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CLINICO-EPIDEMIOLOGICAL, DIAGNOSTIC AND PROGNOSTIC FACTORS OF SURVIVAL IN HYPOPHARYNGEAL SQUAMOUS CELL CARCINOMAS

AN ESSAY (AUTO - REFFERAT)

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The scientific jury of 5 habilitated persons in the respective scientific field on the topic of the dissertation is composed of:

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CONTENTS

LIST OF ABBREVIATIONS USED

ALAT	Alanine aminotransferase
ASAT	Aspartate aminotransferase
AF	Alkaline phosphatase
Chi-square test	Chi-square test
Cox Regression	Cox regression analysis
DALY's	Disease Burden Indicator. One DALY = one year of healthy life lost
ECIS	European Cancer Information System
EU-OSHA	European Agency for Safety and Health at Work
Fisher's exact test	Fisher's exact test
HPV	Human Papillomavirus
LND	Frequency and density of lymph nodes
N	Lymph node
PHLPP	Protein phosphatases, a factor for poor prognosis
PS	General condition
BOND	Bulgarian Oncological Scientific Society BDU No further specifications
BSU	No further details
DCC	Differential blood count
EC	European Commission
EU	European Union
KOC	Comprehensive Cancer Centre
CT	Computed tomography
MZ	Ministry of Health
ICD-10	International Statistical Classification of Diseases and Related Health Problems
MS	COUNCIL OF MINISTERS
NCSOZA	National Centre for Public Health and Analyses
PET–SCAN	Positron emission tomography
PKC	Complete blood count
WHO	World Health Organization
SWE	Erythrocyte sedimentation rate
T	Primary tumour
ENT	Ears, nose, throat
HTZ	Hormone replacement therapy
HPC	Hypopharyngeal squamous cell carcinoma
MRI	Magnetic resonance imaging

INTRODUCTION

As an individual diagnosis, cancer not only has a significant impact on patients, but also reflects on the lives of their families and society as a whole. Europe's population accounts for one tenth of the World's population, but a quarter of global cancer cases are found among it. According to the latest available estimates from the European Cancer Information System (ECIS) for EU countries, unless decisive action is taken, the number of people losing their lives to cancer is expected to rise by 24% by 2035, making cancer the leading cause of death in the EU.

Hypopharyngeal squamous cell carcinoma, as a cancer in Bulgaria, is the third most common of all pharyngeal tumors. Most commonly affected is the age between 50-60 years. The incidence of hypopharyngeal cancer is 0.4 to 0.6 per 100,000 population, of all malignant tumors of the ENT organs, and those of the hypopharynx have an incidence of 10.7.

Hypopharyngeal squamous cell carcinoma is very difficult to be detected and tends to recur and metastasize after surgical treatment, despite the correct and carefully selected surgical intervention and neck dissection.

In Bulgaria, hypopharyngeal cancer is most often detected in advanced clinical stages - III and IV - and is very rarely diagnosed in early clinical stages - I and II, due to which the treatment results are unsatisfactory. The reasons for this are complex - the field of study is less accessible; not enough diagnostic methods are used; it happens that the qualification of doctors is not at the required level; the relatively rare incidence of the disease is largely determined by the lack of experience and oncological thinking of the doctors who study it. Diagnosis is also hampered by initial vague and undefined complaints from patients. So-called "poor" symptomatology is not recognized, not sought and becomes a reason to miss opportunities for early and timely diagnosis. These are the cases in which the tumor is a few millimeters to 1 centimeter in size and has not metastasized to the neck.

Modern methods of diagnosis and treatment of cancer in general significantly increase the quality of cancer care for patients, as well as their quality of life and survival. Globally, scientists have developed and continue to develop numerous tests that can be used to screen for certain types of cancer, but to date, no screening test has been developed and proposed for hypopharyngeal cancer.

According to the WHO, if the necessary measures are taken for prevention, early diagnosis, modern treatment and adequate follow-up care of cancer patients, nearly 7 million cancer patients would be able to benefit from the treatment, souls can be saved from being diagnosed with cancer, including a diagnosis of hypopharyngeal squamous cell carcinoma. The Health Organisation highlighted a wide range of proven interventions to prevent new cases of cancer. At their core are prevention, prophylaxis and the promotion of a healthy lifestyle.

In order to make a difference for all Union citizens, the European Cancer Plan 2021 contains concrete actions that will support, coordinate and complement Member States' efforts to reduce the suffering and loss , caused by the disease. It marks the start of a new phase in cancer prevention and care, where patients have access to high-quality screening and treatment , and doctors have access to state-of-the-art technology and specialisation, while fully respecting Member States' health policy responsibilities.

In Bulgaria, with the successful implementation of the National Programme for the Prevention of Chronic Non-Communicable Diseases 2021-2025 and the National Cancer Control Plan, the health status of the population will improve significantly. This will allow people to study, work and participate longer and more effectively in economic and social life.

The implementation of these strategic documents will require intensive cooperation and collaboration with all stakeholders , whose efforts have the potential to contribute directly , or indirectly to the achievement of the overarching objectives set out therein.

Globally, Europe-wide and nationally, efforts are increasingly coalescing around improving individual and societal health through prophylacsis and prevention, health systems efficiency and engaging both parties - those who provide health care and those who receive it.

I. AIM AND OBJECTIVES, MATERIALS AND METHODS

1. Objective

The aim of this study is to identify and evaluate risk factors for hypopharyngeal squamous cell carcinoma and to propose models for early diagnosis, treatment and screening.

2. Tasks to meet the objective

For the successful accomplishment of the set objective, the following research tasks were formulated:

- Study of literature on the topic in the World, Europe , and in Bulgaria for the purpose of the research and derivation of the traditional model of prevention and prophylaxis in international and Bulgarian practice;
- An analysis of data on patients with hypopharyngeal squamous cell carcinoma and the potential for early diagnosis, screening and prognostic survival factors;
- Developing a model for prevention, early diagnosis and a new treatment algorithm to improve patients" survival and reduce morbidity;
- Development and implementation of a screening model through a survey for the main risk factors for hypopharyngeal squamous cell carcinoma;
- Making recommendations on the prevention of cancer, in particular hypopharyngeal squamous cell carcinoma in Bulgaria.

3. Research framework

3.1. Subject of the study

The subject of the study is the dynamics of the prevalence of hypopharyngeal squamous cell carcinoma as a result of the manifestation of the main types of risk factors - individual, behavioral and environmental.

3.2. Object of the study

Patients with hypopharyngeal squamous cell carcinoma were the subject of the study. The main questions on which individuals were - studied related to clinical, diagnostic and prognostic characteristics of survival, as well as to their health care behaviours - smoking, alcohol use, diet, family burden and individual characteristics.

The target group of respondents was formulated according to a proposed model for screening for hypopharyngeal cancer and provides a representative sample regarding risk factors for the disease and opportunities for prevention and early diagnosis.

The screening for risk factors was performed with an individual questionnaire for testing and with specific parameters for observation in the Complex Oncological Center (COC) - Plovdiv Ltd. and Complex Oncological Center (COC) - Burgas Ltd.

A total of 960 individuals were included in the risk factor study, including 480 patients with a proven diagnosis (hypopharyngeal squamous cell carcinoma) and 480 individuals without a diagnosis (control group). The two groups - patients and controls - were comparable in sex and age.

The study was conducted over a 10-year period - from 2010 to 2020 - in relation to the diagnosis, treatment and prevention of hypopharyngeal cancer, with a focus on addressing the preventable risks of this disease.

All subjects were screened according to the proposed Model for Screening People at Increased Risk for Hypopharyngeal Squamous Cell Carcinoma.

The questionnaire (Appendix 1) contained 9 questions , related to tobacco and alcohol abuse, genetic predisposition, occupational hazards, Epstein-Barr virus lesions, human papillomavirus (HPV), chronic upper respiratory diseases, and culinary preferences.

3.3. Working hypothesis

Risk factors for cancer have specific manifestations among those , studied for the purpose of this dissertation. The main working hypothesis is , that internationally established risk factors influence the prevalence of these diseases, but to different degrees, and statistically significant factors can be identified that play a leading role for certain patients (in the case of hypopharyngeal squamous cell carcinoma).

Traditional prevention models are based on awareness-raising campaigns and population health education , focused on all , or selected risk factors.

The manifestation of specificities, in terms of different degrees of influence of the risk factors subject to risk management, implies the identification of a specific prevention model. The introduction and establishment of a standard methodology for the study of risk factors in the practice of a number of countries, provides an opportunity for further utilization of the generated individual data with the help of modern technologies.

The formulation of an alternative model for prevention will allow the reduction of the risk of cancer (in this case hypopharyngeal squamous cell carcinoma) through health information campaigns, implementation of specific screening programs for early diagnosis, treatment and prognostic data on survival.

4. Sources of information

The study was based on all sources of information and data regarding cancer, in particular hypopharyngeal squamous cell carcinoma. The sources include: official normative documents, specialized professional literature, official statistical data, as well as primary data collected on purpose for the needs of the dissertation - results of own research.

5. Study period and duration

The study of the national statistical information on the dynamics of the disease covers the period 2000-2013.

6. Research methods

During the research process we used the following methods to collect the necessary information:

- System-historical-analysis - review of normative and scientific-applied documentation and literature.
- Documentary method (qualitative content analysis of documents) - official normative and scientific and applied documents , related to oncological diseases; health status analyses, cancer risk assessment materials.
- Conceptual analysis - to clarify terminological issues , related to cancer risk factors.
- Sociological/Inquiry method - conducting a survey of risk factors for CHD , using an individual survey questionnaire and with specific parameters for observation (Appendix 1).
- Statistical method
    - ✓ Descriptive statistics
        - The quantitative variables are represented by the summary statistics - mean (Mean), median (Median) and standard deviation (SD);
        - Absolute frequencies (n) - the number of units in a single group and relative frequencies (%) - the number of units in a single group - relative to the total number of units in the sample were used to summarize the results for the categorical variables.
    - ✓ One-Sample Kolmogorov-Smirnov test - used to check the shape of the frequency distribution. Most often the check is against the shape of the normal distribution.
    - ✓ Chi-square test or Fisher's exact test - when examining relationships between descriptive (categorical) data with two or more categories.
    - ✓ t-test for two independent groups (Independent-Samples t-test) - with normal distribution of the variable under study in the compared groups.
    - ✓ Non-parametric Mann-Whitney test (Mann-Whitney test) when comparing two independent groups - used for rank data , or when the shape of the frequency distribution is different from the shape of the normal distribution.
    - ✓ Kaplan-Meier analysis - to estimate cumulative survival , until the occurrence of the event under study.
    - ✓ Binary Logistic Regression - to quantify the factor dependence of a binary variable and different factor variables (categorical or quantitative). The resulting statistic, Odds Ratio (OR), indicates the degree and direction of the impact of the factor under study on the binary dependent variable.

The threshold level of significance is α=0.05. Statistical significance is assumed when the p-value is less than α.

For the processing of the survey data the SPSS (Statistical Package for the Social Sciences) version 20.0 was used.

II. RESULTS AND DISCUSSION

1. Analysis of the dynamics of the incidence of hypopharyngeal squamous cell carcinoma in Bulgaria by districts for the period 2000-2013.

Malignant tumors of the hypopharynx are of interest , because of their discrete symptomatology and the great difficulties encountered by the otorhinolaryngologist in their diagnosis. In terms of incidence, they rank third out of all pharyngeal tumors. The most commonly affected age group is between 50-60 years. The incidence of hypopharyngeal cancer is 0.4 to 0.6 per 100,000 inhabitants. Of all the malignant tumors of the ENT organs, those of the hypopharynx have an incidence of 10.7% /5,6/. Harmful exogenous habits such as smoking, occupational hazards, alcohol abuse, etc. can be pointed out as ethiological factors for the development of hypopharyngeal cancer.

Most often this type of tumors are primary and histologically originate from the structures (epithelial and mesenchymal) that make up the pharynx, but malignant neoplasms growing from adjacent organs are also possible. Of the epithelial tumors, squamous cell carcinoma is most common: differentiated and undifferentiated, and depending on the degree of differentiation into: well differentiated, moderately differentiated, poorly differentiated and undifferentiated. Adenocarcinoma in the hypopharynx is rare. In addition to these epithelial malignant tumors in the hypopharynx, isolated cases of Nechodchkin's malignant lymphoma (tumors of the lymphoid tissue) have been observed.

In men, hypopharyngeal squamous cell carcinoma is 9 times more common than in women, with a ratio of 9.4:1 .

The study on the dynamics of morbidity covers a large group of patients in its own study. In the epidemiological retrospective study, we found a total of 957 cases of patients,diagnosed for the first time with hypopharyngeal squamous cell carcinoma in Bulgaria and registered by the National Cancer Registry districts for the period 2000-2013.

During the study period about 70 cases were diagnosed annually in Bulgaria.

The standardization was made according to the Segi 1960 World Standard. The International Classification of Diseases, 2003 revision 10 (ICD revision 10 of 2003) was used.

Morbidity and mortality rates are calculated per 100 000 people, both total morbidity and mortality , and morbidity by sex - male and female.

Retrospectively and prospectively, the case histories of 102 patients with hypopharyngeal squamous cell carcinoma, 90 men (88.23%) and 12 women (11.77%) aged between 45 and 70 years, registered at the KOC - Plovdiv, were reviewed.

We found an almost twofold increase in the actual incidence of hypopharyngeal squamous cell carcinoma in Bulgaria by region over the study period - from 0.72 cases per 100 000 population in 2000 to 1.20 cases per 100 000 population in 2013 **(Table No. 1).**

Table No. 1. Incidence of hypopharyngeal squamous cell carcinoma in the period 2000-2013 in the Republic of Bulgaria

Year	**Absolute number of new cases**			**Rate per 100 x population for actual incidence**			**Rate per 100 x population for standard incidence rate**		
	men	**women**	**total**	**men**	**women**	**total**	**men**	**women**	**total**
2000	51	8	59	1.28	0.19	0.72	0.86	0.12	0.47
2001	56	6	62	1.45	0.15	0.72	1.06	0.08	0.55
2002	63	8	71	1.65	0.19	0.90	1.13	0.12	0.60
2003	64	3	67	1.68	0.07	0.85	1.08	0.06	0.53
2004	51	8	59	1.35	0.20	0.76	0.92	0.12	0.49
2005	64	10	74	1.70	0.25	0.96	1.11	0.17	0.61
2006	60	4	64	1.61	0.10	0.83	1.01	0.05	0.55
2007	56	10	66	1.51	0.25	0.86	0.95	0.14	0.52
2008	48	7	55	1.30	0.18	0.72	0.81	0.11	0.44
2009	68	7	75	1.85	0.18	0.99	1.19	0.11	0.61
2010	63	6	69	1.73	0.15	0.92	1.10	0.10	0.56
2011	58	8	66	1.62	0.21	0.90	1.05	0.12	0.57
2012	77	6	83	2.12	0.16	1.14	1.27	0.13	0.66
2013	79	8	87	2.24	0.21	1.20	1.28	0.11	0.66

The standardised incidence of hypopharyngeal squamous cell carcinoma increased from 0.47 cases per 100,000 population in 2000 to 0.66 cases per 100,000 population in 2013.

In men, the actual incidence of hypopharyngeal squamous cell carcinoma increased from 1.28 cases per 100 000 population in 2000 to 2.24 cases per 100 000 population in 2013.

In women, we found a symbolic rate of increase in the incidence of hypopharyngeal squamous cell carcinoma - from 0.19 cases per 100,000 population in 2000 to 0.21 cases per 100,000 population in 2013.

In men, the standardised incidence rate of hypopharyngeal squamous cell carcinoma increased from 0.86 cases per 100 000 men in 2000 to 1.28 cases per 100 000 men in 2013, while in women we found no increase - 0.12 cases per 100 000 women in 2000 and 0.11 cases per 100 000 women in 2013 000 women and 0.14 cases per 100 000 women.

In men by districts in Bulgaria, the highest standardized incidence of hypopharyngeal squamous cell carcinoma was found in the following districts:

- The highest standardized incidence rate of hypopharyngeal squamous cell carcinoma of 3.8 cases per 100 000 men was found in Dobrich district;

- The second place with a high standardized incidence rate of hypopharyngeal squamous cell carcinoma of 3.7 cases per 100,000 men was found in Silistra district;
- In third place with a high standardized incidence rate of hypopharyngeal squamous cell carcinoma of 3.1 cases per 100 000 men, we find Haskovo region;
- The fourth place with a high standardized incidence rate of hypopharyngeal squamous cell carcinoma of 3.0 cases per 100 000 population was found in Gabrovo district.

For women by district, we found the highest standardized incidence rates in the districts as follows:

- The first place with the highest standardized incidence rate of 1.5 cases per 100 000 women is found in Smolyan district;
- Second place with a high standardized incidence rate of 0.6 cases per 100 000 women was found in Vratsa district;
- In third place with a high standardized incidence rate of 0.3 cases per 100 000 women, we find Veliko Tarnovo district;
- In fourth place, with a high standardised incidence rate of 0.2 cases per 100 000 women, we find the districts of Pleven and Stara Zagora;

Hypopharyngeal cancer is most commonly found in the 50-54 and 55-59 age groups. At a young age, up to 29 years, hypopharyngeal cancer was found in single cases in 2000, 2001, 2003, 2005 and 2007 **(Table No. 2).**

Table No. 2. Incidence of the actual incidence of hypopharyngeal squamous cell carcinoma by age groups for the period 2000-2013 in Bulgaria

Year	**Actual incidence of hypopharyngeal cancer by age group for the period 2000-2013 in Bulgaria**								
	0 - 29	**30-39**	**40-44**	**45-49**	**50-54**	**55-59**	**60-64**	**65+**	**total**
2000	1	1	1	4	13	16	5	18	59
2001	2	2	4	11	11	10	11	11	62
2002	0	1	5	8	16	15	11	15	71
2003	1	0	1	6	11	10	15	23	67
2004	0	0	2	10	8	12	12	15	59
2005	1	1	3	8	14	16	12	19	74
2006	0	1	3	13	11	13	13	10	64
2007	1	2	1	2	13	14	13	20	66
2008	0	1	1	6	8	15	7	17	55
2009	0	0	4	7	11	20	9	24	75
2010	0	1	1	9	9	18	11	20	69
2011	0	2	4	8	14	12	10	16	66
2012	0	3	2	7	12	15	18	26	83
2013	0	0	1	9	11	12	16	38	87

By histological type, we found the following structure of hypopharyngeal cancer cases in the period 2000-2013:

- Squamous cell keratinizing without further refinement (CSF) - ranked first in 61.04% of cases;
- Squamous cell carcinoma was second in 27.27% of cases;
- In third place - squamous cell carcinoma, large cell, nonkeratinizing in 9.09% of cases;
- In fourth place, adenocarcinoma BD in 2.60% of cases.

Organ preservation of the pharynx is also a very important part of the treatment of hypopharyngeal squamous cell carcinoma. Therefore, we decided to look forward favourable effects towards 3- and 5-years survival in the treatment of patients with hypopharyngeal squamous cell carcinoma.

Since 1990, there has been a trend to treat hypopharyngeal squamous cell carcinoma by radiotherapy without surgery.

We find that the trend of combined treatment of hypopharyngeal squamous cell carcinoma by surgery and radiotherapy is maintained and remains relatively unchanged.

We find that in a minority of patients with hypopharyngeal squamous cell carcinoma, treatment is only surgery.

We reported the epidemiological measures of the effectiveness of the treatment of hypopharyngeal cancer by examining the actual and standardized mortality of this localization in Bulgaria for the period of 2000-2013 **(Table No. 3).**

Table No. 3. Actual and standardised mortality by sex (men and women) from hypopharyngeal squamous cell carcinoma for the period 2000-2013. in the Republic of Bulgaria

Year	**Number of cases**			**Coefficient of actual mortality per 100 000 men/women**			**Standardised death rate per 100 000 men/women**		
	men	**women**	**total**	**men**	**women**	**total**	**men**	**women**	**total**
2000	39	9	48	0.98	0.22	0.59	0.71	0.14	0.41
2001	51	6	57	1.32	0.15	0.72	0.90	0.07	0.47
2002	33	6	39	0.86	0.15	0.50	0.60	0.08	0.33
2003	52	9	61	1.34	0.22	0.78	0.89	0.11	0.48
2004	56	6	62	1.49	0.15	0.80	0.96	0.08	0.49
2005	35	13	48	0.93	0.33	0.62	0.59	0.14	0.36
2006	53	14	67	1.42	0.35	0.87	0.95	0.18	0.55
2007	44	14	58	1.19	0.35	0.77	0.75	0.22	0.46
2008	34	9	43	0.92	0.23	0.56	0.58	0.14	0.34
2009	40	10	50	1.09	026	0.66	0.72	0.13	0.41
2010	38	7	45	1.04	0.18	0.60	0.65	0.11	0.36
2011	47	10	57	1.31	0.27	0.78	0.77	0.15	0.44
2012	62	6	68	1.74	0.16	0.93	1.05	0.12	0.56
2013	48	3	51	1.36	0.08	0.70	0.75	0.04	0.37

For men, the actual mortality rate increased from a rate of 0.98 cases per 100,000 men in 2000 to a rate of 1.36 cases per 100,000 men in 2013.

For women, we find a decline in the actual mortality rate from a rate of 0.22 cases per 100,000 women in 2000 to a rate of 0.08 cases per 100,000 women in 2013, with a rate of increase of 0.35 cases per 100,000 women in 2006 and 2007 and a rate of 0.33 cases per 100,000 women in 2005.

For men, the standardised mortality rate increased from a rate of 0.71 cases per 100 000 men in 2000 to 0.75 cases per 100 000 men in 2013.

In women, the standardised mortality rate decreased from a rate of 0.14 cases per 100 000 women in 2000 to a rate of 0.04 cases per 100 000 women in 2013. The instantaneous lethality rate that we found takes into account the good clinical effect of any new comprehensive approach , applied in health structures with oncological activity , related to hypopharyngeal cancer.

We also investigated the cumulative survival time as a direct epidemiological measure of the effectiveness of the treatment and the follow-up of the 102 patients with hypopharyngeal cancer , registered in KOC - Plovdiv for the period 2000-2013 **(Table No. 4).**

The cumulative survival time indicator is a direct epidemiological measure of the clinical effect of the application of the complex approach for the treatment of hypopharyngeal cancer in the KOC - Plovdiv, among the population of Plovdiv, Pazardzhik and Smolyan regions with a total population of 1 020 556 inhabitants. It represents the probability that a patient will survive the time period studied for up to 5 years.

The overall survival of the 102 patients we observed in the KOC - Plovdiv for the study period 2000-2013 increased as follows:

- The 1-year survival rate rose to 14.46% of observed cases;
- Over 1-year survival rose to 7.22% of observed cases;
- The 5-year survival rate reached 2.42% of the observed cases.

Table No. 4. Cumulative survival of diagnosed and registered patients with hypopharyngeal squamous cell carcinoma in KOC - Plovdiv for the period 2000-2013.

Group	**Coefficient of cumulative survival**						**Median survival visibility**	**P**
Cancer of the hypopharynx C 13.9	3 months %	6 months %	9 months %	1 year %	Over 1 year %	5 years %		
	36.36	31.82	11.37	9.09	6.84	4.54	23.00	0.16

Cancer of the hypopharynx C 13.2	35. 89	20.52	15.38	20.52	7. 69	0	25. 0	0.16
Overall survival	36. 14	26. 51	13. 25	14.46	7. 22	2. 42	21. 00	0.061

From our clinical-epidemiological study in the period 2000-2013 of the patients registered and dispensed in the KOC - Plovdiv with hypopharyngeal cancer, **we found that only 14.46% of cases reached 1-year survival, and only 2.42% of cases reached 5-year survival.**

- In the period 2000-2013, a total of 957 cases of newly diagnosed hypopharyngeal cancer patients were diagnosed in Bulgaria, or about 70 people per year in total. We find an almost doubling of the incidence rate, with a rate of 0.72 cases per 100,000 population in 2000 and of 1.20 cases per 100,000 population in 2013. The standardised incidence rate increased from 0.47 cases per 100,000 population in 2000 to 0.66 cases per 100,000 population in 2013.
- Hypopharyngeal cancer is 9 times more common in men , compared to women /9.4:1/. The actual incidence rate for men increased from 1.28 cases per 100,000 men in 2000 to 2.24 cases per 100,000 men in 2013. The actual incidence rate for women increased slightly from 0.19 cases per 100,000 women in 2000 to 0.21 cases per 100,000 women in 2013.
- Hypopharyngeal cancer is most commonly found in the 55-64 age group. We find very rare cases of hypopharyngeal cancer up to the age of 45 years, and cases up to the age of 24 years are sporadic.
- The actual mortality rate increased from 0.59 deaths per 100 000 population in 2000 to 0.70 deaths per 100 000 population in 2013. The actual mortality rate for men increased from 0.98 deaths per 100 000 men in 2000 to 1.36 deaths per 100 000 men in 2013. For women, the actual mortality rate decreased from 0.22 deaths per 100 000 women in 2000 to 0.08 deaths per 100 000 women in 2013 000 women in 2013. The standardised mortality ratio decreased overall from 0.41 cases per 100 000 population in 2000. to 0.37 cases per 100,000 population in 2013.
- We propose a project to validate an algorithm for a modern approach to early diagnosis and comprehensive treatment of hypopharyngeal cancer in Bulgaria.

2. Clinical, diagnostic and prognostic characteristics for survival with hypopharyngeal squamous cell carcinoma

We performed a retrospective and prospective analysis **of 215 cases ,** treated in ENT clinics and registered in KOC - Plovdiv and KOC - Burgas in the period 2010-2020.

Of the **215 cases** of hypopharyngeal squamous cell carcinoma studied, 206 were male (95.8%) and 9 were female (4.2%).

We identified the most frequent anatomical localizations of hypopharyngeal squamous cell carcinoma **(Table No. 5).**

Table No. 5. Anatomical localizations of hypopharyngeal squamous cell carcinoma

By №	Localization	Indicators	
		Number	%
1.	Pyriform sinus	166	77.3
2.	Posterior pharyngeal wall	36	16.5
3.	Posterior cricoid area	13	6.2
Total		**215**	**100**

In 166 cases, hypopharyngeal squamous cell carcinoma originated from the pyriform sinus (77.3% of cases).

In 36 cases, hypopharyngeal squamous cell carcinoma originated from the posterior pharyngeal wall (16.5% of cases).

In 13 cases, hypopharyngeal squamous cell carcinoma originated from the posterior cricoid region (6.2% of cases).

We also performed a retrospective analysis of the treatment of hypopharyngeal squamous cell carcinoma. The study group of 215 cases underwent surgical treatment is as follows **(Table No. 6).**

Table No. 6. Operative treatment performed on a study group of 215 cases during the period 2010-2020.

By №	Type of surgical treatment	Indicator	
		Number	%
1.	Partial hypopharyngeal resection	47	21.64
2.	Partial laryngectomy with partial hypopharyngeal resection	15	7.2
3.	Total laryngectomy with partial hypopharyngeal resection	117	54.6
4.	Total laryngectomy with total hypopharyngectomy and gastropharyngeal anastomosis	27	12.4
5.	Total laryngectomy with hypopharyngeal resection and enteropharyngeal anastomosis	9	4
Total		**215**	**100**

Of the 215 patients with hypopharyngeal squamous cell carcinoma that we observed, 47 underwent surgical partial hypopharyngeal resection (21.64% of cases).

15 patients with hypopharyngeal carcinoma underwent partial laryngectomy with partial hypopharyngeal resection (7.2% of cases).

Total laryngectomy with partial hypopharyngeal resection was performed in 117 patients with hypopharyngeal carcinoma (54.6% of cases).

Total laryngectomy with total hypopharyngectomy and gastro-pharyngeal anastomosis was performed in 27 patients with hypopharyngeal carcinoma (12.4% of cases).

9 patients underwent total laryngectomy with hypopharyngeal resection and entero-pharyngeal anastomosis (4.2% of cases).

2.1. Radiotherapy

135 patients with hypopharyngeal carcinoma underwent postoperative radiotherapy in a radiotherapy clinic (62.8% of cases).

2.2. Survival index

Using the Kaplan-Meier method, we performed a survival analysis of the 215 patients with hypopharyngeal squamous cell carcinoma we studied. The results are as follows **(Table No. 7).**

Table No. 7. Mean survival according to surgical intervention in hypopharyngeal squamous cell carcinoma

Group	**Cumulative survival**		**Median survival (in months)**	**p**
	1-year-old (percentage)	**3-year (percentage)**		
General survival with surgical intervention	69	43	20.00 months	0.160
Radical surgical interventions and chemo-radiotherapy	76	56	24.00 months	<0.001

As a next stage of the study, the likely factors influencing overall survival in patients with hypopharyngeal squamous cell carcinoma were analyzed.

Follow-up of this group of 215 patients with hypopharyngeal squamous cell carcinoma reached 90.7% of cases.

We found the 1-year survival rate of cases with hypopharyngeal squamous cell carcinoma with surgical intervention to be 69% and the 3-year survival rate to be 43% of cases. The median survival of patients with hypopharyngeal squamous cell carcinoma is 20 months.

In the second group of operated patients with radical surgical interventions and chemo-radiotherapy, we found the 1-year survival rate of cases with hypopharyngeal squamous cell carcinoma with radical surgical interventions and chemo-radiotherapy to be 76% and the 3-year survival rate to be 56% of cases. The median survival of patients with

radical surgery and chemoradiotherapy for hypopharyngeal squamous cell carcinoma was 24 months.

2.3. Stage of the primary tumor

We found a significant association /p<0.001, Kramer's coefficient=0.311/ between the presence of cervical lymph node metastases, local recurrences and distant metastases in patients with hypopharyngeal squamous cell carcinoma.

The median survival of patients with hypopharyngeal squamous cell carcinoma without cervical and regional metastases was found to be three times that of patients with metastases, and in absolute terms, this was over a 3-year survival for patients **(Table No. 8).**

Table No. 8. Mean survival according to the presence of cervical and regional metastasis in hypopharyngeal squamous cell carcinoma

Metastasis to cervical and regional lymph nodes	**Median survival in months**	**95% fiduciary interval**
No metastases	45.29 months	59.10–85.03
With metastases	19.20 months	15.61–18.30

We also identified the main causes of death in hypopharyngeal squamous cell carcinomas **(Table No. 9).**

Table No. 9. Major causes of death in hypopharyngeal squamous cell carcinoma

By №	**Main causes of death in hypopharyngeal squamous cell carcinoma**	**Indicators**	
		Number	**%**
1.	Cervical lymph node metastases	47	21.9
2.	Local recurrences	81	37.5
3.	Distant metastases	67	31.3

- In our clinical-epidemiological study we found that: cervical metastases were the cause of death in 47 patients (21.9% of cases); local recurrences were the cause of death in 81 patients (37.5% of cases); distant metastases were the cause of death in 67 patients (31.3% of cases).
- The analysis suggests that tumor size and stage of hypopharyngeal squamous cell carcinoma affects , the prognosis , regarding survival in patients
- We find that hypopharyngeal squamous cell carcinoma is detected early with a marked tendency to recur and metastasize rapidly after surgical intervention in patients with this type of carcinoma.
- We found that proper and carefully selected surgical intervention, necessarily with cervical lymph node dissection, along with adjuvant postoperative chemo-

radiotherapy, is the main successful strategy for curative approach in patients with hypopharyngeal squamous cell carcinoma.

- We found that hypopharyngeal squamous cell carcinomas of the posterior pharyngeal wall tend to have a higher incidence of metastasis and recurrence , compared with hypopharyngeal squamous cell carcinomas of the other two sites, the pyriform sinus and the posterior cricoid region.

3. Salvage measures to increase survival in recurrent hypopharyngeal squamous cell carcinoma after surgery and chemoradiotherapy

Despite advances in surgical approaches to the treatment of hypopharyngeal squamous cell carcinoma and the resulting radiochemotherapy, this type of carcinoma has one of the worst prognoses among malignant tumors of the head and neck.

It is very important both to treat the initial disease of hypopharyngeal squamous cell carcinoma and to influence the recurrence, which contributes to the improvement of the applied treatment programs and the overall survival of patients.

We aimed in this study to evaluate the effectiveness of salvage treatment programs in recurrences after initial treatment of hypopharyngeal squamous cell carcinoma.

We included 49 patients treated for recurrent hypopharyngeal squamous cell carcinoma in the KOC - Plovdiv for the period 2010-2020. **The mean time to detection of recurrence from the start** of treatment for hypopharyngeal squamous cell carcinoma was 10.3 months (range 2.1 months to 61.1 months). The overall relapse rate was 45% among the observed group **(Table No. 10).**

Table No. 10. Recurrent squamous cell carcinoma, after initially applied surgical and chemo-radiotherapy in 49 patients, treated for recurrent hypopharyngeal squamous cell carcinomas

By №	**Effectiveness and outcomes of salvage actions in recurrences after initial surgical and chemo-radiotherapy**	**Indicators**	
		Number months	**%**
1.	Mean time to detection of recurrences since the start of treatment	10.3 months	-
2.	By type of recurrence of cases with recurrent hypopharyngeal squamous cell carcinomas: • Local relapses • Locoregional relapses • Regional relapses • Distant relapses	 42 cases 49 cases 11 cases 9 cases	 85 100 23 19

We found significant cumulative tumor-free survival among the group with additional surgery and chemoradiotherapy and no 3-year survival in cases with additional chemoradiotherapy alone **(Table No. 11).**

Table No. 11. Cumulative survival in patients with recurrent CKD and with conducted additional surgery and chemo-radiotherapy, and the cases with additional chemo-radiotherapy only

By №	Cumulative survival	Indicators		95% Confidential interval
		Number	%	
1.	Median survival in patients with surgery and chemoradiotherapy: • 1-year survival rate • 3- year survival	 47 38	 96 79	 16.61– 28.30
2.	Median survival in patients with chemoradiotherapy alone: • 3-year survival	 0	 0	 0

- We found that salvage treatment of recurrent hypopharyngeal squamous cell carcinomas after initial surgical and chemoradiotherapy resulted in increased 1-year and 3-year survival after additional surgical and chemoradiotherapy, 96% of cases for 1-year survival and 79% of cases for 3-year survival, respectively.
- We found no 3-year survival in patients with recurrent hypopharyngeal squamous cell carcinoma and additional chemoradiotherapy alone after their initial treatment.

4. Proposal for a model on early and timely diagnosis of hypopharyngeal squamous cell carcinoma and treatment algorithms

- **Diagnostic algorithms**

1. Anamnesis;

2. Examination of the head and neck by palpation;

3. Examination of the oral cavity and pharynx, by means of devices with mirror images;

4. Performance of hypopharyngoscopy with a flexible fiberoptic laryngoscope;

5. Imaging methods:

- Computed tomography /CT/;

- Nuclear Magnetic Resonance (NMR);

- Positron emission tomography /PET-SCAN/;

- Isotope diagnostics;

- Biopsy of the tumor formation and histological examination.

- **Healing algorithms**

I. Basic treatment strategy in hypopharyngeal squamous cell carcinoma:

- Correct and carefully selected surgical intervention;

- Neck dissection;

- Adjuvant postoperative radiotherapy or chemo-radiotherapy.

II. In early clinical stages (I and II) of hypopharyngeal squamous cell carcinoma, which are extremely rare, radiotherapy is the leading method of treatment:

- Definitive radiotherapy for clinical stage I and II hypopharyngeal squamous cell carcinoma and achieving increased survival , therefore ;

- Clinical stage III hypopharyngeal squamous cell carcinoma: surgical treatment and postoperative radiotherapy and achieving increased survival.

III. In the advanced clinical stages (IV-a and IV-b), the leading method is surgery, followed by radiotherapy or chemoradiotherapy and achieving increased survival.

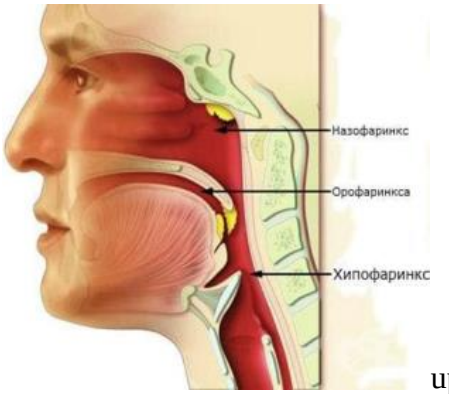
IV. In line with the specificity of surgical treatment, the active application of intensity-modulated radiotherapy appears to be the key for improving the outcome of the overall treatment of hypopharyngeal squamous cell carcinoma and achieving increased survival.

V. Neo-adjuvant chemotherapy with: the two drugs Platinum and Taxane or the three drugs Platinum, Taxane and 5.Flurouracil (5.FU), may be a useful procedure for patients with advanced hypopharyngeal squamous cell carcinoma in order to achieve operability in these patients and the possibility of increasing survival.

5. Screening for early diagnosis of hypopharyngeal squamous cell carcinoma - part of prophylaxis

Screening is used for early diagnosis of cancer, before the first symptoms appear. Worldwide, scientists have developed and continue to develop many tests - that can be used to screen for certain types of cancer. **Unfortunately, to date, there is no screening developed and offered for hypopharyngeal cancer.**

Still nationally, hypopharyngeal cancer is detected in advanced clinical stages (III and IV) and very rarely detected in early clinical stages (I and II). Hypopharyngeal cancer metastasizes very rapidly after surgery and has a poor prognosis and low survival **(Figure No. 1).**



upper -pharynx , meso-pharynx , hypo-pharynx – from up to down

Figure No. 1. Pharinx - anatomical and topographical characterization

The screening test we offer is a test to identify individuals who are at risk for hypopharyngeal cancer and are more likely to suffer from this disease.

The aim of our screening for early diagnosis of hypopharyngeal cancer is to achieve the following results:

1. To reduce the number of people , who develop hypopharyngeal cancer.

2. To reduce the number of people , who die from this disease.

3. To find people at risk , who need screening more often versus people at low risk.

Our future prevention and screening strategies are aimed at early diagnosis of hypopharyngeal cancer in order to reduce morbidity and mortality from this disease.

Raising public awareness of the role of screening, early detection, access to treatment and clinical trials are essential in our strategy to improve outcomes for early diagnosis of hypopharyngeal cancer.

The guiding principle in our strategy for prevention and screening for hypopharyngeal cancer is aimed at addressing the preventable risks for this disease.

Smoking is the most serious but preventable risk of hypopharyngeal cancer. Smoking cessation remains the most important prevention to reduce the risk of hypopharyngeal cancer.

Preventable risks for hypopharyngeal cancer are also the daily use of large amounts of alcohol and the regular consumption of smoked foods.

Our understanding of a healthy lifestyle means educating adolescents and the population towards meaningful habits:

- Use of quality foods;

- Smoking cessation;
- Quitting alcohol;
- Active sports for every age group.

In order to achieve a healthy lifestyle, we consider it necessary to turn to the European institutions, from which we demand psychological support for the population in the Republic of Bulgaria, as a member of the European Union, expressed in the preparation of common programmes:

- to give up smoking and alcohol consumption;
- to supplement with harm reduction methods;
- to develop effective strategies for the prevention of hypopharyngeal cancer in the youngest and adolescent population.

Screening for early diagnosis of hypopharyngeal cancer is an attractive strategy to increase the survival rate of this disease.

6. Chart patterns for screening examination and early diagnosis for hypopharyngeal squamous cell carcinoma

The patient's card from the screening examination for hypopharyngeal carcinoma is completed by the doctor during the history taking, the screening ENT examination, the examination of the medical documentation and, if necessary, an examination by an oncologist, with a view to assessing inclusion and exclusion criteria.

In the patient's card, the following are noted: patient number, date of screening examination, patient's initials and date of birth.

6.1. Questionnaire model for people at increased risk for hypopharyngeal squamous cell carcinoma

1. Prolonged smoking - active and passive.

2. Daily consumption of large amounts of alcohol.

3. Genetic predisposition. Presence of a malignant disease with this location in the family history.

4. Occupational hazards - heavy metals, production of chemical paints, coal dust and asbestos.

5. Specific defeat with the Epstein-Barr virus.

6. Human papilloma virus /HPV/.

7. Chronic diseases of the upper respiratory tract

8. Presence of untreated teeth in the oral cavity.

9. Culinary preferences in the form of certain foods.

- **Symptoms**

1. Swollen lymph nodes in the neck area (first sign of hypopharynx cancer problem in over 50% of all diagnosed cases).

2. Sore throat, localized in only one place, which continues even after treatment.

3. Pain that passes from the throat to the ears.

6.2. An early diagnosis model for hypopharyngeal squamous cell carcinoma

1. History of the disease with local ENT status with biopsy.

2. Pharyngoscopy and/or bronchoscopy.

3. X-ray of the lungs.

4. Computed tomography examination, MRI of the primary tumor.

5. In the presence of enlarged lymph nodes in the neck region, CT/MRI of the upper mediastinum is performed.

6. Ultrasound of abdominal organs.

7. Dental status (rehabilitation and treatment).

8. Bone marrow puncture for staging lymphomas and squamous cell carcinomas G^2 and G^3.

9. Laboratory tests (PCK, ESR, Platelets, ALT, AST, Creatinine, AF, Total bilirubin, Blood sugar, Fibrinogen, Beta 2 microglobulin, Urine test).

7. Risks of screening for hypopharyngeal cancer

Early diagnosis screening for hypopharyngeal cancer helps doctors detect the disease at an earlier stage.

Early diagnosis leads to greater chances of curing hypopharyngeal cancer patients and increasing their survival.

Like any test, screenings also have their risks. These are:

• False positives

Sometimes a screening test can show the presence of a tumor formation, but after the appointment of additional tests, it is established that the tumor is not malignant.

• Overdiagnosis

Additional tests may be ordered that are not necessary. They are appointed in case of false positive results. These procedures can be unpleasant for the patient, lead to additional costs and cause unnecessary stress to the patient.

• Falsely incorrect results

Sometimes screening tests can find that a person does not have hypopharyngeal cancer. As a result, the patients will not receive the treatment they need. This feigned well-being behaviour leads to later diagnosis of hypopharyngeal cancer and reduced survival in these patients.

8. Study of risk factors for cancer of the hypopharynx

The study was conducted over a 10-year period (2010-2020) in relation to the diagnosis, treatment and prevention of hypopharyngeal cancer with a view to addressing the preventable risks of this disease. The subjects were surveyed according to our proposed Model for screening people at increased risk for HSC.

The survey card (Appendix 1) contains 9 questions related to: long-term smoking - active and passive; daily consumption of large amounts of alcohol; genetic predisposition (presence of a malignant disease with this location in the family history); occupational hazards; specific lesion with the Epstein-Barr virus; human papilloma virus /HPV/; chronic inflammatory diseases of the upper respiratory tract; presence of untreated teeth in the oral cavity and culinary preferences in the form of certain foods.

960 people participated in the study - 480 patients with a proven diagnosis and 480 conditionally healthy people, randomly selected (control group).

The distribution of the examined persons, depending on gender, is relatively the same in the two examined groups - patients and controls (p=0.515).

The results are presented in **Table No. 12.**

Table No. 12. Distribution of the subjects, depending on gender, in the two groups - patients and controls and results of the chi-square test.

Gender		Controls	Patients	Total	p
Women	N	50	44	94	0,515
	%	10.4%	9.2%	9.8%	
Men	N	430	436	866	
	%	89.6%	90.8%	90.2%	
Total	N	480	480	960	
	%	100.0%	100.0%	100.0%	

In the test group and in the control group of the examined, men predominate (about 90%), which confirms that men are many times more affected by the disease than women (about 10%).

The subjects - controls and patients - were divided into 6 age groups. The distribution by age groups is presented in **Table No. 13**.

Table No. 13. Distribution of subjects, depending on age, in the two groups - patients and controls and results of the chi-square test

Age Group		Controls	Patients	Total	p
25-34 years	N	2	2	4	1,000
	%	0.4%	0.4%	0.4%	
35-44 years	N	10	10	20	
	%	2.1%	2.1%	2.1%	
45-54 years	N	60	60	120	
	%	12.5%	12.5%	12.5%	
55-64 years	**N**	**350**	**350**	**700**	
	%	**72.9%**	**72.9%**	**72.9%**	
65-74 years	N	50	50	100	
	%	10.4%	10.4%	10.4%	
75 years +	N	8	8	16	
	%	1.7%	1.7%	1.7%	
Total	N	480	480	960	
	%	100.0%	100.0%	100.0%	

The presented table shows that the largest group of patients with hypopharyngeal squamous cell carcinoma is in the age group of 55-64 years.

8.1. Results of the analysis of the relationship between the suspected risk factors and the disease under study (Hypopharyngeal squamous cell carcinoma)

The relationship between the putative risk factors and the disease was examined with the Chi-square test.

• *Prolonged smoking*

The analysis from the study of the relationship between the disease and smoking showed that there was a statistically significant relationship ($p<0.001$). The results are presented in **Table No. 14.**

Table No. 14. Distribution of subjects, depending on smoking, in the two groups - patients and controls and results of the chi-square test

Long-term smoking		Controls	Patients	Total	p
No	N	240	10	250	<0,001
	%	50.0%	2.1%	26.0%	

Active smoker	N	168	408	576	
	%	35.0%	85.0%	60.0%	
Passive smoker	N	72	62	134	
	%	15.0%	12.9%	14.0%	
Total	N	480	480	960	
	%	100.0%	100.0%	100.0%	

In the group of controls, 50% of the examined were non-smokers, and in the patients this percentage was 2.1% (Fig. #2). More than 80% of patients are active smokers, while in the group of controls this share is significantly lower - 35.0%.

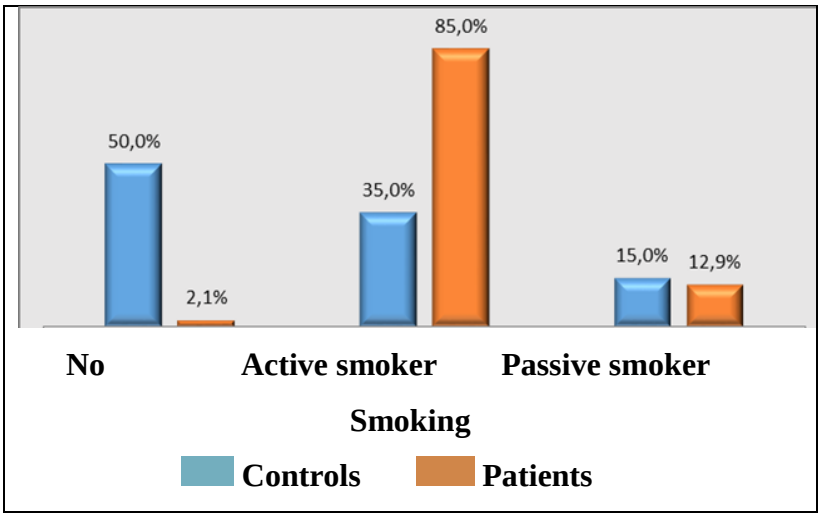


Figure No. 2. Relative share of subjects, depending on smoking, in both groups - patients and controls

• *Daily consumption of large amounts of alcohol*

Daily heavy alcohol consumption was much more common in patients (85.0%) compared to controls (10.0%). This difference is statistically significant (p<0.001). The results of the analysis are presented in **Table No. 15** and **Figure No. 3.**

Table No. 15. Distribution of subjects, depending on alcohol consumption, in the two groups - patients and controls and results of the chi-square test

Daily consumption of large amounts of alcohol		**Controls**	**Patients**	**Total**	**p**
Yes	N	48	408	456	<0,001
	%	10.0%	85.0%	47.5%	
No	N	432	72	504	
	%	90.0%	15.0%	52.5%	

Total	N	480	480	960	
	%	100.0%	100.0%	100.0%	

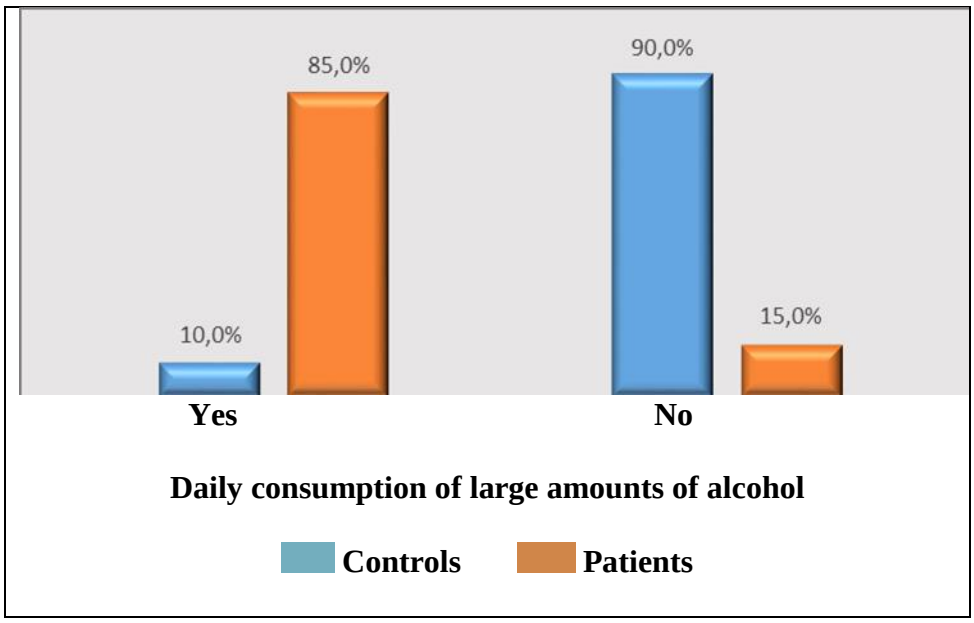


Figure No. 3. Relative share of the examined persons, depending on the use of alcohol, in the two groups - patients and controls

• *Genetic predisposition. Presence of a malignant disease with this location in the family history*

A statistically significant relationship was established between the examined disease and the presence of a malignant disease with this location in the family history (p<0.001) **(Table No. 16).**

Table No. 16. Distribution of the examined persons, depending on the family burden, in the two groups - patients and controls , and results of the chi-square test

Genetic predisposition. Presence of a malignant disease with this location in the family history		**Controls**	**Patients**	**Total**	**p**
Yes	N	58	336	394	<0,001
	%	12.1%	70.0%	41.0%	
No	N	422	144	566	
	%	87.9%	30.0%	59.0%	
Total	N	480	480	960	
	%	100.0%	100.0%	100.0%	

In patients with the presence of a family burden, 70.0% of those examined, and in controls, this percentage is much lower (12.1%) **(Figure No. 4).**

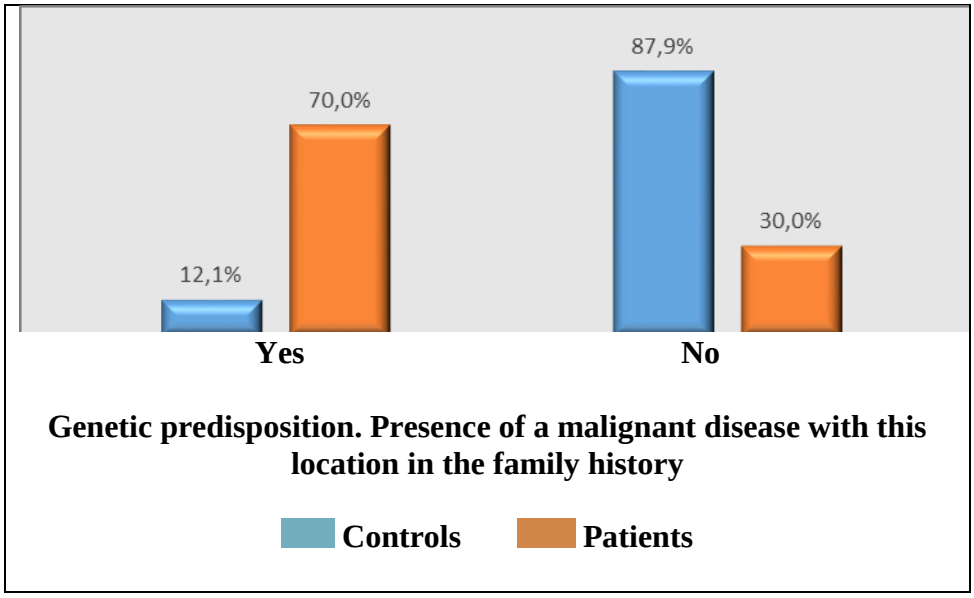


Figure No. 4. Relative share of the examined persons, depending on the family burden, in the two groups - patients and controls

• *Occupational hazards*

The relationship between the disease and the presence of occupational hazards was investigated. The results show that there is a statistically significant relationship ($p<0.001$) **(Table No. 17).**

Table No. 17. Distribution of the examined persons, depending on the occupational hazards, in the two groups - patients and controls and results of the chi-square test

Occupational hazards		Controls	Patients	Total	p
No	N	375	86	461	<0,001
	%	78.1%	17.9%	48.0%	
Heavy metals	N	24	110	134	
	%	5.0%	22.9%	14.0%	
Production of chemical dyes	N	19	43	62	
	%	4.0%	9.0%	6.5%	
Coal dust	N	14	38	52	
	%	2.9%	7.9%	5.4%	
Asbestos	N	10	86	96	
	%	2.1%	17.9%	10.0%	
Asphalt laying	N	14	72	86	
	%	2.9%	15.0%	9.0%	
Glass production	N	24	45	69	
	%	5.0%	9.4%	7.2%	

Total	N	480	480	960	
	%	100,.%	100.0%	100.0%	

In the group of patients, the presence of heavy metals was reported in 22.9%, and in the controls this proportion was significantly lower - 5.0%. Significant differences in the relative shares between patients and controls are also observed for the other occupational hazards. The results are presented in **Figure No. 5.**

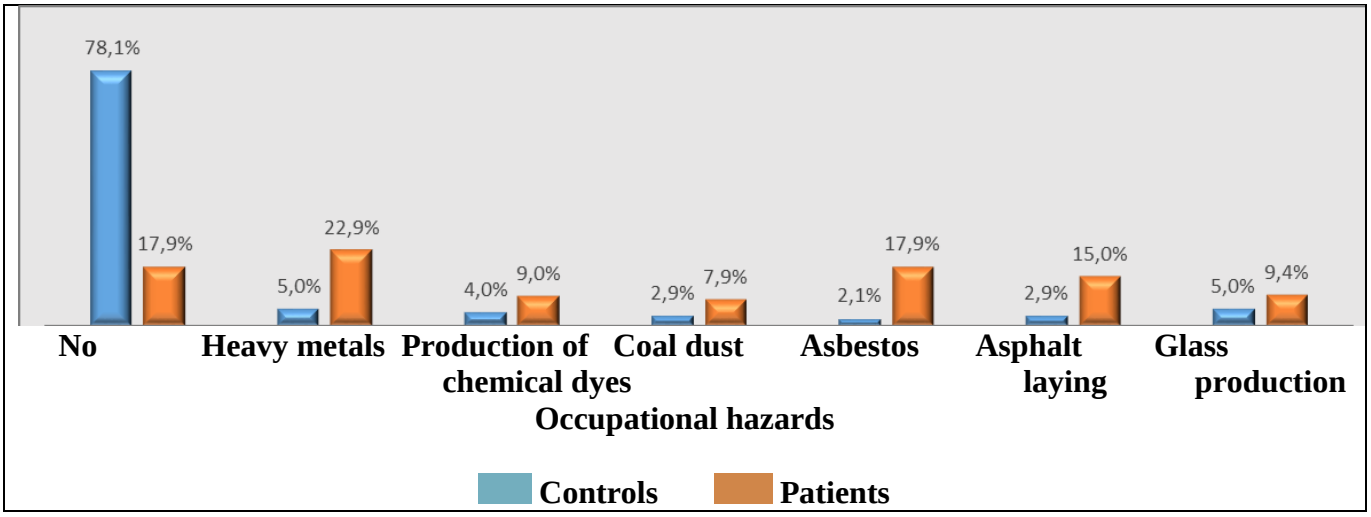


Figure No. 5. Relative share of the examined persons, depending on the occupational hazards, in the two groups - patients and controls

• *Specific lesion with the Epstein-Barr virus*

A statistically significant relationship was also established with the specific lesion with the Epstein-Barr virus (p=0.016). The results are presented in **Table No. 18.**

Table No. 18. Distribution of the examined persons, depending on the specific infection with Epstein-Barr virus, in both groups - patients and controls, and results of the chi-square test

A specific lesion with the Epstein-Barr virus		**Controls**	**Patients**	**Total**	**p**
Yes	N	24	43	67	0,016
	%	5.0%	9.0%	7.0%	
No	N	456	437	893	
	%	95.0%	91.0%	93.0%	
Total	N	480	480	960	
	%	100.0%	100.0%	100.0%	

In 9.0% of the patients there was a specific lesion with the Epstein-Barr virus, and in the controls this share was lower – 5.0% **(Figure No. 6).**

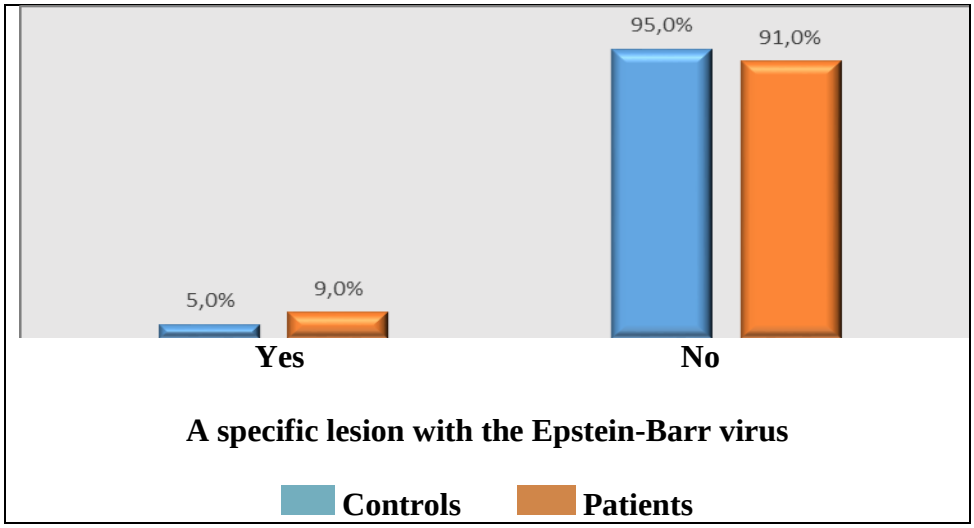


Figure No. 6. Relative share of subjects, depending on the specific lesion with the Epstein-Barr virus, in the two groups - patients and controls

• *Human papilloma virus /HPV/.*

The relationship between the disease and the presence of human papillomavirus was investigated. The results show that this relationship is statistically significant (p=0.031) **(Table No. 19).**

Table No. 19. Distribution of the subjects, depending on the presence of Human papilloma virus, in the two groups - patients and controls , and results of the chi-square test

Human papilloma virus /HPV /		Controls	Patients	Total	p
Yes	N	0	6	6	0,031
	%	0,0%	1,3%	0,6%	
No	N	480	474	954	
	%	100,0%	98,8%	99,4%	
Total	N	480	480	960	
	%	100,0%	100,0%	100,0%	

In the control group there were no persons with the presence of Human papilloma virus, and in the patients this proportion was 1.3% **(Figure No. 7).**

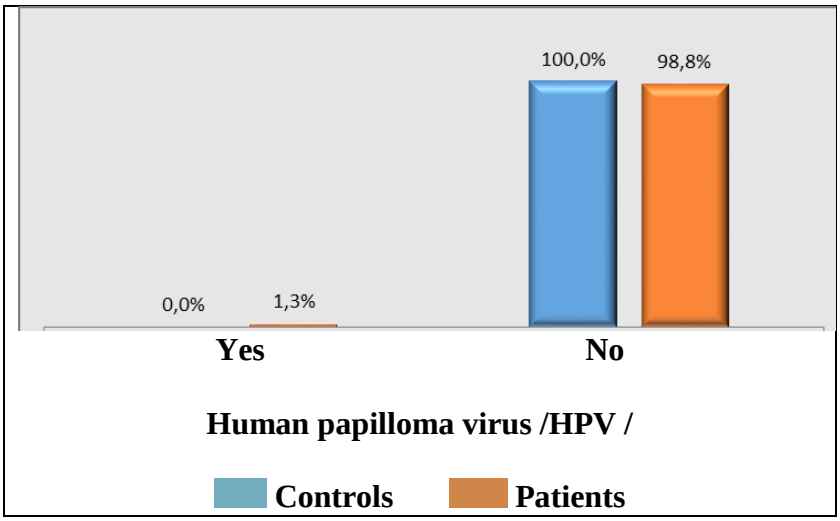


Figure No. 7. Relative share of the surveyed persons, depending on presence of human papilloma virus

• *Chronic inflammatory diseases of the upper respiratory tract*

The analysis shows that there is a statistically significant relationship between the studied disease (Hypopharyngeal squamous cell carcinoma) and the presence of chronic inflammatory diseases of the upper respiratory tract ($p<0.001$) **(Table No. 20).**

Table No. 20. Distribution of the subjects, depending on the presence of chronic inflammatory diseases of the upper respiratory tract, in the two groups - patients and controls , and results of the chi-square test

Chronic inflammatory diseases of the upper respiratory tract		**Controls**	**Patients**	**Total**	**p**
No	N	163	0	163	<0,001
	%	34.0%	0.0%	17.0%	
Sinusitis	N	48	67	115	
	%	10.0%	14.0%	12.0%	
Pharyngitis	N	72	115	187	
	%	15.0%	24.0%	19.5%	
Aphthous stomatitis	N	53	91	144	
	%	11.0%	19.0%	15.0%	
Tonsillitis	N	48	77	125	
	%	10.0%	16.0%	13.0%	
Sore throat	N	96	130	226	
	%	20.0%	27.1%	23.5%	
Total	N	480	480	960	
	%	100.0%	100,0%	100.0%	

In all patients, some chronic inflammatory disease of the upper respiratory tract was found, and in the controls, about 1/3 of the examined were without such disease (Fig. #8). The

most common disease was sore throat, with 27.1% of patients having this disease and 20.0% of controls. In second place is pharyngitis, 24.0% of patients have pharyngitis, and 15.0% of controls. Next is aphthous stomatitis – 19.0% in patients and 11.0% in controls.

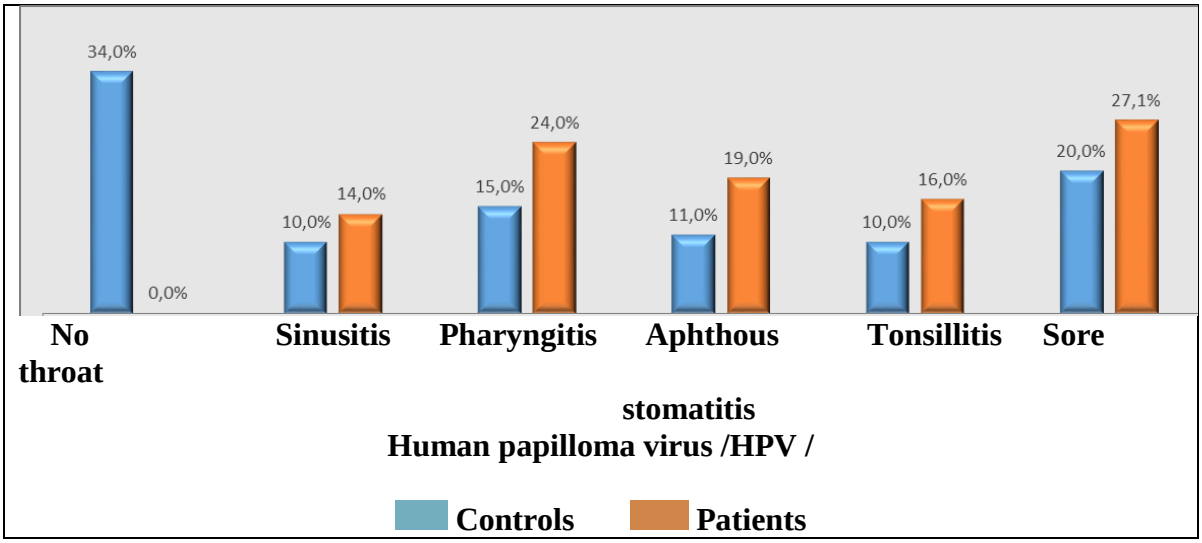


Figure No. 8. Relative share of the examined persons, depending on the presence of chronic inflammatory diseases of the upper respiratory tract, in the two groups - patients and controls

• *Presence of untreated teeth in the oral cavity*

Table No. 21 presents the results of the analysis of the relationship between the presence of untreated teeth and the studied disease. The results show that the relationship is statistically significant (p<0.001).

Table No. 21. Distribution of the subjects according to the presence of untreated teeth in the two groups - patients and controls and results of the chi-square test

Presence of untreated teeth in the oral cavity		**Controls**	**Patients**	**Total**	**p**
Yes	N	192	409	601	<0,001
	%	40.0%	85.2%	62.6%	
No	N	288	71	359	
	%	60.0%	14.8%	37.4%	
Total	N	480	480	960	
	%	100.0%	100.0%	100.0%	

In 85.2% of the patients, untreated teeth were found in the oral cavity, and in the controls this share was significantly lower – 40.0% **(Figure No. 9).**

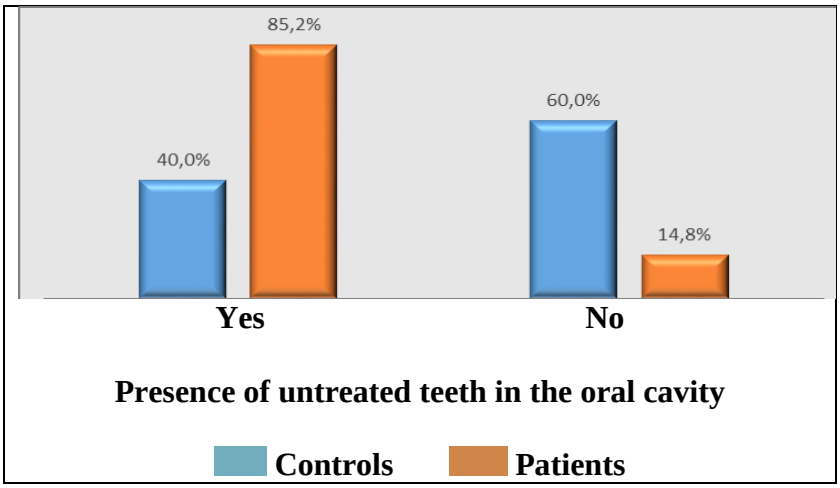


Figure No. 9. Relative share of the examined persons, depending on the presence of untreated teeth, in the two groups - patients and controls

• *Culinary preferences in the form of certain foods*

A statistically significant association of hypopharyngeal squamous cell carcinoma was also established with the consumption of certain foods (hot, spicy, smoked foods) ($p<0.001$). The results are presented in **Table No. 22** and **Figure No. 10.**

Table No. 22. Distribution of subjects, depending on culinary preferences, in the form of certain foods, in the two groups - patients and controls and results of the chi-square test

Culinary preferences in the form of certain foods		**Controls**	**Patients**	**Total**	**p**
Hot foods	N	58	130	188	<0,001
	%	12.1%	27.1%	19.6%	
Spicy foods	N	72	101	173	
	%	15.0%	21.0%	18.0%	
Smoked foods	N	48	168	216	
	%	10.0%	35.0%	22.5%	
Do not specify	N	302	81	383	
	%	62.9%	16.9%	39.9%	
Total	N	480	480	960	
	%	100.0%	100.0%	100.0%	

With the highest relative share among patients are those consuming smoked foods - 35.0%, among controls this share is significantly lower - 10.0%. In second place are hot foods, in patients - 27.1%, in controls - 12.1% **(Figure No. 10).**

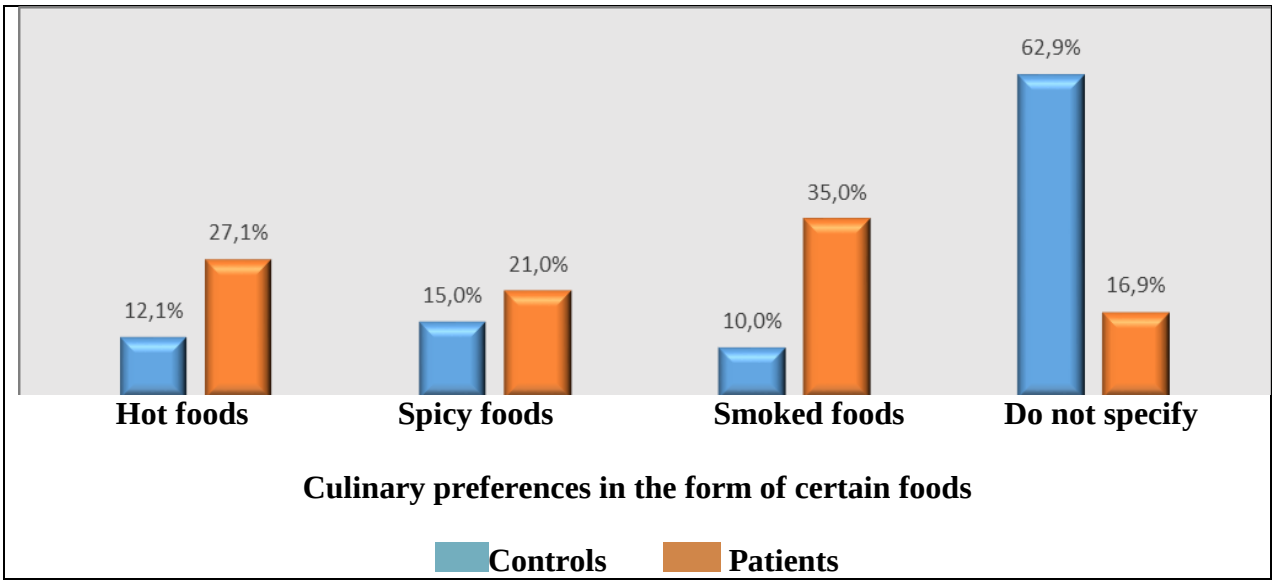


Figure No. 10. Relative share of subjects, depending on culinary preferences, in the form of certain foods, in both groups - patients and controls

8.2. Quantitative assessment of risk factors included in the survey

Analysis was performed with univariate binary logistic regression.

The results show that smoking is the risk factor with the greatest weight, compared to the other investigated and established risk factors **(Table No. 23).**

Table No. 23. Binary logistic regression results

Factor	OR	95% CI		p
Smoking				
Active smoker	58.286	30.198	112.500	<0,001
Passive smoker	20.667	10.080	42.372	<0,001
Daily consumption of large amounts of alcohol	51.000	34.548	75.287	<0,001
Genetic predisposition. Presence of a malignant disease with this location in the family history.	16.977	12.122	23.776	<0,001
Occupational hazards				
Heavy metals	19.985	12.123	32.947	<0,001
Production of chemical paints	9.868	5.478	17.777	<0,001
Coal dust	11.836	6.141	22.809	<0,001
Asbestos	37.500	18.706	75.177	<0,001
Asphalt laying	22.425	12.081	41.628	<0,001
Glass production	8.176	4.726	14.143	<0,001
A specific lesion with the Epstein-Barr virus	1.870	1.116	3.133	0,018
Presence of untreated teeth in the oral cavity	8.641	6.330	11.795	<0,001
Culinary preferences in the form of certain foods				
Hot foods	8.357	5.630	12.403	<0,001

Spicy foods	5.230	3.544	7.719	<0,001
Smoked foods	13.049	8.714	19.541	<0,001

Active smoking increased the chance of hypopharyngeal squamous cell carcinoma by 58.29 times (OR=58.29; 95% CI: 30.20-112.50, p<0.001), compared to non-smokers.

Daily heavy alcohol use was the second most severe risk factor, increasing the chance of developing the disease by 51.00 times (OR=51.00; 95% CI: 34.55-75.29, p<0.001), compared to non-daily drinkers large amounts of alcohol.

In third place as an occupational hazard in terms of influence is asbestos. The increased chance of this factor is 37.50 times (OR=37.50; 95% CI: 18.71-75.18, p<0.001), compared to persons not exposed to this occupational hazard.

Figure No. 11 presents all the researched and established risk factors, arranged by strength of influence.

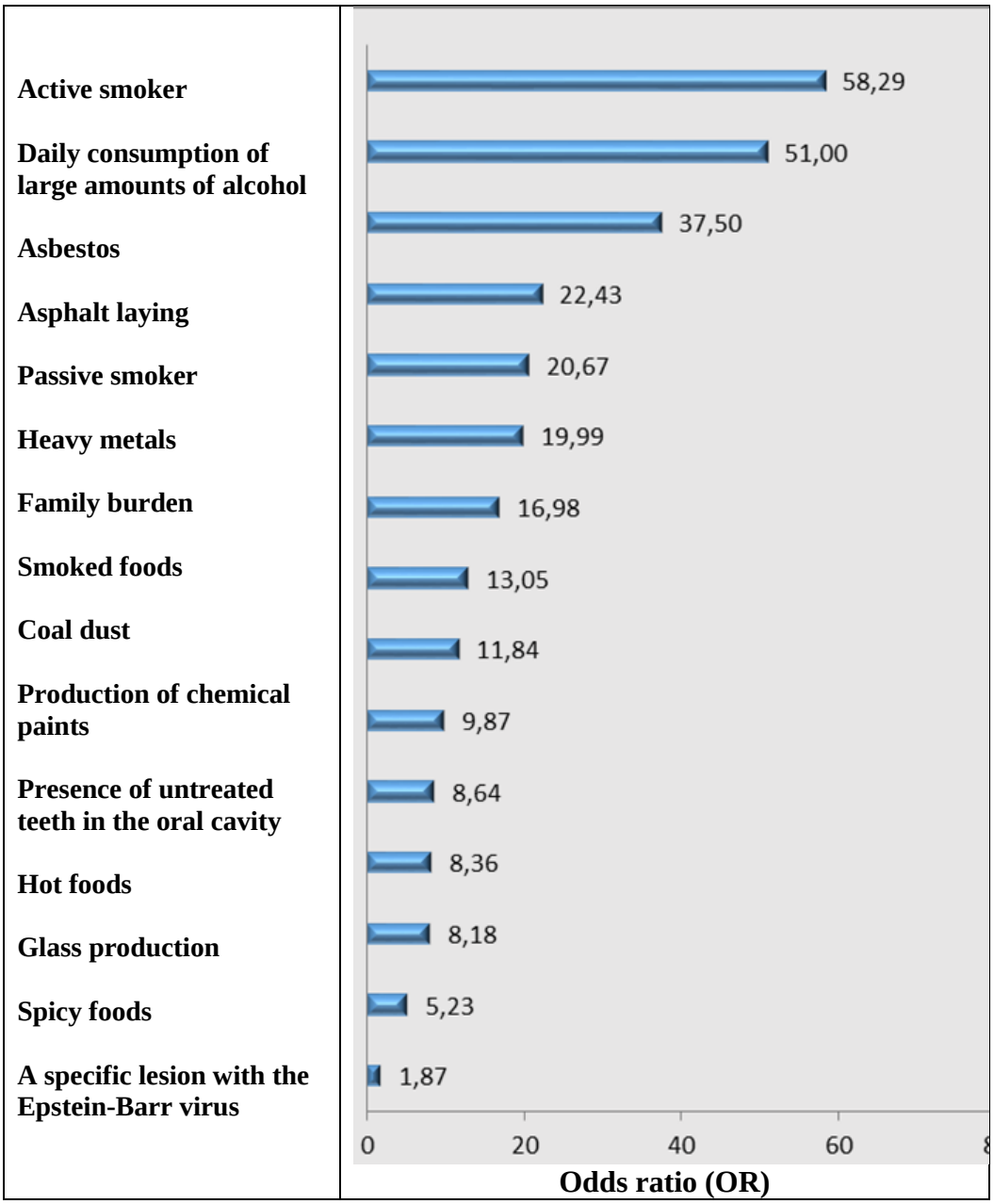


Figure No. 11. Ranking of risk factors by strength of influence on the disease hypopharyngeal squamous cell carcinoma

- The main working hypothesis is confirmed, that the risk factors established in international practice affect the spread of hypopharynx cancer, but to a different degree.
- The statistically significant factors that have a leading role for certain patients with hypopharyngeal squamous cell carcinoma have been identified.
- It is clear from the analysis that hypopharyngeal squamous cell carcinoma occurs many times more often in men than in women

CONCLUSION

The goal of screening programmes for oncological diseases, like all preventive programmes, is the timely detection of precancerous conditions or early stages of the development of the disease, which will lead to fewer cases and fewer deaths.

The World Health Organization (WHO) defines the concept of screening as follows: screening is the (presumed) detection of latent disease through tests and procedures that can be applied rapidly.

According to the WHO, to be successful, screening must be well thought out and organized, cover a significant proportion of healthy people of a certain age who could be at risk and ensure equal access and uniform coverage of all those subject to a given screening test.

For an oncological disease to be subject to screening, it is necessary that the type of cancer is associated with high morbidity and mortality; that there is an effective treatment for the early stages of the disease; the research (screening test) is well accepted by people, is safe and has a low cost.

An important element of any mass screening programme is the presence of a centralized system for collecting and summarizing the data from the screening tests (screening registry), as well as a system for notifying people who should be tested.

WHO promotes the need to create specific screening registries, in which information about all screening tests carried out under a specific screening programme will be stored. This information system makes it possible to compare the results of individuals over a long period of time, analyze the results and evaluate the effectiveness of screening programs. In the register it is necessary to store all the information about the persons invited for examination and the persons , examined.

It is necessary that screening programs target significant parts of a country's population and be conducted in compliance with modern ethical principles and rules for the protection of personal information. Thus, in addition to the beneficial effect in terms of mortality from a certain disease, the screening test may also have negative side effects on some of the people , examined. It is the duty of medical professionals to inform screenees of all possible benefits and risks of tests and procedures, i.e. to obtain appropriate informed consent.

Cancer screening programs also include information campaigns , aimed at both the general public , and medical professionals. These campaigns should begin once the necessary organization is in place to implement the screening program.

CONCLUSIONS

1. Cancer is a global problem. Despite advances in its diagnosis and treatment over the past 20 years, it is still the second leading cause of death.

2. Hypopharyngeal squamous cell carcinoma is very difficult to diagnose in an early clinical stage. Its incidence during the years 2000-2019 is increasing with an average annual percentage change of 1-8% annually.

3. In the basic epidemiological retrospective study conducted in the period 2000-2013, a total of 957 cases of hypopharyngeal squamous cell carcinoma diagnosed for the first time in the country were found. The study is comprehensive in terms of clinical, diagnostic and prognostic characteristics for survival with hypopharyngeal squamous cell carcinoma.

4. The screening test of 960 individuals identified the main risk factors and proved that they are the basis of this disease.

5. Screening, early detection, access to treatment and clinical trials are essential to improve outcomes in early diagnosis of hypopharyngeal cancer.

6. Survival with hypopharyngeal squamous cell carcinoma can increase dramatically with early detection, effective therapy, and supportive care.

RECOMMENDATIONS

To the Ministry of Health

1. After the objective assessment of the dynamics of health-demographic processes in the country and the epidemiological data on the frequency of health risk factors (census 2021), the approach to improving the health of the nation should be based on urgent and broad preventive activities, ensuring long-term changes and sufficient prevention funding.

2. Cancer control models should cover the coordination of health care in all its aspects - the provision of drugs, social support and other measures - with a view to achieving an optimal cost/effectiveness ratio, for which changes in the regulatory framework are necessary.

3. For better health and to reduce the frequency of diseases, it is necessary to introduce more policies that make it difficult to purchase and use tobacco products and alcohol and facilitate healthy eating and physical activity.

4. Through the health promotion partnership, to encourage decision-making for targeted activities and support for appropriate health, social and environmental policy.

DISSERTATION CONTRIBUTIONS

Contributions of original character

1. For the first time in the country, retrospective and prospective clinical-epidemiological studies were conducted, covering 957 patients with hypopharyngeal squamous cell carcinoma for the period 2000-2013 and newly registered in the Republic of Bulgaria.

2. For the first time in our country, a study was conducted among 960 people (a test group of 480 patients with hypopharyngeal squamous cell carcinoma and a control group of 480 conditionally healthy people with complaints), which confirms the identified risk factors for the disease and points to prevention and prophylaxis to prevent them and achieving positive changes to increase overall health outcomes.

Contributions of a theoretical-methodological nature

3. During the period 2010–2020, the clinical and pathological risk factors, among large groups of patients registered in the Plovdiv Oncological Hospital and the Burgas Oncological Hospital, influencing the survival of patients with hypopharyngeal squamous cell carcinoma, individually and integrally, were investigated, and a quantitative assessment of their risk and protective actions.

4. The clinical characteristics and initial therapeutic response in patients with hypopharyngeal squamous cell carcinoma treated with radiotherapy and subsequent chemo-radiotherapy were evaluated.

5. Salvage measures in recurrent hypopharyngeal squamous cell carcinomas and the possibility of prolonging survival in these patients were evaluated.

Contributions of a practical and applied nature

6. A model is proposed regarding early and timely diagnosis of hypopharyngeal squamous cell carcinomas.

7. An algorithm has been developed for the diagnosis and treatment of hypopharyngeal squamous cell carcinomas in the Republic of Bulgaria.

8. Screening for risk factors and for early diagnosis of hypopharyngeal squamous cell carcinoma has been proposed and performed.

9. A patient chart for a screening examination for hypopharyngeal squamous cell carcinoma is suggested.

DISSERTATION RELATED PUBLICATIONS :

1. Stoyanov, St., Ananoshtev, N., 2020, Epidemiology, diagnosis and treatment of malignant tumors of the hypopharynx. /Epidemiology, diagnosis and treatment processes over malignant tumors of the hypopharynx/, Bulgarien Medicine, vol. 10, #2.

2. Stoyanov, St., Ananoshtev, N., 2020, Diagnostic studies in patients with hypopharyngeal carcinoma. /Patients with hypopharyngeal carcinoma – Diagnostic evaluations/. Bulgarien Medicine, vol.10, #2.

3. Stoyanov, St., Ananoshtev, N., Staykova, Zh., 2021, Prognostic factors influencing the results of complex treatment for hypopharyngeal squamous cell carcinoma. /Prognostic factors, influencing the total treatment of the hypopharyngeal squamous cell carcinoma/. Bulgarian Medicine, vol. 11, No. 1.

4. Stoyanov, St., Staykova, Zh., Ananoshtev, N., 2021 Screening for early diagnosis of hypopharyngeal squamous cell carcinoma. Screening for an early diagnosis of hypopharyngeal squamous cell carcinoma. Bulgarian Medicine, vol. 11, No. 2, 2021.

5. Stoyanov St. , Staykova J., Ananoshtev N. , Vizev St.
Helpful Deeds in Recurrent Hypopharyngeal Squamous Cell Carcinoma with Performed Surgical Treatment and Chemoradiotherapy
Annals of Clinical Case Reports (ISSN: 2474-1655), 2023, Volume 8, Issue 1, 2376

APPLICATIONS

Application 1.

A model for screening people at increased risk for hypopharyngeal squamous cell carcinoma - with an individual test card and with specific monitoring parameters

A model for screening people at increased risk for hypopharyngeal squamous cell carcinoma - with an individual test card and with specific monitoring parameters	
Name:…… **Patient No ……** **Date of review:…….** **Date of birth:……**	
1. Prolonged smoking - active and passive.	□ *no* □ *active smoker* □ *passive smoker*
2. Daily consumption of large amounts of alcohol	□ *yes* □ *no*
3. Genetic predisposition. Presence of a malignant disease with this location in the family history.	□ *yes* □ *no*
4. Occupational hazards	□ *no* □ *heavy metals* □ *production of chemical dyes* □ *coal dust* □ *asbestos* □ *asphalt laying* □ *glass production*
5. A specific lesion with the Epstein-Barr virus	□ *yes* □ *no*
6. Human papilloma virus /HPV /	□ *yes* □ *no*
7. Chronic inflammatory diseases of the upper respiratory tract	□ *sinusitis* □ *pharyngitis* □ *aphthous stomatitis* □ *tonsillitis* □ *sore throat*
8. Presence of untreated teeth in the oral cavity	□ *yes* □ *no*
9. Culinary preferences in the form of certain foods	□ *hot foods* □ *spicy foods* □ *smoked foods* □ *do not specify*