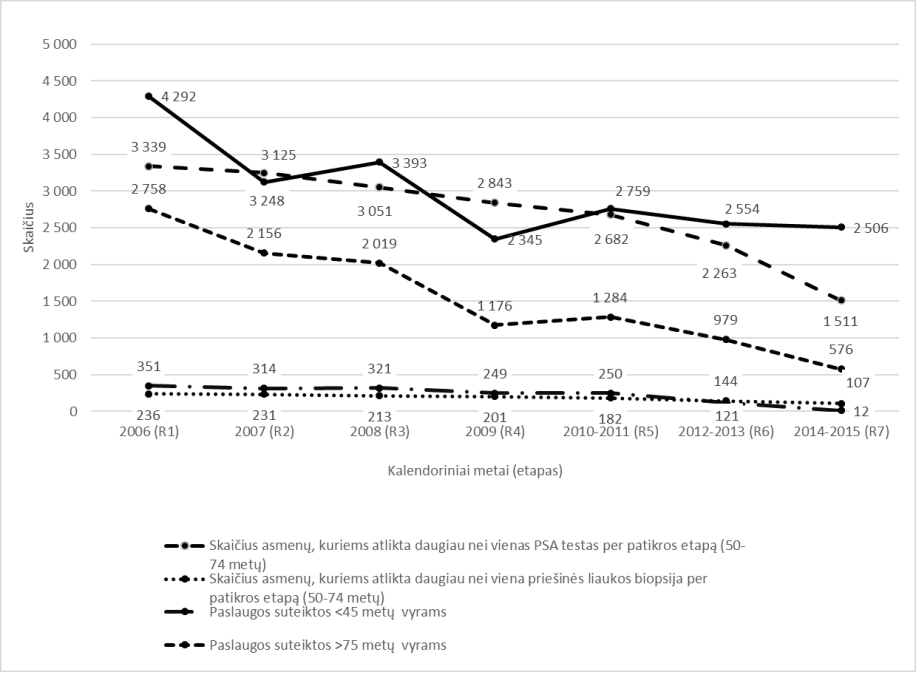


2 pav. Priešinės liaukos vėžio diagnozės nustatymas tikslinėje populiacijoje

Dalis ADP paslaugų buvo suteiktos vyrams, nepriklausantiems tikslinei populiacijai (3 pav.). 2006–2016 metais buvo atlikti 10 498 PSA testai vyrams, vyresniems nei 75 metų, ir 1 618 testų – jaunesniems nei 45 metų. Kiekviename patikros etape neprogramininių paslaugų buvo atliekama nuosekliai mažiau. Pirmajame patikros etape 3,6 % 50–74 metų vyrų buvo atliktas daugiau negu vienas PSA testas (3 339 iš 92 896 vyrų) ir 0,7 % septintajame patikros etape (1 511 iš 223 958). Daugiau nei viena priešinės liaukos biopsija per vieną patikros etapą buvo atlikta 236 (pirmame etape) ir 107 (paskutiniame etape) vyrams. Vykdant ADP, mažėjo ir vyresnių nei 75 metų vyrų, kuriems buvo atlikta patikra, skaičius (atitinkamai nuo 2 758 iki 576 atvejų pirmame ir paskutiniame patikros etapuose). PSA testas buvo naudojamas ir vyrams, kuriems jau nustatytas priešinės liaukos vėžys – atitinkamai 4 292 ir 2506 vyrams pirmame ir penktame patikros etape. Vyrų, kurie patikros metu buvo jaunesni nei 45 metų, skaičius per pirmus penkis patikros etapus svyravo tarp 236 ir 321, tačiau paskui smarkiai sumažėjo.

1 lentelė. Pagrindiniai ADP programos eigos ir vykdymo rodikliai

	Kalendoriniai metai						
	2006	**2007**	**2008**	**2009**	**2010–2011**	**2012–2013**	**2014–2015**
Tikslinė populiacija	413 997	417 832	422 812	429 535	466 557	480 194	492 291
Patikrinta asmenų (50–74 metų)	92 896	99 556	121 871	97 407	184 213	200 079	223 958
Dalyvavusių asmenų dalis (%)	22,4	23,8	28,8	22,7	39,5	41,7	45,5
PSA rezultatai							
PSA < 3 ng/ml (%)	77 188 (83,1)	84 201 (84,6)	105 303 (86,4)	84 666 (86,9)	162 806 (88,4)	176 939 (88,4)	199 968 (89,3)
PSA ≥ 3 ng/ml (%)	15 708 (16,9)	15 355 (15,4)	16 568 (13,6)	12 741 (13,1)	21 407 (11,6)	23 140 (11,6)	23 990 (10,7)
Biopsijos							
Biopsijų skaičius (% nuo asmenų, kuriems padidėjęs PSA)	4 459 (28,4)	5 574 (36,3)	5 934 (35,8)	5 092 (40,0)	8 386 (39,2)	8 750 (37,8)	7 985 (33,3)
Priešinės liaukos vėžys (% nuo biopsijų)	1 509 (35,9)	1 873 (36,1)	1 879 (35,3)	1 647 (35,9)	2 836 (37,6)	3 210 (40,2)	3 107 (42,0)
Priešinės liaukos vėžio dalis tarp asmenų, kuriems padidėjęs PSA (%)	9,6	12,2	11,3	12,9	13,2	13,9	13,0
Priešinės liaukos vėžio dalis tarp patikrintų asmenų (%)	1,6	1,9	1,5	1,7	1,5	1,6	1,4
Priešinės liaukos vėžys tarp bent kartą dalyvavusiųjų patikroje (%)	2 445 (2,5)	3 320 (3,2)	3 242 (2,69)	2 912 (2,9)	4 796 (2,5)	5 143 (2,5)	5 038 (2,2)

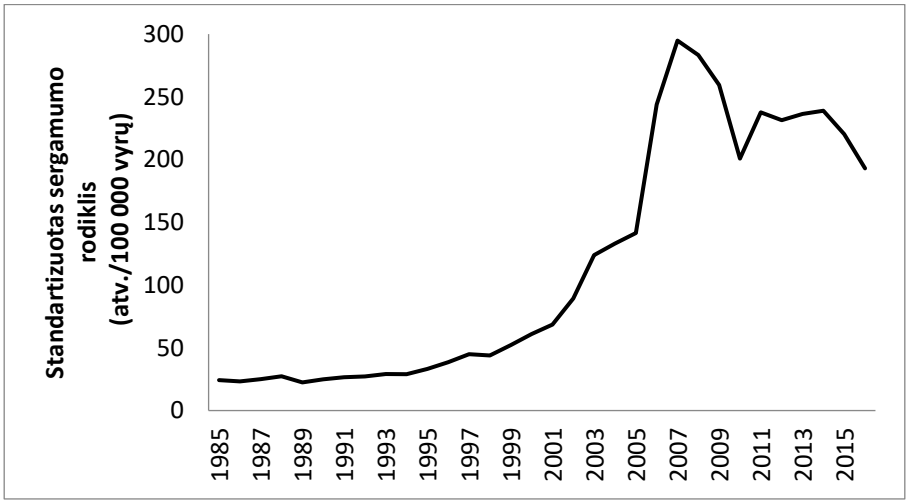


3 pav. ADP paslaugos, suteiktos vyrams, nepriklausantiems tikslinei populiacijai

6.2. Sergamumo priešinės liaukos vėžiu ir mirtingumo nuo jo pokyčiai vykdant priešinės liaukos ADP Lietuvoje

Nuo PSA tyrimo atsiradimo klinikinėje praktikoje ir programos vykdymo pradžios sergamumas priešinės liaukos vėžiu Lietuvoje gerokai pakito (4 pav.). Standartizuotas pagal amžių sergamumo rodiklis nuo 69,32 atv./100 000 vyrų 2000 metais padidėjo iki 279,33 atv./100 000 vyrų (Europos standartas) 2007 metais, vėliau mažėjo, bet liko 161,96 atv./100 000 vyrų 2016 metais [32].

Visą tiriamąjį laikotarpį sergamumas nuosekliai didėjo po 7,4 % kasmet (2 lentelė). 1978–1994 ir 1994–2001 metų laikotarpiais kasmet didėjo atitinkamai po 3,2 % ir 9,8 %. Nuo 2001 metų sergamumas priešinės liaukos vėžiu didėjo spartesniais tempais – 23,0 % kasmet iki 2007 metų, vėlesniais metais kasmet mažėjo po 4,4 % iki tyrimo pabaigos. Didžiausias sergamumo MPP buvo 50–74 metų vyrų grupėje – 2001–2007 metais sergamumas didėjo po 30,8 % kasmet.



4 pav. Sergamumas priešinės liaukos vėžiu Lietuvoje 1985–2015 metais

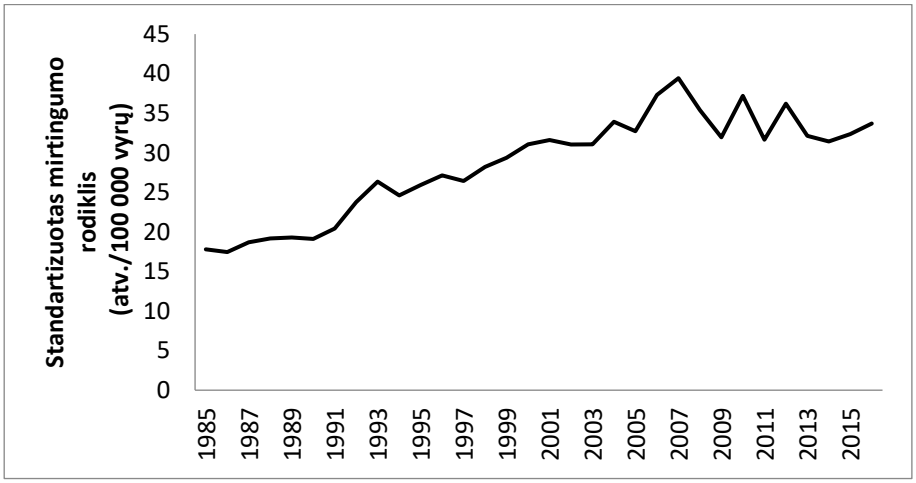
2 lentelė. Sergamumo priešinės liaukos vėžiu pokyčiai ir lūžio taškai 1978–2016 metais

Amžiaus grupės	Standartizuotas rodiklis		Stebėjimo laikotarpis	Pokyčio segmentas	MPP	95 % PI	
	1995–1999	2011–2015					
Visos amžiaus grupės	51,7	203,4	1978–2016	1978–2016	7,4*	6,5	8,3
				1978–1994	3,2*	2,1	4,2
				1994–2001	9,8*	5,1	14,7
				2001–2007	23,0*	16,0	30,3
				2007–2016	–4,4*	–6,6	–2,1
50–74	116,83	686,0	1978–2016	1978–2016	8,8*	7,7	9,9
				1978–1994	3,3*	2,1	4,5
				1994–2001	9,2*	3,5	15,1
				2001–2007	30,8*	22,0	40,3
				2007–2016	–3,5*	–6,2	–0,7
≥ 75	554,0	734,0		1978–2016	4,0*	3,1	4,9
				1978–1984	6,5*	2,7	10,4
				1984–1994	1,6	-0,3	3,6
				1994–2005	12,0*	10,1	13,9
				2005–2016	–7,4*	–8,8	–6,1

* – rezultatai statistiškai reikšmingi.

Nuo 1985 metų iki 2007 metų mirtingumas nuo priešinės liaukos vėžio nuo 17,85 padidėjo iki 39,43 atv./100 000 vyrų, vėliau rodiklis truputį mažėjo, o 2016 metais buvo 33,70 atv./100 000 vyrų (5 pav.). 50–74 metų amžiaus

grupėje mirtingumas didėjo iki 1993 metų po 5,0 % kasmet, vėliau augimo tempai sulėtėjo iki 0,7 % kasmet (3 lentelė). 75 metų ir vyresnių amžiaus grupėje vykę pokyčiai buvo analogiški bendriems mirtingumo pokyčiams: iki 2006 metų atvejų daugėjo vidutiniškai po 4,6 % kasmet ir mažėjo kasmet po 1,7 % iki 2016 metų.



5 pav. Mirtingumas nuo priešinės liaukos vėžio Lietuvoje 1985–2015 metais

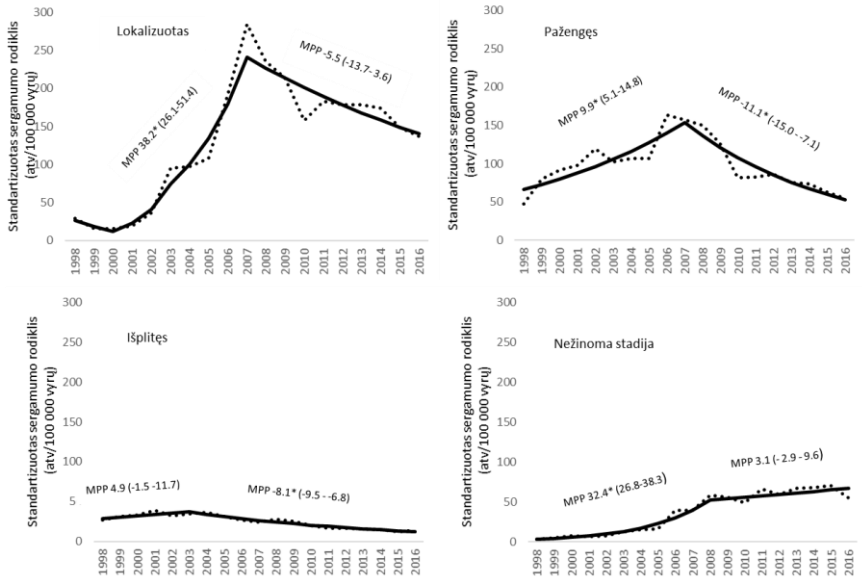
3 lentelė. Mirtingumo nuo priešinės liaukos vėžio pokyčiai ir lūžio taškai 1978–2016 metais

Amžiaus grupės	Standartizuotas rodiklis		Stebėjimo laikotarpis	Pokyčio segmentas	MPP	95 % PI	
	1995–1999	2011–2015					
Visos amžiaus grupės	26,68	31,1	1985–2016	1985–2016	2,3*	1,9	2,8
				1985–2006	3,6*	3,2	4,0
				2006–2016	–1,4*	–2,7	–0,1
50–74	49,7	52,8	1985–2016	1985–2016	1,4*	1,0	1,8
				1985–1993	5,0*	2,4	7,7
				1993–2016	0,7*	0,1	1,2
≥ 75	351,2	445,5		1985–2016	3,0*	2,4	3,6
				1985–2006	4,6*	4,0	5,2
				2006–2016	–1,7	–3,5	0,2

* – rezultatai statistiškai reikšmingi.

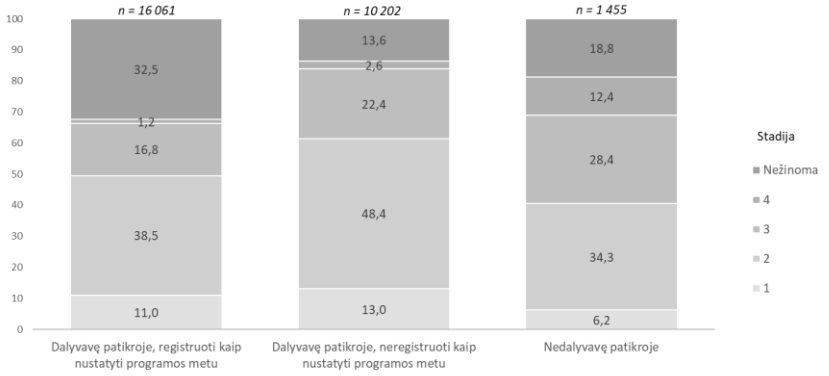
6.3. Priešinės liaukos navikų patologinių charakteristikų pokyčiai

Didžiausi sergamumo priešinės liaukos vėžiu rodiklių pokyčiai nuo ADP vykdymo pradžios buvo lokalaus vėžio grupėje (6 pav.). Lokalaus vėžio grupėje sergamumas iki 2007 metų didėjo vidutiniškai 38,2 % kasmet ir pasiekė 284,6 atv./100 000 vyrų sergamumo rodiklį. Nuo 2007 metų sergamumas mažėjo po 5,5 % kasmet. Sergamumas pažengusios stadijos vėžiu didėjo iki 2007 metų, vėliau pradėjo mažėti po 11,1 % kasmet. Sergamumas išplitusiu vėžiu buvo mažiausias, jis didėjo iki 2003 metų. Nuo 2003 metų sergamumas išplitusiu priešinės liaukos vėžiu mažėjo po 8,1 % kasmet.



5 pav. Sergamumas priešinės liaukos vėžiu 1998–2016 pagal vėžio išplitimo grupes

Iš ankstyvos diagnostikos programoje nedalyvavusių vyrų ketvirtos stadijos vėžiu sirgo 12,4 %, o iš patikroje dalyvavusių ir užregistruotų kaip patikros metu nustatytų sirgo 1,2 % ir 2,6 % tų, kurie dalyvavo patikroje, bet priešinės liaukos vėžys neužregistruotas kaip nustatytas jos metu. Didesnė dalis pirmos ir antros stadijos vėžio atvejų taip pat buvo diagnozuota patikroje dalyvavusių vyrų grupėse (49,5 % ir 61,4 %), palyginti su niekada nedalyvavusiais (40,5 %) (7 pav.).



7 pav. Priešinės liaukos vėžio atvejų pasiskirstymas pagal stadijas

6.4. Priešinės liaukos vėžiu sergančių vyrų mirtingumo rizika

1998–2016 metais buvo diagnozuota 48 819 naujų priešinės liaukos vėžio atvejų – 11 401 atvejis iki pradedant vykdyti ADP ir 37 418 atvejų ją vykdant. Vidutinis tiriamųjų amžius prieš pradedant vykdyti ADP buvo 71,51 metų, didesnis už tiriamųjų amžių vykdant ADP – 67,17 metų (4 lentelė, A dalis). Nedalyvavę ADP asmenys buvo vyresni už tuos, kurie dalyvavo ADP (atitinkamai 76,26 metų ir 65,47 metų) (4 lentelė, B dalis).

4 lentelė. Tiriamųjų grupių charakteristikos: A – pagal tyrimo laikotarpį (1998–2016 metai), B – pagal dalyvavimą ADP (2006–2016 metais)

A	**Iki ADP (1998–2005)**	**ADP metu (2006–2016)**
Asmenys, sergantys priešinės liaukos vėžiu	11 401 (23,35)	37 418 (76,65)
Vidutinis amžius diagnozės nustatymo metu (SN*), metais	71,51 (± 8,44)	67,17 (± 8,87)
Vidutinis amžius mirties metu (SN*), metais	78,16 (± 8,85)	75,61 (± 8,70)
Vidutinis stebėjimo laikas (SN*), dienomis	2 404,78 (± 1 876,44)	1 707 (± 1 160,33)
Mirusiųjų skaičius (%)	8 782 (77,03)	11 079 (29,61)

B	Nedalyvavę ADP	Dalyvavę ADP
Asmenys, sergantys priešinės liaukos vėžiu (%)	5 886 (15,73)	31 532 (84,27)
Vidutinis amžius diagnozės nustatymo metu (SN*), metais	76,26 (± 9,87)	65,47 (± 7,54)
Vidutinis amžius mirties metu (SN*), metais	81,34 (± 8,29)	73,22 (± 7,69)
Vidutinis stebėjimo laikas (SN*), dienomis	1 335,76 (± 1 225,20)	1 776,34 (± 1 134,83)
Mirusiųjų skaičius (%)	3 805 (64,64)	7 274 (23,06)

*SN – standartinis nuokrypis.

Priešinės liaukos vėžiu sergančiųjų mirties dėl visų priežasčių rizika (5 lentelė, A dalis) buvo didesnė nei bendrosios Lietuvos vyrų populiacijos. Asmenims, kuriems priešinės liaukos vėžio diagnozė buvo nustatyta vykdant ADP, mirties dėl visų priežasčių rizika buvo mažesnė (SMS = 1,17 (95 % PI 1,15–1,19)) nei tiems asmenims, kuriems priešinės liaukos vėžio diagnozė buvo nustatyta iki pradedant ADP (SMS = 1,45 (95 % PI 1,42–1,48)). Didesnė mirties dėl visų priežasčių rizika buvo vykdant ADP asmenims, kurie nedalyvavo ADP (SMS = 1,76 (95 % PI 1,71–1,82)), o mirties dėl visų priežasčių rizika ADP dalyviams buvo tokia pati kaip bendrosios Lietuvos vyrų populiacijos (SMS = 1,00 (95 % PI 0,97–1,02)).

Analizuojant mirties dėl visų priežasčių riziką tarp vyrų, kuriems diagnozuotas priešinės liaukos vėžys, pagal piktybinio naviko išplitimą buvo padidėjusi mirties rizika vyrams, kuriems diagnozuotas vietiškai pažengęs arba išplitęs vėžys, rizika statistiškai reikšmingai didėjo didėjant ligos išplitimui ($P < 0,0001$) tarp dalyvavusių ir nedalyvavusių ADP (6 lentelė). Asmenims, kurie nedalyvavo ADP ir jiems buvo diagnozuotas lokalus vėžys, mirties dėl visų priežasčių rizika buvo tokia pati kaip ir bendrosios Lietuvos vyrų populiacijos (SMS = 0,99 (95 % PI 0,92–1,05)). Asmenims, kurie dalyvavo ADP ir kuriems buvo nustatytas lokalus vėžys, mirties dėl visų priežasčių rizika buvo mažesnė nei bendrosios Lietuvos vyrų populiacijos (SMS = 0,72 (95 % PI 0,70–0,75)).

5 lentelė. Mirties dėl visų priežasčių rizika tarp sergančiųjų priešinės liaukos vėžiu: A – pagal tyrimo laikotarpį (1998–2016 metai), B – pagal dalyvavimą ADP (2006–2016 metai)

	Nustatyta	**Tikėta**	**SMS**	**95 % PI**		**Nustatyta**	**Tikėta**	**SMS**	**95 % PI**	
A	**Iki vykdant ADP (1998–2005 metai)**					**Vykdant ADP (2006–2016 metai)**				
Visos priežastys	8 782	6 075,12	1,45	1,42	1,48	1 1079	9 461,78	1,17	1,15	1,19
B	**Nedalyvavę ADP**					**Dalyvavę ADP**				
Visos priežastys	3 805	2 157,04	1,76	1,71	1,82	7 274	7 304,74	1,00	0,97	1,02

6 lentelė. Mirties dėl visų priežasčių rizika tarp sergančiųjų priešinės liaukos vėžiu vykdant ADP pagal ligos išplitimą (2006–2016 metai)

	Nedalyvavę ADP					Dalyvavę ADP				
	Nustatyta	**Tikėta**	**SMS**	**95 % PI**		**Nustatyta**	**Tikėta**	**SMS**	**95 % PI**	
Bendra	3 805	2 157,04	1,76	1,71	1,82	7 274	7 304,74	1,00	0,97	1,02
Lokalus	886	897,05	0,99	0,92	1,05	2 878	3 974,42	0,72	0,70	0,75
Vietiškai pažengęs	1 076	779,70	1,38	1,30	1,46	1 979	1 607,36	1,23	1,18	1,29
Išplitęs	588	107,71	5,46	5,04	5,92	473	114,59	4,13	3,77	4,52
Nežinoma*	1 255	372,58	3,37	3,19	3,56	1 944	1 608,38	1,21	1,16	1,26
			$P < 0,0001$					$P < 0,0001$		

*Į χ^2 testą didėjimo tendencijai neįtraukta.

7. REZULTATŲ APTARIMAS

Lietuvoje visu programos vykdymo laikotarpiu jos paslaugomis bent kartą pasinaudojo maždaug 70 % tikslinės populiacijos vyrų. PSA koncentracija viršijo 3 ng/ml ribą mažiau nei 17 % patikrintų vyrų, iš kurių 10–14 % nustatytas priešinės liaukos vėžys. Didžioji dauguma priešinės liaukos vėžio atvejų buvo diagnozuota ankstyvų stadijų.

Patikros programoje dalyvavusių tikslinės populiacijos asmenų dalis yra vienas svarbiausių profilaktinės patikros vykdymo rodiklių [33,34]. ADP paslaugomis vieno programos vykdymo etapo metu pasinaudojo mažiau nei pusė tikslinės populiacijos vyrų. Patikros programoje dalyvavusių vyrų dalis Lietuvoje didėjo su kiekvienu patikros etapu. Dalyvavusių programoje vyrų dalies padidėjimas, kai patikros pradėtos atlikti kas dveji metai, rodo prailginto patikros intervalo efektą. Kitose šalyse, vykdant profilaktinę priešinės liaukos patikrą, gauti panašūs rodikliai – remiantis JAV medicinos išlaidų apklausa (Medical Expenditure Survey), 2006 metais 49,7 % vyrų, kurių amžius buvo 50–74 metai, bent kartą buvo patikrinti naudojant PSA testą [35]. Japonijoje vykdomos profilaktinės priešinės liaukos vėžio patikros metu buvo patikrinta tik 20 % tikslinės populiacijos vyrų [36].

Reikia pažymėti, kad vykdant ADP jos paslaugos buvo suteiktos ir tiems vyrams, kurie nėra tikslinėje programos populiacijoje arba dažniau negu reikėtų. Tokių paslaugų skaičius mažėjo su kiekvienu patikros etapu. PSA testų atlikimas asmenims, kuriems jau yra nustatytas priešinės liaukos vėžys, rodo ankstyvos diagnostikos programos naudojimą ne patikros, o diagnostiniais tikslais arba vykdant aktyvią stebėseną.

Teigiamų (kai padidėjusi PSA koncentracija) testų dažnis yra tiesiogiai susijęs su ribinėmis vertėmis, kurios yra naudojamos programoje. Yra gerai žinoma, kad PSA koncentracija kraujyje didėja didėjant amžiui [37]. Visų septynių patikros etapų metu naudojant 3 ng/ml ribą, nepaisant asmens amžiaus, teigiamų PSA testų proporcija patikrintoje populiacijoje buvo tarp 9,6 ir 13,9 %. Panašūs rodikliai (11 %) buvo gauti Jungtinėje Karalystėje, kur tyrime 50–69 metų vyrams naudota tokia pati ribinė PSA vertė [38]. Tyrimuose, kurie naudojo ribinę vertę, lygią 4 ng/ml, teigiamų testų dažnis svyravo tarp 8 % [39] ir 17 % [10]. Nuo 2017 metų programos aprašas pakeistas – įtraukti patikros intervalų apribojimai remiantis PSA koncentracija ir paciento amžiumi. Tuo siekiama sumažinti programos išlaidas, klaidingai teigiamų testų tikimybę, kartu tikintis sumažinti hiperdiagnostikos riziką.

Nuo 28,4 % iki 40,0 % vyrų, kuriems nustatyta padidėjusi PSA koncentracija, buvo atlikta priešinės liaukos biopsija. Toks skaičius gali

rodyti, kad urologai, prieš atlikdami priešinės liaukos biopsiją, konsultacijos metu taikė papildomus diagnostikos metodus (pvz., magnetinio rezonanso tomografija, laisvo ir bendro PSA santykis, PSA tankis), siekdami atmesti būkles, kurios galėjo sąlygoti PSA padidėjimą [40].

Priešinės liaukos vėžio dažnis tarp patikrintų asmenų mūsų tiriamoje populiacijoje buvo nuo 1,4 % iki 1,9 %. Šalyse, kuriose buvo vykdoma profilaktinė priešinės liaukos vėžio patikra, gauti panašūs rezultatai: Japonijoje šis rodiklis siekė 0,5–1,1 %, ERPSC tyrime Suomijoje – 2,5 %, Olandijoje – 4,6 % visų patikrintų vyrų [36], [41,42].

Priešinės liaukos vėžio atvejų dalis tarp asmenų, kuriems nustatyta padidėjusi PSA koncentracija, vadinamas teigiama prognostine verte (TPV). Skirtinguose tyrimuose šis rodiklis buvo skaičiuojamas skirtingais būdais: dalijant nustatyto vėžio atvejų skaičių iš biopsijų skaičiaus (ERSPC tyrime) ir dalijant nustatytą vėžio atvejų skaičių iš teigiamų PSA testų skaičiaus (PLCO tyrimas) [10,39]. ERSPC tyrime TPV dalijant iš biopsijų skaičiaus svyravo tarp 35,3 % ir 42,0 %, o dalijant iš testų, rodančių padidėjusią PSA koncentraciją, skaičiaus – nuo 9,6 % iki 13,9 %. Vidutinis TPV tarp ERSPC tyrimo centrų buvo 24,3 % [12]. TPV JAV vykdytame PLCO tyrime dalijant iš teigiamų PSA testų skaičiaus buvo tarp 11,0 % ir 7,3 %, o dalijant iš biopsijų skaičiaus – 36,9 % ir 31,0 % [39].

Lietuvoje sergamumas priešinės liaukos vėžiu pradėtas nagrinėti aštuntame dešimtmetyje. R. Gurevičiaus ir V. Lazutkos straipsnyje analizuotas sergamumas priešinės liaukos vėžiu Lietuvoje 1973–1978 metais, nustatytas sergamumo rodiklis siekė 25,1 atv./100 000 vyrų [43]. Mūsų tyrime 2007 metais sergamumas buvo 279,33 atv./100 000 vyrų. Pirmais ADP vykdymo metais sergamumo pokyčiai Lietuvoje atkartojo sergamumo priešinės liaukos vėžiu Jungtinėse Amerikos Valstijose tendencijas devintajame ir dešimtajame dešimtmetyje [8]. Po staigaus sergamumo rodiklių padidėjimo ėjo sergamumo sumažėjimas. Pagrindinė tokių sergamumo pokyčių priežastis buvo jau esamų populiacijoje priešinės liaukos vėžio atvejų (angl. *prevalent cases*) diagnozavimas per trumpą laikotarpį. Tokį efektą sergamumo rodikliams 2000 metais aprašė *Curtis Metlin* [44]. Naujausioje priešinės liaukos vėžio epidemiologinių tendencijų apžvalgoje sergamumas priešinės liaukos vėžiu Lietuvoje buvo didžiausias iš visų šalių sergamumo rodiklių pasaulyje [2]. Analizuojant sergamumą pagal amžiaus grupes iki 2006 metų buvo matyti sergamumo didėjimas, o vėliau – mažėjimas, tačiau visose grupėse visu tyrimo laikotarpiu vyravo nuosekli sergamumo didėjimo tendencija. Didžiausias metinis procentinis sergamumo pokytis buvo tikslinėje ADP grupėje.

Didžiausi sergamumo priešinės liaukos vėžiu rodikliai pasaulyje yra ekonomiškai išsivysčiusiose šalyse (Šiaurės Amerika, Okeanija ir Šiaurės Europa) ir yra tiesiogiai susijęs su PSA testo naudojimu klinikinėje praktikoje. Todėl šalyse, kuriose atsakingos institucijos pasisakė prieš PSA testo naudojimą profilaktinei patikrai dėl priešinės liaukos vėžio, sergamumo rodikliai paskutinius penkerius metus mažėjo [45].

Mirtingumas nuo priešinės liaukos vėžio pasaulyje nuosekliai mažėja. Tai atspindi patobulėjusias gydymo galimybes, taip pat pagerėjusį gydymo nuo priešinės liaukos vėžio prieinamumą pasaulyje [10]. PSA testavimo poveikis mirtingumui nuo priešinės liaukos vėžio pasaulyje išlieka neaiškus.

Priešinės liaukos vėžys daugiausia yra latentinė, lėtai progresuojanti liga. Todėl atliekant sveikatos priežiūros intervencijas visuomenėje reikia tam tikro laiko, kad tokių intervencijų nauda būtų matoma populiacijoje. Lietuvoje mirtingumas nuo priešinės liaukos vėžio pradėjo mažėti tais pačiais metais, kuriais buvo pradėta vykdyti ADP. Omirtingumo rizika pradėjo mažėti, ERSPC tyrimo duomenimis, devintais stebėjimo metais [10]. Todėl mirtingumo nuo priešinės liaukos vėžio mažėjimas Lietuvoje nuo 2006 metų turėtų būti siejamas ne su PSA tyrimu paremtos patikros efektu, bet su paties PSA tyrimo taikymu klinikinėje praktikoje. Dideli mirtingumo nuo priešinės liaukos vėžio rodikliai Lietuvoje pradėjus vykdyti ADP iš dalies yra ir dėl padažnėjusios priešinės liaukos vėžio, kaip pagrindinės mirties priežasties, nurodymo. Taip pat, taikant intervecijas vienai tikslinei amžiaus grupei, taikytų priemonių rezultatas gali būti matomas kitoje amžiaus grupėje po tam tikro laiko [46]. ADP atveju 2006–2015 metais Lietuvoje 50–74 metų vyrų mirtingumas nemažėjo, tačiau sumažėjo 75 metų ir vyresnių vyrų mirtingumas.

Dėl ADP Lietuvoje nustatyti didžiausi sergamumo lokaliu ir lokaliai pažengusiu priešinės liaukos vėžiu rodikliai 2007 metais. Didžiausi sergamumo išplitusiu priešinės liaukos vėžiu rodikliai buvo 2001 metais, vėliau jie mažėjo. Tokių pokyčių galėjo atsirasti dėl dažnai taikomų transuretrinių priešinės liaukos rezekcijų, vėliau ir dėl PSA naudojimo klinikinėje praktikoje. Staigus sergamumo lokaliai pažengusiu priešinės liaukos vėžiu sumažėjimas rodo teigiamą ADP efektą. Panašūs sergamumo pokyčiai buvo JAV ir Tirolio regione Austrijoje [14,47]. Priešinės liaukos vėžio pasiskirstymo pagal stadijas analizė aiškiai parodė stadijų persiskirstymą (angl. *stage migration*) vykdant ADP, kai gerokai sumažėjo sergamumas lokaliai pažengusiu ir išplitusiu priešinės liaukos vėžiu.

Mirties dėl visų priežasčių rizikos analizė papildo ligai specifinio mirtingumo analizę nagrinėjant patikros dėl priešinės liaukos vėžio efektyvumą. Mirčių dėl visų priežasčių rizika tarp priešinės liaukos vėžiu

sergančių pacientų buvo 28 % didesnė, palyginti su bendrąja Lietuvos vyrų populiacija visu tyrimo laikotarpiu. Taip pat tų, kurie nedalyvavo ankstyvos diagnostikos programoje, mirties rizika buvo 76 % didesnė nei bendrosios Lietuvos vyrų populiacijos, o dalyvavusių rizika nesiskyrė nuo bendrosios Lietuvos vyrų populiacijos mirtingumo. Analizuojant riziką pagal ligos išplitimą, nustatyta, kad mirties rizika didėjo didėjant ligos išplitimui.

Panašaus pobūdžio mirties rizikos dėl visų priežasčių tyrimai atlikti JAV, Europoje, Jungtinėje Karalystėje, Švedijoje ir Suomijoje. Suomių tyrime, kuris apėmė 1985–2009 metus, aptiktas mirties dėl visų priežasčių rizikos sumažėjimas pacientams, kuriems buvo diagnozuotas lokalus priešinės liaukos vėžys [48]. Švedų tyrime rizika analizuota suskirsčius pacientus pagal priešinės liaukos vėžio rizikos grupes ir palyginus juos su priešinės liaukos vėžiu nesergančiais pacientais [49]. Tyrimo rezultatai parodė, kad vyrų, sergančių mažos rizikos priešinės liaukos vėžiu, mirties dėl visų priežasčių rizika yra mažesnė. ERSPC tyrime analizuojant mirties dėl visų priežasčių riziką nebuvo rasta mirties rizikos sumažėjimo [50]. PLCO tyrėjai 2020 metais įvertino profilaktinėje priešinės liaukos vėžio patikroje dalyvavusių asmenų mirties dėl visų priežasčių riziką. Buvo nustatyta didesnė mirties rizika didelės rizikos priešinės liaukos vėžiu sergančiųjų pacientų grupėje, tačiau rezultatai nebuvo statistiškai reikšmingi [51].

Lyginant dvi tiriamųjų grupes (dalyvavę ADP ir nedalyvavę ADP), matyti aiški profilaktinės patikros naudojant PSA tyrimą nauda. Dalyvavusiems ADP pacientams, kuriems buvo diagnozuotas lokalus vėžys, mirties rizika, palyginti su bendrąja Lietuvos vyrų populiacija, buvo mažesnė. Kadangi mūsų tiriamoje populiacijoje pasireiškė vadinamoji „stadijų migracija“ ir didžiausią naujai diagnozuotų priešinės liaukos vėžio atvejų dalį sudaro lokalus vėžys [52,53], galima teigti, kad mažesnė dalyvavusių ADP mirties rizika buvo dėl ankstyvos diagnostikos. Panašūs rezultatai gauti Švedijoje atliktame tyrime, kuriame pacientams, kuriems diagnozuotas ir gydytas lokalizuotas priešinės liaukos vėžys, nustatyta 44,0 % sumažėjusi mirties nuo priešinės liaukos vėžio ir 12,7 % dėl visų priežasčių rizika [54]. Suomių tyrime taip pat buvo matoma ankstyvos diagnostikos nauda, kur mirties dėl visų priežasčių rizika laikotarpiu nuo PSA naudojimo klinikinėje praktikoje pradžios buvo tokia pati kaip bendroje Suomijos vyrų populiacijoje, o nuo 2000-ųjų metų rizika tapo mažesnė [48].

Didesni ADP nedalyvavusių vyrų mirtingumo rizikos rodikliai gali būti socialinių netolygumų priešinės liaukos vėžiu sergančiųjų populiacijoje atspindys [55]. Lietuvoje vykdyto tyrimo duomenimis, mirtingumo rodiklių santykis, lyginant turinčius vidurinį ir mažesnį nei vidurinis išsilavinimą su turinčiais aukštąjį išsilavinimą, buvo didesnis žemesnį nei vidurinis

išsilavinimą turinčių tiriamųjų grupėje [56]. Verta paminėti, kad oportunistinis testavimas taip pat sukelia socialinius netolygumus, nes labiau pasiturintys asmenys gali dažniau testuotis ir taip lengviau pasiekti patikros teikiamą naudą, nei mažiau pasiturintys.

Klinikinių duomenų apie pacientams taikytą gydymą ir tikslias PSA koncentracijos vertes diagnozės nustatymo metu trūkumas buvo pagrindinė priežastis, apribojusi tyrimą ir neleidusi įvertinti hiperdiagnostikos ir hiperterapijos paplitimo ankstyvos diagnostikos programoje dalyvavusių ir nedalyvavusių asmenų grupėse. Lietuvos Vėžio registro duomenų kokybės trūkumai (pvz., didelei daliai priešinės liaukos vėžio atvejų yra nežinoma jo stadija, nežinomas naviko diferenciacijos laipsnis, remiantis Gleasonu) neleido kaip reikiant įvertinti priešinės liaukos vėžio rizikos grupės, tačiau šių duomenų trūkumas nepadarė įtakos pagrindiniams programos efektyvumo vertinimo rodikliams.

Pagrindinis šio tyrimo pranašumas yra tai, kad jame pateikiami programos, įgyvendintos nacionaliniu mastu visoje populiacijoje, rezultatai. Tyrimas apima ilgiausią iki šiol nagrinėtą ankstyvos diagnostikos programos vykdymo laikotarpį, pirmą kartą pateikiami svarbiausi programos vykdymo rodikliai ir mirtingumo rizikos nuo priešinės liaukos vėžio ir visų priežasčių įvertinimas. Nors atsitiktinės atrankos kontroliuojamais tyrimais gaunami aukščiausio įrodymų lygmens rezultatai, realaus gyvenimo duomenų iš populiacinių registrų analizė suteikia unikalią informaciją apie taikomos intervencijos veiksmingumą populiacijoje.

IŠVADOS

1. Lietuvoje vykdoma ADP pasižymėjo mažu patikrintų vyrų skaičiumi iš tikslinės populiacijos, dideliu skaičiumi paslaugų, suteiktų patikros populiacijai nepriklausantiems asmenims, mažu vėžio nustatymo rodikliu.
2. Plačiai naudojamas PSA tyrimas ir šiuo tyrimu paremta ADP padarė didelę įtaką sergamumo priešinės liaukos vėžiu pokyčiams – sergamumo didėjimas atspindėjo PSA tyrimo naudojimo paplitimą. Staigus sergamumo padidėjimas pirmais patikros metais susijęs su dideliu ankstyvo besimptomio vėžio išaiškinimu. Patikros programos įtaka mirtingumo rodikliams nebuvo nustatyta.
3. Vykdant PSA tyrimu paremtą ADP, nustatytas sergamumo ankstyvųjų stadijų priešinės liaukos vėžiu didėjimas ir sergamumo atokiųjų stadijų priešinės liaukos vėžiu mažėjimas.
4. Priešinės liaukos vėžiu sergančių vyrų mirtingumo rizika buvo didesnė nei bendrosios Lietuvos vyrų populiacijos. Atsiradus PSA tyrimu paremtai patikrai, mirtingumo rizika dėl priešinės liaukos vėžio sumažėjo, o ADP dalyvavusių vyrų grupėje mirtingumo rizika nesiskyrė nuo bendrosios Lietuvos vyrų populiacijos mirtingumo rizikos.

SUMMARY

LIST OF ABREVIATIONS

AAPC – average annual percentage change
APC – annual percentage change
DRE – digital-rectal examination
EDP – Lithuanian early detection of prostate cancer program
ERSPC – The European Randomized study of Screening for Prostate Cancer
PLCO – Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial
PPV – positive predictive value
PSA – prostate specific antigen
USA – United States of America
USPSTF – United States Preventive Service Task

THE AIM OF THE STUDY

To evaluate the performance and effectivenes of the prostate cancer early detection program (EDP) and its impact on the epidemiology of prostate cancer in Lithuania.

OBJECTIVES

1. To describe the progress and performance indicators of the EDP;
2. To examine the changes of prostate cancer incidence and mortality during the implementation of the EDP of prostate cancer in Lithuania;
3. To evaluate the changes in the pathological characteristics of prostate tumors during the implementation of the EDP;
4. To assess prostate cancer and other causes of mortality risk in EDP participants and non-participants.

NOVELITY OF THE STUDY

Lithuania is the only country in the world where organized population-based screening for prostate cancer is carried out at the national level. As the effectiveness of the program has not been evaluated since the beginning of the EDP, this study is undoubtedly of scientific interest both on national and international levels. To date, randomized controlled trials have been conducted to examine the effectiveness of screening for prostate cancer.

Efficacy is determined under ideal study conditions, and this is done with the help of randomized controlled trials. Prostate cancer screening trials were limited to study groups and the effectiveness of organized screening in the general population remains unclear. Because efficacy is defined as an assessment of the impact of a specific intervention under normal conditions, and in Lithuania, screening for prostate cancer is performed in the entire population, the study allowed to determine the effectiveness of PSA-based screening.

INTRODUCTION

Prostate cancer is the second most common malignancy in the world and the sixth most common cause of death from malignancy among men. In 2018, approximately 1 276 000 new cases of prostate cancer were diagnosed, while this cancer was responsible for approximately 359 000 deaths worldwide [1]. The incidence of prostate cancer in the world is constantly increasing. In economically developed countries, due to improved the social status of their residents, increasing life expectancy, and declining incidence of malignancies in other localizations, prostate cancer has become the most common cancer site among men. The use of prostate-specific antigen (PSA) is a part of prostate cancer diagnostics, and the increasing incidence of prostate cancer is directly related to the increased use of PSA in clinical practice [2].

PSA is a protein produced in epithelial cells of the prostate gland. An increase in plasma PSA levels may indicate the presence of prostate cancer. PSA was discovered by Ablin and colleagues in 1970 in the United States, but purified and characterized by Wang and colleagues in 1979 [3]. A team of researchers led by Steamey found in 1987 that elevated levels of PSA were associated with the spread of prostate cancer, leading to the use of PSA as a marker in the serum of prostate cancer.[4].

The PSA test was first used as a test to improve diagnostic accuracy in a 1991 study by Catalona and other researchers examining the benefits of the PSA test for screening. The addition of PSA to digital rectal examination (DRT) and ultrasound at that time used for screening was found to diagnose 32% more cases of prostate cancer than with DRT and ultrasound alone [5].

The optimal cut-off value of PSA that should be used in prostate cancer screening is not known to date. Historically, PSA concentrations of 4 ng/ml and above have been used as an indication for prostate biopsy. However, it has been observed that a significant proportion of cases of high-grade prostate cancer are found at PSA concentrations below 4 ng/ml [6]. At a PSA cut-off value of 4 ng/l, the sensitivity of this test in the diagnosis of prostate cancer is

78.7% and the specificity is 59.2% [7]. Increasing the PSA cut-off to 5 ng/ml can archieve PSA test specificity of up to 95% in the diagnosis of prostate cancer, but reduces the sensitivity of the test to 33% [8]. PSA concentration is not an appropriate parameter to distinguish between low- and high-risk cancers [5]. As a result, there is a natural risk of hyperdiagnosis and hypertherapy. Based on the aforementioned studies and in the absence of randomized trials, the PSA was introduced in the United States in the late 1990s for screening for prostate cancer [9].

Following the widespread use of PSA for screening for prostate cancer, its efficacy in randomized controlled trials has also been analyzed. The best-known studies on the effectiveness of screening for prostate cancer are The European Randomized study of Screening for Prostate Cancer (ERSPC) and Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO). The PLCO study involved 10 U.S. centers. The study ran from 1993 to 2001, patients were followed until 2015. The study included 76 693 men who were randomly assigned to groups: some were included in the screening group (annual PSA + DRE), others were assigned to standard follow-up. Prostate biopsy was performed at PSA concentrations greater than 3 ng/ml. After 7 years of follow-up, no differences in mortality were found between study groups; after 13 years of extended follow-up, the results showed the same. The ERSPC study involved 182,000 men aged 50–74 from seven European countries, randomly assigned to screening and control groups. At PSA concentrations greater than 4 ng/ml, subjects underwent prostate biopsy. The examination ran from 2001 to 2006, and patient follow-up is still ongoing. According to this study, after nine, eleven, thirteen, and sixteen years of the study, PSA-based screening reduced the risk of prostate death by 20% in subjects who participated in the study. [10-13].

In addition to the above studies, several smaller studies on the effectiveness of prostate cancer screening were performed. The Tyrol trial in Austria was launched in 1993. All men in the 45–74 age group were offered a free PSA test in the hope that 75% would be tested at least once. This was a follow-up study comparing male mortality in the Tyrolean region with that of the general Austrian male population. A reduction in mortality from prostate cancer was found among the study participants [14]. The independent Gothenburg study, which ran from 1994 to 2004 and was later included in the ERSPC study, included 20 000 men born between 1930 and 1944. The study found that screening based on the PSA study reduced mortality from prostate cancer by 44% [15]. A 1988–1996 study in Quebec, Canada, involving 46 193 men aged 45 to 80, showed that the risk of death from the prostate gland could

be reduced by 62% (compared with the control group) by choosing an annual PSA-based screening [16].

Despite the absence of organized screening for prostate cancer based on the PSA in almost every country in the world, there are attempts to conduct such screenings in an organized manner at the population level. Japan is the only Asian country that has recommended screening for prostate cancer since 2010, which operates in several regions of the country. Up to 20% of men in the screening population participate in screening. The detection rate for prostate cancer ranges from 0.54% to 1.13% [17]. In the Central and South American region, only in Mexico is a screening for prostate cancer recommended for men over the age of 50 [18]. In Australia and New Zealand, screening for prostate cancer is recommended for men up to 70 years of age; 84.9% of men in the screening population have participated in the screening at least once [19,20].

Based on the fact that the PLCO study did not show a reduction in the risk of death from prostate cancer and that the ERSPC study found that achieving the benefits of PSA-based screening requires a large number of participants in screening, in 2012, the United States Preventive Service Task Force (USPSTF) has issued a Level D recommendation against the use of the PSA test for screening for prostate cancer [21]. In response, professional organizations advocated organized population screening for prostate cancer in their guidelines for the diagnosis and treatment of prostate cancer, stating that the decision to participate in a screening should be personalized for each patient, emphasizing the patient-physician consensus on the benefits and potential harm [22]. Following the USPSTF recommendation, there has been a significant reduction in the number of PSA tests performed in the U.S. in academic and community hospitals and primary care facilities. Fewer prostate biopsies were also performed for biopsy-naive patients, and there was a significant reduction in cases of poor cancer differentiation (according to Gleason 7–10) among diagnosed prostate cancers [23]. This recommendation was updated in 2018. The USPTF then recommended a screening for prostate cancer based on the PSA test in men aged 55–59, after careful discussion with the doctor about the possible positive and negative effects of this screening. [24].

The European Association of Urology (EAU), in its guidelines for the diagnosis and treatment of prostate cancer, currently recommends PSA-based prostate cancer screening as part of an individualized, risk-adjusted early diagnosis strategy that can be offered to a well-informed man with a 10- to 15-year survival probability [25].

The PSA test is widely used for the early diagnosis and screening of prostate cancer, but organized screening is not performed in other parts of the world [26]. Recently, the EAU, based on the successful results of an ERSPC trial, proposed that a population-based screening for prostate cancer based on the PSA test be introduced in all countries of the European Union [27].

In Lithuania, a screening for prostate cancer was launched in 2006 – on the basis of the Lithuanian Early Diagnosis Program for Prostate Cancer (EDP). The National Health Insurance Fund periodically evaluates the performance of the program. The evaluation of the program is limited to the criteria for the implementation of the program, the geographical analysis of the ADP services provided, and the report on the funds used [28].

No clear guidelines have yet been developed for evaluating the performance and effectiveness of prostate cancer screening, but a modern evaluation of screening for prostate cancer is primarily performed by assessing changes in mortality from prostate cancer. Changes in the pathological characteristics of prostate malignancies, the performance of the screening, and the proportion of participants in the screening target population are also assessed. Because screening for prostate cancer is a complex set of decisions that are closely related to other health conditions, the risk of death from all causes of death among people with prostate cancer must be considered in a comprehensive way when evaluating the effectiveness of a prostate cancer program [29].

MATERIALS AND METHODS

Data sources

The National Health Insurance Fund (NHIF) database collects information about the insured with compulsory health insurance: primary, secondary and tertiary health care services provided in personal healthcare institutions, applications for emergency care, hospitalization. Data on the prescribing of reimbursable medicines are also collected. Data from the NHIF database, for period 2006–2016, on services provided by EDP for men born in 1931–1966 (program population), date of information services on EDP and PSA test, PSA concentration (<3 ng / ml, ≥3 ng) were used in the study. / ml), date and results of prostate biopsy, vital status, followup, emigration information.

The number of new cases of prostate cancer in Lithuania in 1978–2016 was obtained from the Lithuanian Cancer Registry (according to the International Classification of Diseases (ICD) ICD-9 185, ICD-10 C61). The

Lithuanian Cancer Registry is a population registry whose purpose is to ensure the registration of malignant tumors throughout Lithuania. The database contains information on age at cancer diagnosis, date of diagnosis and tumor stage according to the TNM classification of malignant tumors. Linkage was based on a unique personal identification number that is used throughout all information systems in Lithuania. In the study data on the date, age, stage and differentation of prostate cancer was used.

The number of deaths from prostate cancer and other causes in Lithuania was obtained from the World Health Organization's (WHO) Mortality Database, in five-year age groups from 1985 to 2015 [30].

For the calculation of rates, the data of the Lithuanian Department of Statistics on the number of population in five-year age groups by calendar year were used.

EDP organisation

Screening for prostate cancer in Lithuania is offered by general practitioners when visited for any reason. The EDP is funded by the NHIF, which covers health system activities for almost all residents (98%) of the country. A PSA test was offered to all men aged 50–74 and men aged 45–49 with a family history of prostate cancer. Men with a PSA level of ≥3 ng/ml were consulted by an urologist who referred them for a biopsy after suspicious findings during a digital rectal examination (DRE). Men with a PSA of <3 ng/ml, as well as those who refused biopsies or those with biopsy results indicating no malignant changes, were referred to the next screening round. Screening was offered annually between 2006 and 2009 and biennially between 2010 and 2016. Screening guidelines were modified in 2017, when changes in target population age and the implementation of age-specific PSA cut-offs were introduced.

Study design and statistical methods

For the analysis of performance of the EDP, the study period was divided into seven rounds of the program, which corresponded to the calendar year (2006–2009 annually, 2010–2015 every two years). This choice was due to changes in the frequency of screening during the program (PSA testing was recommended for men in the target population to be performed annually until 2009 and once every two years thereafter). The target population was calculated exactly, i.e., the person was included in the calculation of the reference population on the day of the age of 50 and was excluded on the day

of the age of 75. Men aged 50 and 74 were included in the target population to describe the screening rounds. Information about program participants was obtained from the NHIF database. Participants in the program are those who have been provided with at least one EDP service during the whole study period. Diagnosed cases of cancer were identified from the NHIF database and the cancer registry. For each screening round, the following indicators were calculated among individuals aged 50 to 74 years: screening coverage, proportion of PSA test-positives and test-negatives, ratio between the number of biopsies and PSA test-positives, ratio between detected cancer cases and PSA test-positives, and ratio between detected cancer cases and screened persons.

Changes in the prostate cancer incidence and mortality

Age-standardized incidence and mortality rates (1976 European Standard) were calculated. Rates were calculated for each calendar year in all age groups, in the 50–74 age group, and in the 75 year and older age group. Based on the onset of PSA in clinical practice, for the comparison of incidence and mortality rates, the period of 1995–1999 is named the period before the onset of PSA, and the period of 2011–2015 is named the period after the onset of PSA.

The Joinpoint program was used to estimate the mean percentage changes in incidence and mortality and the points of statistically significant change. The Monte Carlo permutation test was used for the significance test. The APC was considered statistically significant at a p-value of <0.05. Joinpoint analysis was performed in all age groups and separately in the age groups of 50–74 years and 75 years and older. The maximum number of change points was equal to three. Version 4.3.1.0 of the Joinpoint software package was used.

Changes in the pathological characteristics of prostate tumors during EDP

Using a direct standardization method (European Standard 1976), an age-standardized incidence rate was calculated for each group by cancer spread [31]. According to the TNM classification, three groups of prostate cancer spreads were identified according to the TNM classification: local, advanced and distant. The stage and spread of some of the reported cases were not specified. The methodology described in Section *Changes in the incidence*

and mortality of prostate cancer was used for the analysis of AAPC and statistically significant change points.

Mortality risk analysis: all-cause and prostate cancer specific mortality

The study cohort was divided into two periods: patients diagnosed with prostate cancer before the official start date of prostate cancer screening (January 1, 2006) were assigned to the "pre-screening"group, while patients diagnosed after January 1, 2006 were assigned to the "screening" group. In further mortality risk analysis, the screening group was divided into two groups by screening history status – "screened" and "not screened." The definition of "not screened" states that the person who had been diagnosed with prostate cancer has not participated in the Early Prostate Cancer Detection Program in Lithuania.

Person-years were computed from the date of cancer diagnosis to the first of the following events: death, emigration, or end of the follow-up (December 31, 2016). Standardized mortality ratios (SMRs) were calculated by dividing the observed number of deaths among prostate cancer patients by the expected number of deaths estimated from the general population of men, with 95% confidence intervals (CIs). Indirect standardization was used to calculate the expected number of deaths for the study population. Expected numbers were calculated as the multiplication of the exact person-years under observation in the cohort by calendar year- and 5-year-age-groups-specific national cause of death rates.

RESULTS

Between 2006 and 2015, 655 487 men belonged to the target age group of screening (born between the years 1931 and 1966) and 459 667 (70.1%) of them were screened for prostate cancer at least once. A total number of 1 179 283 PSA tests were performed; 1 044 448 tests were performed within the target population; 16 061 (56.7%) prostate cancer cases were registered within the screening program and 10 202 (38.2%) prostate cancers were observed among men who participated in the screening program at least once – however, their prostate cancer cases were not registered within the program.

The proportion of men in the target population who participated in the EDP program ranged from 22.4% to 28.8% at the annual screening and from 39.5% to 45.5% at the biennial screening. The proportion of persons with elevated PSA levels (≥3 ng/ml) among men tested decreased from 16.9% in

the first screening round to 10.7% in the seventh screening round. Of those with elevated PSA, prostate biopsy was performed at 28.4% to 39.2% of men at different stages of the program. Among them, prostate cancer was detected in 35.9–42.0% of cases.

PSA ≥3 ng/ml were detected in 6.3–7.3% of tested men, and prostate cancer was confirmed in 0.3–1.5% of tested individuals. A steady decline in unnecessary screening activities was observed within screening rounds over the time. Among the screened men between 50 and 74 years, 3.6% received more than one PSA test in the first round (3,339/92,896 = 3.6%) and 0.7% in the seventh screening round (1,511/223,958 = 0.7%). Between 236 (first round) and 107 (last round) men received more than one biopsy per screening round. Among those older than 74-year-old men, a decline in screened individuals from 1 751 to 307 was observed. As a test for screening, the PSA test was used in men with already detected prostate carcinomas. The number of younger than 45-year-old men who were screened within the program varied between 236 and 321 in first five rounds and dropped to 12 individuals in the last round.

Since the introduction of the PSA study in clinical practice and at the start of the program, the incidence of prostate cancer in Lithuania has changed significantly. The age-standardized incidence rate increased from 69.32 cases/100 000 men in 2000 to 279.33 cases/100 000 men (European Standard) in 2007, then decreased, but remained at 161.96 cases/100 000 men in 2016 year [32].

A consistent increase in incidence of 7.4% per year was observed throughout the study period. Between 1978 and 1994 and between 1994 and 2001, it increased by 3.2% and 9.8% per year, respectively. From 2001, the incidence of prostate cancer increased at a faster rate – 23.0% per year until 2007, then the incidence decreased by 4.4% until the end of the study. The highest incidence was observed in the group of men aged 50–74 years, where the incidence increased by 30.8% per year between 2001 and 2007.

From 1985 to 2007, prostate cancer mortality has increased from 17.85 to 39.43 cases/100 000 men, then declined slightly, and in 2016 was 33.70 cases/100 000 men. In the 50–74 year age group, mortality increased by 5.0% per year until 1993, then slowed to 0.7%. The changes observed in the age group of 75 years and older were analogous to the general changes in mortality: after an increase until 2006, an average decrease by 1.7% per year was observed until 2016.

The largest changes in the incidence of prostate cancer after the start of EDP were observed in the localized prostate cancer group: the incidence increased on average by 38.2% per year until 2007 and reached the incidence

rate of 284.6 cases per 100 000 men. Since 2007, a decrease in incidence by 5.5% per year has been observed. The incidence of advanced cancer increased until 2007, then began to decline by 11.1% per year. The incidence of distant prostate cancer was the lowest, experiencing a rise up until 2003 and followed by a decline in 8.1% annually.

Among the unscreened men, 12.4% of cases were diagnosed with stage IV disease. In contrast, among prostate cancer registered in screened screen-detected and outside the screening program in men who participated in EDP at least once 1.2 and 2.6% were stage IV.

The all-cause mortality risk was higher among patients with prostate cancer than in the general Lithuanian male population. Individuals diagnosed with prostate cancer during EDP had a lower risk of death from all causes (SMR = 1.17 (95% CI 1.15–1.19)) than individuals diagnosed with prostate cancer before EDP (SMR = 1.45 (95% CI 1.42–1.48)). An increased all-cause mortality risk among prostate cancer patients was observed in the not-screened patient population (SMR = 1.76 (95% CI 1.71–1.82)), while the all-cause mortality risk in the screened patient population was similar to the general population (SMR = 1.00 (95% CI 0.97–1.02)).

Stage group-specific mortality risk from all-causes among men with prostate cancer showed a higher risk of death for patients that were locally advanced and metastatic and risk increased with increasing dissemination (p = <0.0001) among the not-screened and screened patient cohort. For persons with the localized disease in the not-screened cohort, risk of death was similar to the general population (SMR = 0.99 (95% CI 0.92–1.05)) while for the screened person cohort it was significantly lower (SMR = 0.72 (95% CI 0.70–0.75)).

CONCLUSIONS

1. The chracteristis of EDP in Lithuania consisted of a small number of screened men from the target population, a large number of services provided to persons outside the screening population, and a low cancer detection rate;
2. During EDP the widespread use of the PSA test and PSA-based screening for prostate cancer had a significant effect on changes in the prostate cancer incidence, with the increase in incidence reflecting the prevalence of PSA use. The steep increase in incidence in the first year of screening is associated with a high detection of early asymptomatic cancer. The impact of the EDP on mortality rates was not observed;

3. An increase in the incidence of early-stage prostate cancer and a decrease in the incidence of distant prostate cancer were observed after the introduction of EDP;
4. Men with prostate cancer in Lithuania had an excess all-cause mortality risk compared to the general population. After introduction of EDP, the mortality risk of prostate cancer patients decreased; the all-cause mortality risk among screened patients was not higher than in the general population.

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PADĖKA

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DISERTACIJOS TYRIMO REZULTATAI PRISTATYTI MOKSLINĖSE KONFERENCIJOSE

1. 2018 05 17–18 – „Eurasian cancer screening conference“. Minskas, Baltarusija. Pranešimo tema: „Prostate cancer screening in Lithuania“.
2. 2018 06 08 – „Evoliucinė medicina: sveikata ir ligos besikeičiančioje aplinkoje“. Pranešimo tema:„Development of PSA based prostate cancer early detection programme in Lithuania between 2006–2009“.
3. 2018 05 25–26 – „5th Baltic Meeting in conjunction with the EAU“. Pranešimo tema: „Does PSA-based population screening increase suicide risk in prostate cancer patients? National experience from Lithuania early detection programme“.
4. 2019 06 03–05 – „International Cancer Screening Conference 2019“. Rotterdamm, Netherlands. Pranešimo tema: „Changing incidence and stage distribution of prostate cancer in a Lithuanian population – evidence from national screening programme“.
5. 2019 05 24–25 – „6th Baltic Meeting in conjunction with the EAU“, Tallinn, Estonia. Pranešimo tema: „Prostate cancer incidence and mortality trends in the Baltic States and Belarus“. Apdovanotas trečia vieta „Berlin Chemie“ apdovanojimų kategorijoje.
6. 2020 02 24–27 – „Annual Interdisciplinary Localized and Advanced Prostate Cancer Conference“, Vilnius, Lietuva. Pranešimo tema: „The results of Prostate cancer early diagnostic programme in Lithuania“.

PUBLIKACIJŲ KOPIJOS

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Prostate Cancer Screening with PSA: Ten Years' Experience of Population Based Early Prostate Cancer Detection Programme in Lithuania

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Article

Prostate Cancer Screening with PSA: Ten Years' Experience of Population Based Early Prostate Cancer Detection Programme in Lithuania

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Abstract: The aim of this study is to report key performance estimates from the ten years of a population-based prostate cancer screening programme in Lithuania. Retrospective analysis of screening activities recorded in 2006–2015 among men aged 50–74 years was performed. We estimated screening coverage, cancer detection rate, compliance to biopsy, and positive predictive values in each screening round inside and outside the target population. In the first 10 years of screening, 16,061 prostate cancer cases were registered within the screening programme, 10,202 were observed among screened men but reported outside the screening programme, and 1455 prostate cancers were observed in a screening-naïve population. Screening cover reached up to 45.5% of the target population in the recent rounds. The proportion of prostate specific antigen (PSA) test-positive men decreased from 16.9% in 2006 to 10.7% in 2014–2015. Up to 40.0% of PSA test-positive men received a biopsy, of whom 42.0% were positive for prostate cancer. The cancer detection rate was 10.4–15.0% among PSA test-positives and 1.4–1.9% among screened individuals. Screening participants were more likely to be diagnosed with organ-confined disease as compared to non-participants. Despite the unorganized screening practices being employed and low coverage per screening round, 70% of the target population were screened at least once in the first 10 years of screening.

Keywords: prostate cancer; screening; PSA; population-based

1. Introduction

Prostate cancer is the third most common cancer in men [1] and the widespread implementation of prostate specific antigen (PSA) testing has changed the epidemiologic situation of prostate cancer worldwide [2]. Leading to overdiagnosis and overtreatment, PSA-based screening has reduced prostate cancer mortality. Screening practices using PSA are ongoing in many countries, however the benefits of such screening remain debated across communities [3]. In 2011. the United States Preventive Service Task Force (USPSTF) recommended against prostate cancer screening in all age groups [4]. The United States discontinued prostate cancer screening in the same year, but this recommendation was updated in 2018, when it was recommended to screen 55–59-year old men based on a shared decision between the patient and physician [5]. Recently, the European Urology Association expressed their interest for PSA-based prostate cancer screening at the population level in European countries [6]. However, appropriate screening measures to avoid overdiagnosis and overtreatment are yet to be determined.

Population-based screening for prostate cancer is already ongoing in one of a few relatively small Northern-Europe countries. Lithuania, a country with 2.8 million inhabitants in 2019 launched nation-wide PSA-based Early Prostate Cancer Detection Programme (EPCDP) in 2006 that works on an invitation by opportunity basis. According to the programme description, the objective of this programme is to reduce prostate cancer mortality in the target age male population and to diagnose prostate cancer at earlier stages of disease. Since then, Lithuania has experienced a tremendous increase in prostate cancer incidence. Age-standardized prostate cancer incidence peaked to 279 per 100,000 men (European Standard) in 2007 and remained above 160 cases per 100,000 until 2016, the year of data extraction for recently published analysis [7]. During the first years of the EPCDP screening programme, prostate cancer incidence exceeded that observed in the United States in the 1990s [8], making them the highest prostate cancer incidence peaks ever seen in a country. In the most recent analysis, prostate cancer incidence rates in Lithuania were reported to be the highest in the world [2]. While the PSA screening programme in Lithuania has been implemented for more than 10 years, the data published so far are scarce, covering only an analysis of incidence and mortality changes [7,8].

In this paper, we aimed to report for the first time the results of the ten years from the ongoing nation-wide PSA-based screening programme in Lithuania.

2. Materials and Methods

2.1. Early Prostate Cancer Detection Programme (EPCDP)

Screening for prostate cancer in Lithuania is offered by general practitioners when visited for any reason. EPCDP is funded by the National Health Insurance Fund (NHIF) that covers health system activities for almost all residents (98%) of the country. Figure 1 shows a flow chart for EPCDP between 2006 and 2016. A PSA test was offered for all men aged 50–74 and men aged 45–49 with a family history of prostate cancer. Men with a PSA level of ≥3 ng/mL were consulted by a urologist who referred them for biopsy after suspicious findings in a digital rectal examination (DRE). Men with PSA < 3 ng/mL, as well as those who refused biopsy or those with biopsy results indicating no malignant changes, were referred to the next screening round. Screening was offered annually between 2006 and 2009 and biennially between 2010 and 2016. Screening guidelines were modified in 2017 where changes in the target population age and implementation of age-specific PSA cut-offs were introduced. In this analysis, we focus only on years 2006–2015, which corresponds to the first seven screening rounds. The year 2016 was excluded as it comprised only half of the screening round.

2.2. Data Sources

The NHIF database contains demographic data and entries on the primary and secondary healthcare services, emergency and hospital admissions, and prescriptions of reimbursed medications for chronic diseases [9]. We based our analysis on data extracted from the NHIF database between the 1st of January 2006 and the 31st of December 2015. As such, the target population size among those aged 50–74 years old per screening round was extracted together with exact date and PSA test results (<3 ng/mL, ≥3 ng/mL), date and results of biopsy histopathological examination, vital status at the end of follow-up, date of death, and date of emigration when applicable for all men regardless of age.

For a small proportion of men who had multiple screening PSA or biopsies per screening round, only one screening test with most advanced findings was considered. Findings from the repeated PSA tests and biopsies after already confirmed prostate cancer diagnosis were excluded from the analyses.

In addition, data from the NHIF database was linked to Lithuanian Cancer Registry database that contains information on age at cancer diagnosis, date of diagnosis and tumor stage according to the TNM classification of malignant tumors TNM classification. Linkage was based on a unique personal identification number that is used throughout all information systems in Lithuania.

We based this analysis on the first seven screening rounds conducted in the calendar years 2006, 2007, 2008, 2009, 2010–2011, 2012–2013, and 2014–2015. For each screening round, the following

indicators were calculated among individuals aged 50 to 74 years: screening coverage, proportion of PSA test-positives and test-negatives, ratio between number of biopsies and PSA test-positives, ratio between detected cancer cases and PSA test-positives, and ratio between detected cancer cases and screened persons. The same indicators were calculated among men 45–49 years except from screening coverage that was not available due to unknown family history of prostate cancer. Prostate cancer diagnosis in men who participated in screening programme at least once, but cancer was not reported as diagnosed within screening programme were assigned to the screening. Prostate cancer stage distribution was calculated for cases registered in the screening, for cases not registered in the screening among those who participated at least once, and for prostate cancers in a screening-naïve population.

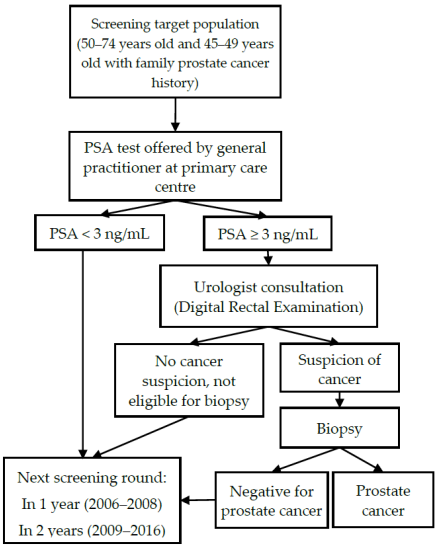

Figure 1. Organizational structure of Early Prostate Cancer Detection Programme in Lithuania between 2006 and 2016; PSA, prostate specific antigen.

2.3. Ethical Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by Vilnius regional biomedical research ethics committee, approval number 158200-16-879-388 on 28th November 2016.

3. Results

Between 2006 and 2015, 655,487 men belonged to the target age group of screening (born between the years 1931 and 1966) and 459,667 (70.1%) of them were screened for prostate cancer at least once. A total of 1,179,283 PSA tests were performed and 1,044,448 tests were performed within the target population.

As seen in the flow chart of the study cohort (Figure 2), 16,061 (56.7%) prostate cancer cases were registered within the screening programme and 10,202 (38.2%) prostate cancers were observed among men who participated in the screening programme at least once, however, prostate cancer was not registered within the program. Overall, 5.8% (=26,896 out of 459,667) of screened men were diagnosed with prostate cancer as compared to 0.7% (=1455 out of 195,820) among screening-naïve individuals. In the group of registered as non-screen detected cancers, 60% of cases were PSA test-positives and prostate cancer diagnosis was reported shortly after the last screening test (median 97 days).

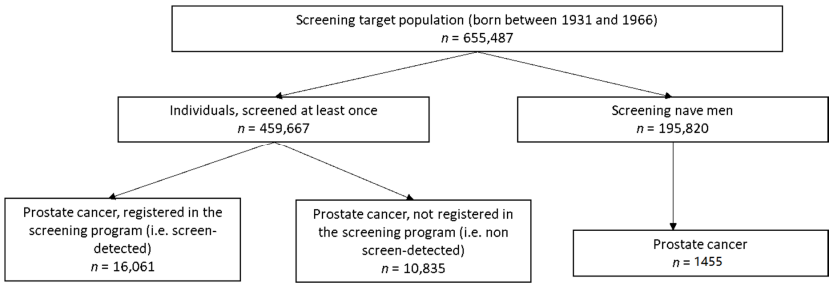

Figure 2. Prostate cancer diagnosis among individuals aged 50 to 74 years in Lithuanian between 2006 and 2015.

The main performance indicators of the prostate cancer screening programme in Lithuania in the first seven screening rounds are shown in Table 1. The participation rate varied from 22.4% to 28.8% between annual screening rounds and from 39.5% to 45.5% between biannual screening rounds. The proportion of PSA test-positive men decreased from 16.9% in first round to 10.7% in the seventh round. Between 28.4% and 39.2% of PSA test-positive men received a biopsy of whom 35.9–42.0% were positive for prostate cancer. The prostate cancer detection rate among PSA test-positive individuals varied between 10.4% and 15.0%.

Table 1. Main performance indicators of of Early Prostate Cancer Detection Programme (EPCDP) in Lithuania in the first seven screening rounds between 2006 and 2015.

	Calendar Year (Screening Round)						
	2006 (R1)	**2007 (R2)**	**2008 (R3)**	**2009 (R4)**	**2010–2011 (R5)**	**2012–2013 (R6)**	**2014–2015 (R7)**
Target population	413,997	417,832	422,812	429,535	466,557	480,194	492,291
Individuals screened (50–74-year-old)	92,896	99,556	121,871	97,407	184,213	200,079	223,958
Coverage (participation rate, %)	22.4	23.8	28.8	22.7	39.5	41.7	45.5
PSA results							
PSA < 3 ng/mL (%)	77,188 (83.1)	84,201 (84.6)	105,303 (86.4)	84,666 (86.9)	162,806 (88.4)	176,939 (88.4)	199,968 (89.3)
PSA ≥ 3 ng/mL (%)	15,708 (16.9)	15,355 (15.4)	16,568 (13.6)	12,741 (13.1)	21,407 (11.6)	23,140 (11.6)	23,990 (10.7)
Biopsy							
Number of biopsies (% of PSA test-positive)	4459 (28.4)	5574 (36.3)	5934 (35.8)	5092 (40.0)	8386 (39.2)	8750 (37.8)	7985 (33.3)
Prostate cancer (% of biopsy)	1509 (35.9)	1873 (36.1)	1879 (35.3)	1647 (35.9)	2836 (37.6)	3210 (40.2)	3107 (42.0)
% prostate cancer of PSA test-positive	9.6	12.2	11.3	12.9	13.2	13.9	13.0
% prostate cancer of screened persons	1.6	1.9	1.5	1.7	1.5	1.6	1.4
Prostate cancer (among screened)	2445	3320	3242	2912	4796	5143	5038
Cancer detection rate	2.5	3.2	2.69	2.9	2.5	2.5	2.2

PSA, prostate specific antigen; R, round.

Screening practices among men aged 45 to 49 years are reported in Supplementary Table S1. PSA ≥ 3 ng/mL were detected in 6.3–7.3% of tested men and prostate cancer was confirmed in 0.3–1.5% of tested individuals. Screening practices outside target groups are shown in Figure 3. A steadily decline in unnecessary screening activities was observed within screening rounds over the time. Among the screened men between 50 and 74 years 3.6% received more than one PSA test in the first round (3339 out of 92,896 = 3.6%) and 0.7% in the seventh screening round (1511 out of 223,958 = 0.7%). Between 236 (first round) and 107 (last round) men received more than one biopsy per screening round. Among older than 74-year-old men, a decline in screened individuals from 1751 to 307 was observed. As screening test PSA test was used in men with already detected prostate carcinoma. Number of

younger than 45-year-old men who were screened within the programme varied between 236 and 321 in first five rounds and dropped to 12 individuals in the last round.

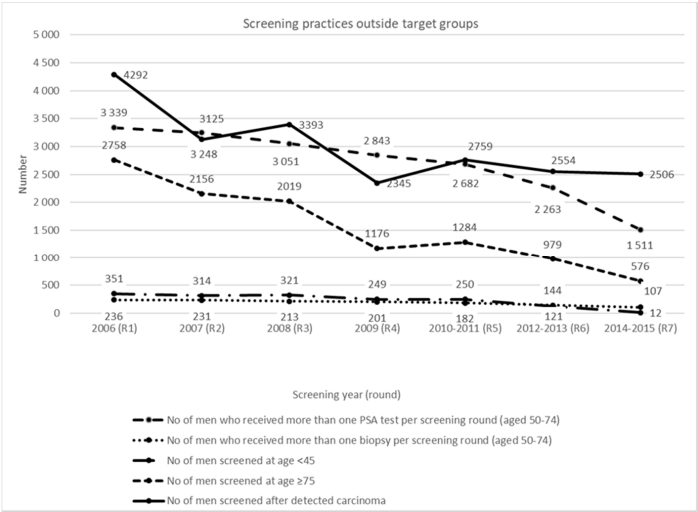

Figure 3. Screening practices outside the target population in the first seven screening rounds (2006–2015).

Figure 4 shows the stage distribution of prostate cancer in screen-detected and screened registered as non-screen-detected and unscreened individuals. Among the unscreened men, 12.4% of cases were diagnosed with stage IV disease. In contrast, 1.2% and 2.6% were stage IV among prostate cancer registered in screened screen-detected and outside the screening programme in men who participated at least once.

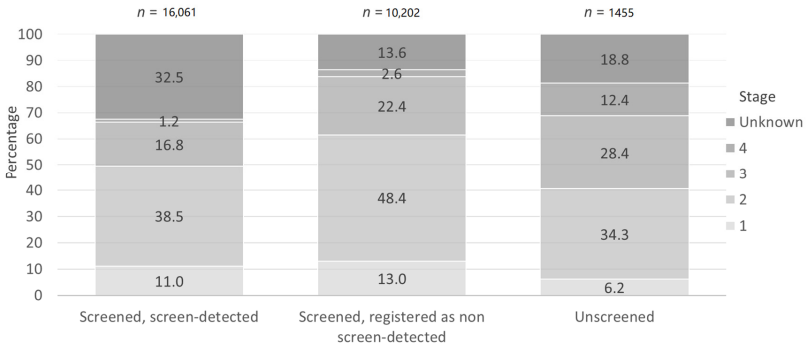

Figure 4. Cancer stage distribution in unscreened, screened non-screen detected and screened, screen detected groups.

4. Discussion

We present the first results from the nation-wide PSA-based screening programme over ten years between 2006 and 2015. In these years, prostate cancer screening in Lithuania covered less than half of the target population in each screening round. Still, 70% of men of age 50–74 years have been screened at least once over the period of 10 years. The PSA test was positive in less than 17% of tested men,

among whom 9–13% were diagnosed with prostate cancer. Majority of screening-detected prostate cancers were detected at early stage.

Reduction in mortality is the main indicator for screening programme effectiveness. In this analysis, we do not report data on mortality as we focused on reporting the screening activities and prostate cancer detection rate in the initial screening years. A longer follow-up period might be needed to observe the effect on mortality rates. Changes in mortality trends have been reported previously [7].

Screening uptake (coverage) is often described as most important factor determining the success of screening programme [10,11]. However, prostate cancer screening when performed in all men without an individual risk-benefit assessment may suffer from substantial overdiagnosis. Therefore, screening uptake in this analysis should be interpreted with caution. Prostate cancer screening coverage in Lithuania increased with every screening round but had not reached half of the target population, that might be due to the unorganized nature and the lack of monitoring system of screening services. An increase in coverage when screening programme switched from annual to biennial screening intervals most likely shows prolonged screening interval effect. According to Medical Expenditure Panel Survey in 2006 in United States, 49.7% of men aged 50–74 years received screening PSA test [12] that is comparable to that observed in Lithuania. In Japan, municipality-based prostate cancer screening coverage reached only 20% of the target population [13].

The number of performed PSA tests increased in conjunction with growing screening attendance over time. Notably, screening was also observed outside target age groups and screening intervals. Such screening practices decreased stepwise with every screening round. It is notable that a small proportion of screening services was performed for patients with already detected prostate adenocarcinoma that may correspond to diagnostic purposes or active surveillance for these cases.

The positivity rate for PSA testing is highly dependent on the cut-off value. It is known that serum PSA concentration level strongly increases with age [14]. Since 2017, age-specific PSA cut off levels were implemented in the screening programme to decrease the costs of screening with possible decrease the likelihood of over-detection and false-positive PSA in older ages. However, in the first seven rounds, the same cut of 3 ng/mL was used for all men regardless of age where the proportion of positive tests ranged from 9.6% to 13.9% between screening rounds. A similar positivity rate was reported in the United Kingdom (11%) using the same PSA cut-off among 50–69-year olds [15] and positivity rates between 8% [16] and 17% [17] were reported from studies using a cut-off 4 ng/mL. Percentage of biopsied PSA test-positive persons in our cohort ranged from 28.4% to 40.0%. A low percentage of compliance to biopsy may show the use of urologist evaluation for other conditions, which may elevate PSA concentration, or the use of additional assessment techniques, e.g., multiparametric magnetic resonance imaging (MRI), free/total PSA ratio, and PSA density, which clinically allowed to decide against prostate biopsy [18]. The percentage of biopsied test-positive (>4 ng/mL.) and test-positive/abnormal DRE persons in the PLCO trial were 30.1–40.2% and 23.5–31.0%, respectively [16]. Total average biopsies/positive test ratio among ERSPC centres was 85.6% [19].

The percentage of cancer among screened persons in our cohort varied from 1.4% to 1.9%, with the average rate of 1.6%. Other countries with prostate cancer screening activities have demonstrated similar prostate cancer detection rates, e.g., in Japan, municipality-based prostate screening detection rate was 0.5–1.1% [13], while the Finland section of ERSPC achieved a 2.5% detection rate with a PSA cut-off level of 4 ng/mL during first three years of the study, whereas the detection rate in the Dutch centre was 4.6%, and in the Italian centre 1.6% of men were screened [20,21]. In the initial four rounds of screening in the PLCO trial, the detection rate for prostate cancer was 4.9% [16]. The proportion of men diagnosed with prostate cancer in the intervention group was 4.3% in England and Wales [15].

The proportion of prostate cancer among PSA test-positives that is a positive predictive value (PPV) of the screening has been reported so far in two different ways, by dividing screen detected cancers by the number of biopsies (ERSPC trial) and by the number of PSA test-positives (PLCO trial) [16,17]. PPV as a proportion of prostate cancer among biopsied individuals ranged from 35.3% to 42.0%, and ratio between screen-detected cancer and PSA-positive varied from 9.6% to 13.9%. PPV of biopsy

among ERSPC study centres in different periods was 21.7–30.2% in Finland, with average ratio among centres being 24.3% [19]. PPV for test positive in PLCO trial among patients with elevated PSA and abnormal DRE findings, has been smaller and decreased from 11% at initial screening round to 7.3% in the fourth round of the screening. PPV for biopsy at the initial screening round was 36.9% and remained at the level of 31.0% in following screening rounds [16].

A positive effect with so-called "stage migration" to a localized form of disease has already been observed in our previous study [22]. Patients in the national Lithuanian prostate cancer cohort were more likely to be diagnosed with localized disease. A higher proportion of organ-confined disease was also observed in the screening group in other studies reporting stage distribution [16,23–25]. The proportion of localized disease is strongly influenced by overdiagnosis, which, according to the literature, is estimated to range from 1.7% to 67% [26].

Our study has several strengths and limitations to be considered. EPCDP is a population-based ongoing prostate cancer screening programme that is unique in this context and reflects real world data, like in an observational study performed in Austria [27]. Data corresponding to the screening programme were collected by a single institution covering more than 98% of country residents. However, some of the major data from the screening were not considered for the registration (e.g., exact PSA concentration, DRE results during urological assessment, and Gleason scores in biopsy were not available). Moreover, a linkage of PSA testing and follow-up procedures outside of the screening programme was not available, making estimation of the screening programme performance somewhat limited.

5. Conclusions

Despite the unorganized screening practices being employed and low coverage per screening round, 70% of men aged 50–74 years have participated in the prostate cancer programme at least once in the first 10 years of the screening. During the study period, in the target population, 94.8% of prostate cancer cases were detected among those who participated in the screening programme. Men participating in the screening were more likely to be diagnosed with organ-confined disease as compared to those not participating.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/9/12/3826/s1, Table S1: Main performance indicators of Early Prostate Cancer Detection Programme (EPCDP) in Lithuania in the first seven screening rounds between 2006 and 2015 for men, aged 45–49 years.

Author Contributions: Conceptualization, A.P. and G.S.; methodology, A.K. and G.S.; formal analysis, A.P.; data curation, G.S.; writing—original draft preparation, A.P.; writing—review and editing, A.K. and G.S.; visualization, A.K. and A.P.; supervision, G.S. All authors have read and agreed to the published version of the manuscript.

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2 publikacija / 2nd publication

Prostate cancer incidence and mortality in the Baltic states, Belarus, the Russian Federation and Ukraine

Patasius A, Innos K, Barchuk A, Ryzhov A, Leja M, Misins J, Yaumenenka A, Smailyte G.

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Prostate cancer incidence and mortality in the Baltic states, Belarus, the Russian Federation and Ukraine

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ABSTRACT

Background Prostate cancer incidence varies internationally largely attributable to differences in prostate-specific antigen (PSA) use. The aim of this study was to provide the most recent detailed international epidemiological comparison of prostate cancer incidence and mortality in six north-eastern European countries (Belarus, Estonia, Latvia, Lithuania, the Russian Federation and Ukraine).

Methods The number of incident prostate cancer cases was obtained from the countries national cancer registries. Prostate cancer mortality and corresponding population data were extracted from the WHO Mortality Database. Age-specific and age-standardised incidence and mortality rates were calculated (European Standard). The joinpoint regression model was used to provide an average annual percentage change and to detect points in time where significant changes in trends occurred. The observation period was between 13 (Ukraine) and 48 (Estonia) years regarding incidence and around 30 years regarding mortality.

Results The comparison of prostate cancer incidence in six European countries showed almost sixfold differences in the age-adjusted rates in most recent years with highest incidence rates in Lithuania and Estonia. Through the observation period, overall a continuous rise was seen in incidence in all countries and a continuous rise in mortality, with a stabilisation in Estonia and a decrease in Lithuania in recent years. Data limitations included a descriptive design using ecological data.

Conclusions A widespread use of PSA testing seems to be responsible for the changes in the epidemiology of the disease in north-eastern European countries. Substantial variation in the incidence of prostate cancer in the Baltic states suggests the possibility that PSA performance and utilisation spread have had a major influence on observed incidence trends, with a lack of effect on prostate cancer mortality.

Strengths and limitations of this study

- ► This is a descriptive international study using national ecological data.
- ► This study provides a detailed updated international epidemiological comparison of age-specific prostate cancer incidence and mortality trends in six north-eastern European countries.
- ► Lack of information on prostate-specific antigen (PSA) testing by age and calendar year for the study countries limits the opportunity for targeted analysis of association for PSA use with incidence data.
- ► Differences in data quality between countries and over time may have influenced the results.
- ► An additional study limitation was the lack of data on tumour stage.

INTRODUCTION

Prostate cancer was estimated to be the third most common cancer site in Europe in 2018 with 450 000 cases being diagnosed and it being ranked as the fifth leading cause of cancer death with 107 000 deaths.[1] Although the aetiology of prostate cancer remains unknown, there are established risk factors for developing prostate cancer, including older age, a black racial background and a family history of the disease.[2] Prevalence of other known risk factors, such as saturated fat intake, sedentary lifestyle and obesity, varies geographically worldwide and plays a role in prostate cancer incidence.[2] Trends in prostate cancer incidence have been strongly influenced by prostate-specific antigen (PSA) testing[3] and widespread use of the PSA test is held responsible for the large rise in prostate cancer incidence in most European countries and worldwide.[4 5] Incidence and mortality trends of prostate cancer have been analysed in several large-scale studies across Europe and worldwide.[6–9] Incidence increase was mostly accompanied by a mortality decrease in western and northern European countries, while in the Baltic states, Belarus, the Russian Federation and Ukraine a steady mortality increase was found.[7 10]

The aim of this study was to provide the most recent detailed international epidemiological comparison of prostate cancer incidence and mortality in six north-eastern European countries (Belarus, Estonia, Latvia, Lithuania, the Russian Federation and Ukraine).

Table 1 Study group characteristics and period range of incidence and mortality data obtained, and availability of incidence data in Cancer Incidence in Five Continents (CI5)

	2011–2015			Available for analysis				
Country	Annual male population (millions)	Average annual number of incident cases	Average annual number of deaths	Incidence	Mortality	Included in CI5	DCO (%)	MV (%)
Belarus	4.4	3621	803	1990–2016	1985–2003 and 2008–2015	1988–2012	–	98.3
Estonia	0.6	1130	260	1968–2015	1985–2015	1968–2012	–	95.6
Latvia	0.9	1118	387	1980–2016	1985–2015	1983–2012	6.0	85.3
Lithuania	1.4	3180	537	1978–2016	1985–2016	1988–2012	1.7	94.5
Russian Federation	66.6	33 039	11 172	1993–2015*	1985–2015	1993–2012	0.1	79.0
Ukraine	20.5	7753	3481	2000–2012†	1985–2012 and 2014–2015	2003–2012	0.5	75.8

*Only from Saint Petersburg, 1998–2012—four cancer registries.
†For later period, not available due to lack of information from occupied regions of Ukraine.
DCO, death certificate only cases; MV, microscopically verified.

METHODS

The number of incident prostate cancer cases (International Classification of Diseases (ICD)-9 185 and ICD-10 C61) by 5-year age groups was obtained from the countries' national cancer registries from the start of data collection to the latest available. The period range of the obtained data is presented in table 1. The breadth of incidence data received from the cancer registries was larger than that included in volumes of 'Cancer Incidence in Five Continents' (CI5),[11] which are submitted to systematic quality control (table 1). Belarus, Estonia, Latvia and Lithuania have a long history of cancer registration, and data from those registries have been published in CI5 for decades. Cancer incidence data from Ukraine at the national level were published in volumes X–XI of the CI5 covering the period of 2003–2012. Four cancer registries from the Russian Federation were included in the latest volume of CI5, whereas previous data were published only from St. Petersburg. For the current analysis, national data aggregated from all regional registries were used. Data from these sources were previously used to evaluate the national cervical and breast cancer burden.[12]

Prostate cancer mortality data were extracted from the WHO Mortality Database by 5-year age groups from 1985 to the latest year available.[13] Data suitable for the analysis of time trends until 2015 or 2016 were available for four countries (Estonia, Latvia, Lithuania and the Russian Federation), but for Belarus, an analysis of time trends was carried out only until 2003 due to data gap in the period 2004–2007. For Ukraine, the mortality data were available from the years 1998–2012, and then for the years 2014 and 2015. The observation period was between 13 (Ukraine) and 48 (Estonia) years for incidence and around 30 years for mortality. Corresponding population data by age and calendar year were also extracted from the WHO Mortality Database.

Age-specific and age-standardised incidence and mortality rates were calculated. Age-standardised incidence and mortality rates per 100 000 person-years were standardised to the European population (Standard of 1976). Age-standardised rates were calculated for each calendar year for all ages combined, and age-specific rates for ages 50–74 and 75+ years. For comparison of mean incidence and mortality rates, years between 1995 and 1999 were defined as the pre-PSA period, and years between 2011 and 2015 as the post-PSA period. The pre-PSA period was defined according to the information on PSA availability in countries under study. The period 2011–2015 was defined as post-PSA under the assumption of widespread use of PSA tests.

Joinpoint regression was used to provide annual percentage changes (APC) and to detect points in time where statistically significant changes in the trends occurred. The average APC (AAPC) is a geometrically weighted average of APC values, with weights based on lengths of each segment during the whole observation period. In the absence of joinpoints, the APC's and AAPC's are equal. The joinpoint regression analysis identifies the best-fitting points ('joinpoints') where a significant change in the linear slope (on a log scale) of the trend is detected. The tests of significance use a Monte Carlo permutation method. Annual per cent changes were considered statistically significant if $p<0.05$. Joinpoint analysis was performed for all ages combined and for the age groups 50–74 and 75+ years. A maximum number of three joinpoints were allowed for estimations. The minimum number of observations from a joinpoint to either end of the data was defined as three, and the

minimum number of observations between two joinpoints as two (excluding any joinpoint that falls on an observation). Joinpoint software V.4.3.1.0 was used.

Patient and public involvement

There was no direct patient involvement. Only aggregated data were used.

RESULTS

Incidence

The comparison of prostate cancer incidence in six European countries showed almost a sixfold differences in the age-adjusted rates in the most recent years (table 2). Based on age-standardised rates in 2011–2015, the countries could be separated into two groups: high-incidence and low-incidence countries (ie, rates per 100 000 above and below 100 cases, respectively). High incidence was observed in the Baltic states and low incidence in Belarus, the Russian Federation and Ukraine. An incidence increase was seen in all countries over the entire study period, with the annual APC ranging between 3.4 in Ukraine and 7.4 in Lithuania. Joinpoint analysis showed a continuous increase in incidence in Ukraine (no joinpoints) and generally increasing trends in Belarus, Latvia and the Russian Federation but with joinpoints suggesting different magnitudes of increase in different periods (see table 2 for joinpoints). Following a continuous rise in incidence and a marked increase, Lithuania and Estonia experienced decreases in incidence.

Prostate cancer incidence showed a general increase in countries in all age groups (figure 1). Among men aged 50–74 years incidence peaks were observed in Estonia and Lithuania, followed by an incidence decrease in Estonia since 2011 and in Lithuania since 2007. Results of detailed joinpoint analysis by age group are presented in online supplementary table 1.

Age-specific incidence distributions in the period 1995–1999 before implementation of PSA in clinical practice indicated the highest incidence in all the countries in the 80–84 years age group, with the highest age-standardised rate of 753.0 cases per 100 000 applying to Estonia (figure 2). During the period 2011–2015, the peak incidence shifted to younger age groups (70–74 and 75–79 years), with the highest age-specific rate of 1261.0 cases per 100 000 in Lithuania applying to the 70–74 years age group.

Mortality

The differences in mortality rates among all countries were relatively small (table 2). As for incidence rates, higher mortality rates were observed in the Baltic states, while lower rates were observed in Belarus, the Russian Federation and Ukraine (ASR above and below 30 cases per 100 000, respectively). All countries experienced a general mortality increase throughout the observation period, but in the most recent years, mortality stabilisation is observed in Latvia and Estonia, and a mortality decrease in Lithuania. Mortality trends in age-specific groups paralleled changes in overall mortality (online supplementary table 1).

Age-specific mortality distributions were similar in both periods, with the highest mortality rates in the age group 85+ years (figure 2). No mortality shift between age groups was observed. Mortality rates differed markedly between two country groups: in the Baltic states, mortality rates were almost three times higher in the period 1995–1999. In the period 2011–2015, observed mortality rates in the oldest age groups doubled; however, the relative difference between the Baltic states and the other countries remained the same.

DISCUSSION

When comparing trends in prostate cancer incidence and mortality across six north-eastern European countries, differences were observed between two groups of countries. In the Baltic states, prostate cancer incidence was higher than in Belarus, the Russian Federation and Ukraine. Throughout the study period, a general rise was seen in incidence in all countries and a general rise in mortality, with a stabilisation in Estonia and decrease in Lithuania in recent years.

Differences in risk factors for specific cancers between regions, in international cancer control plans and in cancer screening strategies may have contributed to incidence and mortality differences between regions.[14] The rising incidence may reflect the increased risk of disease or higher uptake of PSA tests.[7] The incidence trends and patterns may be largely a function of the use of PSA testing.[6 8] Healthcare expenditure availability of medical resources may also be an important contributor to the patterns of international variation in prostate cancer incidence.[15] Differences in data quality between countries and over time may have influenced the results.

Countries included in our study had different profiles of PSA testing uptake. In Lithuania, PSA became available in 2000, and in 2006, a nationwide PSA-based prostate cancer early detection programme was started. Since the start of the programme in the period of 2006–2010, around 72%–78% of the total eligible male population received at least one PSA test. No official prostate cancer screening programme has been introduced in Estonia, although in clinical practice, primary care physicians routinely offer the test to middle-aged and elderly men, and patients themselves actively request the test.[16] According to a population-based health behaviour survey in 2016, the proportion of men who reported to have never had a PSA test was nearly 50% in the age group 55–64 years, and nearly 60% in the age group 45–54 years.[17] In Latvia, PSA tests were not funded by the government and the frequency testing was determined by the urologist.[18] In 2015, it was recommended that PSA testing be used from the age of 50 years onwards. Some prostate cancer screening activity was observed in other countries: Belarus from 2011 to 2012 had a pilot screening project in three regions of the capital city for men aged 50–65

Table 2 Changes in age-standardised prostate cancer incidence and mortality

Country	Age group	Incidence							Mortality				
		ASR 1995–1999	ASR 2011–2015	Observed period	JP linear segment	AAPC/APC	95% CI		ASR 1995–1999	ASR 2011–2015	Observed period	JP linear segment	AAPC/APC	95% CI	
Belarus	All ages	27.2	87.0	1990–2016	1990–2016	7.3*	6.9	7.7	14.9	19.7	1985–2003	1985–2003	3.6*	3.1	4.1
					1990–1998	7.5*	5.9	9.2							
					1998–2001	1.0	−12.1	16.0							
					2001–2014	9.1*	8.2	10.0							
					2014–2016	1.8	−11.4	16.9							
Estonia	All ages	58.4	158.3	1968–2015	1968–2015	5.4*	5.0	5.8	26.09	35.1	1985–2015	1985–2015	2.6*	2.1	3.1
					1968–1989	2.7*	1.8	3.6				1985–1989	−3.4	−11.4	5.4
					1989–2011	7.9*	7.0	8.8				1989–2004	4.3*	2.9	5.6
					2011–2015	−3.4	−13.2	7.4				2004–2015	0.5	−1.4	2.3
Latvia	All ages	39.4	102.2	1980–2016	1980–2016	5.4*	4.9	5.8	22.19	35.1	1985–2015	1985–2015	3.0*	2.6	3.5
					1980–1985	6.0*	2.1	10.0				1985–1998	1.7*	0.5	2.8
					1985–1994	0.6	−1.3	2.4				1998–2004	8.3*	3.4	13.5
					1994–2005	10.2*	8.8	11.6				2004–2015	0.1	−1.3	1.5
					2005–2016	2.4*	1.2	3.6							
Lithuania	All ages	51.7	203.4	1978–2016	1978–2016	7.4*	6.5	8.3	26.68	31.1	1985–2016	1985–2016	2.3*	1.9	2.8
					1978–1994	3.2*	2.1	4.2				1985–2006	3.6*	3.2	4.0
					1994–2001	9.8*	5.1	14.7				2006–2016	−1.4*	−2.7	−0.1
					2001–2007	23.0*	16.0	30.3							
					2007–2016	−4.4*	−6.6	−2.1							
Russian Federation	All ages	18.6	55.2	1993–2015	1993–2015	7.1*	6.8	7.4	12.24	19.2	1985–2015	1985–2015	2.6*	2.5	2.8
					1993–2002	6.3*	5.1	7.4				1985–2000	2.1*	1.8	2.4
					2002–2015	7.5*	6.9	8.2				2000–2010	3.6*	3.0	4.1
												2010–2015	1.0	−0.3	2.4
Ukraine	All ages	N/A	36.2†	2000–2012	2000–2012	3.4*	2.7	4.2	11.38	16.1	1985–2012	1985–2012	3.8*	3.7	4.0
												1985–1990	5.4*	3.7	7.0
												1990–1996	2.4*	0.8	4.0
												1996–2012	4.2*	3.9	4.5

*Statistically significant.
†2008–2012.
AAPC, average annual percentage change (applicable for the whole period); APC, annual percentage change (applicable for segment between two joinpoints); ASR, age-standardised rate; JP, joinpoint; N/A, not available.

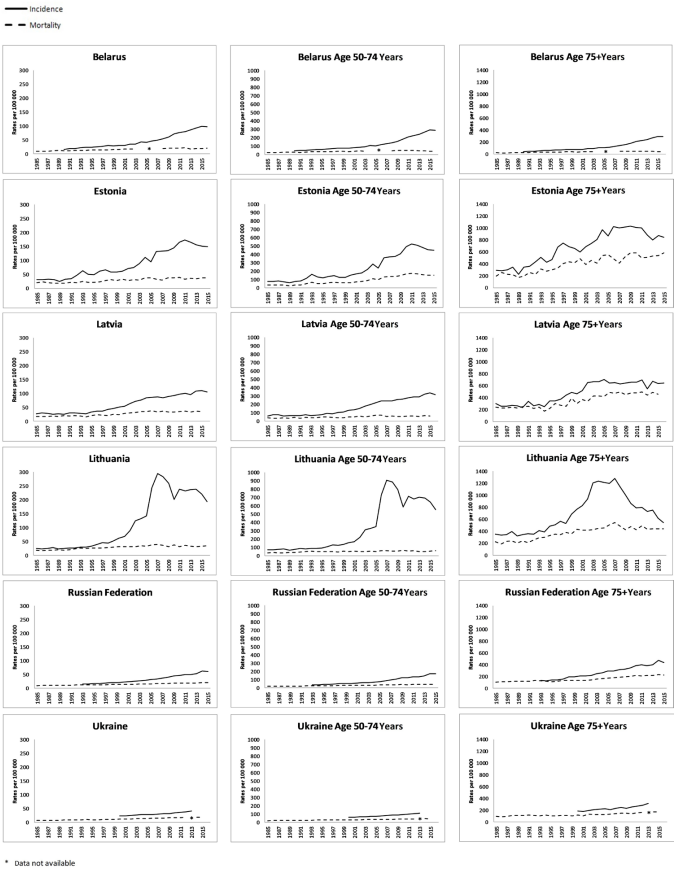

Figure 1 Trends in age-adjusted and age-specific prostate cancer incidence and mortality in six European countries.

years, with a PSA cut-off of 4 ng/mL.[19] In the Russian Federation, PSA testing was introduced in the 1990s. Furthermore, PSA has been included in the national health check-up programme since 2013. This programme included other tests for other cancers and no formal and detailed information about the PSA cut-off value or settings for check-ups in this programme are available. In Ukraine, PSA check-ups for the population started quite late, compared with other countries. Formally, the PSA test was added to national guidelines for diagnostics of different locations and the state oncology programme of Ukraine, although no information regarding implementation and results of screening is available.

During the past 20 years, due to more extensive endoscopic benign prostate hyperplasia surgery, developing imaging techniques and PSA testing, higher prostate cancer rates have been observed in developed countries.[5] A rapid increase in prostate cancer incidence appears mostly to be associated with the widespread use of the PSA test since the middle of 1980s.[3 5–7] PSA use in clinical practice in north-eastern European countries began in the mid-to-late 1990s which reportedly reached almost 70% of males in some populations.[7 16 18 20] There were sporadic occurrences of prostate cancer screening in the study countries.[19] In Lithuania, in 2006, a prostate cancer early detection programme was introduced as part of a nationwide opportunistic PSA test-based prostate cancer screening initiative. Incidence changes in Lithuania paralleled changes in prostate cancer incidence in the USA reported for the early 1990s.[18] There was a rapid incidence peak after the start of the screening programme, followed by a decrease thereafter. It was caused by initial detection

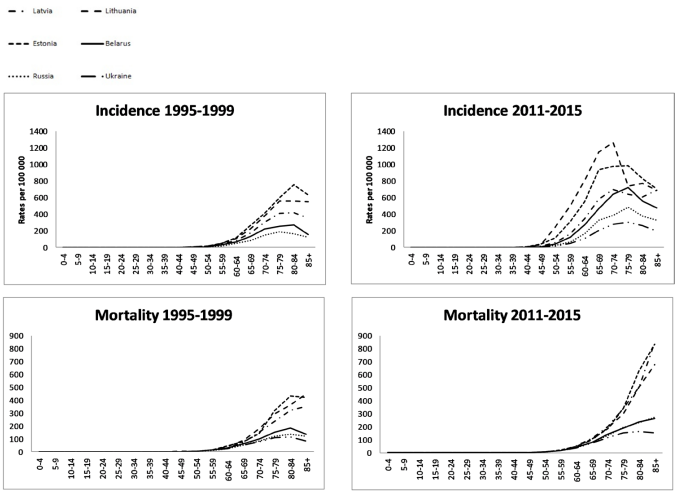

Figure 2 Age-specific incidence and mortality in periods 1995–1999 and 2011–2015.

of a so-called 'backlog' of prevalent cancers that had accumulated as a result of previous years' incidence, described by Mettlin.[21] It is notable that similar incidence changes have been observed in Estonia, where the PSA uptake is relatively high in the male population, according to a health behaviour study reported in 2016.[17] The role of PSA-testing in incidence trends is further supported by the fact that the incidence increase in Estonia was shown to be limited to localised cancers.[16]

Besides the tangible benefits of PSA testing, which appears to be small based on recent mortality data, the test may also cause unwanted harms, such as overdiagnosis or detection of indolent tumours,[22] and as a consequence of overdiagnosis, overtreatment[23] and reduction in life quality.[24] Although PSA screening may be beneficial in an organised setting,[25] the net effect of a higher PSA uptake at a population level could be negative due to side effects.

For the most part, prostate cancer is a latent, slowly progressing disease. A long period of time might be necessary before the mortality declines at the population level. Also, such a decline may occur in a different age group rather than the age at diagnosis.[8] In our analysis, no mortality decrease was found in Lithuania in the age group 50–74 years and a slight mortality slope was observed in the age group 75+ years after 2006. This is consistent with the US data where a decrease in the mean age at diagnosis followed PSA use.[23] The same effect is observed in our study. The highest age-specific incidence rates observed before implementation of PSA testing in clinical practice were seen in the 80–84 years age group in all countries. However, in more recent years, peak incidence rates shifted to younger age groups (ie, 60–64 and 70–74 years). By comparison, peak mortality rates shifted to older age groups from 80–84 to 85+ years after implementation of PSA testing in clinical practice. These changes could be a reflection of the PSA screening effect.

The Baltic states during the last decades have experienced a steep average incidence increase with a rather stable mortality,[5] although mortality in our study in the Baltic countries has had a continuous growth, with stabilisation in Estonia and Latvia and a decrease in Lithuania since 2006 by 1.4% annually. The year when decrease started, coincidently, is the same as the start of the prostate cancer early detection programme in Lithuania. This could be misinterpreted as a success of the early effect of this programme. However, according to the data from randomised controlled PSA screening trials, the first mortality reduction is observed at least 9 years after the beginning of the trial.[26] The mortality decrease in Lithuania, starting in the same year the screening started, is, therefore, unlikely to be due to the PSA-based screening. The high mortality rates observed after implementation of the PSA-based screening could be possibly due to the over-reporting of prostate cancer as an underlying cause of death in death certificates. Similarly, this was noted in the USA in 1991, when many men with undetected prevalent cancers were diagnosed with prostate cancer and were more likely to have prostate cancer assigned as a cause of death when dying.[27] In a study in Norway, over-reporting of prostate cancer deaths was estimated to be 33%, with significantly higher misattribution among older patients, who represent the large majority of prostate cancer deaths.[28] Misattribution of the cause of death in Estonia was one explanation for increasing prostate cancer mortality.[16]

CONCLUSIONS

A widespread use of PSA testing seems to be responsible for the changes in the epidemiology of prostate cancer in north-eastern European countries. Substantial variation in the incidence of prostate cancer in the Baltic countries likely reflects the use of the PSA test in detecting prostate cancer. A lack of effect on prostate cancer mortality was observed. Guidelines for the use of the PSA-test as an early detection tool, including a joint and informed decision process of the physician and the patient, should be developed and adhered to in all the participating countries. This would help to minimise the harm associated with overdiagnosis, and to ensure that Belarus, the Russian Federation and Ukraine will not experience the marked incidence increases seen in the Baltic states.

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3 publikacija / 3rd publication

Changing Incidence and Stage Distribution of Prostate Cancer in a Lithuanian Population—Evidence from National PSA-Based Screening Program

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Changing Incidence and Stage Distribution of Prostate Cancer in a Lithuanian Population—Evidence from National PSA-Based Screening Program

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Abstract: Background: The aim of this study was to examine the impact of screening introduction on prostate cancer incidence changes, and changes in stage distribution in Lithuania between 1998–2016. Methods: Age-standardized incidence as well as stage-specific incidence rates were calculated. Joinpoint regression was used to estimate the annual percentage change in the incidence changes by determined stage: Localized, advanced, distant and unknown. Results: Over the study period, a total number of 48,815 new prostate cancer cases was identified. Age-standardized incidence rose from 51.9 per 100,000 in 1998 to 279.3 per 100,000 in 2007 (by 20.3% per year) and then decreased thereafter by 3.8% annually. Highest incidence rates after introduction of prostate specific antigene (PSA)-based screening was found for localized disease, followed by advanced. Incidence of localized disease rose by 38.2% per year until 2007 reaching the highest rate of 284.6 per 100,000, with a subsequent decrease of 5.5% every year thereafter. Advanced stage of disease experienced rise till 2007, and continuous decrease by 11.1% every year thereafter. Incidence of disease with distant metastasis was lowest, and rose till 2003, thereafter incidence significantly decreased by 8.1% every year. Conclusions: To our knowledge, this is the first report of stage migration effect in Lithuania, following the introduction of nationwide PSA-based screening. Prostate cancer screening substantially increased the overall incidence and incidence of localized cancer.

Keywords: incidence; prostate cancer; PSA-based screening; stage migration

1. Introduction

Prostate cancer was estimated to be the third most common cancer in Europe in 2018, with 450,000 cases, as well as the fifth leading cause of cancer death, with 107,000 deaths [1]. Widespread implementation of prostate specific antigen (PSA) testing has changed the epidemiologic situation of prostate cancer worldwide. There has been a noted incidence rise in prostate cancer in most European countries and worldwide [2,3]. Despite recommendation from international health authorities [4], in 2006, Lithuania started the Early Prostate Cancer Detection Program (EPCDP). Lithuania is the only country in the world with a running nation-wide PSA-based prostate cancer screening program. Asymptomatic men with PSA levels >3 ng/mL are offered further urological evaluation, including digital rectal examination and transrectal ultrasound. The decision to perform a prostate biopsy is at the discretion of the consulting urologist. The EPCDP experienced several modifications for check-up frequency. At first, screening annually targeted men aged 50–75 years and younger men (>45 years) with a family history of prostate cancer. From 2009 to 2016, screening was performed every two years By the end of 2010, 72 to 78% of the total eligible male population received at least one PSA test [5].

Costs of EPCDP varied between 1.26 million euros in 2006 to 2.1 million euros in 2008 [6]. Changes of prostate cancer incidence and mortality have been analyzed and interpreted: Lithuania experienced continuous increase of prostate cancer incidence steadily, from 37.03 per 100,000 in 1994, to 75.66 per 100,000 in 2001. During the period between 2001–2007, there was a rapid annual increase of 23% in prostate cancer incidence. A peak incidence rate of 279.33 per 100,000 (European standard) was reached in 2007, after the start of the screening program. Thereafter, these incidence changes led to a decrease in the incidence rate. Mortality in Lithuania had been continuously growing, however, in 2006 mortality started to decrease by 1.4% annually [7]. This decrease is unlikely attributable to the success of the early effects of EPCDP, as the start of decrease is the same as the start of the program. However, analyzed changes are lacking detailed information about disease distribution by stage. The aim of this study was to examine the impact of screening introduction on prostate cancer incidence changes, and changes in stage distribution in Lithuania between 1998–2016.

2. Materials and Methods

The study is based on all new prostate cancer cases identified in the Lithuanian Cancer Registry during 1998–2016. The Lithuanian Cancer Registry is a population-based registry which contains personal and demographic information (place of residence, sex, date of birth, vital status), as well as information on diagnosis (cancer site, date of diagnosis, stage of disease, method of cancer verification) and death (date of death, cause of death) of all cancer patients in Lithuania. Age-standardized incidence, as well as group-specific incidence rates were calculated using the direct method (Europe standard population) [8]. Corresponding population data by age and year were available from Statistics Lithuania. We determined three prostate cancer groups by cancer stage and TNM (Tumor, Node, Metastasis): Localized (T1-T2N0M0 or stage I–II), advanced (T3-T4N0M0 or stage III), distant (any T, N1 or M1, or stage IV) and unknown. Changes in overall incidence, and incidence changes by stage of disease were examined.

The joinpoint regression model was used to provide estimated annual percentage change (APC), and to detect points in time where significant changes in the trends occur. For each of the identified trends, we also fitted a regression line to the natural logarithm of the rates, using calendar year as a regression variable. Joinpoint regression analysis is often used when the temporal trend of a given quantity—like incidence, prevalence and mortality—is the field of interest. Permutation tests for joinpoint regression analysis were introduced and proposed to be applied to cancer rates by Kim et al. in the 2000s [9]. A maximum number of one joinpoint was decided a priori, in order to identify the most important time point at which stage incidence changes occurred. Using 95% confidence intervals, APC was calculated. Changes were considered statistically significant if $p < 0.05$. A Monte Carlo permutation method was used for the tests of significance [9]. Joinpoint analysis was performed for all age groups and for each outspread group of prostate cancer. Joinpoint software version 4.3.1.0 (Information Management Services, Inc., Calverton, MD, USA) was used.

3. Results

Over the study period, a total number of 48,815 new prostate cancer cases was identified. Description of study population is presented in Table 1. Age-standardized incidence rose from 51.9 per 100,000 in 1998 to 279.3 per 100,000 in 2007 (by 20.3% per year), and then decreased thereafter by 3.8% annually (Figure 1). Figure 2 shows trends of prostate cancer incidence by stage of disease. Highest incidence rates after introduction of PSA-based screening were found for localized disease, followed by advanced. Incidence of localized disease rose by 38.2% per year until 2007, reaching the highest rate at 284.6 per 100,000, with a subsequent decrease by 5.5% every year. Advanced stage of disease experienced a rise until 2007, followed by a continuous decrease by 11.1% every year thereafter. Incidence of disease with distant metastasis was lowest and rose till 2003, and significantly decreased by 8.1% every year thereafter.

Table 1. Study group characteristics.

		Number of Cases	%	Before Screening (1998–2005)	%	During Screening (2006–2016)	%
	Overall	48,815	100.00	11,400	100.00	37,415	100.00
By stage	Localized	22,095	45.26	3706	32.51	18,389	49.15
	Advanced	12,593	25.80	4910	43.07	7683	20.53
	Distant	3150	6.45	1688	14.81	1462	3.91
	Unknown	10,977	22.49	1096	9.61	9881	26.41
By age group	**<50 years**	509	100.00	67	100.00	442	100.00
	Localized	314	61.69	25	37.31	289	65.39
	Advanced	68	13.36	16	23.88	52	11.76
	Distant	38	7.47	19	28.36	19	4.30
	Unknown	89	17.49	7	10.45	82	18.55
	50–74 years	37,006	100.00	7204	100.00	29,802	100.00
	Localized	18,349	49.58	2582	35.84	15,767	52.91
	Advanced	8646	23.36	3028	42.03	5618	18.85
	Distant	1934	5.23	1045	14.51	889	2.98
	Unknown	8077	21.83	549	7.62	7528	25.26
	>75 years	11,300	100.00	4129	100.00	7171	100.00
	Localized	3432	30.37	1099	26.62	2333	32.53
	Advanced	3879	34.33	1866	45.19	2013	28.07
	Distant	1178	10.42	624	15.11	554	7.73
	Unknown	2811	24.88	540	13.08	2271	31.67

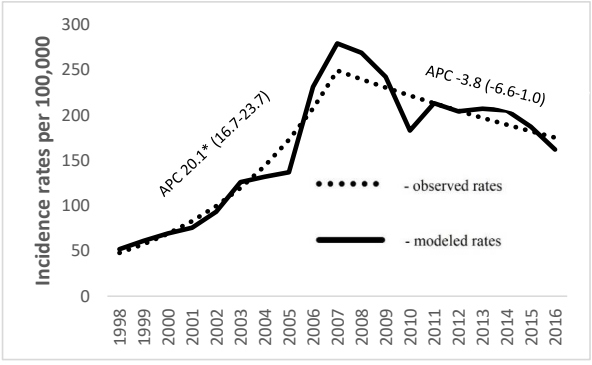

Figure 1. Age-adjusted prostate cancer incidence rates in Lithuania from 1998 to 2016 (* statistically significant; APC: Annual percentage change).

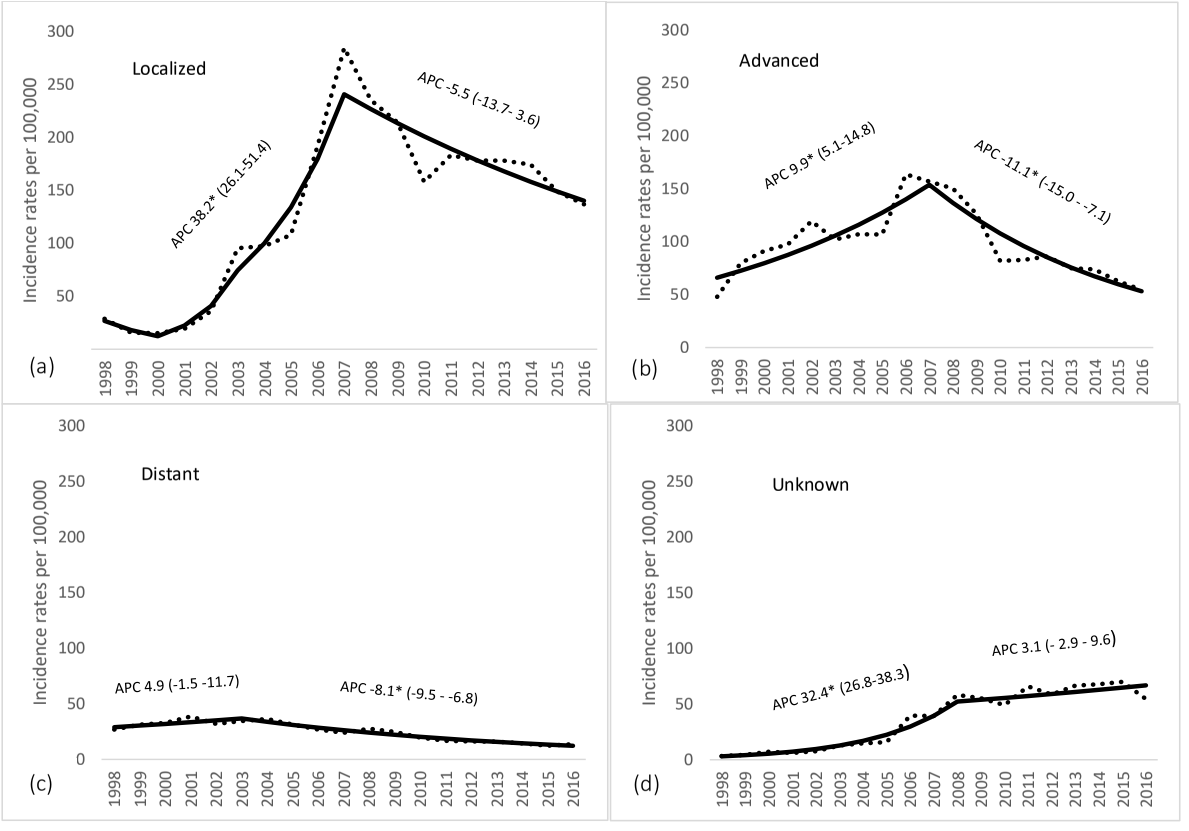

Figure 2. Changes in incidence rates of prostate cancer by stage in Lithuania 1998–2016; ((**a**): Localized; (**b**): Advanced; (**c**): Distant; (**d**): Unknown) (* statistically significant; APC: Annual percentage change).

4. Discussion

The results of this analysis provide an overview of the incidence changes in stage distribution of prostate cancer in Lithuania over the past two decades, following the introduction of a national PSA-based screening program. One of the main endpoints of successful screening, and sign of the effectiveness of PSA in detecting significant new cancers is a reduction of mortality from prostate cancer [10–12]. The existing evidence from the European Randomized Study of Screening for Prostate Cancer has showed, that screening results led to a 21% prostate cancer mortality reduction in an intention-to-treat analysis [13]. However, mortality risk reduction in randomized prostate cancer screening trials remains weakly tangible [14]. Other signs of successful screening, that appear much earlier than mortality reduction can be seen, are increase of incidence of disease followed by decrease thereafter, and a downward shift in age and in the stage of disease at diagnosis [12]. Results of our study show an incidence decrease in advanced and distant forms of the disease, with an overall increase of localized disease after the introduction of PSA-based screening at the population level.

Incidence peak, seen after introduction of prostate cancer screening, was observed in the United States in the early 1990s [15]. This phenomena is called "backlog", described by A. Farkas in 1998 and C.Mettlin in 2000. The wide use and utilization of PSA testing as a screening tool detects clinically insignificant cancers, and results in a largely increasing incidence for this disease. As soon as this backlog is diagnosed, incidence exhibits a downfall, reaching true level of incidence which is higher than in the pre-screening era [16,17]. Overall, prostate cancer incidence changes in Lithuania mimicked changes of incidence in the USA in the early 1990s [1]. There has been a rapid incidence peak since the start of screening program, followed by a decrease thereafter. In Lithuania, PSA became available in 2000, and in 2006, a nationwide PSA-based prostate cancer early detection program was started [7]. Since the start of the program, in the period between 2006–2010 around 72–78% of the total eligible male population received at least one PSA test [5].

Introduction of the EPCDP in Lithuania resulted in an incidence peak in 2007 for advanced and localized cancer stages. The incidence peak for distant stage of disease was seen in 2001, although incidence for systemic disease had continuously decreased from 2003 to 2016. Observed changes in incidence could be a result of an increase in transurethral resection of the prostate for obstructive symptoms, and later because of PSA introduction into clinical practices in 2000. Rapid decline in incidence of advanced stage disease shows early detection related effect before the start of the national EPCDP. Similar incidence changes by stage were observed in the United States and Tyrol (Europe), after introduction of population-based prostate cancer screening [18]. Analysis of stage distribution in Lithuania after implementation of PSA into clinical practice and introduction of EPCDP, revealed clear incidence reduction of advanced disease and stage with distant metastasis.

The main limitation of this study is the proportion of unknown stages of disease and/or staging by TNM classification. Based on the results of our recent study, patients with a lack of staging information are likely to live like patients in the advanced stage group. It suggests that patients with an unknown stage of disease are not presenting a metastatic status of the disease [5]. It is notable that incidence in the unknown stage group rose from the beginning of the study to 2008.

Not only can the improvement in age and stage distribution be attributable to the test itself, but also to an overall improvement in the knowledge and cancer awareness at the population level. Often screening programs are accompanied by the widespread publication of screening information. Studies from other cancer site screening programs, analyzing degree of caution in stage I disease, showed that the proportion of stage I diseases may well reduce with consecutive screening rounds [19].

5. Conclusions

To our knowledge, this is the first report of stage migration effect in Lithuania, following the introduction of the nationwide PSA-based screening. Prostate cancer screening substantially increased the overall incidence and incidence of localized cancer.

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All-cause mortality risk in national prostate cancer cohort: an impact of population-based prostate cancer screening

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All-Cause Mortality Risk in National Prostate Cancer Cohort: An Impact of Population-Based Prostate Cancer Screening

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Abstract: The aim of this study is to evaluate all-cause mortality risk differences before and during prostate cancer screening, with a profound focus on the differences between screened and not-screened patient groups. Prostate cancer cases diagnosed between 1998 and 2016 were identified from the population-based Lithuanian Cancer Registry and linked with screening status in the National Health Insurance Fund database. The analysis was stratified by a period of diagnosis and screening status. Standardized mortality ratios (SMRs) were used to assess all-cause and cause-specific mortality risk. The SMRs were calculated by dividing the observed number of deaths among prostate cancer patients by the expected number of deaths from the general population. All-cause SMR (1.45 (95% CI 1.42–1.48)) in the pre-screening period was higher compared to the screening period (SMR = 1.17 (95% CI 1.15–1.19)). An increased all-cause mortality risk among prostate cancer patients was observed in the not-screened patient population (SMR = 1.76 (95% CI 1.71–1.82)), while all-cause mortality risk in the screened patient population was similar to the general population (SMR = 1.00 (95% CI 0.97–1.02)). Screened patients with localized stage of disease had lower all-cause mortality risk than the general population (SMR = 0.72 (95% CI 0.70–0.75)). In conclusion, men with prostate cancer in Lithuania had excess all-cause mortality risk compared to the general population. The all-cause mortality risk among screened patients was not higher than expected.

Keywords: prostate cancer; screening; mortality risk; cause-specific mortality; all-cause mortality

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1. Introduction

The main factor determining the incidence of prostate cancer is the utilization of prostate specific antigen (PSA) test in clinical practice and public health interventions [1]. Despite the wide use of PSA testing in many countries, the benefits of PSA-based screening remain debatable [2]. The best indicator for success against cancer is a decreasing mortality rate in the population [3]. European randomized study of screening for Prostate Cancer (ERSPC) based on the PSA test showed 20% significant reduction in prostate cancer mortality in the screened patient arm compared to not-screened patient arm. Although the ERSPC trial has demonstrated a reduction in cause-specific mortality, a reduction in all-cause mortality was not demonstrated relative to comparing higher risk groups with lower risk groups [4]. In the study from The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, higher other and all-cause mortality risk was observed in the high risk prostate cancer group [5]. The trial presupposes that a large sample size in a trial is required in order to demonstrate a significant reduction in all-cause mortality. Disease-specific mortality is biased in favor of screening and all-cause mortality is a more exact endpoint than disease-specific mortality in cancer screening trials [6]. Increased detection of cancer in the screened patients group presupposes a greater likelihood of a death being classified as caused by cancer in this group which leads to ascertainment or so called "sticky diagnosis" bias [7,8]. All-cause mortality is often used as an outcome

measure to study the effects of different interventions on the course of prostate cancer in contemporary register-based prostate cancer studies [9]; however, only five studies from the USA, Europe, UK, Sweden, and Finland reported their results [10–12].

Lithuania has operated the national Early Prostate Cancer Detection Program (EPCDP) since 2006 [13]. This program works in the setting of nationwide PSA test-based screening and 70% of men aged 50 years to 74 years have participated in the prostate cancer program at least once in the first 10 years of the screening. During the screening period, prostate cancer incidence exhibited a dramatic increase in incidence and reached 279.33 cases per 100,000 (from 69.32 cases per 100,000 in 2000, European standard), with slowly decreasing prostate cancer mortality since 2007 [14]. However, all-cause and other cause mortality risk differences after implementation of prostate screening in Lithuania have never been investigated.

The purpose of this study is to evaluate all-cause and other cause mortality risk differences before and during prostate cancer screening, with a profound focus on all-cause mortality risk differences between screened and not-screened patient groups.

2. Materials and Methods

Cause-specific and all-cause mortality risk among patients with prostate cancer in Lithuania were evaluated using a retrospective cohort study design. Primary prostate cancer cases diagnosed between 1998 and 2016 were identified from the population-based Lithuanian Cancer Registry, which covers the entire population (3 million individuals in 2011) of the country and has been in operation since 1984. Available data for this analysis included age, date of diagnosis, date, and cause of death. Underlying causes of death were obtained from death certificates. Screening status (participated at least once in the screening program) was received from the National Health Insurance Fund (NHIF).

The study cohort was divided into two periods: Patients diagnosed with prostate cancer before the official start date of prostate cancer screening 1 January 2006 were assigned to the group "pre-screening", and patients diagnosed after 1 January 2006 assigned to group the "screening". In further mortality risk analysis, the screening group was further divided into two groups by screening history status which are "screened" and "not-screened". The definition of what falls under "not-screened" is an individual who had been diagnosed with prostate cancer but has not participated in the Early Prostate Cancer Detection Program in Lithuania.

Person-years were computed from the date of cancer diagnosis to the first of the following events: death, emigration, or end of the follow-up (31 December 2016). Standardized mortality ratios (SMRs) were calculated by dividing the observed number of deaths among prostate cancer patients by the expected number of deaths estimated from the general population of men, with 95% confidence intervals (CIs). Indirect standardization was used to calculate the expected number of deaths for the study population. Expected numbers were calculated as the multiplication of the exact person—years under observation in the cohort by calendar year—and 5-year-age-groups-specific national cause of death rates [15].

For stage group-specific standardized mortality ratios (SMRs) analysis, we determined three prostate cancer groups by cancer stage and TNM: localized (T1-T2N0M0 or stage I–II), advanced (T3-T4N0M0 or stage III), distant (any T, N1 or M1 or stage IV), and unknown stage. A χ^2-test for trend was performed to evaluate all-cause mortality risk among prostate cancer patients over stage groups [16].

All statistical analyses were carried out using STATA 15 statistical software (StataCorp LLC. 2020 rev. Stata Statistical Software: Release 15.0., College Station, TX, USA). The study was conducted following the Declaration of Helsinki and the protocol was approved by the Vilnius Regional Biomedical Research Ethics Committee with the approval number 158200-16-879-388 on 28 November 2016. Data analyzed were based on record-linkage information and, as such, the Ethics Committee waived the need for informed consent of the study subject.

3. Results

In the Table 1 are the presented characteristics of the study groups. In part A are the described patient cohorts by period. The mean population age before screening was 71.51 years and it was higher compared to the prostate cancer population during the screening —67.17 years. In part B demonstrates patient cohorts by screening status during the screening period. Not-screened prostate cancer patients were older than screened (76.26 vs. 65.47 years). All-cause mortality risk before and during the screening period (Table 2, part A) among prostate cancer patients was higher compared to the general population, however, during screening period all-cause mortality risk was lower than in the pre-screening period (SMR = 1.45 (95% CI 1.42–1.48) vs. SMR = 1.17 (95% CI 1.15–1.19)). An increased all-cause mortality risk among prostate cancer patients (Table 2, part B) was observed in the not-screened patient population (SMR = 1.76 (95% CI 1.71–1.82)) while all-cause mortality risk in screened patient population was similar to general population (SMR = 1.00 (95% CI 0.97–1.02)).

Table 1. Study group characteristics of men diagnosed with prostate cancer during pre-screening and screening period (A) and of screened and not-screened persons (B).

A	Pre-Screening (1998–2005)	Screening (2006–2016)
Patients diagnosed with prostate cancer (%) (N [1])	11,401	37,418
Median age at prostate cancer diagnosis (IQR [2]), years.	72 (66; 77)	67 (61; 73)
Mean follow-up time (IQR), days.	2076 (613; 4222)	1728 (859; 2802)
Number of deaths (%)	8782 (77.03)	11,079 (29.61)
B	**Not-Screened**	**Screened**
Patients diagnosed with prostate cancer (%) (N [1])	5886	31,532
Median age at prostate cancer diagnosis (IQR [2]), years.	78 (73; 82)	66 (60; 71)
Mean follow-up time (IQR), days.	1093 (261; 2377)	1811 (983; 2852)
Number of deaths (%)	3805 (64.64)	7274 (23.06)

[1] Number; [2] IQR—interquartile range.

Table 2. Standardized all-cause mortality ratios during pre-screening and screening period (A) and of screened and not-screened persons (B).

	Obs [1]	Exp [2]	SMR [3]	95% CI [4]		*p* Value [5]	Obs	Exp	SMR	95% CI		*p*-Value [2]
A	**Pre-screening (1998–2006)**						**Screening (2006–2016)**					
All-causes	8782	6075.12	1.45	1.42	1.48	<0.001	11,079	9461.78	1.17	1.15	1.19	<0.001
B	**Not-Screened**						**Screened**					
All-causes	3805	2157.04	1.76	1.71	1.82	<0.001	7274	7304.74	1.00	0.97	1.02	<0.001

[1] Obs, observed; [2] Exp, expected; [3] SMR, standardized mortality ratio; [4] CI, confidence interval; [5] Chi-square test.

Stage group-specific standardized mortality ratio (Table 3) from all-causes among men with prostate cancer showed a higher risk of death for patients that were locally advanced and metastatic as well as for patients with the unknown stage of disease and risk increased with increasing dissemination (p = <0.0001) among the not-screened and screened patient cohort. For persons with the localized disease in not-screened cohort, risk of death was similar to the general population (SMR = 0.99 (95% CI 0.92–1.05)) while for the screened person cohort it was significantly lower (SMR = 0.72 (95% CI 0.70–0.75)).

Table 3. Stage-specific standardized mortality ratios of screened and not-screened persons.

	Not-Screened						Screened					
Stage Group	**Obs**	**Exp**	**SMR**	**95% CI**		***p*-Value** [2]	**Obs**	**Exp**	**SMR**	**95% CI**		***p*-Value** [2]
Overall	3805	2157.04	1.76	1.71	1.82	<0.001	7274	7304.74	1.00	0.97	1.02	<0.001
Localized	886	897.05	0.99	0.92	1.05	0.712	2878	3974.42	0.72	0.70	0.75	<0.001
Locally-advanced	1076	779.70	1.38	1.30	1.46	<0.001	1979	1607.36	1.23	1.18	1.29	<0.001
Distant	588	107.71	5.46	5.04	5.92	<0.001	473	114.59	4.13	3.77	4.52	<0.001
Unknown	1255	372.58	3.37	3.19	3.56	<0.001	1944	1608.38	1.21	1.16	1.26	<0.001
			p [1] < 0.0001						p [1] < 0.0001			

[1] χ^2 test for trend, [2] Chi-square test.

Supplementary materials Tables S1 and S2 show standardized mortality ratios for specific causes of death. Increased mortality risk for malignant neoplasms was found (Supplementary Table S1). During the pre-screening period, mortality risk was increased for bladder cancer, colorectal neoplasms, prostate, and kidney and renal pelvis cancer although the cancer risk increase was insignificant for colorectal neoplasms and kidney cancer. During the screening period, an increased mortality ratio was observed for kidney and renal pelvis cancer, colorectal neoplasms, prostate, and bladder cancer although the risk increase for bladder cancer was insignificant.

During the screening period, among the screened and not-screened patients, standardized mortality ratios for specific causes of death were increased for malignant neoplasms: colorectal, kidney, renal and pelvis, and bladder cancers among the not-screened patients; and for bladder cancer among screened patients (Supplementary Table S2). SMR's for the diseases of the circulatory system was not higher than expected from the general population during the whole study period and in different screening status groups.

4. Discussion

This national cohort study involved 48,819 men with prostate cancer and was followed-up for almost 250,000 person-years and with over 19,000 deaths. Mortality risks were analyzed from 1998 to 2016. The large study cohort allowed us to investigate a wide range of mortality outcomes and compare them to the general population.

The study showed that people with prostate cancer had a 28% increased risk of death from all causes. Higher mortality risk was observed for patients before prostate cancer screening. All-cause mortality for prostate cancer patients was higher among not-screened patients, while screened patient mortality risk was similar to the general population. Stage group-specific all-cause mortality risk increased with disease severity.

Prostate cancer incidence in Lithuania is often compared with the incidence in the United States of America, where opportunistic PSA screening played a crucial role in prostate cancer diagnostics. Incidence changes in Lithuania in 2007 mimicked prostate cancer incidence changes in the late 1980s and early 1990s in the United States. There was a rapid incidence peak in Lithuania after the beginning of the screening program, followed by a decrease thereafter. It was caused by a so-called "backlog" of prevalent cancers that had accumulated as a result of previous years' incidence although mortality changes between the United States and Lithuania were different. In the United States there was an observed increase in prostate cancer mortality from the initiation of PSA based prostate screening, which is likely caused by the labelling of prostate cancer diagnosis to death certificates for older men population as opposed to true increases. These changes were followed by a mortality decrease by 37% from baseline prostate cancer mortality level [6]. In Lithuania, there was observed increasing mortality trend from 1985 to 2006 by 3.6% annually and decreasing mortality trend from 2006 by 1.4% annually [14].

All-cause mortality risk among prostate cancer patients was analyzed in studies from Sweden, the USA, Europe (ERSPC), and Finland. In the study from Finland, significant all-cause mortality decreases over the period from 1985 to 2009 and the mortality risk reduction among patients with the localized disease was observed [12]. The study from Sweden compared risk-specific prostate cancer groups with prostate cancer-free control

male group [11]. They have found that all-cause mortality was lower in men with low-risk prostate cancer compared with the corresponding prostate cancer-free men. Investigators from the ERSPC trial, comparing different risk groups, have found that prostate cancer screening attendees have lower all-cause mortality rate and a higher probability of a prostate cancer diagnosis than non-attendees although they stated that correction for attendance in screening status is important if the calculation of all-cause mortality risk is to be used in conjunction with disease-specific mortality analysis [4]. The PLCO trial in 2020 reported results of other cause and all-cause mortality risk among prostate cancer patients who participated in the PLCO trial. They have found that other cause survival was higher in lower risk disease compared to higher risk disease although results were statistically insignificant [5].

In the study from Sweden [11] comparing risk-stratified prostate cancer groups with controls, higher cardiovascular mortality risk was observed. It is well known, that one of the treatment modalities—androgen deprivation therapy—which is the treatment keystone of metastatic prostate cancer, has a causal relationship with increased mortality risk from cardiovascular diseases (CVD) [17,18]. In our study, during the pre-screening period and during screening, there was an observed lower mortality risk from diseases of the circulatory system than in the general population. Not-increased mortality risk from diseases of the circulatory system was found by comparing screened and not-screened patient cohorts. These findings differ from findings in other study and this could be explained by the high prevalence of cardiovascular diseases in the population of men in Lithuania [19].

Increased mortality risk due to kidney cancer, bladder cancer, and colorectal cancer was observed during the study period. Patients who are participating in the screening program often tend to be more aware of the benefits of health check-ups and they often undergo additional medical examination [20]. During the diagnostic process of prostate cancer, various imaging modalities are used and, therefore, patients could be incidentally diagnosed with kidney cancer or colorectal cancer [21–24]. Since those patients have worsened survival outcomes compared to prostate cancer alone, the more likely cause of death is different than for prostate cancer alone. Increased SMR for bladder and colorectal cancer among not-screened persons could be linked to a greater likelihood of second primary cancer due to pelvic radiotherapy, which is used as one of the modalities to treat advanced prostate cancer [25].

In the comparison of two different cohorts of prostate cancer patients (screened and not-screened), the benefit of screening can be observed. Even stage group-specific mortality risk analysis showed higher mortality rates in the not-screened patient cohort. More surprisingly, among screened patients with the localized stage of the disease there was an observed lower all-cause mortality risk compared to the general population. The so called "stage migration" was described in our previous studies [13,26] and the biggest proportion in our population-based screening cohort was localized disease. Therefore, we could assume that lower mortality risk in the screened patient population is mainly caused by earlier diagnosis. The benefit of the treatment of localized disease is seen in a large study from Sweden [27] that combined radical prostatectomy, radiation therapy, and active surveillance where surgery reduced the risk of death due to prostate cancer by 44% and all-cause mortality by 12.7%. In the study from Finland, benefits from early diagnostics were observed as well and the SMR's for localized disease became similar to the general Finnish male population since the introduction of PSA; furthermore, since the early 2000s, the SMR was lower compared to the SMR in the Finnish male population [12].

Higher stage-specific SMR rates in the not-screened patient cohort might be a reflection of social inequalities in men with prostate cancer population [28]. In Lithuania, age-adjusted incidence rate ratios (IRR) were reported to be higher among men with higher education and a lower risk among men with secondary and lower than secondary education (IRR = 0.70 (95% CI 0.64–0.76) and IRR = 0.49 (95% CI 0.46–0.53)) [29]. Mortality rate ratio comparing secondary and lower than secondary levels of education to prostate cancer patients with higher education was higher in lower than the secondary level of education

group (MRR = 1.40 (95% CI 1.13–1.72)). It is worth mentioning that opportunistic testing brings social inequalities as well when the more affluent can more readily obtain the benefits of testing than the less affluent.

Our study has limitations and strengths. The large proportion of men with unknown prostate cancer stage and bias encountered with SMR calculation where the true relative risk can be underestimated for relatively common diseases somewhat limited our analysis; however, it is unlikely to have affected the main conclusions drawn. Lower mortality rates in the screened patient group might be affected by earlier diagnosis and lead-time bias. The lack of clinical data regarding diagnostic modalities used and treatments of prostate cancer, which have largely evolved during study period, somewhat limited our study. The strengths of this study are the analyses based on real-life data, which covers a large national prostate cancer patient cohort, in line with a unique experience from ongoing population-based prostate cancer screening program and long follow-up of patients. Despite that, randomized controlled trials provide the highest level of evidence and analyses of real-world data from population-based registries provide unique information for the management of the effects of diagnosis at the population level.

5. Conclusions

In conclusion, men with prostate cancer in Lithuania had excess mortality risk compared to the general population. Population-based prostate cancer screening in Lithuania resulted in a mortality risk decrease in the time frame and mortality risk among screened patients was similar to that expected from the general population. Prostate cancer screening program participants with localized disease experienced mortality risk reduction.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/jcm10112459/s1, Table S1: Cause-specific standardized mortality ratios of men diagnosed with prostate cancer during pre-screening and screening period, Table S2: Cause-specific standardized mortality ratios of screened and not-screened persons.

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