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RETROSPECTIVE STUDY

Prostate cancer in Slovakia: last decade overview

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ABSTRACT
BACKGROUND: Prostate cancer is a significant health issue worldwide, with varying incidence and mortality rates across different regions. This study focuses on Slovakia, a country with an increasing trend in number of prostate cancer cases. The manuscript aims to provide a comprehensive overview of the burden of prostate cancer in Slovakia, encompassing epidemiological trends, economic impact, diagnostic approaches, and treatment modalities. The study emphasizes the need for effective management strategies and healthcare policies to address the increasing burden of this disease in the Slovak population.
METHODS: This retrospective study utilized data from various Slovak health databases, including the National Cancer Registry, hospital records, and insurance claims from 2009 to 2022. We employed epidemiological measures such as incidence, prevalence, and mortality rates to evaluate the burden of prostate cancer. Economic analysis involved assessing direct costs (hospitalizations, treatments, diagnostics) and indirect costs (lost productivity, disability). Additionally, the study reviewed cost of current diagnostic methods in Slovakia.
RESULTS: The study revealed a steady increase in prostate cancer incidence in Slovakia, with a notable rise in cases among men aged 50 and above. Mortality rates showed a moderate increase, highlighting the disease's impact on the healthcare system. The economic analysis indicated substantial direct and indirect costs, with a significant portion allocated to advanced treatments and productivity loss. Diagnostic methods showed improvements over time, with increased utilization of advanced imaging techniques.
CONCLUSIONS: The burden of prostate cancer in Slovakia is significant and growing, with rising incidence and economic costs posing challenges to the healthcare system. The study underscores the need for improved and early access to effective diagnostic and treatment options, and robust health policies to manage the rising burden. Additionally, public health initiatives focusing on awareness and early detection could play a crucial role in reducing the impact of prostate cancer in Slovakia. The findings of this study contribute valuable insights for policymakers and healthcare providers in developing targeted strategies to mitigate the burden of prostate cancer in the Slovak population *(Tab. 7, Ref. 53)*. Text in PDF www.elis.sk
KEY WORDS: prostate cancer, burden of disease, direct costs, indirect costs, societal impact.

Introduction

Prostate cancer represents a significant global health challenge, marked by its variable incidence, prevalence, and mortality rates worldwide. This variability is even more pronounced when comparing global data with specific regions such as Europe. The worldwide incidence of prostate cancer was 25.3 per 100,000 in 2007, with mortality rates at 8.1 per 100,000 (1). In contrast, Europe represents a distinct epidemiological profile. The crude annual incidence of prostate cancer in the European Union is 78.9 per 100,000 men, significantly higher than the global average, and the mortality rate stands at 30.6 per 100,000 men/year (2). The increasing incidence and prevalence of prostate cancer in Europe, ranging from 3% to 10% per annum, contrast with the global scenario where the increase is more gradual. This increase in Europe is accompanied by stable or decreasing mortality rates, except for the Baltic states, indicating improvements in diagnosis and treatment (3). The age-standardized incidence in the European Union was 65 per 100,000 men in 2008, with mortality rates ranging from 15 to 37 per 100,000, reflecting the regional variations within Europe (4). Additionally, prostate cancer in Europe has the sixth highest cause of cancer-related deaths in men, with an incidence rate of 93 per 100,000 (5). The 5-year prevalence is projected to increase from approximately 1.0 million in 2012 to 1.3 million in 2026, indicating a growing burden of this disease in the region (6). The dynamics of prostate cancer in Europe compared to global patterns underscore the need for tailored public health strategies and clinical practices. It highlights the importance of understanding regional epidemiology to effectively address this widespread and impactful disease. While global trends provide a broad perspective, the European context demonstrates the necessity for region-specific approaches in managing prostate cancer. The increasing incidence and prevalence of prostate cancer in Europe, along with the high mortality rates, emphasize the need for effective diagnosis and treatment strategies specific to the European region.

Cost perspective of Prostate cancer imposes a substantial economic and societal burden globally, with significant impacts in all

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geographical areas. This burden encompasses not only healthcare costs but also productivity losses, informal care, and long-term side effects of treatment. Therefore, it is crucial for policymakers and healthcare professionals in Europe to prioritise the development and implementation of comprehensive strategies to effectively manage prostate cancer and mitigate its impact on individuals and society. In the European Union, prostate cancer had an economic cost of €843 billion in 2009, including healthcare costs, productivity losses, and informal care. This figure reflects the substantial resources allocated to managing this disease across EU member states (7). In the USA, the total costs of early-stage prostate cancer range annually from $US1.72 billion to $US4.75 billion, demonstrating the significant financial implications of early intervention and ongoing management (8). For example, Canada faces similar challenges, with estimated lifetime costs including clinical staging, initial treatments, complications, follow-up cancer therapies, routine outpatient care, and palliative care following metastatic disease. This comprehensive approach to cost estimation underlines the long-term economic impact of prostate cancer management (9). In Australia, men diagnosed with prostate cancer reported median expenses of A$8000 for cancer treatment, with 75% of them spending up to A$17,000. This financial toxicity highlights the personal economic burden faced by individuals undergoing treatment (10). The Nordic countries, Central Eastern Europe, and the European Union collectively demonstrate a significant clinical and economic burden due to prostate cancer. Over-treatment and long-term side effects such as impotence and impaired urinary and/or bowel function compound this burden (11).

In the context of developed countries, treatments like radiotherapy, surgical treatment, and hormone therapy account for the greatest per capita costs. (12). In 2008, male costs due to premature cancer-related mortality in Europe were €49 billion, almost twice the female costs, underscoring the gendered impact of cancer mortality on economic productivity (13). Prostate cancer represented 5% of the overall cancer costs in the European Union, with healthcare accounting for 36% of these costs (14). Overall, the economic and societal cost of prostate cancer is a significant consideration in healthcare planning and policy development across these regions. The data from the USA, Canada, Australia, Nordic countries, Central Eastern Europe, and the European Union illustrate the multifaceted nature of this burden, encompassing direct medical costs, long-term care, lost productivity, and personal financial impact on patients. This highlights the necessity for efficient resource allocation and targeted strategies to mitigate the economic and societal impact of prostate cancer globally.

Diagnostic and therapeutic approaches

Diagnostic approaches

Diagnosis of prostate cancer involves several consecutive steps. It begins with interviewing the patient about their symptoms, overall health, and family history of prostate cancer in male relatives (15). A digital rectal examination (DRE) of the prostate provides information about the size, consistency, symmetry, and local extent of the disease. A hard, asymmetrical prostate with a rough surface often indicates cancer. However, the DRE is influenced by subjective factors and primarily reflects the examiner's personal experience

The examination of prostate-specific antigen (PSA) is a significant advancement in the diagnosis of prostate cancer. However, PSA is not exclusively a marker for prostate cancer but rather a marker for prostate tissue, as no other tissues produce PSA. PSA exists in the blood in two forms: free and bound to blood proteins. A free-to-total PSA ratio below 10% suggests the possibility of prostate cancer. This test is particularly valuable in distinguishing prostate cancer from benign prostatic hyperplasia in patients with PSA levels between 4.0 and 10.0 ng/ml.

PSA density (PSA D) correlates with prostate volume, with a value greater than 0.15 indicating a higher likelihood of prostate cancer. PSA velocity measures the change in PSA levels over time, and a PSA doubling time (PSA DT) of less than one year indicates an increased risk of prostate cancer. The shorter the PSA DT, the higher the likelihood of aggressive prostate cancer. The prostate health index (PHI), calculated from proPSA, total PSA, and free PSA values, allows for the early detection of prostate cancer (16). If the digital rectal examination is suspicious or PSA levels are elevated, the next step in diagnosis is a prostate biopsy.

A prostate biopsy is performed using either a transrectal or perineal approach. Typically, twelve tissue samples are taken, although the optimal number is not predefined. During a fusion prostate biopsy, images from magnetic resonance imaging (MRI) are combined with ultrasonographic images to allow for a more precisely targeted biopsy. Once the pathologist confirms the presence of prostate cancer, the diagnosis is definitive. The Gleason scoring system is then used to assess the aggressiveness of the disease (17).

After histological confirmation of prostate cancer, the next step is to determine the extent of the disease. This involves assessing whether the cancer is localized to the prostate or has spread to the pelvic lymph nodes or distant parts of the body. Prostate cancer most commonly metastasizes to the bones, where the metastases are usually sclerotic, though occasionally osteolytic. Skeletal scintigraphy using Technetium 99m is effective in detecting or ruling out bone metastases.

Ultrasonography of the prostate has low sensitivity and specificity in diagnosing prostate cancer but is useful during prostate biopsy. A CT scan can determine the extent of metastases in local lymph nodes. Magnetic resonance imaging (MRI), particularly its multiparametric variant, provides detailed information on prostate structure and lesions, with high sensitivity. Local changes are graded on a scale of 1 to 5, with grades 3 to 5 being suspicious for prostate cancer (18).

Positron emission tomography (PET CT) is used for whole-body staging of the disease and is considered the most precise method for detecting pelvic lymph node and distant metastases of prostate cancer (19).

For prognosis establishment and decision on prostate cancer treatment, the combined evaluation of the clinical stage, Gleason score and PSA values is used. Prostate cancer with very low risk

includes T1c cancer, Gleason score less than 6, PSA less than 10 ng/ml with less than three positive biopsy samples with less than 50% of cancer infiltration Prostate cancer with low risk – T1 –T2a cancer, Gleason score less than 6, Gleason grade 1, PSA less than 10 ng/ml. Prostate cancer with middle risk – this group includes T2b-T2c cancers with Gleason score (3+4), Gleason grade 2 or Gleason score 7 (4+3), Gleason grade 2 and PSA 10 to 20 ng/ml. Prostate cancers with high risk include patients with prostate cancer T3a, Gleason score 8, Gleason grade 4 or Gleason score 9 and 10, Gleason grade 5 and PSA more than 20 ng/ml. Prostate cancer with very high risk – T3b-T4 cancer, Gleason grade 5 or Gleason score 8 to 10 in more than 4 biopsy samples (19).

Therapeutic approaches

Before deciding on treatment, several factors are considered: the patient's age, general health status, clinical stage of the disease, risk of progression, PSA levels, Gleason score, number of positive biopsy samples, and the patient's attitude towards the proposed treatment after evaluating the potential benefits and possible side effects (20).

Certain prostate cancers progress very slowly, often taking more than 15 years without causing any symptoms. For these patients, treatments such as surgery, radiotherapy, or hormonal therapy can result in overtreatment, with complications that may be more severe than the disease itself. Patients under active surveillance are regularly monitored, and actual treatment is initiated only if the disease progresses. It is essential to discuss all aspects of active surveillance with the patient.

In a radical prostatectomy, the entire prostate, along with the seminal vesicles and pelvic lymph nodes, is removed. This procedure can be performed using open surgical techniques, laparoscopy, or robot-assisted laparoscopy, with all methods yielding similar oncological and functional results. Radical prostatectomy is recommended for patients with localized prostate cancer who have an expected survival of at least 10 years. It has also been found beneficial for patients with oligometastatic or locally advanced disease. In these cases, adjuvant radiotherapy or hormonal therapy may be necessary. The source of radiation is external to the patient's body.

The newest technique of external radiation therapy involves modulated intensity radiation therapy (IMRT), often combined with hormonal therapy. In this approach, the source of radiation is placed directly in the patient's prostate, with the isotopes of palladium-103 or iodine-125 being the most frequently used.

Hormonal therapy is the cornerstone of metastatic prostate cancer treatment. Although hormonal therapy does not cure the patient, it can slow the disease's progression (21). The principle of hormonal treatment is to either remove the source of testosterone (via bilateral orchiectomy) or block the production of testosterone in the testicles (pharmacological castration). The somatic and psychological consequences of castration are significant and include loss of libido and potency, gynecomastia, hot flashes, osteoporosis with pathological fractures, obesity, impaired glucose tolerance, increased incidence of diabetes, hypertension, arrhythmias, and a higher risk of cardiovascular diseases.

Pharmacological castration is achieved through the administration of LHRH agonists or LHRH antagonists, which halt the production of luteotropic hormone and testosterone. The effect of pharmacological castration is equivalent to bilateral orchiectomy. Castration-level testosterone is achieved four weeks after administering LHRH agonists and one day after administering LHRH antagonists. Antiandrogens, which block the binding of testosterone to receptors on prostate cancer cells, allow the level of testosterone in the body to remain unchanged, which is beneficial for other bodily systems (22).

Maximum (combined) androgen blockade aims to eliminate the influence of all androgens (both testicular and adrenal) in treating prostate cancer. LHRH agonists or antagonists stop testosterone production by the testicles, while antiandrogens block the effects of androgens produced by the adrenal glands. The lowest androgen levels are typically achieved after 6 to 9 months of hormonal treatment.

Hormonal treatment can be administered continuously or intermittently. Intermittent hormonal treatment is paused based on PSA values, possibly offering advantages such as fewer side effects and a better quality of life (23).

Primary treatment of metastatic prostate cancer is hormonal treatment. After 12 to 24 months – despite hormonal treatment – prostate cancer progresses. Progression is diagnosed by an increase of PSA at the castration level of testosterone. Progress is observed through an increased number metastases or of their size. Hormonal treatment must continue also in patients with hormone resistant prostate cancer. Chemotherapy with docetaxel is considered the standard treatment of castrate resistant prostate cancer. Two medicaments (abiraterone and enzalutamide) blocking the androgen receptors significantly prolong patients´ survival with acceptable quality of life. Hormonal treatment increases bone resorption, decreases bone density and increases the risk of skeletal fractures. Other cause of skeletal complications are bone metastases. In prevention and management of skeletal complications of prostate cancer, bisphosphonates and denosumab are used (24). Molecular therapy is emerging as a potential approach for treating primary prostate cancer. Research on the PAR-4 gene has shown promise in this regard (25). In cases of castration-resistant prostate cancer, initial androgen-deprivation therapy with docetaxel is considered the standard approach (26). Immunotherapy has also become an important treatment modality for advanced prostate cancer, with the approval of novel agents by the FDA (27).

Additionally, molecular imaging techniques like PET-CT or PET-MRI are increasingly being used for detecting local recurrence, lymph node involvement, or distant metastasis (28). Radioligand therapy (RLT) with 177Lu-PSMA is a relatively novel method of treating prostate cancer. It's part of a concept called Theranostics, which combines specific diagnostic method with specific therapeutical approach. Both use the same, or very similar PSMA ligand which target PSMA as a transmembrane protein, highly expressed on the prostate cancer cells. Current indication for this type of treatment is mCRPC after exhausting all other available treatment options. But there are data available from recent trials like VISION or TheraP, that show superior performance over the

best standard of care and chemotherapy. More studies are currently underway, which test the use of 177Lu-PSMA in early stages of the disease – in hormone sensitive and oligometastatic settings and also in neo-adjuvant setting before radical prostatectomy. Based on the interim results, it is expected to promote in the near future the use of RLT in earlier stages of the disease.

Methodology

Burden of disease methodological approach

The cost of illness (COI) methodology for prostate cancer encompasses various components to provide a comprehensive understanding of the economic impact of the disease. This approach includes the total cost of care, encompassing hospitalization for skeletal-related events, treatment costs, and the economic impact of long-term effects of the disease. It also investigates the cost-effectiveness of novel treatment options. Benefits of the COI methodology include providing a detailed understanding of the economic burden of prostate cancer on healthcare systems and society. It helps in identifying the most significant cost drivers, which can inform healthcare policy and resource allocation. This methodology also assists in evaluating the cost-effectiveness of new treatments and interventions, aiding in decision-making for healthcare providers and policymakers (29). However, the COI approach has limitations. It may not fully account for the indirect costs associated with lost productivity, the impact on caregivers, and the quality of life of patients and their families. Additionally, this methodology often relies on averages and may not capture the variability in costs among different patient populations and healthcare settings. There is also a challenge in accurately forecasting future costs, especially with rapidly evolving treatment modalities and technologies (12).

Analysis framework and data sources

This retrospective, prevalence-based cost-of-illness analysis for prostate cancer in Slovakia was conducted from the perspectives of both third-party payers and society with published methodology adjusted to Slovak conditions (30, 31). From the third-party payer perspective, the study encompassed all direct medical costs covered by insurance companies. Additionally, the societal perspective included the total societal loss attributable to prostate cancer, employing the Value of Statistical Life Year (VSLY) methodology (32). However, patient co-payments and out-of-pocket expenses were excluded from this study. The analysis covered all costs and healthcare resources used between 2013 and 2022, provided data were available. All costs were aggregated annually and presented in euros, with no application of cost discounting.

Prostate cancer was classified according to the World Health Organization's ICD-10 guidelines as code C61. The study included patients at all stages of disease severity. Prevalence data from 2009 to 2022 were sourced from the National Health Information Center (33). Additionally, age-sex structure and epidemiological data were obtained from both the National Health Information Center and the Statistical Office of the Slovakia (33, 34). A comprehensive analysis of reimbursement expenditures from 2014 to 2022 was conducted, based on data from the National Health Information Center, which included the costs of outpatient diagnostic and medical procedures. Indirect costs, calculated from data on paid sick leave and disability due to prostate cancer, were provided by the Social Insurance Agency (www.socpoist.sk).

Costs

In this analysis, both direct medical costs and indirect costs related to prostate cancer were considered. Direct medical costs included inpatient care, pharmacotherapy, diagnostic and medical procedures, medical devices, dietary supplements, and transport costs. Specifically, these encompassed all hospital admissions exceeding 48 hours with prostate cancer as the primary diagnosis, along with additional reimbursed services. Costs of outpatient diagnostics and procedures included a range of tests and examinations covered by health insurance. However, the study did not assess direct non-medical costs due to the absence of data in Slovakia. Indirect costs incorporated short-term and long-term work absences, as well as early retirement. Productivity loss due to absenteeism was estimated by multiplying the number of days on paid sick leave by the national average salary. Disability costs were calculated based on the proportion of individuals with prostate cancer receiving disability pensions.

Indirect costs included in the analysis were: costs of short-term absence from work, long-term absence from work, and early retirement. Productivity loss due to absenteeism was estimated as the number of days spent on paid sick leave from work due to C61.XX diagnosis multiplied by the national average salary in the available years. The disability costs were calculated as a proportion of the total number of people with C61.XX who were granted an invalidity pension multiplied by lump sum benefit provided by the Slovakian Social Insurance Agency for the disability.

Data analysis

Data analysis was performed retrospectively using anonymized electronic health insurance data from all Slovak health insurance companies. These companies collectively cover healthcare services for the entire population. Data for nine consecutive years, from 2014 to 2022, were collected upon official request from the NCZI. This dataset included every insured individual who received reimbursed care for prostate cancer, encompassing both outpatient and inpatient services. Unfortunately, out-of-pocket costs, such as drug co-payments and travel expenses, were not included due to the lack of comprehensive data collection in this area. Additionally, no current research presents these expenses for a representative sample of Slovak patients with prostate cancer. The dataset owners relied on the accuracy of diagnosis and cost information provided in the healthcare providers' monthly claims. Data on indirect costs related to absenteeism and disability were sourced from the Social Insurance Agency, segmented into costs associated with illness-related absenteeism and disability pensions, verified annually. Additionally, the datasets included average work absences from 2014 to 2022.

Tab. 1. Prostate cancer incidence in Slovakia from 2012 till 2021, in absolute numbers (51).

	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Incidence C61	1859	1964	1877	2071	2166	2707	2520	2810	2392	2802
Incidence C60-63	2183	2332	2211	2381	2495	3154	2865	3128	2757	3161
C61 incidence % from all cancer diagnosis (C00-96) incidence (in %)	5.94	6.42	5.90	5.92	6.05	7.00	6.67	7.37	6.96	7.66

Tab. 2. Prostate cancer mortality in Slovakia from 2012 till 2021, in absolute numbers (34, 51).

	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Mortality C61	637	626	737	696	696	712	699	727	738	677
Mortality C60-63	678	666	783	748	740	759	740	766	787	720
C61 mortality % from C60-63 group (in %)	5.31	4.75	5.56	5.15	5.18	5.27	5.10	5.47	5.35	5.29

Societal burden methodology

The methodologies for calculating Years of Potential Life Lost (YPLL), Years of Potential Productive Life Lost (YPPLL), and Disability-Adjusted Life Years (DALY) are crucial for understanding the impact of diseases, including prostate cancer, on public health and economies. These metrics offer valuable insights into the burden of diseases and play a significant role in various aspects of health planning, resource allocation, and intervention evaluation. Years of Potential Life Lost (YPLL) is determined by subtracting the age at death from a predetermined end point age, typically the average life expectancy. This method quantifies premature mortality by measuring the number of years not lived due to early death. However, YPLL calculations can vary among authors, depending on the chosen end point age and the data source for life expectancy (35).

Years of Potential Productive Life Lost (YPPLL) modifies the YPLL approach by incorporating the working-age population, typically considering ages between entering the workforce and retirement. This metric focuses on the economic impact of disease by measuring the loss of productive years. Calculating YPPLL often involves adjusting YPLL based on the proportion of the population within the working-age range, which can vary by country and economic context (36).

Disability-Adjusted Life Years (DALY) is a composite measure that combines Years of Life Lost (YLL) due to premature mortality and Years Lived with Disability (YLD) due to illness or injury.

The DALY formula is DALY = YLL + YLD.

YLL is calculated similarly to YPLL, considering the age at death and expected lifespan, while YLD is calculated by multiplying the duration of the disease with a disability weight factor reflecting the disease's severity. DALY captures both mortality and morbidity aspects of a disease, offering a comprehensive measure of disease burden (37).

These methodologies have unique strengths and limitations. YPLL and YPPLL provide insights into the impact of premature mortality on society and lost productivity. However, they do not consider the quality of life or disability associated with a disease. In contrast, DALY offers a more holistic view by including both mortality and morbidity but requires detailed data on disease prevalence, duration, and disability weights for calculation. All metrics are instrumental in quantifying the impact of diseases like prostate cancer from different perspectives, contributing to public health planning, resource allocation, and the evaluation of intervention effectiveness.

Results

From the epidemiology aspect of the prostate cancer the Table 1 shows a year-by-year account of prostate cancer incidence in Slovakia. Notably, there's a gradual increase in incidence over the years, with a significant rise observed in 2017. The incidence data are divided into two categories: C61 and C60-63, both showing an upward trend, highlighting the growing prevalence of prostate cancer in the country. The lowest recorded incidence for C61 was 1,859 in 2012, and the highest was 2,810 in 2019. The percentual increase from 2012 to 2021 is 33.7%. For C60-63, the lowest incidence was 2,183 in 2012, with the highest at 3,161 in 2021, reflecting a 30.9% increase over the period. In 2021, percentage of prostate cancer incidence cases created 7.66% part of total cancer incidence cases in Slovakia.

Table 2 details the mortality rates due to prostate cancer during the same period. Mortality C61 had its lowest at 626 in 2013 and peaked at 738 in 2020, an increase of 15.2%. For C60-63, the numbers ranged from 666 in 2013 to 787 in 2020, marking a 15.4% increase. Like the incidence, there's an observable increase in mortality rates over the years. The mortality data, categorized as C61 and C60-63, indicate a persistent and concerning health issue in Slovakia with increasing trend in deaths due to prostate cancer. In 2021, percentage of prostate cancer total mortality cases created 5.29% part of total cancer mortality cases in Slovakia and keeps steady trends over last decade.

Results provide also a more population-adjusted view of the incidence and mortality rates, offering a clearer understanding of the impact of prostate cancer relative to the total population. The lowest incidence rate per 100,000 was 71 in 2012 and 2014, and the highest was 106 in 2019. The percentual increase was 32.4%.

Tab. 3. Prostate cancer incidence and mortality in Slovakia from 2012 till 2021 per 100.000 men (34, 51).

	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Incidence C61	71	75	71	78	82	102	95	106	90	105
Mortality C61	24	24	28	26	26	27	26	27	28	25

Tab. 4. Direct costs associated with the prostate cancer in Slovakia from 2014 till 2022 in EUR (33).

	2014	2015	2016	2017	2018	2019	2020	2021	2022
Out-patient costs diagnostics	6 782 698	7 440 586	8 945 696	9 919 817	11 141 790	11 839 724	13 064 251	16 738 777	18 267 511
In-patient care hospitalization	3 340 133	3 398 771	3 621 046	4 997 606	5 648 737	6 177 478	5 827 382	6 669 668	7 095 733
Pharmaceutical treatment	10 423 253	11 465 569	13 418 206	15 023 972	17 060 957	18 583 747	18 934 591	22 455 589	28 177 989
Medical devices	107 988	105 171	96 783	106 562	90 227	111 070	122 314	135 159	105 395
Dietetical supplements	87 230	98 896	99 687	80 897	84 891	100 153	90 465	105 136	133 136
Transportation costs	228 565	203 213	204 695	213 635	264 487	314 876	331 808	318 897	325 435
Total	20 969 865	22 712 207	26 386 113	30 342 489	34 291 089	37 127 048	38 370 811	46 423 227	54 105 198

Tab. 5. Sick leaves and disability cost associated with the prostate cancer diagnosis in Slovakia from 2014 till 2022 in EUR (52).

	2014	2015	2016	2017	2018	2019	2020	2021	2022
Sick-leaves	1 199 672	1 201 701	1 167 621	1 517 309	1 773 681	1 972 857	2 123 390	2 238 685	2 122 042
Disability	589 443	674 107	544 577	613 711	727 486	755 375	751 447	858 047	897 619
Total	1 789 115	1 875 808	1 712 197	2 131 020	2 501 166	2 728 233	2 874 837	3 096 732	3 019 661

The mortality rates varied from 24/100 000 in 2012 to 28/100 000 in 2020, a 14.3% increase. The increase in both incidence and mortality per 100,000 men emphasizes the growing burden of this disease in Slovakia (Tab. 3).

Highlighting the economic burden, Table 4 presents the direct costs associated with prostate cancer, including outpatient costs, inpatient care, pharmaceutical treatments, medical devices, dietary supplements, and transportation. The direct costs of prostate cancer showed a significant increase, with the lowest in 2014 at €17,586,602 and the highest in 2021 at €28,938,742, amounting to a 64.67% increase. There's a noticeable increase in total costs over the years, indicating rising healthcare expenditures related to prostate cancer management with 169% increase in primary care costs including the diagnostic costs, 112% increase in inpatient costs and 170% increase in drug costs in 2022 compared to 2014.

From the perspective of the indirect economic impact of prostate cancer, Table 5 shows the costs associated with sick leaves and disability. There's a clear trend of increasing costs over the years, underscoring the broader economic and societal impacts of the disease beyond direct medical expenses. The indirect costs due to sick leaves and disability increased from €1,789,115 in 2014 to €3,019,661 in 2021, marking a 68.76% increase. The costs associated with sick leaves that are paid from our social security system almost doubled in a decade from € 1,2 mil. to € 2,1 mil. Similar trend is visible also with disability costs (Tab. 7).

The years of potential life lost (YPLL) increased from 6,947 in 2013 to 8,368 in 2019, then decreased to 6,128 in 2021. The disability-adjusted life years (DALYs) showed a decrease from 8,427 in 2013 to 7,144 in 2021. The data reveal the substantial impact of prostate cancer on life expectancy and quality of life in Slovakia (Tab. 6).

Tab. 6. Years of potential life lost, Years of potential productive life lost and Disability-adjusted life years associated with the prostate cancer in Slovakia from 2013 till 2021, in absolute numbers.

	2013	2014	2015	2016	2017	2018	2019	2020	2021
YPLL	6947	7749	7756	7533	7661	7385	8368	7893	6128
YPPLL	1141	1073	1238	881	1064	971	957	1181	841
DALY	8427	9560	9493	8688	8997	8873	9870	9324	7144

The Table 7 estimates the societal loss expressed by the Value of Statistical Life Year (VSLY) due to prostate cancer, calculated as 4 times the GDP per capita for each year. The VSLY increased from €283,194,199 in 2013 to €414,679,348 in 2019, before decreasing to €307,961,134 in 2021.The figures are substantial, highlighting the immense societal and economic value of life years lost to prostate cancer as well as a need for more prudent and tailored actions at the field of prostate cancer diagnostic and treatment.

Discussion

The economic burden of prostate cancer is multifaceted, encompassing both direct and indirect costs, which vary significantly based on treatment modalities, disease stage, and geographical location. Prostate cancer has some of the highest mean direct medical costs, as observed in Taiwan, where the mean direct medical cost was $28,464, and the total costs reached $81,775, that was higher than many other cancers (38). Considering only new patients in Slovakia, the average direct cost for 1 new patient was approx. € 19 500 in 2022. In Sweden, societal costs due to prostate cancer were estimated to be €64 million euro in 2016, with direct medical costs representing 62.2% of the total costs (39). Indirect costs, such as disability costs and sick leave, are more challenging to determine but represent a significant portion of the economic burden. The treatment of men with benign prostatic hyperplasia, for instance, places a significant burden on employees and employers through direct medical costs and lost work time, with total direct and indirect costs estimated at 3.9 billion dollars (40, 53). Family labor expended in caring for a patient with cancer is a major component of indirect costs in home care costs for prostate cancer (41).

The YPLL and YPPLL due to prostate cancer provide critical insight into the impact of this disease on population health, both worldwide and in Europe. In Europe, the life expectancy of fatal cases in prostate cancer was found to be 7.7 years for patients

Tab. 7. Expected societal loss expressed by Value of statistical life year due to prostate cancer in Slovakia, in EUR using 4x GDP per capita for each year separately.

	2013	2014	2015	2016	2017	2018	2019	2020	2021
VSLY	283 194 199	332 099 048	355 222 825	330 112 118	347 493 710	364 799 292	414 679 348	373 741 877	307 961 134

aged 65-74 years, indicating a significant loss of potential life years in this age group (42). In patients with grade 1 tumors, the years lost due to prostate cancer ranged from 11.0 to 1.2 in the youngest and oldest age strata, respectively (43). Ten years of remaining life expectancy was reached between 68 and 76 years in Europe and the United States, with varying ratios of additional diagnoses/avoided deaths (44). Globally, prostate cancer causes a cumulative loss of expected life years of around 90,000 per annum in the UK and worldwide. The number of years of potential life lost due to prostate cancer deaths is projected to increase by 226.1% from 291,853 in 2004 to 951,753 in 2050 (45). These studies highlight the significant premature mortality burden associated with prostate cancer. The YPLL due to prostate cancer underscores the need for effective screening, early detection, and improved treatment strategies to reduce the impact of this disease on life expectancy and public health. Prostate cancer screening can be cost-effective when limited to two or three screens between ages 55 to 59 years, with a predicted lifetime mortality reduction of 13%. This reduction in mortality could potentially decrease the YPPLL associated with prostate cancer (46). These findings underscore the substantial impact of prostate cancer on the productive years of life, particularly among younger patients. The increasing YPPLL due to prostate cancer highlights the importance of early detection, effective treatment, and potential screening programs to reduce the burden of this disease on individuals and society.

The disability-adjusted life years (DALYs) lost due to prostate cancer provide a comprehensive measure of the disease's impact by combining years of life lost due to premature mortality and years lived with disability. Globally, prostate cancer contributed significantly to the total cancer burden, accounting for an estimated 1693 million years of healthy life lost, which is 18-50% of the total cancer burden worldwide (47). In Tunisia, for instance, the burden of prostate cancer in 2017 was high, with 6548 DALYs lost due to the disease (48). In Europe, prostate cancer was responsible for 10.2% of the lost DALYs in a large sample of middle-aged and older adults, indicating its substantial impact on the population's health (49). In Norway and Bulgaria, prostate cancer was a major contributor to DALYs, representing 54% and 45% of the totals, respectively (47). Spain also saw a significant impact, with 61% of its cancer-related DALYs being due to prostate cancer (50). The substantial burden of prostate cancer on global and European health, necessitates continued efforts in prevention, early detection, and effective treatment to reduce its impact on DALYs.

Conclusions

The study's findings indicate a significant and escalating burden of prostate cancer in Slovakia, characterized by increased incidence and mortality rates. This trend underscores the need for robust healthcare policies and management strategies tailored to the Slovak demographic. The economic analysis revealed substantial direct and indirect costs, highlighting the financial impact on both the healthcare system and the broader society. The evolving patterns in diagnosis and treatment suggest improvements in diagnostic and medical practice, but also point to the necessity for more accessible and advanced options. Enhanced screening programs and public health initiatives focusing on awareness and early detection are crucial in addressing this growing concern. Overall, the study provides comprehensive insights into the prostate cancer landscape in Slovakia, offering valuable information for policymakers and healthcare providers. It emphasizes the importance of a multi-faceted approach encompassing efficient resource allocation, patient education, and improved clinical practices to mitigate the impact of prostate cancer. The findings also lay a foundation for further research, particularly in optimizing diagnostic and treatment protocols and exploring preventive measures. The study's outcomes are instrumental in shaping future strategies to improve prostate cancer management and care in Slovakia.

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