



The association between Epstein-Barr virus contributing to diagnosis of Hodgkin's Lymphoma in young adults

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ABSTRACT

Background: Hodgkin's lymphoma is a cancer of the immune system accounting for less than 1% of cancers worldwide. In Hodgkin's lymphoma, cells in the lymphatic system grow abnormally due to an excess number of Reed-Sternberg cells, and may spread beyond the lymphatic system, affecting one's ability to fight infection. This disease is most prevalent in young adults between 15-35 years and after the age of 55. Although Hodgkin's lymphoma has no confirmed risk factors, it has been suggested that Epstein-Barr virus may increase an individual's risk of developing Hodgkin's lymphoma. Epstein-Barr virus, best known for causing infectious mononucleosis, has been linked to other types of immune system related cancers as well.

Objective: A review of the literature was done to assess the evidence regarding the association between Hodgkin's lymphoma and Epstein-Barr virus in young adults.

Methods: A structured literature review was conducted to find evidence of an association between Epstein-Barr virus and Hodgkin's lymphoma. Peer-reviewed articles were collected from SCOPUS, using the keywords "Epstein-Barr", "Hodgkin's Lymphoma", "female" and "young". Articles were assessed to meet inclusion criteria through publication date, language, and title and abstract scope.

Results: The literature search revealed that there is an association between a positive Epstein-Barr virus infection and Hodgkin's lymphoma in young adults. Studies indicate differences in the strength of the association reported in young adults diagnosed with Hodgkin's lymphoma. The literature shows evidence of a stronger association in certain geographical regions around the world.

Conclusion: The literature provides evidence of an association between Hodgkin's lymphoma and Epstein-Barr virus in young adults. Further studies are needed to show the strength of association, specifically targeting young adults between the ages of 15-35, as Hodgkin's lymphoma peaks in this age group.

INTRODUCTION

How is Epstein-Barr virus (EBV) related to Hodgkin's lymphoma (HL)? Although HL has no confirmed risk factors, it has been suggested that EBV may increase an individual's risk of developing HL [2]. Studies show that the frequency of EBV in patients diagnosed with HL is highly variable, ranging from 18-100% in different countries [4].

What is Epstein-Barr virus? EBV, a virus among the herpes virus family, has been historically seen as a possible causative agent of HL, as HL patients were more likely to report EBV infection than non-HL patients [4]. EBV has been implicated in several types of cancers and autoimmune diseases, due to its impact on the immune system [5]. Furthermore, EBV-positive Hodgkin's lymphoma is characterized by a high incidence in underdeveloped countries and has a male predominance [4].

Research question: Is there an association between Epstein-Barr virus and the diagnosis of Hodgkin's lymphoma in young adults?

RESULTS

Study Name (year)	Study Design	Population	Primary Findings	Limitations	Quality Rating
Chen et al. (1997) [1]	Cohort Study	4997 cases in Connecticut, USA 57% male 43% female 95% white	<ul style="list-style-type: none"> Molecular studies consistently report EBV is detectable in 18-49% of cases. EBV does not explain the increase in HL in young adults and the diverse trend between males and females. Currently identified major risk factors such as SES, EBV, and HIV infections, cannot adequately explain the increase in incidence in young adults. 	<ul style="list-style-type: none"> Cohort-effect: changes of exposure to risk factors during the period of the study. Sampling bias: predominantly white population. 	4.5
Čičkušić et al. (2007) [2]	Retrospective Cohort Study	81 participants	<ul style="list-style-type: none"> All cases of HL diagnosed in the first decade of life are EBV+. The frequency of HL association with EBV infection in children is 80%. 	<ul style="list-style-type: none"> Population: age and gender not properly defined. Selection bias: all participants could not have been EBV+. 	4.0
Claviez et al. (2005) [3]	Retrospective Cohort Study	842 participants	<ul style="list-style-type: none"> MCHL subtype was strongly associated with high rates of EBV positivity (75% of boys and 52% of girls were EBV+). EBV infection was significantly associated with younger age. Only 44 (17%) of 266 adolescents older than 15 years were EBV infected. Correlation of young age with EBV infection in HL. 	<ul style="list-style-type: none"> Many studies used come to different conclusions. 	4.5
Glaser et al. (2005) [4]	Case-Control Study	268 women 211 young adults between 19-44 years	<ul style="list-style-type: none"> EBV was detected in 11% of young adults. EBV+ were more likely than EBV- to be older, to be non-white. 	<ul style="list-style-type: none"> Sampling bias: predominantly white women. 	3.75
Koh et al. (2012) [5]	Cohort Study	159 participants Children and young adults: 22 male and 21 female	<ul style="list-style-type: none"> Out of the 43 participants, 16% had EBV associated disease. EBV+ adults with advanced disease had poorer survival outcome than those who were EBV-. 	<ul style="list-style-type: none"> Small sample size of young adults. No clear distinction was made in regards to the peak age groups that are affected by the disease. 	3.5
Lee et al. (2014) [6]	Meta-analysis	119 Studies Divided HL cases into paediatric and adult groups (14-15 year old considered adults)	<ul style="list-style-type: none"> The frequency of EBV infection was 69.7% in paediatric patients with HL and 41.1% in adult patients with HL. EBV+ HL according to the geographic regions, the prevalence of EBV+ HL was more than 70% in paediatric patients from Africa, Asia, and Central America. EBV+ HL occurs in young adults (15-34 years) in developed countries indicating a delayed exposure to EBV. EBV+ HL is approximately two times more prevalent in Africa and Central South America than in North America and Europe. 	<ul style="list-style-type: none"> Some studies included in the meta-analysis influenced the results positively. Funnel chart illustrates some publication bias in some studies that have been included in the analysis. 	4.5
Qi et al. (2013) [7]	Case-Control Study	59 total 27 adolescent patients: 18 males and 9 females	<ul style="list-style-type: none"> Out of the 27 young cases, 96.3% exhibited EBV + results. There was 96.6% EBV + reported in Indian children and 90.3% in Brazilian children. 	<ul style="list-style-type: none"> Small sample size. No mention on methods of recruitment of participants. Study design was not clearly mentioned. 	3.25
Souza et al. (2010) [8]	Retrospective Cohort Study	97 participants 58 male 39 female	<ul style="list-style-type: none"> EBV in Reed-Sternberg cells was detected in 52.5% of all cases (51/97). Incidence of EBV-related HL in developing countries is different from that in developed countries. The majority of cases (Brazilian population) had advanced disease at diagnosis (63%). 	<ul style="list-style-type: none"> Small sample size in age groups. No emphasis on specific age groups affected. 	4.0
Thomas et al. (2002) [9]	Systematic Analysis	Not stated	<ul style="list-style-type: none"> Several studies suggest that EBV may be a transforming agent in HL; patients with a history of EBV related infectious mononucleosis are 2-3X at a higher risk of development of HL. In Western countries, about 50% of HL cases are EBV+ vs. ≥ 90% EBV+ in developing countries. 	<ul style="list-style-type: none"> Information bias: number of articles analyzed was not specified in article. 	3.5
Vassallo et al. (2001) [10]	Cohort Study	78 patients 15-75 years	<ul style="list-style-type: none"> EBV was detected in 50 cases (64.1%). EBV expression in patients is similar to that of other developing regions, probably related to patients' SES; with an ethnically heterogeneous population. 	<ul style="list-style-type: none"> Population used does not focus specifically on the younger age range. 	4.0

Figure 1. Epstein-Barr virus positive = EBV+. HL = Hodgkin's Lymphoma. Quality rating assigned based on a checklist of 10 items, with some items referenced from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(6): e1000097. doi:10.1371/journal.pmed1000097

METHODS

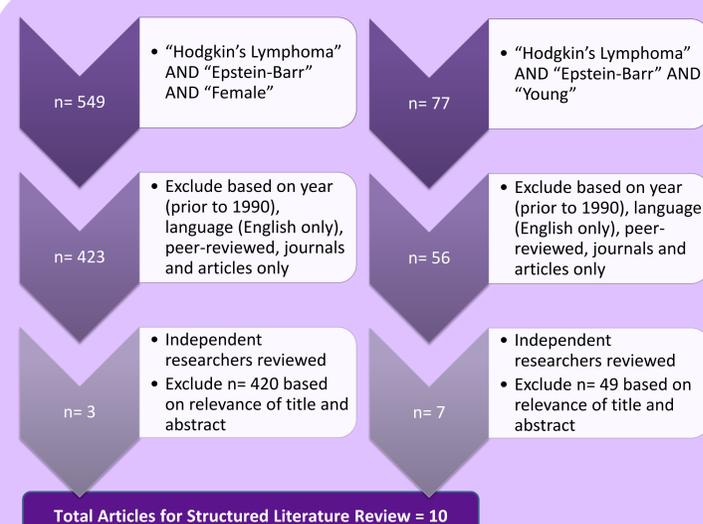


Figure 2. Flow charts illustrating the process of selecting studies for inclusion in the structured literature review. Database was selected based on accessibility through the University of Ottawa, and was limited to one due to the large number of articles available. Studies [2], [9], and [10] were selected from the original search criteria, including female as a keyword. All other studies were selected from the secondary search criteria, including young as a keyword.

Quality ratings were assigned based on a checklist of 10 items: relevance of title, relevance of abstract, type of study stated, population was distinct, data collection process stated, references were listed, no risk of bias identified, results stated, limitation section included (within discussion or conclusion acceptable), and peer-reviewed article. Each item is worth 0.5, and final score is out of 5 points. Some items were referenced from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(6): e1000097. doi:10.1371/journal.pmed1000097.

Agreement: two independent researchers rated the studies, and had a kappa score of $\kappa = 0.94$, indicating an almost perfect agreement.

DISCUSSION

- Studies [2-3, 6-7 & 9] show a large association with Epstein-Barr virus (EBV) and Hodgkin's lymphoma (HL).
- Studies [1,4-5, 8] do not show evidence of a strong association with EBV and HL.
- Study [10] is inconclusive about the association between EBV and HL.
- Studies [1, 6-10] show that there is a greater association with EBV positive and younger adults.
- The studies were limited by the study designs used; this included mainly cohort and retrospective studies.
- There was bias included in many of the studies. Publication bias was illustrated in the meta-analysis through a funnel plot (i.e. negative results not published). Other biases found include small sample size and very specific sample sizes in several of the studies analyzed.
- An unanticipated finding in several studies included a higher rate of EBV and HL in developing countries in young adults [1, 6-10].
- The burden of disease is not well defined between the two populations (young vs old) in studies comparing younger and older adults.
- The quality rating system consisted of 10 items that were selected based on the criteria necessary to analyze the studies. This allowed for rigorous and systematic approach of analyzing the data.
- It was necessary to broaden the population from young female adults to young adults because of the lack of research readily available.
- Strengths of our structured literature review: two independent researchers rigorously went through each article individually, limitations of studies were analyzed by both researchers, and a quality rating scale was used to determine the strength of each study analyzed.
- Limitations of our structured literature review: only one database was used due to the large number of search results, researchers were limited in the time to analyze each article for inclusion, and only articles where both researchers agreed on were included for further analysis.
- Future research is needed to establish the significance of the association between EBV and HL in the populations where it is most prevalent (i.e. 15-35 and over the age of 55).
- Future studies should focus on methodological rigour in order to determine the strength of the association.

CONCLUSION

- In conclusion, this structured literature review revealed that there is a large distribution in the association between EBV and HL.
- Studies range from 11% [4] association to 100% [2] association of positive EBV and HL in young adults.
- Positive EBV is associated with lower survival rates, relative to patients with negative EBV, in patients with HL [5, 9].
- Other factors, such as low socioeconomic status and living in a developing country contribute to an increased association between positive EBV and HL in young adults [1, 6-10].
- The literature reveals that there may be a stronger association between positive EBV and HL in older adults, relative to younger adults [4].
- Although EBV is not a confirmed risk factor of HL, it is clear that there is an association between EBV and HL. Other risk factors may contribute to an increase or decrease in the association.

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