Rīgas Stradiņa Universitāte

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THE ANALYSIS OF BASIC EPIDEMIOLOGY AND GENETIC CHARACTERISTICS OF PROSTATE CANCER IN LATVIA

Summary of the Doctoral Thesis
for obtaining the degree of a Doctor of Medicine

Speciality – Surgery

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SUMMARY

Prostate cancer is a common medical condition throughout the world. In many countries of the world, prostate cancer is the leading type of cancer by incidence and the second after lung cancer by mortality. Prostate cancer is morphologically, genetically, and clinically heterogeneous disease, and its clinical progress, response to therapy, and prognosis are directly dependent on its heterogeneous nature.

Despite the multitude of studies devoted to prostate cancer worldwide, as well as some studies that were performed in Latvia, the information about its epidemiological trends in Latvia is incomplete and outdated.

Even though studies were conducted about the genetic features of inherited prostate cancer in Latvia, insufficient comparative data are available about the familial and sporadic prostate cancer according to the criteria of survival rates, age, T stage, and tumour cell grade.

The gene *CHEK2* participates in cell repair and acts as a tumour suppressor. The del5395 mutation of *CHEK2* has been linked to elevated risk of prostate cancer in several Central and Eastern European studies. There is a lack of data about the effect of del5395 mutation in *CHEK2* on the development of prostate cancer in Latvian population.

The goal of this study was to perform a population-based study of trends in prostate cancer epidemiology in Latvia between the years 1990 and 2014, to compare familial prostate cancer with sporadic prostate cancer in Latvia, and to investigate the effects of del5395 mutation in *CHEK2* gene on the development of prostate cancer cases in Latvia.

The study results indicate that the incidence, prevalence, and mortality due to prostate cancer in Latvia have increased from year 1990 to 2014. The largest increase in the incidence of prostate cancer was observed in the population under 60 years of age. Also, the largest increase in the prevalence of

prostate cancer was observed in the population under 60 years of age. The mortality due to prostate cancer decreased in the populations that were 70–79 and 80 + years of age. The 5, 10, and 15 year survival rates improved in the considered time period, while the share of unspecified (TX) stage decreased, and the share of early stages (T1 and T2) increased. The mortality of patients in Latvia during the first year after diagnosis of prostate cancer has decreased in the considered time period.

The familial type of prostate cancer had statistically significantly higher survival rate and earlier start of disease than the sporadic type of prostate cancer, but no differences were found in the T stages and the tumour cell grade.

The del5395 mutation of *CHEK2* gene is the common founder mutation in Latvia, but no statistically significant effect of this mutationon on the risk of prostate cancer development was identified in the Latvian population.

CONTENTS

ABBREVIATIONS USED

AAPC	Average Annual Percent Change
APC	Annual Percent Change
USA	United States Of America
BRCA1	Breast Cancer 1
BRCA2	Breast Cancer 2
CHEK2	Checkpoint Kinase 2
CSS	Cancer-Specific Survival
DNA	Deoxyribonucleic Acid
FG	Family Group
IARC	International Agency for Research on Cancer
CRC	Colorectal Cancer
CUH	Clinical University Hospital
BC	Breast Cancer
OR	Odds Ratio
OS	Overall Survival
PCR	Polymerase Chain Reaction
p.y.	Person-Years
PLCO	Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial
HPC	Hereditary PC
PSA	Prostate Specific Antigene
PCL	Prostate Cancer Lethality
PC	Prostate Cancer
SD	Standard Deviation
SEER	Surveillance, Epidemiology and End Results

SG	Sporadic PC Group
SSM	Share of Specific Mortality
ICD-10	International Statistical Classification of Diseases
CI	Confidence Interval
TP53	Tumour Protein P53
TRUS	Transrectal Ultrasonography
TURP	Transurethral Prostatectomy

1. INTRODUCTION

1.1. Relevance of the problem

Prostate cancer (PC) is generally recognized as an important medical problem worldwide. The global epidemiological trends of PC have been widely studied. PC is the fourth most common cancer by worldwide incidence, with 1.1 million new cases annually (7.9% of all cancers), and it is the eight most common cancer-related cause of death, with 30 7000 deaths (3.7% of the total mortality due to cancer) (Ferlay et al., 2015; Ferlay et al., 2013). Among males, PC was the second most frequently diagnosed cancer in year 2012 (15% of all newly diagnosed cancers) after lung cancer, and the fifth most common cancer-related cause of death for males (6.6% of all cancer deaths) after lung, liver, stomach, and colorectal cancers (Ferlay et al., 2015; Ferlay et al., 2013). The incidence of PC shows a trend of long-term growth in most countries of the world, even though in some regions – Finland, New Zealand, North America, and Australia the incidence of PC has stabilized or even decreased over the last two decades (Center et al., 2012). The mortality due to PC tended to decrease over the last two decades in many regions – North America, Australia, New Zealand and Oceania, most of Northern Europe and Western Europe (Center et al., 2012), which was attributed to early detection and improved treatment (Collin et al., 2008; Etzioni et al., 2008).

A multitude of studies worldwide have been devoted to the genetic features of PC. These data indicate that about 10% of PC cases can be considered to be hereditary, and hereditary PC typically develops 6–7 years earlier than sporadic PC (Hemminki, 2012). The criteria for identification of hereditary PC are the following: at least three cases of PC among first-degree relatives or PC in three sequential patrilinear or matrilinear generations, or cases of PC afflicting at least 2 biological relatives who are younger than 55

years of age (Carter et al., 1993). The criteria for suspected hereditary or familial type PC are the following: two cases of PC among first degree relatives or one case of PC among relatives who are younger than 55 years of age.

Approximately 100 genes are known that can affect the development of PC (Eeles et al., 2013). The gene *CHEK2* is localized in the long shoulder of 22nd chromosome and is involved in cell repair, acting as a tumour suppressor. It is activated by exposure to toxic factors when the cellular DNA is damaged, resulting in the arrest of cell division until the time when DNA repair is attempted by DNA repair enzymes. In the case if DNA repair is not successful, apoptosis occurs (Bartek and Lukas, 2003). The effect of del5395 mutation in *CHEK2* gene on the risk of PC development has been investigated in Poland, Czech Republic, Slovakia, Belarus (Cybulski et al., 2006; Cybulski et al., 2013; Walsh et al., 2006), and it has been proposed that del5395 mutation may affect the risk of PC development in Ukraine, Russia, Balkan region, and the Baltic states (Cybulski et al., 2006).

Despite the large volume of research results available about PC worldwide, the data about epidemiological trends of PC in Latvia are limited to the time period from 1980 until 2004 (Lietuvietis, 2006; Lietuvietis et al., 2002), and there is a lack of more recent epidemiological information about PC in Latvia.

Even though studies have been conducted about the genetic features of hereditary PC in Latvia (Abele et al., 2011), no comparative data are available with regard to the local rates of survival, patient age, disease stages, and the tumour cell grade in familial and sporadic PC in Latvia.

The role of del5395 mutation in *CHEK2* gene for the development of PC has been studied in several Central and Eastern European countries in populations of Slavic ethnicity, but there is a lack of data about the effect of this mutation on development of PC in the population of Latvia.

1.2. Goals of the work

To perform analysis of basic prostate cancer epidemiology parameters, familial prostate cancer and del5395 mutation of *CHEK2* gene in Latvia for the time period from year 1990 until 2014.

1.3. Tasks to be accomplished

1. To determine the total and age-resolved dynamics of PC incidence, prevalence, and mortality in Latvia from year 1990 until 2014.
2. To determine the overall and cancer-specific survival of patients with PC in Latvia from year 1990 until 2014.
3. To determine the relative dynamics of T stages in Latvia from year 1990 until 2014.
4. To compare familial PC and sporadic PC according to the criteria of patient age, survival rate, and tumour cell grade.
5. To determine the prevalence of del5395 mutation of *CHEK2* gene in the Latvian population and to establish the effect of this mutation on the development of PC (as well as the risk of ovarian, breast, and colorectal cancer).

1.4. Working hypotheses

1. The incidence, prevalence, and mortality of PC has increased from year 1990 until 2014, while the survival rate has improved, and the fraction of late diagnoses has been reduced.
2. The patient age, survival rate, and tumour cell grade in familial PC and sporadic PC are different.

3. The del5395 mutation of *CHEK2* gene is the founder mutation in the population of Latvia, the presence of this mutation increases the risk of PC development (as well as the risk of ovarian, breast, and colorectal cancer).

1.5. Scientific merit of the study

This work contains a broad population-based analysis of PC in Latvia from the year 1990 until 2014, with the following epidemiological parameters of PC evaluated:

- incidence, prevalence, mortality – both overall and age-specific;
- overall and cancer-specific survival rates both during the entire analyzed time period, as well as according to T stages (separately considering the data for early and late T stages), and according to the year of first diagnosis;
- the fraction of PC-specific mortality;
- lethality of PC;
- changes in first year mortality due to PC;
- changes in the fraction of T stages.

These data supplement and update the previously available information about the trends of PC epidemiology in Latvia.

This is the first study of differences between familial PC and sporadic PC in Latvia, according to the patient age, survival rates, and the tumour cell grade.

It was found that the del5395 mutation of *CHEK2* gene has a founder effect in Latvia.

This is the first evaluation of the link between del5395 mutation of *CHEK2* gene and the risk of PC development (as well as the risk of ovarian, breast, and colorectal cancer) in Latvia.

2. MATERIAL AND METHODS

The study consists of three parts: 1) description and analysis of PC epidemiology in Latvia; 2) comparison of familial and sporadic PC in Latvia; 3) establishing the link between the del5395 mutation of *CHEK2* gene and PC development in Latvia.

The study was performed at the Oncology Institute of Rīga Stradiņš University. The study was authorised by the Clinical Research Ethics Committee of the Research Society at P. Stradins Clinical University Hospital (authorisation No. 151209-5L).

2.1. Description and analysis of PC epidemiology in Latvia

2.1.1. Study group

A retrospective cohort study was performed to analyze the changes of epidemiological and other parameters of patients with PC in the time period from year 1990 until 2014. This study was based on information about the persons registered during this time period at the cancer patient database of the Latvian Centre for Disease Prevention and Control. The information about 16 902 persons diagnosed with PC according to ICD-10 was included in the study.

The necessary information about the male population of Latvia, changes of age structure, as well as the total mortality data for each year was obtained from the database of Central Statistical Bureau of Latvia, available on the Internet at http://www.csb.gov.lv/dati/statistikas-datubazes-28270.html.

The obtained data were binned according to the age structure in groups of 10 years, while checking for adequate homogeneity of each age group. The age-specific parameters were analysed in the following age groups: < 60; 60–69; 70–79; 80 + years, due to the low incidence of PC in the youngest and oldest age groups.

The prostate cancer stages T1a, T1b, T1c were combined in stage T1. The prostate cancer stages T2a, T2b, T2c were combined in stage T2. The prostate cancer stages T3a, T3b were combined in stage T3. The stages were combined due to the similar prognosis for the respective patients. The stages of PC that were described as TX and those cases of PC where the T stage was not indicated were combined as stage TX.

The early PC stages T1 and T2 were grouped together as (T1 + T2), while the locally advanced stages T3 and T4 were grouped together in the second category as (T3 + T4). The occurrence of the aforementioned stages among newly diagnosed cases per year was calculated, and the survival rates were analyzed.

2.1.2. Statistical methods

The statistical average, median, and mode of age of first diagnosis and death of patients was calculated. The data are presented as the average age and standard deviation. In order to prevent fluctuations of the annual values used for comparison of age and survival rates, the average values of the first and last three years were used at the beginning and end of the considered time period, and the Mann-Whitney U test was used for quantitative data, while the Chi-squared test was used for qualitative parameters.

The specific epidemiological parameters of PC: the incidence, prevalence, and mortality were calculated for 100 000 person-years according to methods that are widely described in many literature sources and textbooks. Further comparison of data was based on age-standardized parameters that were calculated by using the world standard population 2000 (Ahmad et al., 2001) and the method of direct standardization.

The mortality due to PC was characterised by the folowing parameters:

- The share of PC-specific mortality – the number of deaths due to PC relative to the total number of deaths in Latvia during each year;
- Lethality of PC– the number of deaths due to PC relative to the prevalence of PC.

The Joinpoint regression method was used for the evaluation of incidence, prevalence, and mortality trends during the study period. The age-specific parameters were compared among all groups in pairs, with the purpose of detecting the presence of statistically similar (parallel) trends in age groups, or identifying differences.

The analysis of survival rates was performed with the Kaplan–Meier method, calculating the overall 5, 10, 15, and 20-year survival rates, as well as survival rates separated by stages of the disease, while excluding from the analysis any cases of PC that were diagnosed at the time of death (n = 864). The cancer-specific survival rate was calculated for cancer patients with the cause of death reported as C61 (ICD-10 classification), while ignoring other causes of death. While evaluating the link between the survival rates and year of diagnosis, the results were averaged over three-year periods, in order to suppress annual fluctuations. The survival rate graphs were analysed for statistically significant differences by using the log-rank test.

During the evaluation of contributions by T stages and the early or locally advanced stages, the results were also averaged over three-year periods, in order to suppress annual fluctuations.

2.2. Comparison of the sporadic and familial PC

2.2.1. The study group

There were 16 229 new cases of PC registered at the Centre for Disease Prevention and Control in the time period from 1990 until 2014. The family history survey form was completed at the Oncology Institute of Rīga Stradiņš University by 1175 PC patients of all stages (with PC diagnosed between the years 2000 and 2012). The inclusion criteria were: histologically verified PC, signed consent form for the study. Exclusion criteria: other oncological diseases, unknown family history, or the mental condition of the patient not adequate for giving informed consent.

The information about T stage and Gleason score for patients who died during the study was obtained from the database of the Centre for Disease Prevention and Control. The observation period was continued until February, 2013.

Out of the 1175 PC patients, only 12 matched the criteria for hereditary PC and 203 corresponded to familial PC. Taking into account the fact that only few cases matched the criteria for hereditary PC, thus preventing adequate statistical analysis, the groups of hereditary PC and familial PC were combined in one family group (FG) with 215 PC patients, comprising 18.3% of all PC patients in this study. On the other hand, the group of sporadic PC (SG) included 960 PC patients, comprising 81.7% of all PC patients in the study.

The Gleason score was available for 622 patients.

2.2.2. Statistical methods

The T stages and Gleason scores for FG and SG were compared by using the Chi-squared test; the patient age at the time of diagnosis was compared between the groups by using the t-test. The cancer-specific survival

rate between the groups was analysed by using the Kaplan–Meier method; the log-rank test was used for evaluating statistically significant differences between the survival rate graphs.

2.3. Analysis of the *CHEK2* gene

2.3.1. The study group

Volunteers for the participation in the study were recruited among breast cancer (BC), colorectal cancer (CRC), ovarian cancer (OC), and prostate cancer (PC) patients at the Oncology Institute of Rīga Stradiņš University, Latvian Oncology Centre, and Daugavpils Oncological Hospital in the time period from year 2010 until 2012. A total of 1824 patients with various types of cancer took part in the study. The BC group included 438 patients, the CRC group – 568 patients, OC group – 399 patients, and the PC group – 419 patients.

Two study groups of volunteers were recruited between the years 2010 and 2012 at the Outpatient Center, Occupational Health Center, and Urology Center of Pauls Stradins Clinical University Hospital, comprising 531 people involved in the radioactive contamination clean-up after Chernobyl disaster, and 444 geriatric patients (older than 60 years).

The control group was recruited from 526 healthy male blood donors from the blood bank of Pauls Stradins Clinical University Hospital, who volunteered for the study.

All study participants gave written consent for DNA analysis.

2.3.2. Isolation of DNA

DNA was isolated from a 2 ml venous blood sample of each study participant with the Qiagen FlexiGene DNA Kit (250) according to the user's manual.

DNA from tissue samples was isolated with the Qiagen QIAamp DNA mini Kit (250) according to the user's manual. The quality of isolated DNA was verified on 1% agarose gel, and the concentrations were determined with Nanodrop 1000 spectrophotometer (Thermo Fisher Scientific).

2.3.3. Determination of the del5395 mutation

The del5395 mutation was determined by using PCR, and the positive samples were verified by sequencing.

The multiplex PCR was performed with previously used primers (Cybulski et al., 2006), which were complementary to the DNA sequences at introns 8 and 10 of the *CHEK2* gene. The normal alleles (without deletion) amplified 379 bp and 522 bp long fragments. In the case of deletion, a third fragment with 450 bp was amplified (due to the forward primer of exon 8 and reverse primer of exon 10). The PCR products were separated on a 1% agarose gel.

2.3.4. DNA sequencing

DNA sequencing was performed with ABI PRISM 3130 Genetic Analyzer, using the Big Dye v3.1 Sequencing kit according to the user's manual. The forward primer for exon 8 or the reverse primer for exon 10 were used for the sequencing reactions.

2.3.5. Statistical methods

All cancer groups, the Chernobyl group and the geriatric group were compared with the control group comprising healthy blood donors, using the Fisher's exact test. The odds ratio (OR) and 95% confidence intervals (CI) were calculated.

In all of the cases, the differences were evaluated at the statistical significance level of $p < 0.05$ or 95% (the differences were recognized as statistically significant when the reliability intervals did not overlap).

Data analysis was performed with MS Excel, SPSS version 22.0, Joinpoint Regression Program version 4.04, and R version 3.0.3. (Bioconductor, http://www.bioconductor.org) software.

3. RESULTS

There were 16 229 new cases of PC diagnosed between years 1990 and 2014. The average age of patients at the time of PC diagnosis during the entire considered time period was 70.0 years (SD 8.6 years). The average age of PC patients at the time of diagnosis was 71.1 years (SD 9.1 years) over the time period from 1990 to 1992, then slightly decreased and reached 69.0 years (SD 9.0 years) ($p < 0.001$) between the years 2012 and 2014. More detailed information about the average age of patients at the time of PC diagnosis during the considered time period can be found in Figure 3.1.

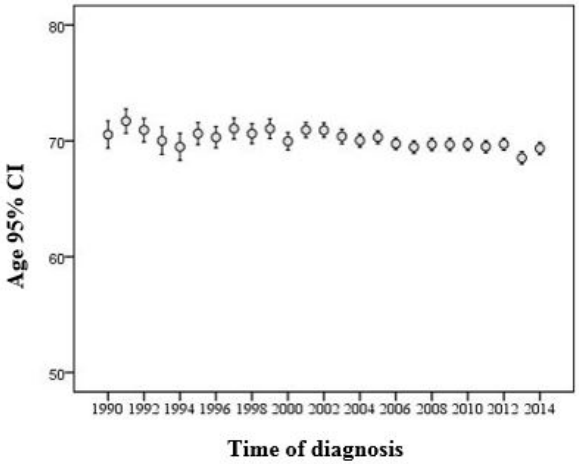

Figure 3.1 **The average age of PC patients at the time of diagnosis**

The total number of deaths among PC patients was 9852 during the time period between year 1990 and 2014, while PC was identified as the cause of death in 6731 cases. The average age of death for PC patients was 75.1 years (SD 8.9 years) over the entire considered time period. The average age of death

for PC patients from year 1990 until 1992 was 74.6 years (SD 9.3 years), then the age of death increased and reached 76.3 years (SD 8.6 years) ($p < 0.001$) in the time period from year 2012 until 2014. The average age of death due to PC in the entire considered time period was 74.0 years (SD 8.9 years). The average age of death due to PC from year 1990 until 1992 was 73.4 years (SD 92 years), then it increased and reached 75.7 years (SD 8.8 years) in the time period from year 2012 until 2014 ($p < 0.001$). Detailed information about the average age of death in the considered time period is shown in Fig. 3.2.

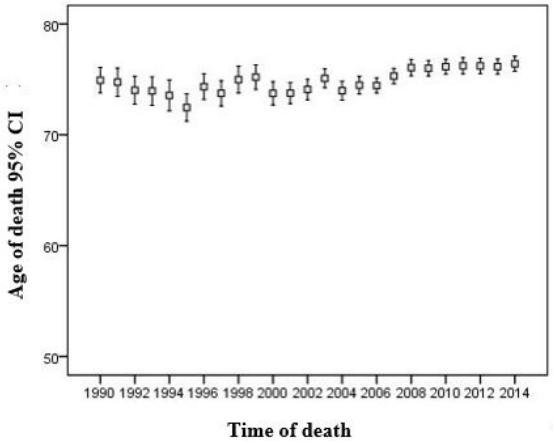

Figure 3.2 **The average age of death for PC patients**

3.1. Incidence

There were on average 270 new cases of PC diagnosed per year at the beginning of the considered time period. Starting in 1994, the number of new PC cases sharply increased until 2005, when the number of new PC cases had increased by 3.5 times. The increase in the number of new PC cases has slowed down after 2005, reaching on average of 1070 new PC cases per year at the end

of the considered time period, at four times the rate in 1994. More detailed information about the changes in number of new PC cases in the considered time period is presented in Fig. 3.3.

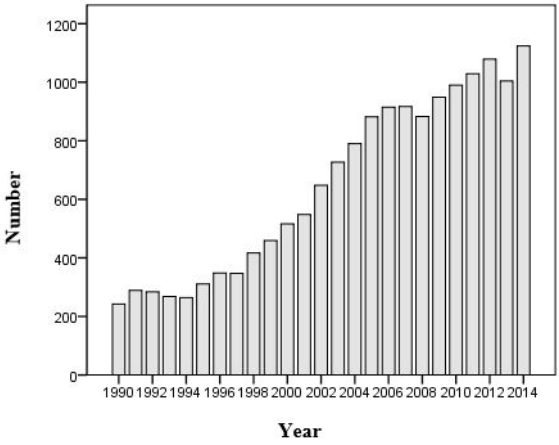

Figure 3.3 **The number of new PC diagnoses per year**

The largest number of new PC cases in the considered time period was found in patients who were 70–79 and 60–69 years old (the number of new PC cases was 6440 (40%) and 5783 (36%), respectively). There were 2153 (13%) new cases of PC diagnosed in men older than 80 years during the considered time period; the smallest fraction of new PC cases were diagnosed among patients younger than 60 years of age (1853 (11%)).

The incidence of PC in the year 1990 was 19.5 per 100 000 person-years, representing the lowest incidence in the considered time period. The increase of incidence was small until year 1994, and not considered statistically significant. There was a rapid increase of PC incidence from year 1994 until 2005, at the APC rate of 12.4, and PC incidence reached 85.5 (per 100 000 p.y.) in 2005. The increase of PC incidence slowed to 4.0 APC from year 2005 to

2014, but remained statistically significant also in this time period.The incidence of PC reached the highest value in 2014, at 122.7 (per 100 000 p.y.). During the entire considered time period, AAPC was 7.4 (95% CI 6.1; 8.7). More details about the incidence of PC are given in Figure 3.4.

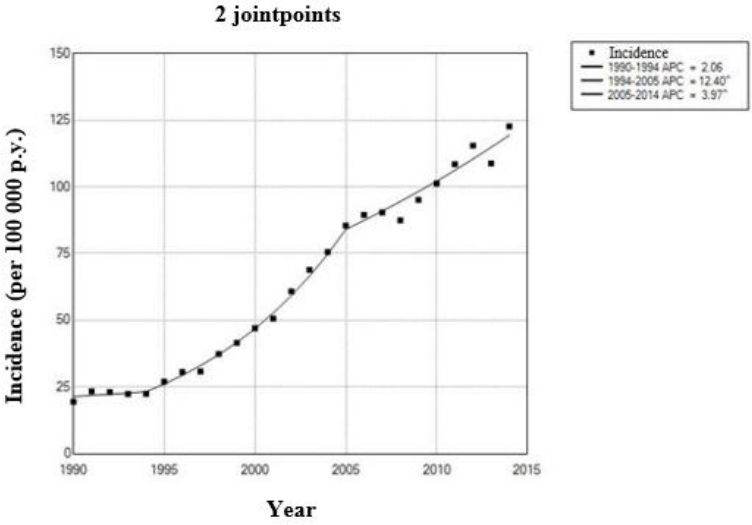

Figure 3.4 **The changes of PC incidence by year**

The trends of standardized incidence are presented in Table 3.1.

Table 3.1

The trends of prostate cancer incidence, prevalence, and mortality in Latvia from year 1990 until 2014 (jointpoint analysis).

	Trend 1		Trend 2		Trend 3		AAPC
	Years	APC	Years	APC	Years	APC	1990–2014
Incidence	1990–1994	2.1	1994–2005	12.4*	2005–2014	4.0*	7.4* (6.1; 8.7)
Standardized incidence	–	1.3	–	10.0*	–	2.8*	5.8* (4.8; 6.8)
Age group							
< 60	1990–2014	10.3*	–	–	–	–	10.3* (9.3; 11.3)
60–69	1990–1997	3.4*	1997–2006	13.3*	2006–2014	3.4*	7.0* (5.8; 8.2)
70–79	1990–2005	7.9*	2005–2014	– 0.27	–	–	5.0* (3.3; 6.8)
80 +	1990–2003	8.4*	2003–2014	– 0.42	–	–	4.9* (3.3;6.6)
Prevalence	1990–1997	6.8*	1997–2006	13.9*	2006–2014	10.3*	10.6* (9.8 – 11.4)
Standardized prevalence	1990–1998	6.0*	1998–2005	12.0*	2005–2014	8.0*	8.5* (7.2; 9.8)
Age group							
< 60	1990–1998	4.1	1998–2014	15.9*	–	–	11.8* (9.7; 13.9)
60–69	1990–1998	5.0	1998–2012	13.3*	2010–2014	8.0*	10.2* (8.9; 11.5)
70–79	1990–1996	3.1*	1996–2005	10.8*	2005–2014	7.6*	7.6* (6.7; 8.5)

Continuation of Table 3.1

	Trend 1		Trend 2		Trend 3		AAPC
	Years	APC	Years	APC	Years	APC	1990 – 2014
80 +	1990–2006	8.7*	2006–2014	1.8*	–	–	6.4* (5.9; 6.8)
Mortality	1990–2006	6.6*	2006–2014	2.8*	–	–	5.3* (4.4; 6.2)
Standardized mortality	1990–2006	4.8*	2006–2014	─ 0.5	–	–	3.0* (2.1; 3.9)
Age group							
< 60	1990–2014	1.8*	–	–	–	–	1.8* (0.2; 3.5)
60–69	1990–2014	2.5*	–	–	–	–	2.5* (1.5; 3.5)
70–79	1990–2006	4.7*	2006–2014	─ 2.0	–	–	2.4* (1.4; 3.4)
80 +	1990–2007	6.2*	2007–2014	─ 0.6	–	–	4.2* (2.8; 5.6)

APC – annual percent change; AAPC – average annual percent change

* APC or AAPC was statistically significantly different from 0

The patient group who were < 60 years of age did not show major fluctuations of the increase of incidence over the considered time period, with AAPC 10.3 (95% CI 9.3; 11.3). The age group of 60–69 years experienced a small but statistically significant growth of PC incidence in the time periods from year 1990 to 1997 and from year 2006 to 2014, with APC 3.4. The largest increase of incidence in the considered time period among all age groups was observed in the group of 60–69 years old patients between the years 1997 and 2006, with APC 13.3. The group of 70–79 years old patients had a statistically

significant increase of PC incidence from year 1990 until 2005, with APC 7.9. Starting in year 2005, the group of 70–79 years old patients showed a statistically insignificant decrease of PC incidence, with APC ─ 0.27. Similar observations were also made for the group of patients who were older than 80 years, where a statistically significant increase of PC incidence with APC 8.4 was observed between the years 1990 and 2003, followed by a statistically insignificant reduction of PC incidence until year 2014, with APC ─ 0.42. Comparison of the incidence dynamics among age groups showed similar trends in the groups of patients who were 70–79 years old and over 80 years old, as shown in detail in Figure 3.5, while the trends were different in the groups of patients who were 60–69 years and 70–79 years old, as shown in detail in Fig. 3.6.

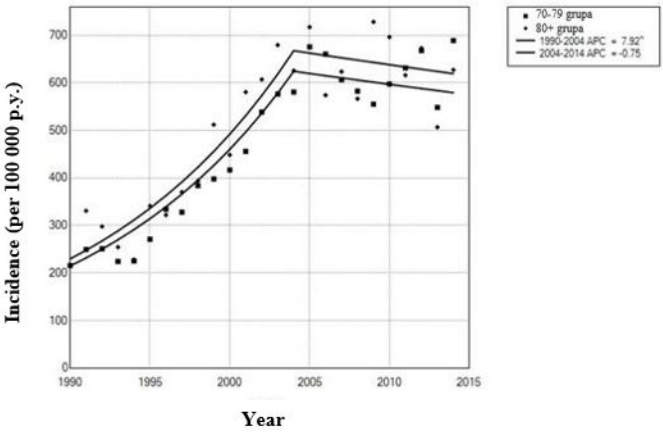

Figure 3.5 **Comparison of the PC incidence trends in age groups of 70–79 and 80 + years**

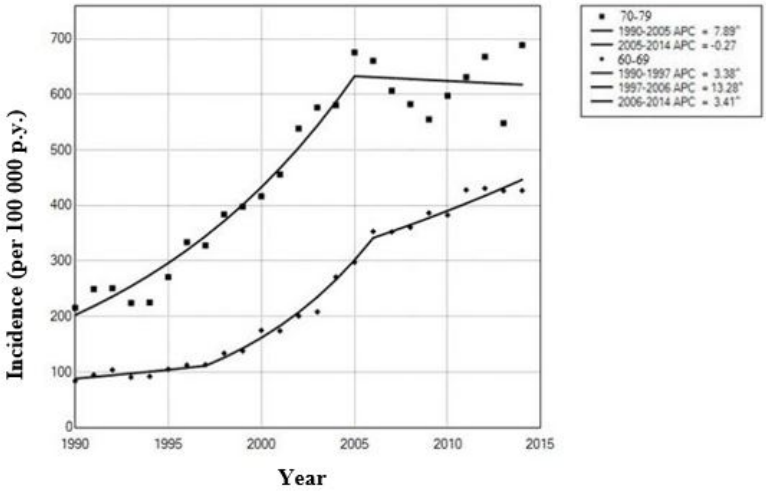

Figure 3.6 **Comparison of the PC incidence trends in age groups of 60–69 and 70–79 years**

More details about the PC incidence and age-specific incidence trends is shown in Table 3.1.

3.2. Prevalence

The number of PC patients at the beginning of the considered time period did not exceed 1 thousand. However, the number of PC patients rapidly increased from the year 1997 until 2006, and reached 3.6 thousand patients in 2006. The growth in the number of PC patients slowed down between year 2006 and 2014, and the total number of patients reached 7 thousand at the end of the considered time period; thus, the number of patients has increased by a factor of seven over the entire considered time period. Divided by age groups, the largest number of PC patients was among 70–79 years old men (3 thousand, 43%) and among 60–69 years old men (2 thousand, 29%).

The prevalence of PC in the year 1990 was 72.1 (per 100 000 p.y.), representing the lowest value in the considered time period. A small but statistically significant increase of incidence was observed from the year 1990 until 1997 (APC 6.8), and the prevalence of PC in the year 1997 was 113.0 (per 100 000 p.y.). The rate of increase for PC prevalence doubled from 1997 to 2006, with APC 13.3, and reached 358.2 (per 100 000 p.y.) in 2006. The growth of PC prevalence somewhat slowed down from the year 2006 to 2014, with APC 10.3, with the prevalence equal to 770.6 (per 100 000 p.y.) in 2014. More details about PC prevalence are shown in Fig. 3.7.

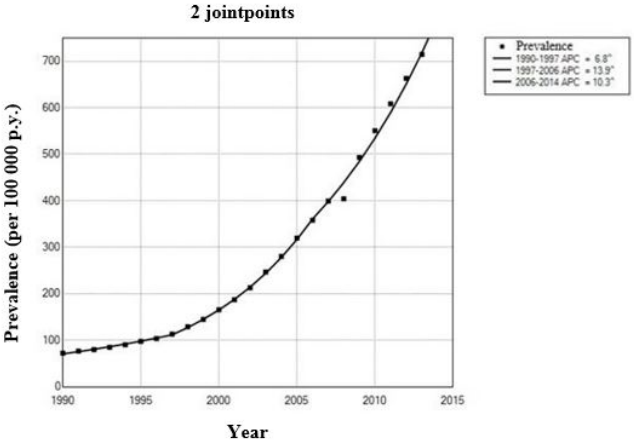

Figure 3.7 **The changes of PC prevalence by year**

The trends of standardized prevalence values are shown in Table 3.1.

The age-specific prevalence in the age group of < 60 years showed no statistically significant increase between the years 1990 and 1998, but a sharp rise occurred from year 1998 until 2014, with the greatest APC 15.9 among all age groups. As a result, this age group experienced the largest growth of age-specific prevalence over the considered time period, with AAPC 11.8

(95% CI 9.7; 13.9). The age-specific prevalence in the age group of 60–69 years showed no statistically significant growth between the years 1990 and 1998, while a sharp increase of age-specific prevalence occurred between the years 1998 and 2014, resulting in the second largest AAPC 10.2 (95% CI 8.9; 11.5) for the age group of 60–69 years during the considered time period. The age-specific prevalence in the age group of 70–79 years showed statistically significant growth over the entire considered time period, with APC fluctuations from 3.1 to 10.8, with the AAPC 7.6 (95% CI 6.7; 8.5). The age-specific prevalence in the age group of 80 + years during the entire considered time period showed a statistically significant growth, with APC fluctuations from 1.8 to 8.7, with AAPC 6.4 (95% CI 5.9; 6.8). The analysis of age-specific prevalence showed different trends in all age groups. More details about the prevalence trends in age groups of 60–69 years, 70–79 years, as well as 80 + years can be found in Figures 3.8. and 3.9., respectively.

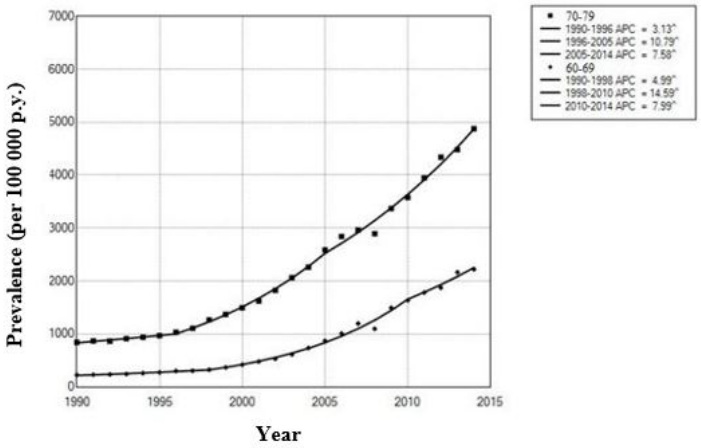

Figure 3.8 **Comparison of prevalence trends in age groups of 60–69 and 70–79 years**

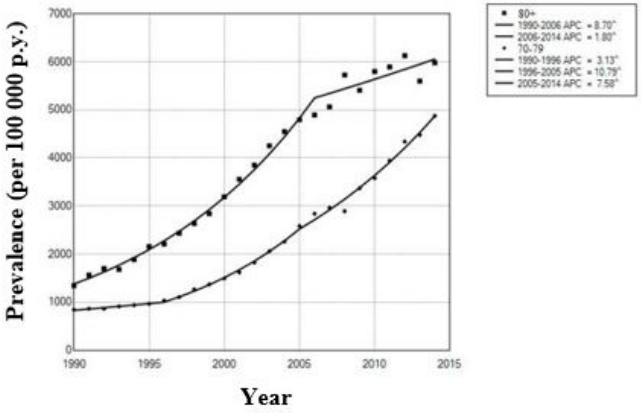

Figure 3.9 **Comparison of prevalence trends in the age groups of 70–79 and 80 + years**

More detailed data about the trends of PC prevalence and age-specific prevalence are shown in Table 3.1.

3.3. Mortality

There were on average 230 deaths per year due to PC at the beginning of the considered time period. The number of deaths among PC patients rapidly increased after 1998, up to three times the initial rate at the end of the considered time period, reaching on average 600 deaths per year. More detailed data about the number of deaths is shown in Fig. 3.10.

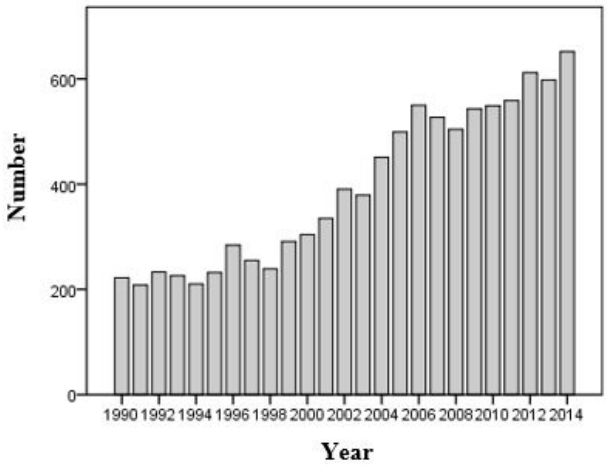

Figure 3.10 **The number of deaths among PC patients**

At the beginning of the considered time period, there were on average 180 deaths per year due to PC among the patients. Starting from the year 1998, there was a rapid increase in the number of deaths due to PC, doubling until the end of the considered time period, and reaching an average of 370 deaths due to PC per year. More detailed data about the number of deaths due to PC are shown in Fig. 3.11.

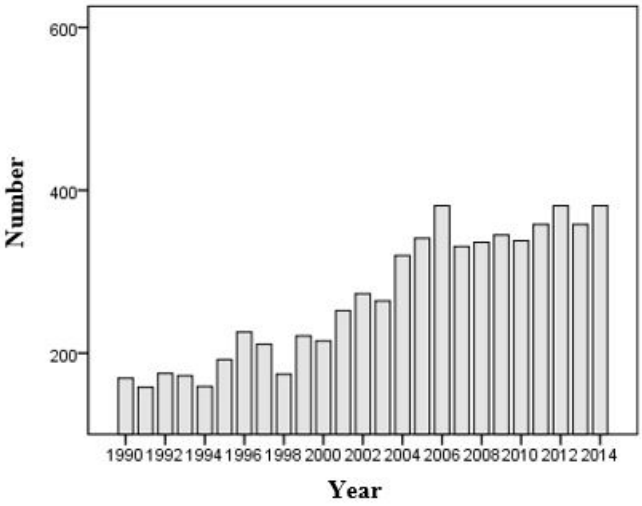

Figure 3.11 **The number of deaths due to PC**

The mortality of PC was 13.6 (per 100 000 p.y.) in 1990. The mortality continued to increase at APC 6.6 until 2006 and reached 37.3 (per 100 000 p.y.). The rate of PC mortality increase slowed from the year 2006 until 2014 to APC 2.8. The PC mortality was 41.8 per 100 000 p.y. in 2014, the highest value in the considered time period. It should be noted that the standardized mortality showed a slight, statistically insignificant decrease from year 2006 until 2014, with APC ─ 0.5. However, during the entire considered time period generally there was a statistically significant increase of both mortality and standardized mortality with AAPC 5.3 (95% CI 4.4; 6.2) and 3.0 (95% CI 2.1; 3.9), respectively. More details about PC mortality are shown in Fig. 3.12.

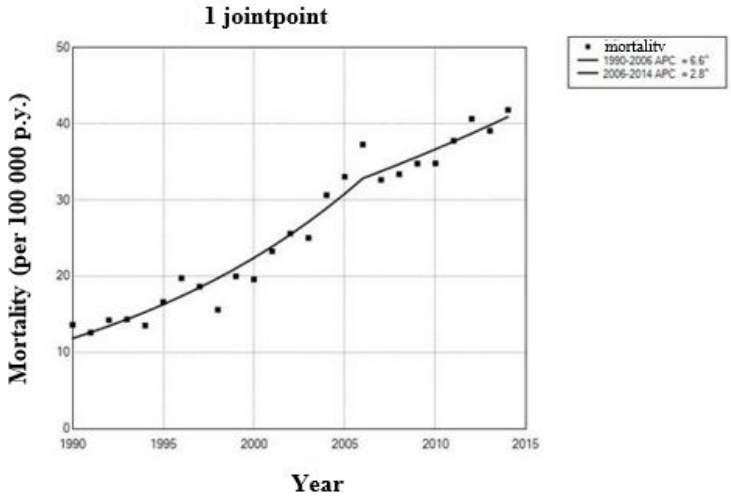

Figure 3.12 **The changes of PC mortality by year**

More details about the standardized mortality are shown in Fig. 3.13.

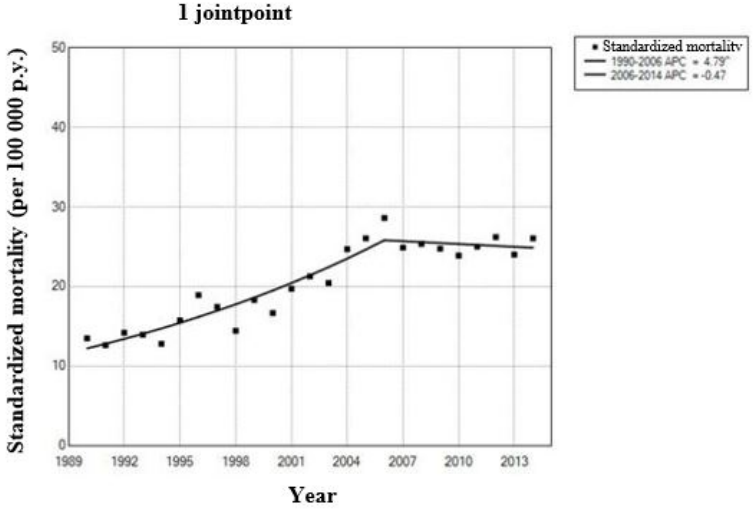

Figure 3.13 **Changes of the standardized PC mortality by year**

The trends of standardized mortality are shown in Table 3.1.

The age-specific mortality in age groups of < 60 and 60–69 years showed a stable growth over the entire considered time period, with AAPC 1.8 (95% CI 0.2; 3.5) and 2.5 (95% CI 1.5; 3.5), respectively. In turn, the age groups of 70–79 and 80 + years showed a statistically significant increase of mortality over the time periods from year 1990 to 2006 and from 1990 to 2007, respectively, followed by a statistically insignificant reduction of mortality until year 2014, with APC ─ 2.0 and ─ 0.6, respectively. By comparing the changes of mortality among the age groups, similar trends could be identified in the age groups of 60–69 and 70–79 years, as shown in Figure 3.14., and different trends occurred in the age groups of 70–79 and 80 + years, as shown in more detail in Fig. 3.15.

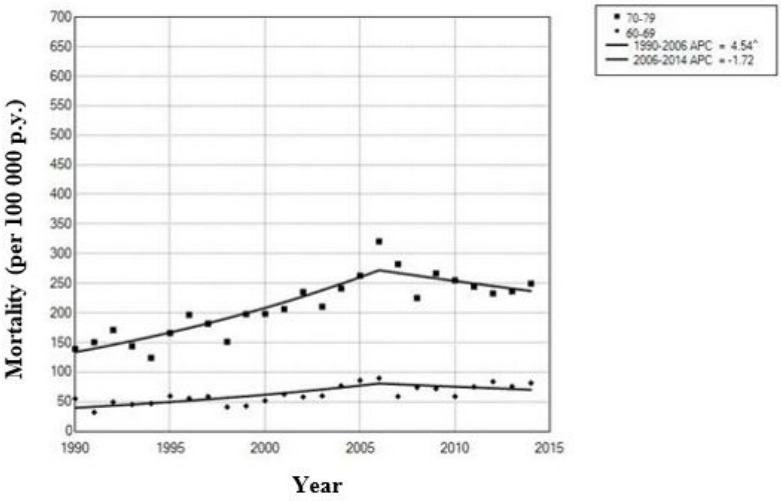

Figure 3.14 **Comparison of mortality trends in the age groups of 60–69 and 70–79 years**

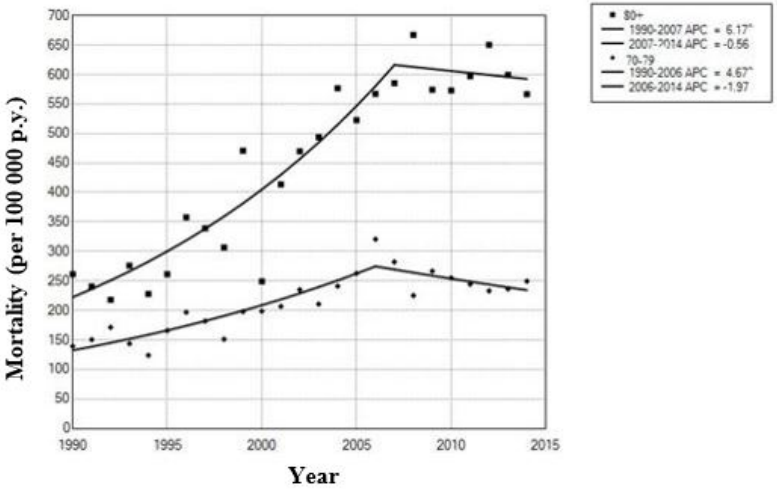

Figure 3.15 **Comparison of mortality trends in the age groups of 70–79 and 80 + years**

More details about the trends of PC mortality and age-specific mortality are shown in Table 3.1.

The PC specific share of mortality (SSM) was the lowest from year 1990 until 1995, when the SSM value was between 0.7% and 1.0%. The SSM value gradually increased after 1995, reaching 2.8% in 2014. The lethality of PC (PCL) was 69.8% in 1990, which was the highest lethality during the entire considered time period. The PCL indices remained high between the years 1990 and 1997, and were above 60%. Starting in 1998, PCL rapidly decreased, and has been around 35% since 2010, reaching 34.1% in 2014 – the lowest value during the considered time period. More details about the SSM and PCL indices of PC are shown in Table 3.2.

Table 3.2.

The PC specific share of mortality and lethality

Year	Total number of deaths in population	PC-specific share of mortality	PC lethality
1990	16 951	1.0%	19.0%
1991	17 146	0.9%	16.6%
1992	17 978	1.0%	18.2%
1993	20 462	0.8%	17.3%
1994	22 182	0.7%	15.3%
1995	20 343	0.9%	17.3%
1996	17 509	1.3%	19.2%
1997	16 715	1.3%	16.7%
1998	16 942	1.0%	12.2%
1999	16 453	1.3%	13.9%
2000	16 155	1.3%	12.0%
2001	16 537	1.5%	12.6%
2002	16 423	1.7%	12.2%
2003	15 893	1.7%	10.2%
2004	15 890	2.0%	11.1%
2005	16 601	2.1%	10.4%
2006	16 621	2.3%	10.5%
2007	16 360	2.0%	8.2%
2008	15 432	2.2%	8.4%
2009	14 539	2.4%	7.2%
2010	14 561	2.3%	6.5%
2011	13 857	2.6%	6.3%
2012	13 801	2.8%	6.2%
2013	13 518	2.7%	5.5%
2014	13 723	2.8%	5.5%

The share of postmortem PC diagnoses was 5% during the entire considered time period, and did not exceed 10%. The average mortality due to PC in the first year after diagnosis during the entire considered time period was 19%, while it was 26% at the beginning of the considered time period. The percentage of deaths due to PC during the first year after diagnosis gradually decreased since 1998, reaching on average 15% at the end of the considered time period. The share of PC patients who were actively treated (excluding the cases diagnosed postmortem) and died during the first year was 21% at the beginning of the considered time period, and 14% on average for the entire period. The share of actively treated patients who died during the first year gradually decreased since 1998, reaching on average of 10% at the end of the considered time period. More detailed data about the changes in the number of deaths due to PC are presented in Fig. 3.16.

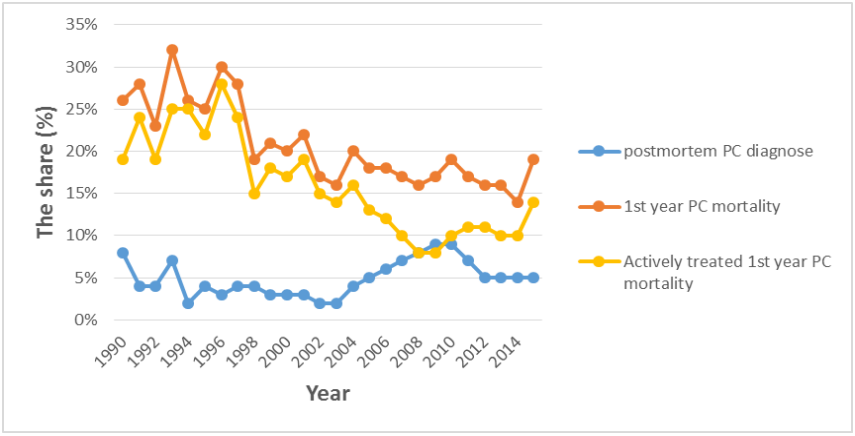

Figure 3.16 **The changes in death rate during the first year after diagnosis of PC**

3.4. Survival rate

3.4.1. Overall survival rate

The median overall survival rate of PC patients during the study period was 5.3 (95% CI 5.2; 5.5) years (Fig. 3.17.).

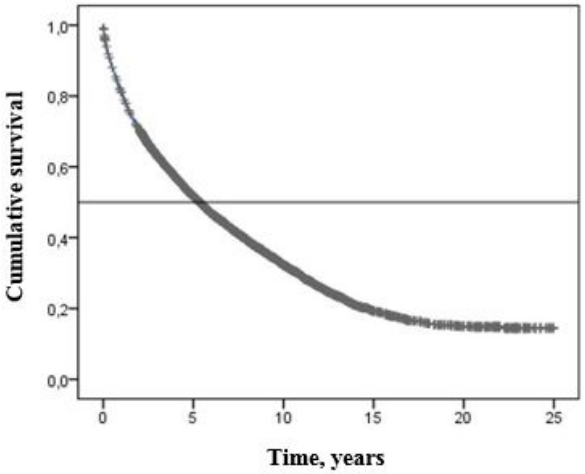

Figure 3.17 **Cumulative overall survival rate of PC patients**

The median overall survival rate by stages was: T1 stage – 11.5 (95% CI10.3; 12.7) years, T2 stage – 10.3 (95% CI9.8; 10.7) years, T3 stage – 4.2 (95% CI4.0; 4.5) years, T4 stage – 1.1 (95% CI0.9; 1.2) years, TX stage – 2.8 (95% CI2.5; 3.0) years; these differences are statistically significant ($p \leq 0.005$) (Fig. 3.18.).

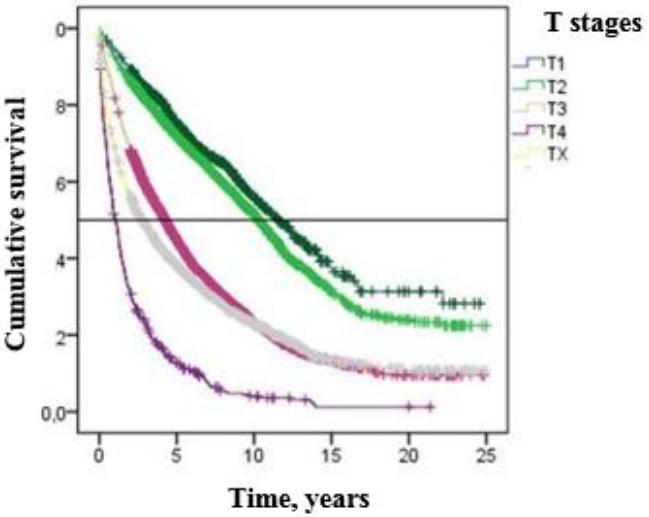

Figure 3.18 **Cumulative overall survival rate of PC patients by T stages**

More details about the overall 5, 10, 15, and 20 year survival rate by T stages are shown in Table 3.3.

Table 3.3

Overall and cancer-specific PC survival rate by T stages

Life expectancy			Total	Stages				
				T1	T2	T3	T4	Tx
5 years	OS	Percentage	51.7	74.8	71.9	44.8	12.8	38.2
		95% CI	(50.7–52.7)	(71.7–77.9)	(70.5–73.3)	(43.2–46.4)	(10.1–15.5)	(36.6–39.8)
	CSS	Percentage	63.0	89.3	83.9	55.8	16.4	49.5
		95% CI	(62.0–64.0)	(87.1–91.5)	(82.7–85.1)	(54.2–57.4)	(13.3–19.5)	(47.7–51.3)

Continuation of Table 3.3

Life expectancy			Total	Stages				
				T1	T2	T3	T4	Tx
10 years	OS	Percentage	32.3	55.8	51.7	23.1	4	22.7
		95% CI	(31.3–33.3)	(51.5–60.1)	(49.5–53.9)	(21.5–24.7)	(2.2 –5.8)	(21.1–24.3)
	CSS	Percentage	50.3	81.9	73.7	37.4	7.5	39
		95% CI	(49.1–51.5)	(78.4–85.4)	(71.7–75.7)	(35.4–39.4)	(4.8 – 10.2)	(37.0–41.0)
15 years	OS	Percentage	19.2	37.3	30.9	13.3	1.2	13.4
		95% CI	(18.0–20.4)	(31.2–43.4)	(27.6–34.2)	(11.7–14.9)	(0.0 – 2.8)	(11.6–15.2)
	CSS	Percentage	41.8	73.5	61.7	29.4	–	32.7
		95% CI	(40.2–43.4)	(66.8–80.2)	(57.6–65.8)	(26.9–31.9)	–	(30.2–35.2)
20 years	OS	Percentage	14.9	31.3	24	9.6	–	10.8
		95% CI	(13.5–16.3)	(24.2–38.4)	(20.3–27.7)	(7.8–11.4)	–	(8.8–12.8)
	CSS	Percentage	37.5	67.8	56	25.8	–	29.5
		95% CI	(35.3–39.7)	(58.0–77.6)	(50.5–61.5)	(22.5–29.1)	–	(26.2–32.8)

OS – overall survival

CSS – cancer-specific survival rate

The median overall survival rate for early stages of PC (T1 + T2) was 10.5 (95% CI 10.0; 10.9) years, for advanced stages (T3 + T4) – 3.6 (95% CI 3.4; 3.8) years; these differences are statistically significant ($p < 0.001$) (Fig. 3.19.).

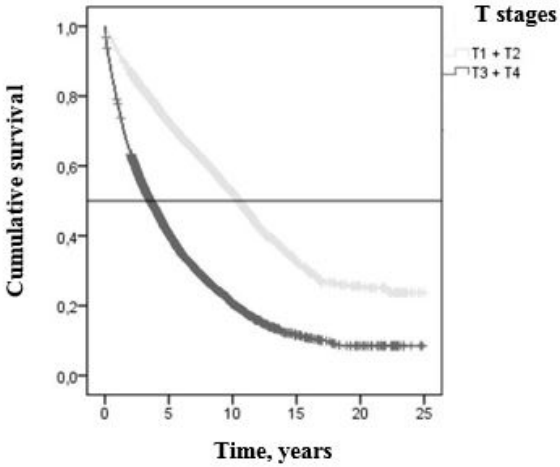

Figure 3.19 **Cumulative overall survival rate of PC patients at early stages and locally advanced stages**

More details about the overall 5, 10, 15, and 20 year survival rate for early stage and advanced stage PC patients are presented in Table 3.4.

Table 3.4

The overall and cancer-specific survival rate of patients at early stages and locally advanced stages of PC

Life expectancy			Stages	
			T1 + T2	T3 + T4
5 years	OS	Percentage	72.4	40.6
		95% CI	(71.0–73.8)	(39.2–42.0)
	CSS	Percentage	84.9	50.4
		95% CI	(83.7–86.1)	(48.8–52.0)
10 years	OS	Percentage	52.5	20.6
		95% CI	(50.5–54.5)	(19.2–22.0)
	CSS	Percentage	75.2	33.6
		95% CI	(73.4–77.0)	(31.8–35.4)
15 years	OS	Percentage	32.7	11.7
		95% CI	(30.0–35.4)	(10.3–13.1)
	CSS	Percentage	64.1	26.5
		95% CI	(60.6–67.6)	(24.3–28.7)
20 years	OS	Percentage	25.9	8.5
		95% CI	(22.6–29.2)	(6.9–10.1)
	CSS	Percentage	58.4	23.3
		95% CI	(53.7–63.1)	(20.4–26.2)

OS – overall survival rate

CSS – cancer-specific survival rate

3.4.2. Cancer-specific survival rate

The median cancer-specific survival rate of PC patients during the entire considered time period was 10.0 (95% CI 9.5; 10.6) years (Fig. 3.20.).

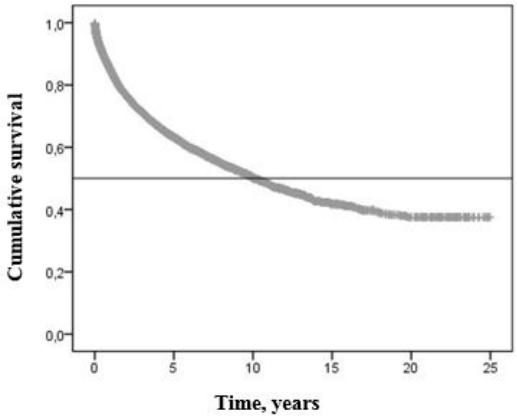

Figure 3.20 **Cumulative cancer-specific survival rate of PC patients**

The median cancer-specific survival rate during the considered time period could not be determined for stages T1 and T2, for stage T3 it was 6.1 (95% CI 5.7; 6.5) years, for stage T4 it was 1.2 (95% CI 1.0; 1.4) years, in the case of TX it was 4.8 (95% CI 4.3; 5.4) years; these are statistically significant differences ($p \leq 0.005$) (Fig. 3.21.).

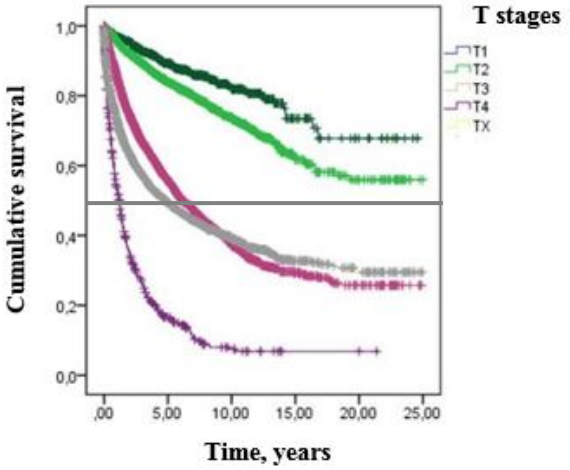

Figure 3.21 **Cumulative cancer-specific survival rate of PC patients by T stages**

More details about the cancer-specific 5, 10, 15, and 20 year survival rate by T stages are shown in Table 3.4.

The cancer-specific median survival rate during the considered time period could not be evaluated for the early PC stages (T1 + T2), while for advanced stages (T3 + T4) it was 5.2 (95% CI 4.8; 5.5) years; these were statistically significant differences ($p < 0.001$) (Fig. 3.22.).

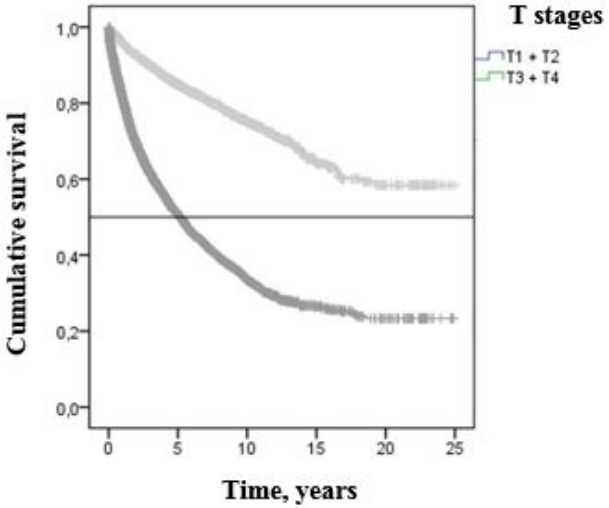

Figure 3.22 **Cumulative cancer-specific survival rate of PC patients at the early stages and locally advanced stages**

The cancer-specific 5, 10, 15, and 20 year survival rate by early and advanced stages is shown in Table 3.5.

3.4.3. Survival rate during the first year after diagnosis of PC

The overall 5 and 10 year survival rates were the lowest for cases of PC that were diagnosed at the beginning of the considered time period (from the year 1993 until 1995) – 33.2% (95% CI 29.9; 36.0) and 19.9% (95% CI 18.2; 21.6), respectively. The overall 5 and 10 year survival rates improved during all the considered time period, and the overall 5 year survival rate reached 65.0% (95% CI 65.0; 67.0) for the cases of PC diagnosed in the time period from year 2008 until 2010, while the overall 10 year survival rate reached 31.2% (95% CI 29.2; 33.2) for the cases of PC diagnosed between the years 2002 and 2004. The overall 15 year survival rate was the highest for the

PC cases diagnosed at the beginning of the considered time period, from the year 1990 until 1992 – 15.3% (95% CI 12.6; 18.0). The overall 15 year survival rate then decreased to 9.6% (95% CI 7.9; 11.4) for the cases of PC diagnosed between the years 1996 and 1998.

The cancer-specific 5 and 10 year survival rate was the lowest at the beginning of the considered time period, from year 1993 until 1995 – 40.3% (95% CI 36.8; 43.8) and 29.3% (95% CI 25.8; 32.8), respectively. The cancer-specific 5 and 10 year survival rates improved during the considered time period, with the 5 year cancer-specific survival rate reaching 75.1% (95% CI 73.3; 76.9) in the time period from year 2008 until 2010, and the cancer-specific 10 year survival rate reaching 49.9% (95% CI 47.5; 52.3) in the time period between years 2002 and 2004. The cancer-specific 15 year survival rate was the lowest at the beginning of the considered time period (from year 1993 until 1995) – 25.1% (95% CI 23.5; 26.7). The cancer-specific 15 year survival rate subsequently increased to 30.9% (95% CI 27.8; 34.0) from year 1999 until 2001. More details about the overall and cancer-specific survival rates depending of the year of diagnosis are shown in Table 3.5.

Table 3.5

The overall and cancer-specific 5, 10, and 15 year PC survival rates by year of diagnosis

Year of diagnosis	5 years		10 years		15 years	
	OS (95% CI)	CSS (95% CI)	OS (95% CI)	CSS (95% CI)	OS (95% CI)	CSS (95% CI)
1990–1992	35.1 (31.8–38.4)	43.6 (39.9–47.3)	20.7 (17.8–23.6)	32.9 (29.2–36.6)	15.3 (12.6–18.0)	27.9 (24.2–31.6)
1993–1995	33.2 (29.9–36.0)	40.3 (36.8–43.8)	19.9 (18.2–21.6)	29.3 (25.8–32.8)	13.4 (11.0–15.8)	25.1 (23.5–26.7)

Continuation of Table 3.5

Year of diagnosis	5 years		10 years		15 years	
	OS (95% CI)	CSS (95% CI)	OS (95% CI)	CSS (95% CI)	OS (95% CI)	CSS (95% CI)
1996–1998	41.5 (38.4–44.6)	51 (47.3–54.7)	23.6 (20.5–26.7)	37.7 (33.8–41.6)	9.6 (7.9–11.4)	27.4 (25.8–29.0)
1999–2001	41.1 (38.2–44.0)	54 (50.7–57.3)	24.4 (21.9–26.9)	40.5 (37.2–43.8)	12.5 (10.5–15.0)	30.9 (27.8–34.0)
2002–2004	50.6 (48.1–53.1)	63.4 (60.9–65.9)	31.2 (29.2–33.2)	49.9 (47.5–52.3)	–	–
2005–2007	58.3 (56.3–60.8)	70.7 (68.9–73.2)	–	–	–	–
2008–2010	65 (65.0–67.0)	75.1 (73.3–76.9)	–	–	–	–

OS – overall survival rate

CSS – cancer-specific survival rate

3.5. Comparison by T stages

At the beginning of the considered time period, the largest fraction of PC patients (43.2%) were identified as stage TX. This fraction decreased by more than 2 times until the end of the considered time period, down to 16.9% ($p < 0.001$). The average fraction of stage TX during the entire considered time period was 28.2%, and has rapidly decresed since year 2011 (see the Table in Annex 1). The stage T4 was identified in the smallest fraction of patients (3.7%) at the beginning of the considered time period, increasing to 7.2% by the middle of the first decade, and decreasing to 2.8% ($p < 0.001$) by the end of the considered time period; the average fraction of stage T4 during the entire considered time period was 4.3%.

The fraction of T1 stage at the beginning of the considered time period was 5.1%, and increased by more than 2 times until the end of that time period,

reaching 11.9% ($p < 0.001$); the average fraction of T1 stage was 7.1%. The fraction of T2 stage at the beginning of the considered time period was 25.0%, increasing by two thirds to 42.9% ($p < 0.001$) at the end of that time period; the average fraction of stage T2 during all the considered time period was 31.1%. The fraction of stage T3 at the beginning of the considered time period was 22.7%, increasing to 39.4% by the end of the first decade, then decreasing to 25.5% ($p < 0.001$) by the end of the considered time period; the average fraction of stage T3 during all the considered time period was 29.3%. The occurrence of different T stages by year is shown in Fig. 3.23.

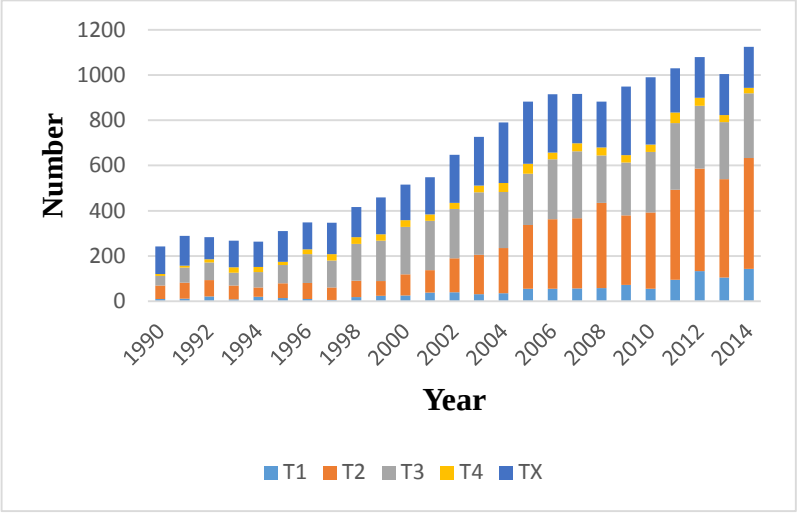

Figure 3.23 **The occurrence of different T stages by year**

The fraction of early PC stages at the beginning of the considered time period was 53.6%, followed by a decrease to 30.6% by the end of the first decade; then the fraction of early stages increased to 65.9% ($p < 0.001$) by the end of the considered time period. The average fraction of early PC stages during all the considered time was 53.6% (see the Table in Annex 2). The

fraction of advanced PC stages at the beginning of the considered time period was 46.4%, increasing to 69.4% by the end of the first decade; then decreasing to 34.1% ($p < 0.001$) until the end of the considered time period. The average fraction of advanced PC stages during all the considered time period was 46.4%. The occurrence of early and advanced PC stages by year is shown in Fig. 3.24.

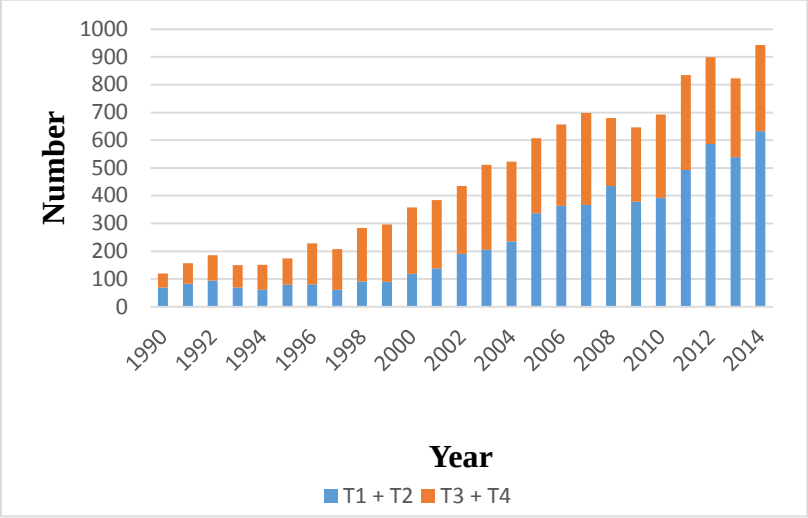

Figure 3.24 **The occurrence of early and advanced PC stages by year.**

3.6. Comparison of sporadic and familial PC

The average age of familial PC patients (FG) at the time of diagnosis was 58.9 years (95% CI 57.8; 60.1); the average age of sporadic PC patients (SG) was 67.2 years (95% CI 66.7; 67.6). Thus, the FG patients were on average 8.3 years younger than the SG group patients; the difference was statistically significant ($p < 0.0001$).

The T stage was known for a total of 980 patients, among them 191 patients was assigned to the FG and 789 patients were assigned to the SG group. The T stage was not known for a total of 195 patients, among them 24 FG patients and 171 SG patients. The Gleason score was known for a total of 622 PC patients, among them 130 FG patients (20.9% of all PC patients with known Gleason score) and 492 SG patients (79.1% of all PC patients with known Gleason score). There were no statistically significant differences in the fraction of patients with known Gleason score and known T stage between both groups (p=0.712 and p=0.084, respectively). The comparison of patient age, Gleason score, and fraction of T stages between the FG and SG groups is presented in Table 3.6.

Table 3.6

Comparison of age, Gleason score and Tstage between the FG and SG groups

	FG	SG	p-value
Age at the time of diagnosis			
All patients (1175)	215 (18.3%)	960 (81.7%)	
Average	58.9 (95%TI 57.8–60.1)	67.2 (95%TI 66.7–67.6)	< 0.0001
Range	28–85	46–92	
Gleason score			0.712
Patients with known Gleason score (622)	130 (20.9%)	492 (79.1%)	
1–4	12 (9.2%)	57 (11.6%)	
5–7	97 (74.6%)	352 (71.5%)	
8–10	21 (16.2%)	83 (16.9%)	

Continuation of Table 3.6

	FG	SG	p-value
T stages	191 (19.5%)	789 (80.5%)	0.084
T1	10 (5.2%)	40 (5.1%)	
T2	138 (72.3%)	511 (64.8%)	
T3	43 (22.5%)	224 (28.4%)	
T4	0 (0%)	14 (1.8%)	

The 5 year cancer-specific survival rate in FG was 92% (95% CI 0.88; 0.97), while it was 88% in SG (95% CI 0.86; 0.91), with no statistically significant difference. The 10 year cancer-specific survival rate in FG was 92% (95% CI 0.88; 0.97), while it was 69% in SG (95% CI 0.60; 0.78). Thus, the 10 year cancer-specific survival rate in FG was higher by 23% than in SG, with p = 0.0237. A comparison of cancer-specific survival rate in FG and SG is shown in Fig. 3.25.

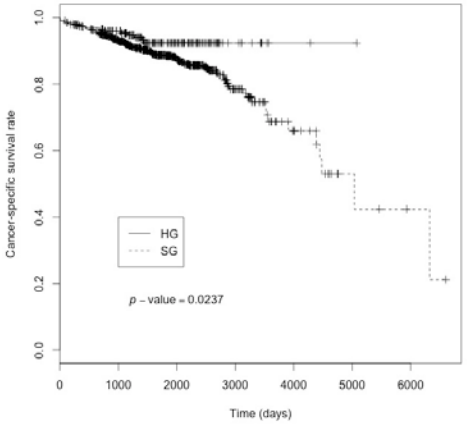

Figure 3.25 **Comparison of cancer-specific survival rate in FG and SG**

3.7. Analysis of del5395 mutation in *CHEK2* gene

The average age (range) of CRC patients was 67 (18–88) years; the del5395 mutation of *CHEK2* gene was found in 2 out of 568 (0.35%) CRC patients.

The average age (range) of BC patients was 62 (28–89) years; the del5395 mutationof *CHEK2* gene was found in 3 out of 435 (0.68%) BC patients.

The average age (range) of OC patients was 57 (16–86) years; the del5395 mutation of *CHEK2* gene was found in 4 out of 399 (1.0%) OC patients.

The average age (range) of PC patients was 66 (42–91) years; the del5395 mutation of *CHEK2* gene was found in 1 out of 419 (0.24%) PC patients.

The average age (range) of people involved in radioactive contamination cleanup after the Chernobyl disaster was 54 (43–76) years; the del5395 mutation of *CHEK2* gene was found in 4 out of 531 (0.75%) Chernobyl cleanup survivors.

The average age (range) of geriatric group was 73 (60–97) years; the del5395 mutation of *CHEK2* gene was found in 3 out of 444 (0.68%) geriatric group patients.

The average age (range) of blood donors serving as control group was 35 (18–65) years; the del5395 mutation of *CHEK2* gene was found in 4 out of 524 (0.76%) members of the blood donor group.

The largest risk due to the del5395 mutation of *CHEK2* gene among the cancer patients was associated with ovarian cancer (OR = 1.32, 95% CI 0.24; 7.13, p = 0.73), while the lowest risk was for prostate cancer (OR = 0.31, 95% CI 0.06; 3.70, p = 0.39). Among the cancer patients, only those with ovarian cancer had a higher incidence of del5395 mutation of

CHEK2 gene, compared to the control group with OR > 1. The risk due to the del5395 mutation of *CHEK2* gene was not statistically significant in any of the cancer patient groups, with the p value ranging from 0.39 to 1.00.

Compared to the control group, there was no statistically significant risk of del5395 mutation in *CHEK2* gene among the Chernobyl cleanup survivors (OR = 1.09, 95% CI 0.20; 5.90), nor in the geriatric group (OR = 0.89, 95% CI 0.13; 5.28) (p = 1).

The frequency of del5395 mutation in *CHEK2* gene among all study groups is shown in Table 3.7.

Table 3.7

The frequency of del5395 mutation in *CHEK2* gene

Groups of cancer patients	Age		del5395 mutation	Frequency (%)	OR	95% CI	p-value
	average	range					
Colorectal	67	18–88	2/568	0.35	0.46	0.04–3.23	0.43
Breast	62	28–89	3/435	0.68	0.90	0.13–5.35	1.00
Ovarian	57	16–86	4/399	1.00	1.32	0.24–7.13	0.73
Prostate	66	42–91	1/419	0.24	0.31	0.06–3.70	0.39
Combined for all groups of cancer patients	63	16–91	10/1824	0.55	0.75	0.28–1.94	0.52

Continuation of Table 3.7

Groups of cancer patients	Age		del5395 mutation	Frequency (%)	OR	95% CI	p-value
	average	range					
Chernobyl cleanup survivors	54	43–76	4/531	0.75	0.99	0.18–5.35	1.00
Geriatric group	73	60–97	3/444	0.68	0.89	0.13–5.28	1.00
Control group							
Healthy blood donors	35	18–65	4/524	0.76	–	–	–

OR: odds ratio; 95% CI: 95% confidence interval.

There were 51 patients with different types of malignant tumours among the Chernobyl cleanup survivors. The del5395 mutation of *CHEK2* gene was not found in any of these cases.

4. DISCUSSSION

4.1. Epidemiology

Prostate cancer is one of the most common types of malignant tumours among males worldwide. A large number of publications describe the global trends of PC epidemiology, bet there is a lack of data about the situation in Latvia over the last decade, and the available information must be updated. Our analysis of trends in PC epidemiology in Latvia over 25 years provides a perspective on the contributions and accomplishments of urological care in Latvia starting from the restoration of Latvian independence (when the implementation of European Association of Urology guidelines was started) until the current time.

The analysis of epidemiology is based on the data from the Latvian Centre for Disease Prevention and Control and the Central Statistical Bureau. Both of these institutions maintain databases that are essentially unique for Latvia and aggregate information from the entire country, and the obtained epidemiological data are relevant for the entire country, thus considered to be reliable. The epidemiological data registered between the years 1990 and 1993 may be incomplete due to the transition from Soviet epidemiological records to the newly formed cancer patient register of independent Latvia.

The standardized incidence of PC increased over the entire considered time period with AAPC of 5.8 (95% CI 4.8; 6.8). An especially rapid increase in the incidence of PC was observed from the year 1994 until 2005, with APC of 12.4. Such a rapid increase in the incidence of PC could not be linked to any of the proven risk factors for PC: age, genetic traits or race. The average life expectancy for males in Latvia has not substantially changed during the study (63–68 years), the influence of other races on the ethnic composition of Latvian population is insignificant. Thus, it can be concluded that the reason for the

rising incidence of PC is the recent emphasis on search for PC cases (the education of society and medical professionals, especially general practice doctors, the increased interest of urologists in Latvia about the problem, theoretical and practical advancement of urologists during the study time frame), and improved diagnostics (widespread introduction of PSA testing in 1997, the common application of TRUS in combination with prostate biopsy since 1998). The growth of PC incidence slowed after year 2005 to APC of 2.8. This trend can be explained by several factors: population screening with the PSA test was discontinued at the same time and the efforts by urologists to diagnose PC in patients over 75 years of age were stopped, because PSA testing after this age becomes less clinically significant or economically justified (Schaeffer et al., 2009).

In most of the world, similarly as in Latvia, a long-term growth of PC incidence has been observed, although the incidence of PC in several countries did not show statistically significant changes, but rather stabilized. A statistically insignificant decrease of PC incidence was observed in Finland, New Zealand, and India (Chennai province), with AAPC of ─0.2, ─1.2, and ─0.5, respectively (Center et al., 2012). On the other hand, there was a statistically insignificant increase of PC incidence in USA, Canada, and Australia, with AAPC of 0.1, 0.9, and 0.1, respectively (Center et al., 2012). It does not mean that there were no variations of PC incidence in these countries, just the opposite: when the PSA test was introduced in these countries at the end of 1980's and the start of the 1990's, screening for PSA led to greatly increased observed incidence of PC. The APC of PC incidence in Australia and New Zealand at this time was 24.8 and 27.5, respectively (Center et al., 2012). A substantial decrease of PC incidence was observed in these countries in the middle and end of the 1990's (with the greatest APC of -10.4 in Australia), followed by a stabilization of PC incidence (Baade et al., 2009; Center et al., 2012; Etzioni et al., 2002).

The dynamics of PC incidence in Latvia have been rather similar to the countries of Western and Northern Europe, where the variations of PC incidence were not that significant. In those countries, similarly to Latvia, the PSA test was introduced several years later and was not used as widely (Bray et al., 2010; Center et al., 2012; Melia et al., 2004).

The incidence of PC in Asia is generally lower than in Latvia (Israel is an exception), PSA test is used less commonly, but still there is a long-term rise of PC incidence in the whole region, probably explained by the increasing impact of Western lifestyle and diet (Center et al., 2012; Hsing et al., 2000).

The major differences of PC incidence worldwide (up to 25 times) can be attributed mostly to the different practices of PC diagnostics in different regions. The rate of PC diagnoses in the more developed regions of the world increased by 81% after the introduction of PSA testing, compared to the digital rectal examination alone (Baade et al., 2009; Catalona et al., 1994; Kvale et al., 2007; Potosky et al., 1995). This has enabled the detection of a large number of clinically insignificant cases of PC, thus resulting in massive hyperdiagnosis. Prior to the introduction of PSA testing, cases of PC in the more developed regions of the world were often discovered while performing surgery for benign prostate hyperplasia (TURP), when the stage of PC was interpreted as T1a or T1b, with the PC component in the histologically examined material comprising < 5% or > 5%, respectively (Potosky et al., 1990). It has been established that 23 – 42% of PC cases in Europe and the USA have been detected due to hyperdiagnosis by the commonly used PSA test (Draisma et al., 2009; Etzioni et al., 2002). Comparing the PC diagnostics worldwide and in Latvia, it can be concluded with certainty that hyperdiagnosis is a problem in Latvia as well, as indicated by the increased fraction of patients with T1 stage of PC.

Considering the global trends and comparing the dynamics of PC incidence in Latvia and worldwide, it is clear that the data about the incidence

of PC in Latvia have been subjected to essentially the same fluctuations as observed in the more developed regions of the world. The only major difference is the delay by 5–15 years, which generally can be explained by the later introduction of PSA testing and other state-of-art technologies and surgical techniques (TRUS, TURP) in Latvia.

The trends observed for different age groups in Latvia are not the same: there has been a steady increase of PC incidence in patients younger than 60 years of age, with AAPC 10.3 (95% CI 9.3; 11.3), which is the highest indicator among all age groups. This trend can be explained by the long efforts to draw the attention of Latvian society to the problem of PC and the recommendations for men to undergo scheduled health check-ups (after 50 years of age at the end of the 20th century and the beginning of the 21st century), currently it is recommended already for men over 40 years of age, and even 5 years earlier for men with family history of PC. On the other hand, in the age groups of 70–79 and 80 + years an increasing incidence of PC was observed until year 2005 and 2003, respectively, followed by a statistically insignificant decrease of PC incidence in both of these groups. It can be asserted that this decrease in the incidence of PC was due to the long known and implemented concept promoted by European Urological Association that the PSA test is not economically justified and thus not recommended for men over 75 years of age. Certainly, it does not mean that PSA tests are not prescribed for patients older than 75 years of age, if they show the clinical signs of PC. Both of these trends should be viewed as positive, because cases of PC in younger men are diagnosed at earlier stages, when the life expectancy is relatively long and watchful waiting or radical therapy can be prescribed, depending on the risk group for PC. On the other hand, older men are spared unnecessary stress and medical expenses by foregoing the search for PC that will not be their likely cause of death.

The standardized prevalence of PC increased from the year 1990 until 2014 with AAPC 8.5 (95% CI 7.2; 9.8). A particularly rapid increase of PC prevalence was observed from the year 1998 until 2005, with APC 12.0. Such dynamics of PC prevalence can be explained by the synergy of several factors, the interaction of which have increased the prevalence of PC. Undeniably, such an increase of PC prevalence can be linked to the increase of PC incidence due to the reasons that were already described. However, the number of PC patients has grown seven-fold during the considered time period, which cannot be explained with the improved diagnostics of PC. It is very important to note that PC is relatively less lethal than other malignant tumours. That was reflected first of all in the mortality during the first year after diagnosis, which at the beginning of the considered time period practically did not exceed 30%, but at the end of the same time period was 15% on average. This relatively good prognosis was also clearly reflected in the 5, 10, and 15 year cancer-specific survival. The lethality of PC, which directly indicates the ratio between the number of deaths caused by PC and the occurrence of PC, decreased fourfold during the considered time period, once again confirming the relatively good prognosis of PC and indirectly pointing to the increased fraction of early PC stages.

The standardized prevalence of PC revealed by prevalence studies in Europe at the beginning of the considered time period was typically 3 times higher than in Latvia (in Sweden – even 7 times higher) (Forman et al., 2003; Micheli et al., 2002). Even though there was a sharp increase of PC prevalence in Latvia, there was an increase in other European countries as well. According to IARC data, the highest standardized prevalence of PC in year 2012 was observed in Scandinavian countries and in France, surpassing the prevalence in Latvia by approximately 2 times. Thus, it is certain that Latvia will not approach such a high prevalence of PC in the near future, because the average life expectancy of males in these countries differs from that in Latvia by more

than 10 years, leading to a high prevalence of PC, which may further increase in the future.

The prevalence of PC is growing in all age groups, but the most rapid increase of prevalence was observed in the group of men <60 years old, with AAPC 11.8 (95% CI 9.7; 13.9), which was explained by the largest increase of PC incidence in this group.

According to the Central Statistical Bureau of Latvia, there were 412 592 deaths of males in Latvia from year 1990 until 2014, of which 1.5% died from PC. The share of PC deaths among malignant tumours during year 1990 was 5.6%, but almost doubled by 2009, reaching 10.8%.

The standardized mortality of PC increased from year 1990 until 2006 with APC 4.8%, reaching 28.6 (for 100 000 p.y.) in 2006, one of the highest mortalities in the world along with the other Baltic countries, Scandinavia, and the Caribbean region (Center et al., 2012; Ferlay et al., 2015; Hsing et al., 2000). Such an increase of mortality as in Latvia is characteristic for countries with similar practices of PC diagnostics and therapy, when the initiation of active campaigns for the diagnostics of PC initially result in increased mortality following the growth of observed incidence. After the rapid increase of standardized mortality in Latvia, a statistically insignificant decrease was observed until year 2014, with APC ─ 0.5. Even though the decrease of PC mortality was small, it should be considered as a positive trend, at least as a sign of stabilization. This trend was also characteristic for other countries with similar practices of PC diagnostics and treatment, only these trends were delayed in Latvia, the same as the rising incidence of PC. The decrease of standardized mortality due to PC was also observed in most of the North and South America, as well as in Western and Northern Europe (Center et al., 2012; Ferlay et al., 2015; Hsing et al., 2000). It is believed that the stabilization or decrease of mortality both in Latvia and elsewhere in the world must be linked to the successful early diagnostics of PC that enables

effective treatment of average and high-risk PC cases, as well as the introduction of advanced medications for the treatment of castration-resistant PC, which statistically significantly improve the survival. Also, it is clear that the decrease of PC mortality was also affected by the large number of identified low risk PC cases, where the 10-year cancer-specific survival exceeded 90% even with watchful waiting and no treatment. The explanation of standardized PC mortality trends has been also confirmed by an interesting difference between the cancer-specific PC mortality and lethality trends. The fraction of cancer-specific mortality due to PC increased three-fold during the considered time period (the larger the number of identified PC cases, the larger will be the long-term number of deaths due to PC), while the lethality due to PC decreased almost five-fold (as a result of early diagnosis, partially hyperdiagnosis, and effective treatment).

The mortality due to PC in the age groups of < 60 years and 60–69 years increased during all the considered time period, while in the age groups of 70–79 and 80 + years the relatively large increase up to the year 2006 was followed by a decrease in PC mortality. These similar trends in the two younger and two older age groups can be explained by the transition of successfully treated or monitored patients from the younger age groups to the next age groups, thus reducing the cancer-related mortality in the older age groups.

Previous studies of the trends in PC epidemiology in Latvia demonstrated a growth of incidence, prevalence, and mortality until year 2004 (Lietuvietis, 2006; Lietuvietis et al., 2002). Our analysis has shown that the age-specific incidence and standardized overall mortality decreased in several age groups after year 2004, which can be definitely attributed to the successful efforts by urologists in Latvia.

The fraction of patients who died during the first year after diagnosis decreased by nearly 2 times over the considered time period. This observation

allows us to conclude that an increasing number of cases have benefitted from early diagnosis.

The overall and cancer-specific 5 year survival rate of PC patients improved (nearly doubled) when comparing the beginning and end of the considered time period, reaching 65.0% (95% CI 65; 67) and 75.1% (95% CI 73.3; 76.9), respectively for the PC patients diagnosed between years 2008 and 2010. Similar trends were also observed for the overall and cancer-specific 10 year survival rate, which increased by approximately 50% when comparing the beginning and end of the considered time period, reaching 31.2% (95% CI 29.2; 33.2) and 49.9% (95% CI 47.5; 52.3), respectively for the PC patients diagnosed between years 2002 and 2004. The cancer-specific 15 year survival rate during the considered time period showed a slower increase, only by 3%. Despite the generally positive trends of improving survival rates, these results are still inadequate, because the cancer-specific 5 year survival rate in countries using the PSA test has exceeded 90% (Paquette et al., 2002). During a study about the natural progression of early stage PC in Scandinavian countries, the patients either did not receive therapy, or were treated with hormonal drugs in the case of locally advanced or metastatic PC. The overall 15 year survival rate in that study was 21.5%, and the cancer-specific 15 year survival rate was 80.3% (Popiolek et al., 2013). On the other hand, the overall 15 year survival rate in Latvia never exceeded 16%, while the cancer-specific 15 year survival rate did not exceed 31%. It should be taken into account that a 5% difference in the overall 15 year survival rate results in a nearly three-fold difference in the cancer-specific 15 year survival rate. This massive difference in results can be explained by the simultaneous influence of several factors. The Scandinavian study included patients at stages T1 and T2, while the study in Latvia considered all cases of PC, including those at locally advanced stages and metastatic PC. It is also of clear importance that, according to the Central Statistical Bureau of Latvia, the average life expectancy of males in Latvia

during the considered time period varied from 63 to 68 years, which was shorter by 3 to 8 years than the average age of PC diagnosis. It is clear that the data about mortality and cancer-specific survival rates are often controversial, because the actual cause of death for many PC patients may be different, as in the aforementioned Scandinavian study, where only 17% of patients died specifically of PC over 32 year time period (Popiolek et al., 2013). Our opinion was also supported by a study from USA with PC patients at stages T1 and T2, where the cancer-specific 10 year mortality was relatively low and varied between 8.3% and 25.6%, depending on the tumour cell grade (Lu-Yao et al., 2009).

The analysis of T stages revealed a great excess of the unspecified TX stage at the beginning of the considered time period, which decreased by more than 2 times until the end of the considered time period, primarily due to the introduction of advanced diagnostics of PC, and also improved statistics. Certainly, all stages of PC were represented in the TX category, but indications of the actual prevalence can be found from the analysis of overall and cancer-specific survival rates by individual T stages in Figures 4.18. and 4.21. As clearly shown by both graphs, both the overall and cancer-specific survival rates show very similar curves for the TX stage and T3 stage, and is quite different from the curves characteristic for other stages. This finding allows to confirm that the TX stage mostly contained advanced cases of PC. Thus, it can be concluded that the share of early stage PC cases in Latvia during all the considered time period was less than 50%, providing an additional explanation for the relatively low survival rates of PC patients in Latvia.

It can be stated with certainty that the relative dynamics of the known T stages clearly reflected the beginning of PSA testing in Latvia in the middle of 1990s, when the fraction of stages T1 and T2 started to increase. Without a doubt, the relative increase of stage T1 was also facilitated by transurethral prostate surgery, introduced in Latvia and rapidly promoted in the middle of

1990s, leading to the formation of subtypes T1a and T1b of the T1 stage. Nevertheless, the fraction of T1 stage did not exceed 10% prior to year 2010. This can be explained by the fact that the clinical cT1 stage was typically treated surgically prior to 2010, and the pathological stage had definitely advanced past stage T1, and was probably T2 or T3, as reflected by the dynamics of stages T2 and T3: these stages showed the largest growth during the considered time period both by occurrence and the share of the total patient population. The fraction of stage T1 still clearly increased after year 2010, reaching 13% in year 2014, and it can be concluded with certainty that its fraction will continue to rise. This view is also supported by the fact that an increasing number of patients with PC that is deemed to have a low risk of progression are offered watchful waiting with anticipated radical therapy in the future, when the analyses will indicate a moderate or high risk of PC progression. The current concept of "active surveillance" appeared in the guidelines of European Association of Urology for the first time in 2008, and was previously known as " active monitoring". Even though active monitoring is a common approach worldwide, it is often difficult or impossible to convince oncological patients in Latvia that treatment should be postponed, despite the high probability that the treatment will decrease the quality of life, with the most significant problems being urinary incontinence and erectile dysfunction.

The relative dynamics of early and locally advanced stages of PC also reflect the previously mentioned influence of PSA testing on the diagnosis of PC at early stages, which is essentially the whole purpose of PSA testing. The fraction of early PC stages has increased since 1997, exceeding 50% after 2005, and continues to increase, which certainly is a positive trend. A comparative study of cancer-specific mortality based on data from the SEER cancer register in the USA showed that the introduction of routine PSA testing has reduced the cancer-specific 10 year mortality of PC patients by more than 50% (Lu-Yao et al., 2009). The results in Latvia have been less striking, but

nevertheless optimistic, because the standardized mortality since year 2006 has shown a slight decrease with APC ─ 0.5, which is statistically insignificant, but proves that the standardized mortality due to PC has not increased after 2006.

The overall and cancer-specific survival rate of PC patients at early stages and locally advanced stages significantly differed (by up to 3 times), as should have been expected. Although the overall survival rate and cancer-specific survival rate at early stages of PC was significantly better than at locally advanced stages, these results cannot be considered satisfactory, because the cancer-specific 15 year survival rate in a Swedish study of early-stage PC exceeded 80% (in Latvia – 64.1%) (Popiolek et al., 2013). An explanation for this difference was based on the analysis of survival rates independently of the T stages.

The evaluation of epidemiological data must account for the considerable migration that occurred in Latvia immediately after the restoration of independence in 1990 and continues to this day. The true scale of migration is difficult to calculate, because various information sources indicate a significant role of undocumented migration, which is not reflected in the official statistics. This situation can certainly affect the data about PC incidence, prevalence, and mortality.

4.2. Comparison of familial and sporadic PC

Among the 1175 PC patients included in the study, 12 (1.02%) matched the criteria of definitive hereditary PC. Other studies have shown that 9–10% of all PC cases are hereditary (HPC) (Hemminki, 2012). This difference is quite considerable, and should be due to the relatively low number of family members in Latvia. The fertility index in Latvia between years 2000 and 2012 varied within the range of 1.22–1.59. Certainly, the low birth rate and small families for several generations do not affect the real percentage of hereditary

PC, but often prevent the clinical identification of such cases. The situation is similar to the identification of other types of hereditary cancers in Latvia. For example, only 1.7% of sequential breast cancer patients in Latvia match the criteria for hereditary breast cancer (Gardovskis et al., 2005), but determination of BRCA1 founder mutation for all patients of this group revealed that up to 5.5% of breast cancer cases were hereditary. It should be pointed out that the share of hereditary breast cancer in epidemiological study performed in the Valka region of Latvia was determined to be as high as 6.8%, despite the fact that the majority of identified families lacked founder mutations in the BRCA1 gene (Vanags et al., 2010). Similarly, mutations of the BRCA2 gene were found in breast cancer patients with family history that did not indicate the hereditary nature of this cancer (Berzina et al., 2013). Even more difficult was the identification of Lynch syndrome in the families of Latvia: many families with medical history pointing to hereditary cancers lacked mutations of DNA repair genes, but families with less pronounced medical history carried these mutations (Berzina et al., 2012).

Population studies performed in the Valka region about hereditary and familial cancer cases identified the same problem and the authors concluded that due to the small size of families in Latvia, it is often difficult to arrive at justified conclusions about potentially hereditary conditions by using only the medical history of the family (Vanags et al., 2010). The data of that study indicated that 0.6% of PC cases matched the criteria of HPC (Vanags et al., 2010). We should note that this number was very close to our result of 1.02%

Thus, it has been reliably established that the identification of hereditary PC cases in Latvia is complicated by the small family size with poorly known medical history (relatives are often unaware about the medical history of their parents and, especially, grandparents and/or offer contradictory information), the lack of founder mutations, as well as the lack of clear “leader genes”

(for example, BRCA1 in the cases of breast and ovarian cancer), as only about 30% of familial PC cases can be attributed to the 100 genes known to potentially contain cancer-promoting mutations (Eeles et al., 2013).

Therefore, it can be reliably concluded that the majority of hereditary PC cases remain unknown, and the true prevalence of hereditary PC in Latvia cannot yet be determined.

Since no statistically significant differences of Gleason's score could be found between the groups of familial and sporadic PC, we concluded that the different cancer-specific survival rates of these groups are not determined by the tumour cell grade.

The average age of patients in the FG at the time of diagnosis was lower by 8.3 years than in SG. Our data are very similar to other studies of hereditary and familial PC (Gronberg et al., 1996; Hemminki, 2012).

The cancer-specific 10 year survival rate in the FG was 23% higher than in the SG, and could be explained by the better awareness of family members in the FG about the cancer risk and importance of screening. For this reason, the men in families affected by PC more reliably and regularly undergo check-ups by general practice doctors and urologists, performing the necessary tests for prevention and early diagnosis of PC.

The groups of familial and hereditary PC represent a small fraction of the general population, thus it can be asserted that state-sponsored PC screening of these groups is entirely justified both medically and economically.

4.3. The analysis of del5395 mutation in *CHEK2* gene

The current results confirm the assumption that *CHEK2* del5395 is the founder mutation in Latvian and Eastern European populations, but no statistically reliable link of this mutation with increased risk of prostate, colorectal, breast, or ovarian cancer development was found. The frequency of

CHEK2 del5395 mutation in BC patients (0.68%) was somewhat lower than in studies from Poland (Cybulski et al., 2007; Myszka et al., 2011), Czech Republic, and Slovakia (Walsh et al., 2006), while the frequency of *CHEK2* del5395 mutation among patients of ovarian cancer (1.0%) was similar to that reported in the aforementioned studies.

The relatively higher frequency of *CHEK2* del5395 mutation in the control group of blood donors, against which the other groups were compared, decreased the OR value for all groups of tumours.

The survivors of Chernobyl cleanup suffered high levels of radiation exposure that has been linked with DNA damage or double-strand breaks, increasing the risk of malignant tumours (Eglite et al., 2009). Ionizing radiation is one of the factors that activate the *CHEK2* gene. It encodes a protein that interacts with a cascade of other proteins, including the tumour suppressor p53 protein (encoded by TP53 gene). These proteins arrest cell division and determine the extent of DNA damage. DNA repair is initiated, if possible. In case if the DNA damage is irreparable and the integrity of DNA cannot be restored by the cell, a self-destruction of cell or apoptosis is initiated. Such a process prevents further proliferation of cells carrying mutations or damaged DNA, resulting in tumour prevention (Bartek and Lukas, 2003). If there is a link between mutations in the *CHECK2* gene and development of malignant tumours, it should be manifested most clearly in the group of Chernobyl cleanup survivors. It was assumed that the carriers of *CHEK2* del5395 mutation should be more sensitive to ionizing radiation, thus more likely to develop malignant tumours. There were 51 patients (9.6%) with various types of malignant tumours among the Chernobyl survivors, but none of them were carriers of the *CHEK2* del5395 mutation.

The geriatric group was formed to evaluate the potential effect of *CHEK2* del5395 mutation on the mortality. If there was a correlation between the presence of *CHEK2* del5395 mutation and increased incidence of malignant

tumours and mortality in the population, the geriatric group should have a lower incidence of *CHEK2* del5395 mutation. However, no statistically significant difference was found between the frequency of *CHEK2* del5395 mutation in the control group of blood donors and the geriatric group (OR = 0.89; 95% CI 0.13 – 5.28; p = 1). The results of both non-oncological study groups thus did not confirm the role of *CHEK2* del5395 mutation in the initiation of tumour development, at least in the population of Latvia. Even though no close link was discovered between the *CHEK2* del5395 mutation and the risk of prostate, colorectal, breast, or ovarian cancer development, further research should take into account the environmental and genetic factors that together with the *CHEK2* del5395 mutation may increase the risk of malignant tumour development.

5. CONCLUSIONS

1. The incidence and prevalence of PC in Latvia increased from year 1990 until 2014 (especially in the age group of < 60 years old patients), but the mortality decreased (especially in the age group of 70–80 + years).
2. The cancer-specific 5, 10, and 15 year survival rate of PC patients in Latvia increased from year 1990 to 2014, while the mortality in the first year after diagnosis decreased.
3. The fraction of PC cases in Latvia that were at unknown stage decreased from year 1990 until 2014, while the fraction of early stages (T1, T2) increased.
4. The patients with familial PC were younger by 8.3 years than the patients with sporadic PC, and the cancer-specific 10 year survival rate for patients with familial PC was 23% higher than that of patients with sporadic PC ($p = 0.0237$).
5. The *CHEK2* del5395 mutation has founder effect in the Latvian population, but it does not affect PC (as well as ovarian, breast, and colorectal cancer) incidence and mortality.

6. PRACTICAL RECOMMENDATIONS

1. Men with family history of hereditary or familial PC should start testing for PC prevention from the age of 42 years.
2. Men with family history of hereditary or familial PC should consult with physician specialized in hereditary cancer.
3. The costs of prophylactic testing for men with family history of hereditary or familial PC should be covered from the budget of the Ministry of Health.

REFERENCES

1. Abele, A., Vjaters, E., Irmejs, A., Trofimovics, G., Miklasevics, E. and Gardovskis, J. Epidemiologic, clinical, and molecular characteristics of hereditary prostate cancer in Latvia. *Medicina (Kaunas)*. 2011, 47(10), 579–585.

2. Ahmad, O. B., Boschi-Pinto, C., Lopez, A. D., Murray, C. J., Lozano, R. and Inoue, M. AGE STANDARDIZATION OF RATES: A NEW WHO STANDARD. *World Health Organization GPE Discussion Paper*. 2001, 31.

3. Baade, P. D., Youlden, D. R. and Krnjacki, L. J. International epidemiology of prostate cancer: geographical distribution and secular trends. *Mol Nutr Food Res*. 2009, 53(2), 171–184. doi:10.1002/mnfr.200700511

4. Bartek, J. and Lukas, J. Chk1 and Chk2 kinases in checkpoint control and cancer. *Cancer Cell*. 2003, 3(5), 421–429.

5. Berzina, D., Irmejs, A., Kalniete, D., Borosenko, V., Nakazawa-Miklasevica, M., Ribenieks, K. and Miklasevics, E. Novel germline MLH1 and MSH2 mutations in Latvian Lynch syndrome families. *Exp Oncol*, 2012, 34(1), 49–52.

6. Berzina, D., Nakazawa-Miklasevica, M., Zestkova, J., Aksenoka, K., Irmejs, A., Gardovskis, A. and Miklasevics, E. BRCA1/2 mutation screening in high-risk breast/ovarian cancer families and sporadic cancer patient surveilling for hidden high-risk families. *BMC Med Genet.* 2013, 14, 61. doi:10.1186/1471-2350-14-61

7. Bray, F., Lortet-Tieulent, J., Ferlay, J., Forman, D. and Auvinen, A. Prostate cancer incidence and mortality trends in 37 European countries: an overview. *Eur J Cancer*. 2010, 46(17), 3040–3052. doi:10.1016/ j.ejca.2010.09.013

8. Carter, B. S., Bova, G. S., Beaty, T. H., Steinberg, G. D., Childs, B., Isaacs, W. B. and Walsh, P. C. Hereditary prostate cancer: epidemiologic and clinical features. *J Urol.* 1993, 150(3), 797–802.

9. Catalona, W. J., Richie, J. P., Ahmann, F. R., Hudson, M. A., Scardino, P. T., Flanigan, R. C. et al. Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. *J Urol.* 1994, 151(5), 1283–1290.

10. Center, M. M., Jemal, A., Lortet-Tieulent, J., Ward, E., Ferlay, J., Brawley, O. and Bray, F. International variation in prostate cancer incidence and mortality rates. *Eur Urol.* 2012, 61(6), 1079–1092. doi:10.1016/j.eururo.2012.02.054

11. Collin, S. M., Martin, R. M., Metcalfe, C., Gunnell, D., Albertsen, P. C., Neal, D. and Donovan, J. Prostate-cancer mortality in the USA and UK in 1975–2004: an ecological study. *Lancet Oncol*, 2008, 9(5), 445–452. doi:10.1016/s1470-2045(08)70104-9

12. Cybulski, C., Wokolorczyk, D., Huzarski, T., Byrski, T., Gronwald, J., Gorski, B. and Lubinski, J. A large germline deletion in the Chek2 kinase gene is associated with an increased risk of prostate cancer. *J Med Genet.* 2006. 43(11), 863–866. doi:10.1136/jmg.2006.044974

13. Cybulski, C., Wokolorczyk, D., Huzarski, T., Byrski, T., Gronwald, J., Gorski, B. and Lubinski, J. A deletion in CHEK2 of 5,395 bp predisposes to breast cancer in Poland. *Breast Cancer Res Treat.* 2007, 102(1), 119–122. doi:10.1007/s10549-006-9320-y

14. Cybulski, C., Wokolorczyk, D., Kluzniak, W., Jakubowska, A., Gorski, B., Gronwald, J. and Lubinski, J. An inherited NBN mutation is associated with poor prognosis prostate cancer. *Br J Cancer.* 2013, 108(2), 461–468. doi:10.1038/bjc.2012.486

15. Draisma, G., Etzioni, R., Tsodikov, A., Mariotto, A., Wever, E., Gulati, R. and de Koning, H. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. *J Natl Cancer Inst.* 2009, 101(6), 374–383. doi:10.1093/jnci/djp001

16. Eeles, R. A., Olama, A. A., Benlloch, S., Saunders, E. J., Leongamornlert, D. A., Tymrakiewicz, M. and Easton, D. F. Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array. *Nat Genet.* 2013, 45(4), 385–391, 391e381-382. doi:10.1038/ng.2560

17. Eglite, M. E., Zvagule, T. J., Rainsford, K. D., Reste, J. D., Curbakova, E. V. and Kurjane, N. N. Clinical aspects of the health disturbances in Chernobyl Nuclear Power Plant accident clean-up workers (liquidators) from Latvia. *Inflammopharmacology*. 2009, 17(3), 163–169. doi:10.1007/s10787-009-0001-4

18. Etzioni, R., Penson, D. F., Legler, J. M., di Tommaso, D., Boer, R., Gann, P. H. and Feuer, E. J. Overdiagnosis due to prostate-specific antigen screening: lessons from U.S. prostate cancer incidence trends. *J Natl Cancer Inst.* 2002, 94(13), 981–990.

19. Etzioni, R., Tsodikov, A., Mariotto, A., Szabo, A., Falcon, S., Wegelin, J. and Feuer, E. Quantifying the role of PSA screening in the US prostate cancer mortality decline. *Cancer Causes Control.* 2008, 19(2), 175–181. doi:10.1007/s10552-007-9083-8

20. Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., Rebelo, M. and Bray, F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer.* 2015, 136(5), E359–386. doi:10.1002/ijc.29210

21. Ferlay, J., Soerjomataram, I. and Ervik, M., et al. GLOBOCAN 2012 cancer incidence and mortality worldwide. *IARC cancerbase No. 11*. 2013.

22. Forman, D., Stockton, D., Moller, H., Quinn, M., Babb, P., De Angelis, R. and Micheli, A. Cancer prevalence in the UK: results from the EUROPREVAL study. *Ann Oncol*. 2003, 14(4), 648–654.

23. Gardovskis, A., Irmejs, A., Miklasevics, E., Borosenko, V., Bitina, M., Melbarde-Gorkusa, I. and Gardovskis, J. Clinical, molecular and geographical features of hereditary breast/ovarian cancer in Latvia. *Hered Cancer Clin Pract*. 2005, 3(2), 71–76. doi:10.1186/1897-4287-3-2-71

24. Gronberg, H., Damber, L. and Damber, J. E. Familial prostate cancer in Sweden. A nationwide register cohort study. *Cancer*. 1996, 77(1), 138–143. doi:10.1002/(sici)1097-0142(19960101)77:1<138::aid-cncr23>3.0.co;2-5

25. Hemminki, K. Familial risk and familial survival in prostate cancer. *World J Urol*. 2012, 30(2), 143–148. doi:10.1007/s00345-011-0801-1

26. Hsing, A. W., Tsao, L. and Devesa, S. S. International trends and patterns of prostate cancer incidence and mortality. *Int J Cancer*. 2000, 85(1), 60–67.

27. Kvale, R., Auvinen, A., Adami, H. O., Klint, A., Hernes, E., Moller, B. and Bray, F. Interpreting trends in prostate cancer incidence and mortality in the five Nordic countries. *J Natl Cancer Inst.* 2007, 99(24), 1881–1887. doi:10.1093/jnci/djm249

28. Lietuvietis, V. (2006). *Priekšdziedzera vēzis (saslimstība, diagnostisko metožu lietderība riska grupas vīriešiem, kuru PSA serumā 4,0-20,0 ng/ml: promcijas darbs - specialitāte - ķirurģija.* Rīga: Rīgas Stradiņa universitāte, 2006.

29. Lietuvietis, V., Vaganovs, P., Stengrevics, A. un Gardovskis, J. Prostatas vēzis Latvijā: populācijas pētijums 20 gados. *Latvijas Ķirurģijas žurnāls*. 2002, 2(2).

30. Lu-Yao, G. L., Albertsen, P. C., Moore, D. F., Shih, W., Lin, Y., DiPaola, R. S. and Yao, S. L. Outcomes of localized prostate cancer following conservative management. *Jama*. 2009, 302(11), 1202–1209. doi:10.1001/jama.2009.1348

31. Melia, J., Moss, S. and Johns, L. Rates of prostate-specific antigen testing in general practice in England and Wales in asymptomatic and symptomatic patients: a cross-sectional study. *BJU Int.* 2004, 94(1), 51–56. doi:10.1111/j.1464-4096.2004.04832.x

32. Micheli, A., Mugno, E., Krogh, V., Quinn, M. J., Coleman, M., Hakulinen, T. and Capocaccia, R. Cancer prevalence in European registry areas. *Ann Oncol*. 2002, 13(6), 840–865.

33. Myszka, A., Karpinski, P., Slezak, R., Czemarmazowicz, H., Stembalska, A., Gil, J. and Sasiadek, M. M. Irrelevance of CHEK2 variants to diagnosis of breast/ovarian cancer predisposition in Polish cohort. *J Appl Genet.* 2011, 52(2), 185–191. doi:10.1007/s13353-010-0013-1

34. Paquette, E. L., Sun, L., Paquette, L. R., Connelly, R., McLeod, D. G. and Moul, J. W. Improved prostate cancer-specific survival and other disease parameters: impact of prostate-specific antigen testing. *Urology.* 2002, 60(5), 756–759.

35. Popiolek, M., Rider, J. R., Andren, O., Andersson, S. O., Holmberg, L., Adami, H. O. and Johansson, J. E. Natural history of early, localized prostate cancer: a final report from three decades of follow-up. *Eur Urol.* 2013, 63(3), 428–435. doi:10.1016/j.eururo.2012.10.002

36. Potosky, A. L., Kessier, L., Gridley, G., Brown, C. C. and Horm, J. W. Rise in prostatic Cancer Incidence Associated With Increased Use of Transurethral Resection. *Journal of the National Cancer Institute.* 1990, 82(20), 1624–1628. doi:10.1093/jnci/82.20.1624

37. Potosky, A. L., Miller, B. A., Albertsen, P. C. and Kramer, B. S. The role of increasing detection in the rising incidence of prostate cancer. *Jama.* 1995, 273(7), 548–552.

38. Schaeffer, E. M., Carter, H. B., Kettermann, A., Loeb, S., Ferrucci, L., Landis, P. and Metter, E. J. Prostate specific antigen testing among the elderly – when to stop? *J Urol.* 2009, 181(4), 1606–1604. doi:10.1016/j.juro.2008.11.117

39. Vanags, A., Strumfa, I., Gardovskis, A., Borosenko, V., Abolins, A., Teibe, U. and Gardovskis, J. Population screening for hereditary and familial cancer syndromes in Valka district of Latvia. *Hered Cancer Clin Pract.* 2010, 8(1), 8. doi:10.1186/1897-4287-8-8

40. Walsh, T., Casadei, S., Coats, K. H., Swisher, E., Stray, S. M., Higgins, J. and King, M. C. Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer. *Jama.* 2006, 295(12), 1379–1388. doi:10.1001/jama.295.12.1379

PUBLICATIONS

Publications

1. Plonis, J., Kalniete, D., Nakazawa-Miklasevica, M., Irmejs, A., Vjaters, E., Gardovskis, J. and Miklasevics E. The CHEK2 del5395 is a founder mutation without direct effects for cancer risk in the latvian population. *Balkan J Med Genet.* 2015, 18(2), 33–36. doi: 10.1515/bjmg-2015-0083
2. Plonis, J., Nakazawa-Miklasevica, M., Malevskis, A., Vaganovs, P., Pildava, S., Vjaters, E., Gardovskis, J., Miklasevics, E. Survival rates of familial and sporadic prostate cancer patients. *Exp Oncol*. 2015, 37(2), 154–155.
3. Plonis, J., Bokums, K., Cauce, V., Miklasevics, E., Vaganovs, P., Irmejs, A., Gardovskis, J., Vjaters, E. Prostate cancer trends in Latvia during 1990-2012: incidence, prevalence, mortality, and survival rates. *Medicina (Kaunas).* 2014, 50(6), 313–317. doi: 10.1016/j.medici.2014.11.002

International abstracts

1. Plonis, J., Malevskis, A., Miculis, K., Nakazawa-Miklasevica, M., Vaganovs, P., Pildava, S., Abele, A., Gardovskis, J., Vjaters, E., Miklasevics, E. Survival rates of hereditary and sporadic prostate cancer patients. *Eur Urol Suppl*. 2015, 14(3), e1124.
2. Plonis, J., Malevskis, A., Miculis, K., Kalniete, D., Nakazawa-Miklasevica, M., Aksenoka, K., Vaganovs, P., Irmejs, A., Pildava, S., Gardovskis, J., Miklasevics, E., Vjaters, E. CHEK2 del5395 is a founder mutation with no direct effects for cancer risk in Latvian population. *Eur Urol Suppl*. 2015, 14(3), e1125.

3. Abele, A., Plonis, J., Miklasevics, E., Vjaters, E., Irmejs, A., Gardovskis, J., Trofimovics, G. BRCA2 gene mutation characterization in hereditary prostate cancer patients in Latvia. *Eur. Urol. Suppl*. 2009, 8, 569.

Local abstracts

1. Plonis, J., Bokums, K., Cauce, V., Šrubalko A., Geldners, I., Vaganovs, P., Miklaševičs, E., Vjaters, E., Gardovskis, J. Prostatas vēža ārstēšanas īpatnības Latvijā pēdējos 20 gados. *RSU zinātniskās konferences tēzes*. 2013, 253.
2. Plonis, J., Bokums, K., Cauce, V., Vaganovs, P., Miklašēvics, E., Geldners, I., Vjaters, E., Gardovskis, J. Prostatas vēža epidemioloģija Latvijā: izmaiņas pēdējos 20 gados. *RSU zinātniskās konferences tēzes*. 2013, 250.