Epidemiological situation of Hodgkin's lymphoma with predictive modeling of global incidence and mortality in 2040

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ABSTRACT

The aim of the work: The aim of our work was to describe the current epidemiological situation of Hodgkin's lymphoma (HL) with a possible global prediction for the year 2040.

Methods: We obtained data on incidence and mortality of HL using the GLOBOCAN database. The rating was done specifically for men and women and together, with an age range of 0–85+ years. For the possibility of international comparison, the data are evaluated in the format of age standardized incidence/mortality (Age Standardized Rate – ASR) related to the world population – ASR (W).

Results: In the period 2000–2010, the incidence of the lowest values in the male population in Sweden reached 1.90 ASR (W), the highest values reached 3.45 ASR (W) in Italy. In the female population, the lowest incidence was reported in Malta 1.63 ASR (W), the highest in Italy 3.34 ASR (W). The lowest mortality in the male population was reported in Norway at 0.21 ASR (W), the highest value was in Bulgaria at 0.85 ASR (W). In the female population, the lowest mortality value was reported in Iceland 0.09 ASR (W), the highest value in Poland 0.43 ASR (W). In 2040, 19,788 new cases of HL will be reported in Europe (104,317 in the world), the number of deaths will be 4,633 deaths in 2040 (34,237 in the world).

Conclusion: HL in Europe shows a continuously increasing trend of incidence in the prescription period 2000–2010, but continuously decreasing trend in mortality. In 2020, within Europe, the lowest incidence value was reported in Central and Eastern Europe, the highest incidence value was reported in Southern Europe. In the same year, the lowest value of mortality was reported in Western Europe, the highest value was reported in Central and Eastern Europe. Modeling the epidemiology of the disease for the world for the year 2040 is important, as the disease will continue to be more common in the male population in the future.

KEYWORDS

Hodgkin lymphoma – epidemiology – incidence – mortality – Europe

SOUHRN

Kolařík L., Horáková D., Vlčková J., Matoušková I.: Epidemiologická situace Hodgkinova lymfomu s prediktivním modelováním globální incidence a mortality v roce 2040

Cíl práce: Cílem naší práce bylo popsat současnou epidemiologickou situaci Hodgkinova lymfomu (HL) s možnou globální predikcí pro rok 2040.

Metodika: Data o incidenci a mortalitě HL jsme získali pomocí databáze GLOBOCAN. Hodnocení bylo provedeno speciálně pro muže a ženy a společně, ve věkovém rozmezí 0–85+ roků. Epidemiologická data naznačují mírný kontinuální nárůst incidence HL s mírně klesajícím trendem mortality onemocnění v ekonomicky vyspělých zemích.

Výsledky: V Evropě vykazovala incidence HL v recentním období 2000–2010 mírný rostoucí trend u obou pohlaví. Nejnižší incidence v mužské populaci byla pozorována ve Švédsku, v ženské populaci na Maltě. Nejvyšší hodnota incidence byla pro obě pohlaví pozorována v Itálii. Nejnižší hodnota mortality HL v mužské populaci byla pozorována v Norsku, v ženské populaci na Islandu. Nejvyšší hodnota mortality byla v mužské populaci v Bulharsku, v ženské populaci v Polsku. Vyšší hodnoty incidence i mortality byly evidovány v populaci mužů. V roce 2040 bude v Evropě hlášeno 19 788 nových případů HL (104 317 ve světě), počet úmrtí bude v roce 2040 4 633 úmrtí (34 237 ve světě).

Závěr: HL v Evropě vykazuje v preskripčním období 2000–2010 kontinuálně rostoucí trend incidence, ale kontinuálně klesající trend v mortalitě. V roce 2020 byla v rámci Evropy nejnižší hodnota incidence hlášena ve střední a východní Evropě, nejvyšší hodnota incidence byla hlášena v jižní Evropě. Ve stejném roce byla nejnižší hodnota úmrtnosti hlášena v západní Evropě, nejvyšší hodnota byla hlášena ve střední a východní Evropě. Modelování epidemiologie onemocnění pro svět pro rok 2040 je důležité, protože onemocnění bude i v budoucnu běžnější u mužské populace.

KLÍČOVÁ SLOVA

Hodgkinův lymfom – epidemiologie – incidence – mortalita – Evropa

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INTRODUCTION

Lymphomas are generally less common cancer. Of all cancers, lymphomas account for 6% of new cases, of which 5% are non-Hodgkin's lymphomas and only 1% represent Hodgkin's lymphomas (HLs). The disease has a bimodal age distribution, occurring mainly in young adults (16–34 years) and patients over 55 years of age. The disease is more frequent in males. The disease primarily affects the lymph nodes, most commonly those in the cervical region. Based on immunophenotype, neoplastic cell morphology, and cellular background, two main types of Hodgkin's lymphoma (HL) are recognized: classical HL (CHL) and nodular lymphocyte-predominant HL (NLPHL). The CHL was further categorized into four subtypes according to histological appearance. There are the subtypes CHL: nodular sclerosis classic Hodgkin lymphoma (NSCHL), lymphocyte-rich classic Hodgkin lymphoma (LRCHL), mixed cellularity classic Hodgkin lymphoma (MCCHL) and lymphocyte-depleted classic Hodgkin lymphoma (LDCHL) [1].

HLs account for approximately 15–20% of all lymphomas, in Asia 10% of lymphomas. The CHL subtype accounts for approximately 90% of all HL cases. The etiology of HL is not fully understood. Increased risk is observed in EBV (Epstein-Barr virus) and human immunodeficiency virus (HIV) infections, autoimmune diseases, or immunosuppressive conditions (organ and bone marrow transplantations). The association between EBV and HL is variable in different geographical areas and correlates with older age and higher Human Development Index (HDI). The proportion of EBV-positive HL cases ranges from 30% to 50% in the United States of America (USA) and Europe, reaching 100% in Vietnam, the Republic of Kenya and Honduras. In the literature, it is classified as a highly curable malignancy with a bimodal incidence curve in more economically developed countries. The hallmark of this disease is the presence of neoplastic Hodgkin and Reed-Sternberg cells (HRS) derived from germinal center B-cells. Hodgkin's lymphoma can occur in the general population as well as in immunocompromised individuals [1].

Risk factors are an important factor influencing the epidemiological situation of the disease. HL risk factors can be divided into uncontrollable and controllable risk factors. Uncontrollable risk factors include e.g. age, gender and ethnicity. Influenceable risk factors are mainly related to an individual's lifestyle, e.g. obesity or smoking. The importance and strength of risk factors depend on the geographic location of the population being evaluated [1].

Certain childhood infectious diseases may show a negative correlation or even provide a protective effect (chickenpox, measles, mumps, rubella, and whooping cough). Recent genetic studies point to familial risk factors, with same-sex siblings of a patient with HL having a 10-fold increased risk of developing the disease [1, 2, 3].

The aim of our study was to evaluate the epidemiological situation of HL in Europe. The partial goal of our study was to model the possible development of the epidemiological situation of HL in the world in 2040.

MATERIAL AND METHODS

To assess the epidemiology of HL in Europe and worldwide, we used data from the GLOBOCAN registry, which provides incidence and mortality data for 36 cancer types in 185 countries. The registry is operated by the World Health Organization's International Agency for Research on Cancer. Data in the GLOBOCAN registry are obtained from national and subnational population-based registries. Individual diagnoses are coded according to the International Classification of Diseases and Related Health Problems, 10th Revision.

The *Cancer Over Time-Trends* application was used to assess trends in incidence and mortality for 2000–2010. In our study, we chose the recent period 2000–2010 because during this period, incidence and mortality data were available in the GLOBOCAN registry for all countries included in the study. To allow international comparison, data were evaluated using the age-standardized rate (ASR) relative to the world standard population ASR (W) per 100,000 person-years. The standard population used was the 1966 Segi–Doll World. Data version 1.0 was used to obtain the data. A total of 23 European countries were included in the assessment. The numbers of new cases (incidence) and deaths (mortality) were extracted from 18 age groups (0–4, 5–9... 80–84, and 85+). The total number of included countries and the time range were limited by the availability of reported data. Data were analyzed separately and together for males and females. Based on the data obtained, graphs were created in MS Excel that illustrate the trends in incidence and mortality for over the period of interest.

The *Cancer Today-Multi Bars* application was used to estimate incidence and mortality in 2020. For international comparison, data were evaluated using the ASR (W) per 100,000 person-years (GLOBOCAN 2020 data). A total of 40 European countries were assessed. The countries were divided into 4 geographical regions of Europe (Northern Europe, Central and Eastern Europe, Western Europe, and Southern Europe). The geographical grouping of countries followed the GLOBOCAN 2020 methodology.

For modeling the prediction of incidence and mortality of HL in Europe and in the world, the *Cancer Tomorrow-Trends* and *Cancer Tomorrow-Bar Chart* applications, respectively, were used. To allow international comparison of the prediction of incidence and mortality in the world and in Europe, data were evaluated using the

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number of cases (GLOBOCAN 2020 data). The modelling was performed for 40 countries. The prediction was modeled for the years 2020–2040, with the interpreted data used for 2040. Data analysis was performed separately for males and females. The age range for the male and female populations was set to 0–85+. Data for the 2040 world prediction were evaluated based on individual cases. The data were obtained from GLOBOCAN 2020. Six world regions (Africa, Asia, Europe, Latin America and the Caribbean, Oceania, and North America) were assessed. The prediction was modeled for the year 2040. Data analysis was performed separately for males and females. To show trends in incidence and mortality by sex, data were processed in MS Excel.

Data from the GLOBOCAN registry must be interpreted with caution because the data reported are only as valid as the data entered. Data obtained from national and subnational population registries may be skewed, mainly by under-reporting of cases, especially in regions with low and very low HDI.

RESULTS

Incidence – trends in 2000–2010 in Europe

The incidence of HL in the 23 countries over the period 2000–2010 showed a slightly increasing trend for both sexes (Figure 1). In the male population, the incidence was 2.51 ASR (W) in 2000 and 2.85 ASR (W) in 2010. In females, the rates were 1.92 ASR (W) and 2.29 ASR (W), respectively.

The lowest average incidence for the period 2000–2010 in male was reported in Sweden at 1.90 ASR (W), followed by Latvia and Lithuania (2.03 ASR (W)), and Slovakia (2.22 ASR (W)). The highest average incidence for the period 2000–2010 in male was in Italy at 3.45 ASR (W) (Figure 2).

The lowest average incidence for the period 2000–2010 in female was reported in Malta at 1.63 ASR (W), followed by Bulgaria (1.64 ASR (W)) and Sweden (1.65 ASR (W)). As in males, the highest average incidence for the period 2000–2010 in female was in Italy at 3.34 ASR (W) (see Figure 2).

Over the period 2000–2010, the incidence rate was higher in males at 2.55 ASR (W) than in females at 2.12 ASR (W).

When assessing the incidence rates for individual age groups, the peak incidence of HL for both sexes in 2010 was observed in the age group 15–34 years. In males, the second peak incidence was more pronounced in the 60+ age group. The peak incidence in those aged 15–34 years was expected as 70% of CHL cases were NSCHL, typically showing the peak incidence in this age group.

Mortality – trends in 2000–2010 in Europe

Over the period 2000–2010, HL mortality in the 23 countries showed a slightly decreasing trend for both sexes (see Figure 1). In the male population, mortality decreased from 0.56 ASR (W) in 2000 to 0.38 ASR (W) in 2010. In females, the decrease was from 0.34 ASR (W) in 2000 to 0.25 ASR (W) in 2010.

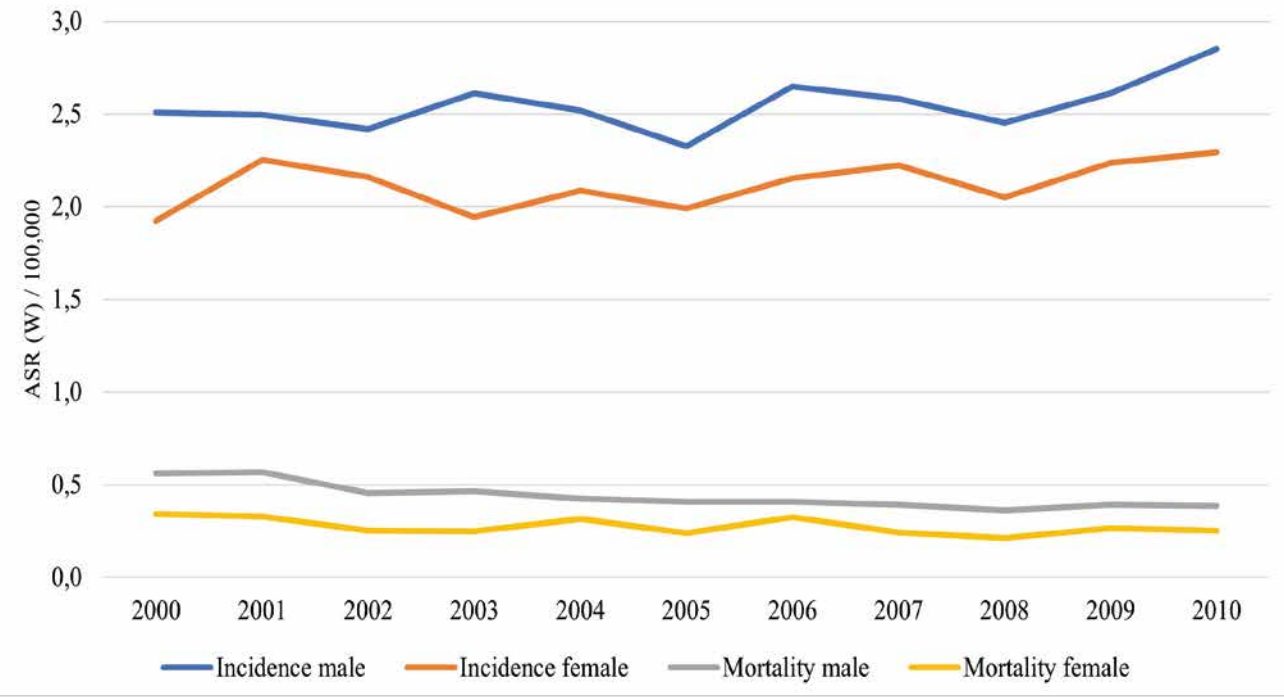


Figure 1. Trends in the incidence and mortality of Hodgkin's lymphoma in males and females in Europe for the period 2000–2010 (data source: GLOBOCAN 2020, custom design)

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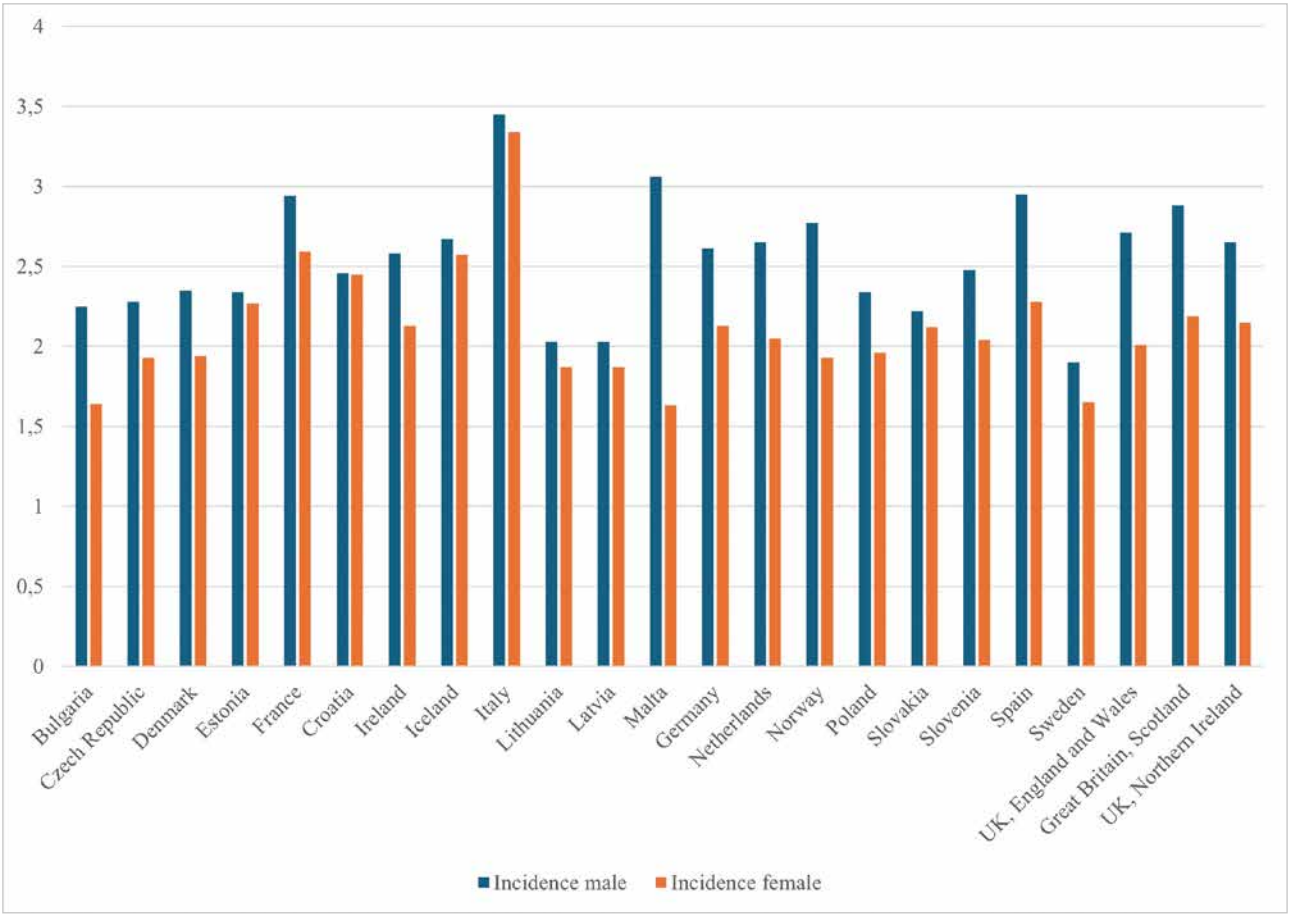


Figure 2. Average incidence of Hodgkin's lymphoma in Europe 2000–2010

(data source: GLOBOCAN 2020, custom design)

The lowest average mortality for the period 2000–2010 in male was reported in Norway at 0.21 ASR (W), followed by Sweden (0.25 ASR (W)) and Germany (0.27 ASR (W)). The highest average mortality for the period 2000–2010 in male was in Bulgaria at 0.85 ASR (W) (Figure 3).

The lowest average mortality for the period 2000–2010 in female was reported in Iceland at 0.09 ASR (W), followed by Norway (0.12 ASR (W)) and Sweden (0.15 ASR (W)). The highest average mortality for the period 2000–2010 in female was in Poland at 0.43 ASR (W) (see Figure 3).

The Nordic countries reported the lowest mortality rates for both sexes. Over the period 2000–2010, mortality was higher in males at 0.44 ASR (W) than in females at 0.27 ASR (W).

Looking at mortality rates by age group in 2010, there was a continuous increase in mortality for both sexes from the 60–64 age group.

Assessment of HL incidence and mortality in Europe in 2020

The assessment of incidence and mortality of Hodgkin lymphoma in 2020 was conducted for 40 countries in Europe, divided into four geographical regions: Northern, Central and Eastern, Western, and Southern Europe.

Northern Europe

The lowest male and female incidence rates were in Iceland at 1.10 ASR (W) and in Sweden at 1.70 ASR (W), respectively. When evaluating both sexes together, the lowest rate was 1.80 ASR (W) for Sweden and Lithuania (Figure 4).

The highest incidence rates were 3.30 ASR (W) in the United Kingdom and Latvia for males and 2.70 ASR (W) in Iceland for females. When evaluating both sexes, the highest rate was reported in the United Kingdom at 2.90 ASR (W) (see Figure 4). Higher incidence rates in females were in Estonia and Iceland.

The lowest mortality rates were reported in Sweden at 0.16 ASR (W) for males and in Norway and Estonia at 0.08 ASR (W) for females. When evaluating both sexes together the lowest rate in Norway and Estonia at 0.14 ASR (W) (see Figure 4). The highest mortality rates for both males (0.52 ASR (W)) and females (0.47 ASR (W)) were in Latvia; the overall mortality rate was 0.48 ASR (W) (Figure 4). Higher mortality in female population was observed in Lithuania.

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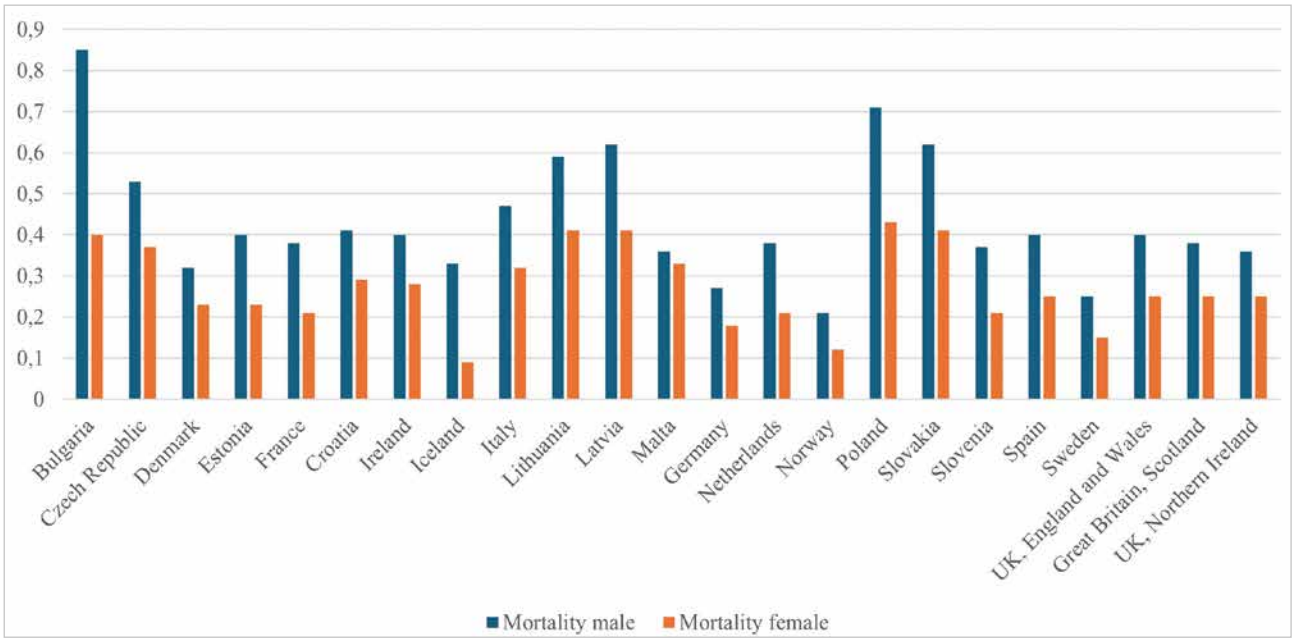


Figure 3. Average mortality of Hodgkin's lymphoma in Europe 2000–2010

(data source: GLOBOCAN 2020, custom design)

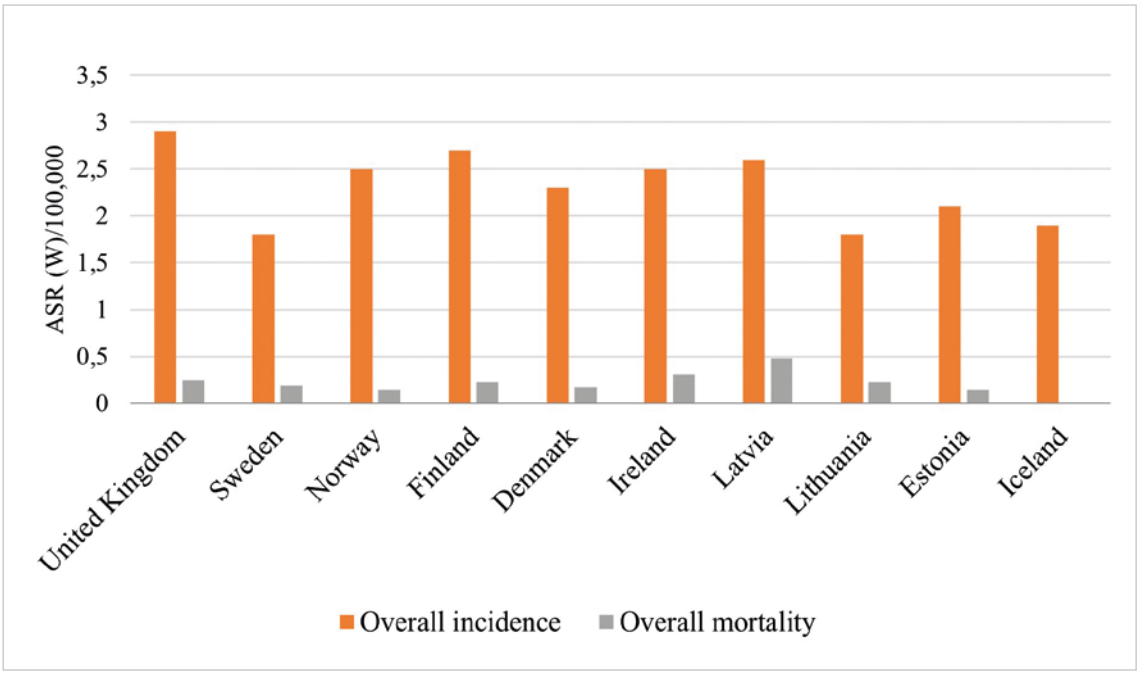


Figure 4. Overall incidence and mortality of HL Northern Europe 2020

(data source: GLOBOCAN 2020, custom design)

Central and Eastern Europe

The lowest incidence rates were noted in the Republic of Moldova (1.20 ASR (W)) for males and in Romania (0.86 ASR (W)) for females. For both sexes combined, the lowest incidence was in the Republic of Moldova (1.10 ASR (W)) (Figure 5). The highest incidence rates in the male and female populations were reported in Slovakia (2.80 ASR (W)) and Ukraine (2.70 ASR (W)), respectively. When evaluating both sexes together, the highest rates were 2.50 ASR (W) for Slovakia and Ukraine (see Figure 5). Higher incidence rates in females were observed in Ukraine, Belarus and Bulgaria.

The lowest mortality rates were in the Czech Republic and Hungary (0.25 ASR (W)) for males and in Romania and Hungary (0.19 ASR (W)) for females. The lowest mortality rate for both sexes together was reported in

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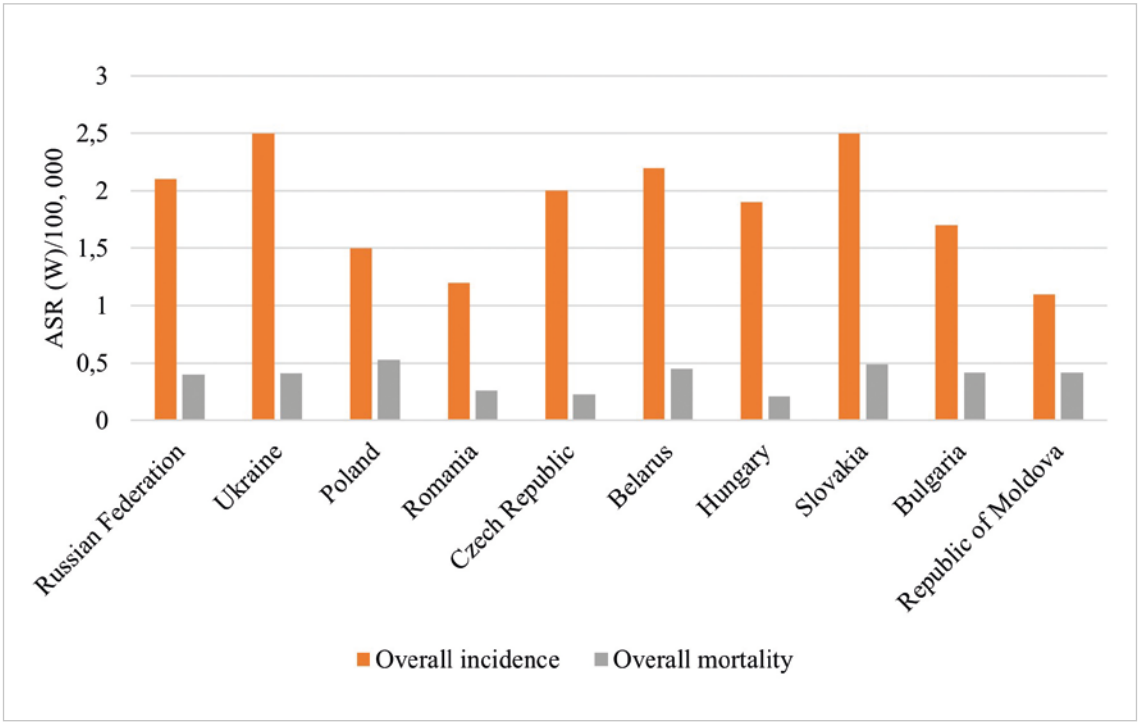


Figure 5. Overall incidence and mortality of HL Central and Eastern Europe 2020
(data source: GLOBOCAN 2020, custom design)

Hungary at 0.21 ASR (W) (see Figure 5). The highest mortality rates for males and females were in Slovakia (0.65 ASR (W)) and Poland (0.46 ASR (W)), respectively. For both sexes together, the highest mortality rate was 0.53 ASR (W) in Poland (see Figure 5). Higher mortality in the female population was reported in Poland.

Western Europe

Austria showed the lowest incidence rates for both males (1.40 ASR (W)) and females (1.50 ASR (W)), whereas France had the highest rates for both males (3.50 ASR (W)) and females (2.50 ASR (W)). Higher incidence rates in the female population were observed in Austria and Luxembourg.

The lowest mortality rates were in Austria (0.12 ASR (W)) for males and in Belgium and Switzerland (0.09 ASR (W)) for females. The lowest mortality rate for both sexes combined was seen in Austria (0.12 ASR (W)) (Figure 6). The highest male and female mortality rates were found in France (0.32 ASR (W)) and in Austria (0.13 ASR (W)), respectively. When both sexes were evaluated together, the highest mortality rate was in France at 0.21 ASR (W) (see Figure 6). The mortality rate in the female population was higher in Austria.

Southern Europe

The lowest incidence rate in the male population was in Albania at 1.40 ASR (W); the lowest rate in the female population (1.60 ASR (W)) was in Albania and North Macedonia. When both sexes were evaluated together, the lowest rate was reported in Albania at 1.40 ASR (W) (see Figure 7). The highest incidence rates were 3.60 ASR (W) in Italy for males and 3.20 ASR (W) in Cyprus for females. When combining the two sexes, the highest rate was seen in Italy (3.40 ASR (W)) (see Figure 7).

Higher incidence rates in the female population were found in Greece, Slovenia, and Cyprus.

Slovenia showed the lowest mortality rates: 0.10 ASR (W) for males, 0.13 ASR (W) for females, and 0.11 ASR (W) for both sexes combined (see Figure 7). The highest mortality rates were reported in Montenegro (0.95 ASR (W)) for males and in Serbia (0.42 ASR (W)) for females. The assessment of both sexes together showed the highest mortality rate in Serbia at 0.62 ASR (W) (see Figure 7).

Looking at Europe as a whole, the lowest incidence of HL was reported in Iceland for the male population and in Romania for the female population; the highest incidence rates were in Italy and Cyprus, respectively. The lowest male and female mortality rates were observed in Slovenia and Estonia, respectively. The highest mortality rates were in Montenegro for males and in Latvia for females.

Prediction of HL incidence in 2040

The incidence of HL in 2040 has been predicted for a total of 40 countries. In 2040, a total of 19,788 new cases of HL are expected to be reported. Of those, males would account for 11,141 new cases and females for 8,647 new cases (Figure 8).

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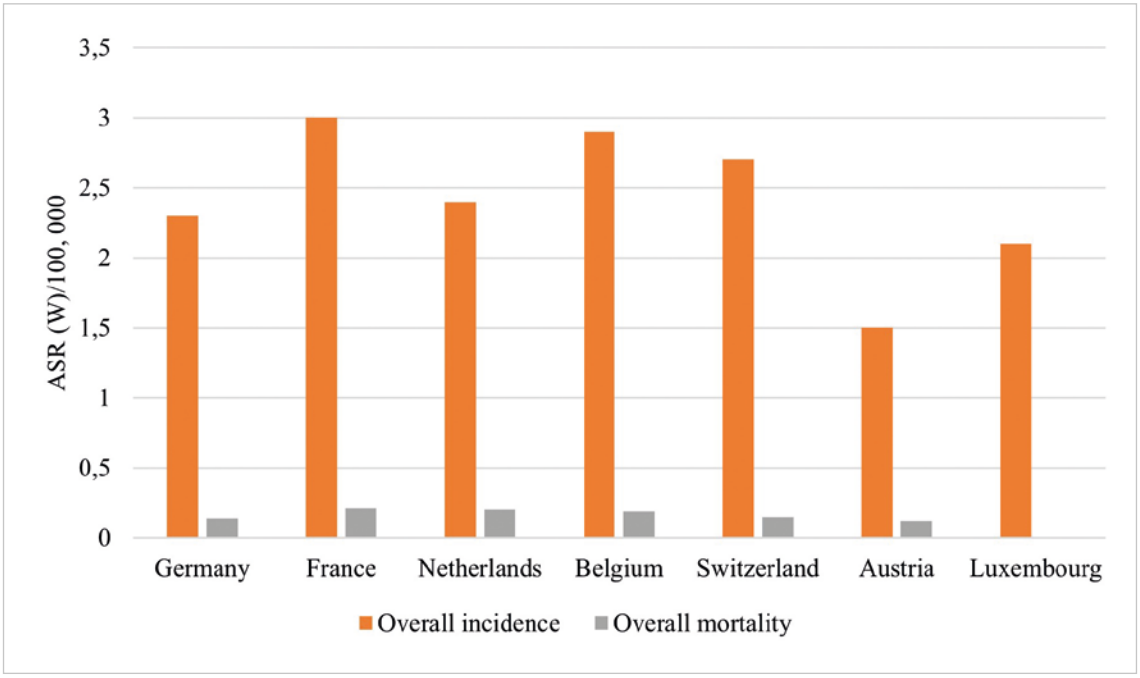


Figure 6. Overall incidence and mortality of HL Western Europe 2020
(data source: GLOBOCAN 2020, custom design)

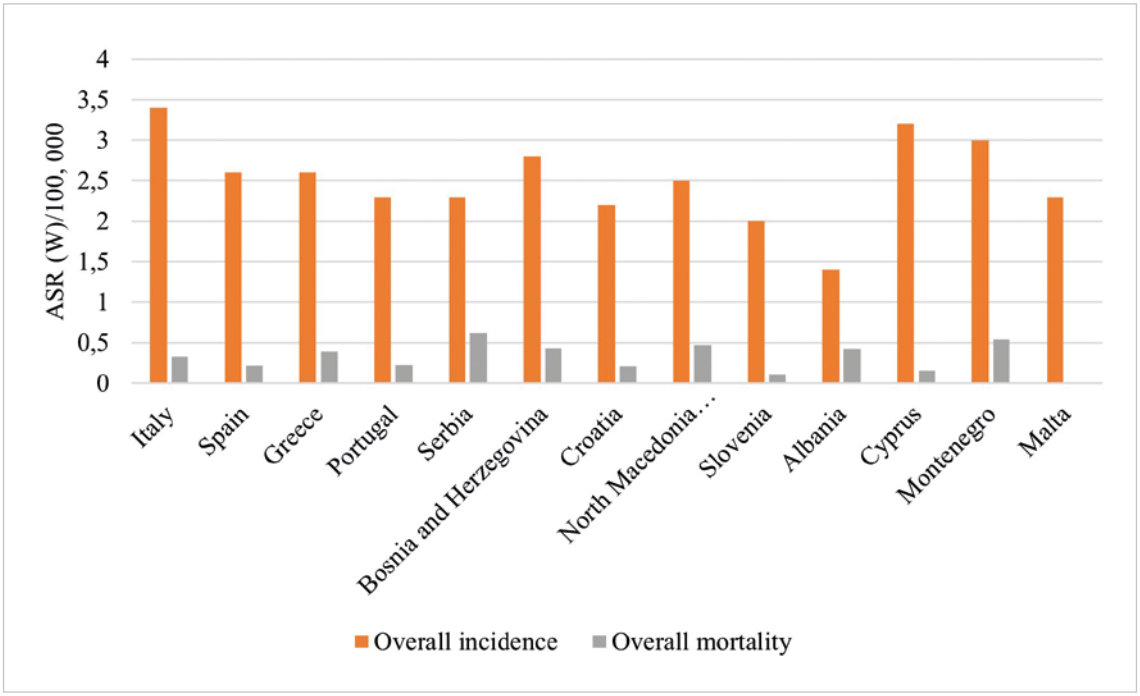


Figure 7. Overall incidence and mortality of HL Southern Europe 2020
(data source: GLOBOCAN 2020, custom design)

Predictions of male incidence indicate that the lowest rate would be in Iceland, followed by Estonia, Malta, Luxembourg, and Montenegro. In contrast, the highest incidence rate would be in Russia at 1.60 ASR (W). Predictions for the female population show that the lowest incidence rate would be seen in Malta, followed by Iceland, Luxembourg, and Montenegro. As in males, the highest incidence rate would be reported in Russia at 1.50 ASR (W).

When extending the prediction of HL incidence in 2040 to the entire world, Europe is expected to rank second. The other regions would rank as follows (in

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descending order): Asia (40,934 new cases), Africa (18,249), Latin America and the Caribbean (13,751), North America (10,346), and Oceania (1,248) (see Figure 8).

Prediction of HL mortality in 2040

Additionally, deaths from HL have been predicted for the same 40 countries. In 2040, a total of 4,633 people is projected to die from HL, of whom 2,702 would be males and 1,931 females (Figure 9).

Predictions of male HL mortality showed that the lowest rates would be reported in Estonia, Malta, Iceland, Cyprus, and Luxembourg. On the other hand, the highest mortality rate is expected to be seen in Russia (0.49 ASR (W)). Predictions for the female population indicate that the lowest mortality rates would be observed in Estonia, Iceland, Malta, Cyprus, Luxembourg, and Montenegro. As with the male population, the highest mortality rate would be in Russia (0.40 ASR (W)).

Extending the prediction to the whole world in 2040 shows that Europe would rank third. The highest rates are expected to be reported in Asia (15,944 deaths), followed by Africa (7,567), Europe, Latin America and the Caribbean (4,328), North America (1,556), and Oceania (208).

The predictions for Europe have shown that Russia will be faced with the highest HL incidence and mortality rates in 2040 see (Figure 9).

DISCUSSION

This article provides a brief overview of the epidemiological situation of Hodgkin's lymphoma, with a prediction of its incidence and mortality in 2040.

The study produced several findings:

1. Permanently increase incidence trend HL in Europe,
2. Permanently decreasing mortality trend HL in Europe,
3. Prediction of HL incidence and mortality in 2040 confirms higher incidence and mortality values in the male population,
4) In 2040, the most of new disease cases and deaths from the disease will be reported in Asia. Europe will be 2nd in the number of new cases, 3rd in the number of deaths.

Even though the first scientific description of the disease dates to 1832, the cause remains unknown. The disease is characterized by specific patterns of incidence associated with patient age, socioeconomic status, sex, and the presence of EBV and HIV also regarding to different histological subtypes of CHL. Despite the absence of a known cause, there are both uncontrollable (age, gender, ethnicity and genetic predisposition) and controllable risk factors (obesity, smoking tobacco products, and HIV status) that may contribute to the development of the disease.

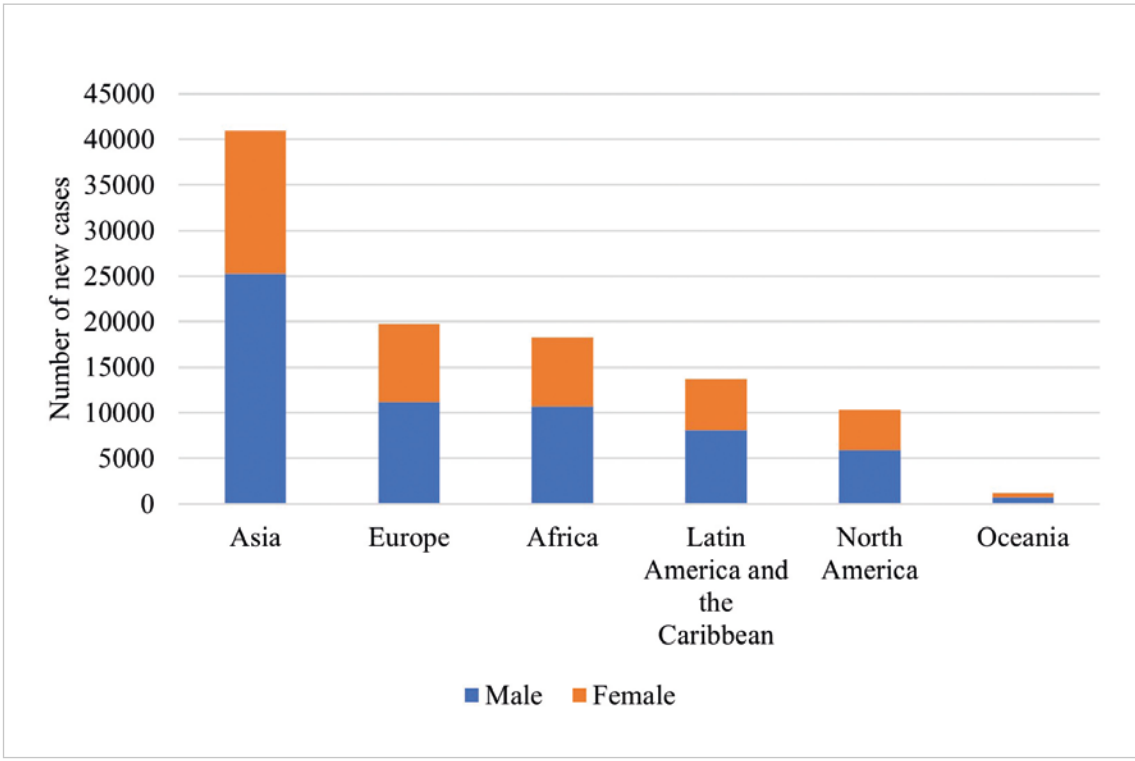


Figure 8. Prediction of male and female incidence world 2040

(data source: GLOBOCAN 2020, custom design)

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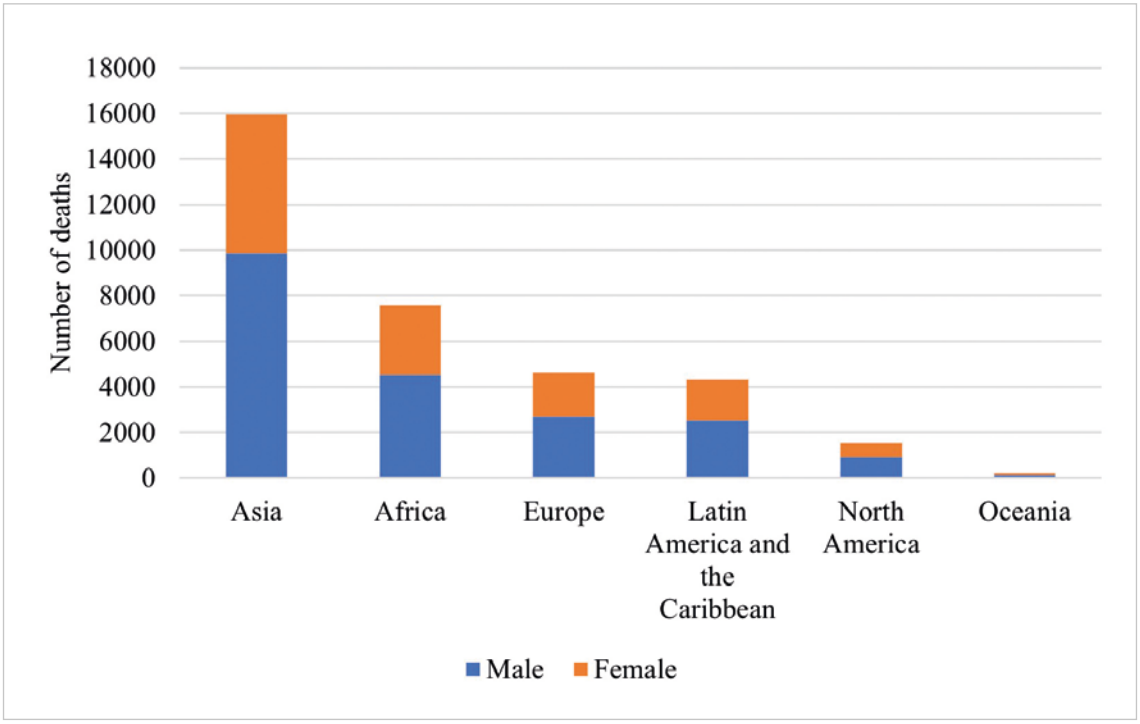


Figure 9. Prediction of male and female mortality world 2040

(data source: GLOBOCAN 2020, custom design)

Obesity

Obesity is associated with chronic inflammation, which may play a role in promoting the growth and survival of HRS cells and may also impair the accumulation of immune cells in the cellular background of HL. Chronic inflammation is accompanied by elevated levels of interleukin 6, which is considered a risk factor for HL. Endocrine and paracrine mechanisms associated with obesity may influence the microenvironment and thus the growth and proliferation of HRS cells. Willett et al. concluded that obesity (as defined by body mass index) is a risk factor for the development of HL. Individuals with class II or III obesity had odds ratio (OR) OR = 2.2 (95% CI 1.1–4.3). An increased risk was observed in persons over 35 years of age, especially males with OR = 2.8 (95% CI 1.2–6.5) compared to females with OR = 1.1 (95% CI 0.3–3.8). A study by Walk et al. showed an increased risk of HL only in overweight male patients with a standardized incidence ratio of 3.3 [4, 5, 6, 7].

Smoking tobacco products

Studies have yielded considerably inconsistent findings as to whether tobacco smoking is a risk factor for HL. This may be explained by methodological limitations (e. g. small sample sizes, uneven distribution of histological variants of HL, limited statistical power, or definitions of current and former smokers). Important factors influencing study results are patient age and the presence of EBV in HRS cells. Smoking as a risk factor for HL has been demonstrated especially in patients older than 35 years of age. A meta-analysis by Castillo et al. evaluated the relationship between smoking and developing HL using an odds ratio (OR). The OR for HL in current smokers was increased at 1.37 (95% CI 1.22–1.54; P < 0.001) as compared to OR = 0.72 (95% CI 0.61–0.86; P<0.001) in former smokers. A cutoff of 20 cigarettes per day was used to demonstrate the dose-risk relationship; once again, heterogeneity between studies was observed. Current smokers of less than 20 cigarettes per day had OR = 1.27 (95% CI 1.09–1.49; P = 0.002). Those who smoked more than 20 cigarettes per day had OR = 1.51 (95% CI 1.16–1.98; P = 0.002). Individuals smoking less than 10 cigarettes per day had OR = 1.09 (95% CI 0.88–1.35; P = 0.45). An empirical cut-off of 20 years of active smoking was used to demonstrate the relationship between exposure duration and risk. Individuals who had smoked for less than 20 years had OR = 1.12 (95% CI 0.93–1.36; P = 0.23) and those who had smoked for more than 20 years had OR = 1.84 (95% CI 1.47–2.32; P < 0.001). The effect of smoking as a risk factor was higher in males (OR = 1.78; 95% CI 1.46–2.17; P < 0.001) than in females (OR = 1.16; 95% CI 0.89–1.51; P = 0.28). There was a relationship between smoking and EBV infection; in current smokers, the OR for EBV-positive HL was 2.26 (95% CI 1.69–3.02; P < 0.001) and the OR for EBV-negative HL was 1.40 (95% CI 1.08–1.81; P < 0.001). Regarding histological subtypes of CHL, smoking was shown to be a risk factor especially for MCCHL and NSCHL [8, 9, 10].

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Alcohol consumption

Epidemiological studies have shown that alcohol consumption is not a risk factor for developing HL and has a protective effect observed across all age groups. In a study by Besson et al., the protective effect of alcohol was observed in regular drinkers with OR = 0.61 (95% CI 0.43–0.87). Regarding age, the results were as follows: OR = 0.63 (95% CI 0.37–1.09) for the age group < 35 years and OR = 0.58 (95% CI 0.35–0.94) for those > 35 years of age. As for the type of alcohol regularly consumed, the highest protective effect was associated with wine consumption in the age group < 35 years (OR = 0.49; 95% CI 0.22–1.10) and with beer consumption in the age group > 35 years (OR = 0.51; 95% CI 0.28–0.92). The protective effect was observed for NSCHL but not for MCCHL. The discussion mechanism of the protective effect of alcohol on HL includes proapoptotic properties based on the inhibition of the transcription factor nuclear factor kappa-B (*NF-κB*). This factor initiates the transcription of anti-apoptotic genes (e.g. *bcl-2*), which subsequently allows HRS cells to block their apoptotic pathway. Inhibition of active *NF-kB* reduces the proliferative activity of HRS cells, leading to spontaneous apoptosis of HRS cells [8].

An important factor in the development and prognosis of HL is the patient's socioeconomic status. Higher incidence rates (depending on the histological subtype) are observed in regions with high HDI. This trend may be explained by a dramatic increase in the incidence of metabolic diseases and the associated epidemic of obesity in high HDI regions. When HL develops in low HDI countries, it affects individuals of higher socioeconomic status. The mortality rates are lower in high HDI areas than in low HDI areas, suggesting that patients' prognosis improves with the level of the health care system. Important factors influencing mortality are early diagnosis and the availability of modern therapies [10, 11].

The effect of HDI was observed by Hjalgrim et al. who examined changes in the incidence of HL in Singapore between 1968 and 2004. During that time, Singapore experienced a significant socioeconomic transition in lifestyle like that seen in high HDI countries. The increase in socioeconomic level resulted in an increase in the incidence of HL in the 15–19 and 20–24 age groups [12].

Socioeconomic risk factors

In 2020, the global incidence of HL was 83,087 cases. The rates were higher in areas with high HDI, depending on the subtype of HL. In very high HDI countries, the incidence was highest at Age ASR = 2.0, compared with low HDI countries (ASR = 0.83), high HDI countries (ASR = 0.79), and medium HDI countries (ASR = 0.69). The regions with the highest incidence of HL were Southern Europe (ASR = 2.8), Northern Europe (ASR = 2.6), Australia and New Zealand (ASR = 2.6), and Western Europe (ASR = 2.5). The lowest incidence of HL was observed in East Asia (ASR = 0.44), Southeast Asia (ASR = 0.45), Central Africa (ASR = 0.46), and Melanesia (ASR = 0.59).

The effect of high HDI was most pronounced in NSCHL, which accounted for as many as 70% of CHL cases. This subtype of CHL occurred predominantly in areas with high HDI. When occurring in low HDI areas, the disease affects people of high socioeconomic status. In cases of higher incidence rates for CHL subtypes (MCCHL, LDCHL) in low HDI areas, there was an obvious association with the presence of EBV or HIV in the affected individuals. The MCCHL subtype accounted for up to 25% of CHL cases and was associated with EBV (and HIV) in 75% of cases. LDCHL represented the rarest subtype of CHL. In developing countries, the prevalence of HIV was as high as 15.1% in LDCHL cases (the overall HIV prevalence in HL was 3.8%) [1, 13, 14].

In 2020, HL was responsible for a total of 23,376 deaths (ASR = 0.26). The differences in mortality between geographical areas were smaller than those for incidence. In contrast to incidence, mortality rates were lower in very high HDI areas. Regions with very high and high HDI had the lowest rates, at ASR = 0.23, compared to medium HDI (ASR = 0.27) and low HDI regions (ASR = 0.43). The lowest mortality rates were in East Asia (ASR = 0.13), Southeast Asia (ASR = 0.14), North America (ASR = 0.15), and Western Europe (ASR = 0.17). The highest rates were observed in West Asia (ASR = 0.59), North Africa (ASR = 0.53), West Africa (ASR = 0.45), and Central America (ASR = 0.42) [13].

Since HL is a well-treatable disease with the highest incidence in young adulthood, or at a time of education, family formation, and the establishment or strengthening of social relationships, numerous articles have been published in the last decade that address the quality of life of long-term survivors after successful treatment of HL, most of which are systematic reviews [15, 16, 17].

Future research should focus on the possibility of elimination of the three risk factors (obesity, tobacco smoking, and HIV) which could lead to a change in the epidemiological situation of HL in both high and low HDI regions. In addition to the identification of individual risk factors, it is essential to clarify the biological and epidemiological roles of other determinants associated with EBV and thus HL. Approximately 90–95% of the world's adult population has been exposed to EBV, but only a small percentage of the affected individuals develop HL. Therefore, it can be assumed that biological and epidemiological determinants other than EBV alone are involved in the development of HL [18].

Although HL is not a very prevalent cancer, it is the most common malignancy in the 15–19 age groups. In the USA, HL accounts for 7% of childhood cancers, with a 1% mortality rate [19].

This study has several limitations. The first limitation represents analysed data from the GLOBAN registry.

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The indicative value is dependent on the reporting mechanism within national registries. A common problem that can occur is the "signing off" of data. The second limitation follows the number of reports and the periodicity of sending data from individual national registers to the GLOBOCAN register. For some states, we observed only the transmission of data on mortality, but not on incidence.

CONCLUSION

Incidence of Hodgkin's lymphoma in Europe in the last period 200–2010 gradually slightly increasing trend. However, in the same period to a slight decrease in mortality. The increase in the incidence of the disease is influenced on the one hand by risk factors, especially lifestyle, but at the same time the impact of influencing the availability and level of the healthcare system can be increased. The influence of the health system on the epidemiological situation of the disease is confirmed by the decreasing trend of mortality. Early diagnosis of the disease represents one of the most important prognostic factors of the disease.

Looking at the incidence of HL in 2020, the lowest value was reported in the Republic of Moldova, the highest value was reported in Italy. Looking at mortality, the lowest value was reported in Slovenia, the highest value mortality was reported in Serbia.

In 2020, the lowest incidence value was reported in Central and Eastern Europe, the highest incidence values were reported in Southern Europe. The lowest mortality value was reported in Western Europe and the highest value in Central and Eastern Europe.

Modelling of the prediction of incidence and mortality of HL in 2040 shows that the disease will continue to be more frequent in the male population, including a higher mortality rate. Most new cases and deaths will be reported in Asia.

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Conflict of interest
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