Annals of Epidemiology 25 (2015) 275–292

Contents lists available at ScienceDirect

Annals of Epidemiology

journal homepage: www.annalsofepidemiology.org

Review article

A critical review of the epidemiology of Agent Orange or 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and lymphoid malignancies

Ellen T. Chang ScD [a,b,*], Paolo Boffetta MD, MPH [c], Hans-Olov Adami MD, PhD [d], Jack S. Mandel PhD, MPH [a]

[a] *Health Sciences Practice, Exponent, Inc., Menlo Park, CA*
[b] *Division of Epidemiology, Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA*
[c] *Institute for Translational Epidemiology and the Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY*
[d] *Department of Epidemiology, Harvard School of Public Health, Boston, MA*

ARTICLE INFO

Article history:
Received 19 September 2014
Accepted 9 January 2015
Available online 30 January 2015

Keywords:
Lymphoma
Lymphoma, Non-Hodgkin
Lymphoma, Hodgkin
Multiple myeloma
Tetrachlorodibenzodioxin
Agent Orange
Epidemiology

ABSTRACT

Purpose: Establishing a causal relationship between 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and risk of specific lymphoid cancers, including non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), and multiple myeloma (MM), would be useful for risk assessment.
Methods: This article systematically and critically reviews epidemiologic studies of the association between exposure to TCDD or TCDD-contaminated herbicides and risk of lymphoid malignancies. These include studies of military, industrial, accidental environmental, and general environmental exposure to Agent Orange or TCDD.
Results: Collectively, the epidemiologic evidence from industrial cohorts suggests a positive association with NHL mortality, but results are not consistent across other studies, a clear exposure-response gradient is not evident, and data are insufficient to conclude that the association is causal. Furthermore, available studies provide little information on NHL incidence or specific NHL subtypes. Epidemiologic studies do not show an association of TCDD exposure with HL, whereas the indication of a positive association with MM in a limited number of studies, but not others, remains to be confirmed in additional research. Exposure classification error and small numbers are important limitations of the available epidemiologic studies.
Conclusions: Overall, a causal effect of TCDD on NHL, HL, MM, or subtypes of these lymphoid malignancies has not been established.

Introduction

Lymphoid malignancies, which are classified broadly as non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), and multiple myeloma (MM), comprise a heterogeneous group of clonal tumors of mature B cells, T cells, and natural killer cells [1]. Although occupational exposure to pesticides in general has long been studied as a risk factor for NHL [2–4], HL [5,6], and MM [7–9], no causal association has yet been established with any specific pesticide.

Agent Orange, an herbicide used by the U.S. military for strategic defoliation during the Vietnam War in the period 1962 to 1971 [10], was contaminated by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Since 1991, the U.S. Institute of Medicine Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (IOM Committee) has conducted comprehensive reviews and evaluations of the available scientific and medical evidence on associations between specific health outcomes and exposure to Agent Orange and other herbicides used by the military in Vietnam. In each of these biennial reviews, the IOM Committee has determined that "evidence is sufficient to conclude that there is a positive association" between herbicides and both NHL and HL, such that "chance, bias, and confounding could be ruled out with reasonable confidence" [10–19]. For MM, the IOM Committee considers the evidence of an association with herbicides to be "limited or suggestive."

Of note, the IOM Committee is charged specifically with determining "whether a statistical association with herbicide exposure exists, taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiologic methods used to detect the association" (emphasis added) [10]. The

* Corresponding author. Health Sciences Practice, Exponent, Inc., 149 Commonwealth Drive, Menlo Park, CA 94025. Tel.: +1-650-688-6734; fax: +1-650-688-1799.
E-mail address: echang@exponent.com (E.T. Chang).

http://dx.doi.org/10.1016/j.annepidem.2015.01.002
1047-2797/

IOM Committee "fully recognize(s) that an association does not establish a causal relationship and that the rigor of the evidentiary database needed to support a finding of statistical association is weaker than that needed to establish causality." Moreover, any association is not necessarily specific to Agent Orange or other herbicides that contain TCDD.

The epidemiologic evidence on Agent Orange or TCDD and risk of lymphoid malignancies is complex. A detailed examination of this relationship is necessary for informed risk assessment and public health regulatory decision making. Although high-level exposure to TCDD and other polychlorinated dibenzo-*p*-dioxins is rare in general populations, due in large part to restrictions on the manufacture and use of chlorinated compounds, low-level exposure to dioxins is widespread, presumably through diet [20]. Moreover, the results on HL and MM have not been subject to recent systematic reviews, and the potential adverse health effects of Agent Orange exposure in Vietnam continue to be a focus of public concern and controversy [21–24]. Therefore, to clarify the current state of the science, this article systematically reviews the epidemiologic evidence on Agent Orange or TCDD exposure and risk of lymphoid malignancies.

Epidemiology of lymphoid malignancies

As the 10th most common malignancy worldwide, NHL is diagnosed in approximately 386,000 new patients and causes approximately 200,000 deaths each year [25]. MM and HL are substantially less common, with the former affecting approximately 114,000 new patients and causing approximately 80,000 deaths annually, and the latter being responsible for 66,000 new cases and 25,000 deaths annually. However, half of incident HL cases occur between ages 15 and 44 years, making HL the 11th most common malignancy in that age group worldwide and the sixth most common in economically more developed regions [25].

NHL incidence rates vary by more than 20-fold internationally, and HL and MM incidence rates vary by more than 30-fold, with generally higher rates of all three lymphoid malignancies in Israel, North America, Australia and New Zealand, and northern and western Europe and lower rates in Africa and East and Southeast Asia [25]. However, certain NHL subtypes, such as Burkitt lymphoma and adult T-cell leukemia/lymphoma, are more common in the latter regions [26,27].

In most countries with cancer registries, the incidence rate of NHL increased during the second half of the 20th century, followed by a plateau in many regions [28]. The incidence rate of MM also followed the same pattern in several geographic areas. These trends are believed to be at least partially explained by improvements in case ascertainment, reporting, and diagnosis [29,30]. By contrast, no clear international time trends are evident for HL incidence, either overall or for ages 15 to 44 or 45 to 85 years and greater [28].

Established risk factors for NHL analyzed as a single disease entity include older age, male sex, family history of hematopoietic malignancy, severe congenital or acquired immune suppression (e.g., ataxia telangiectasia, HIV or AIDS, or organ transplantation), and certain autoimmune disorders (e.g., Sjögren syndrome) [31–34]. In addition to HIV, which increases the risk of numerous NHL subtypes [35,36], other specific infectious agents are also etiologically linked to certain NHL subtypes. Causal relationships have been established between Epstein-Barr virus (EBV) and immunodeficiency-associated NHL, Burkitt lymphoma, and extranodal nasal natural killer/T-cell lymphoma; between human herpesvirus 8 (Kaposi sarcoma herpesvirus) and primary effusion lymphoma; between human T-cell lymphotropic virus 1 and adult T-cell leukemia/lymphoma; between *Helicobacter pylori* and gastric mucosa–associated lymphoid tissue lymphoma; and between hepatitis C virus and certain B-cell NHL subtypes [37–40].

Other relationships that are not established as causal include positive associations with type 2 diabetes mellitus [41,42], trichloroethylene exposure [43–45], and certain genetic polymorphisms in the tumor necrosis factor, lymphotoxin-alpha, interleukin 10 genes [46,47], and an inverse association with sun exposure [48,49]. In addition, higher body mass index is associated with increased risk of diffuse large B-cell lymphoma [50], cigarette smoking is associated with increased risk of follicular lymphoma [51], and alcohol consumption is associated with lower risk of Burkitt lymphoma [52]. Genomewide association studies have identified 16 genetic variants associated with risk of common NHL subtypes [53–59]. Other potential risk factors, such as other infectious agents [37,38,60], specific pesticides [2,61], diet [62], and reproductive and hormonal factors [63,64], are not consistently associated with risk of NHL or specific NHL subtypes.

HL incidence varies bimodally by age, with an initial peak in young adults under 40 years and a second peak after around the age of 50 years [65,66]. HL incidence patterns differ by age group, with young-adult HL occurring more often in whites and slightly more often in women but older-adult HL occurring more often in nonwhites and men [67,68]. These patterns are reflected in histologic subtype-specific patterns. Nodular sclerosis HL, the most common subtype, affects mainly younger adults, whereas mixed-cellularity HL, the second most common subtype, occurs more frequently in older adults.

Some established risk factors for HL are shared with NHL, including a family history of hematopoietic malignancy, severe congenital or acquired immune suppression, and certain autoimmune disorders [68–71]. EBV is an established cause of HL [40], with a higher proportion of EBV-positive (and mixed cellularity) tumors among older adults, young-adult males, nonwhites, and less economically developed populations [72]. Young-adult HL risk is consistently associated with indicators of a childhood social environment that favors delayed infection with common childhood infectious agents [68–71]. Delayed EBV infection, which manifests as infectious mononucleosis, increases the risk of tumor EBV–positive HL by approximately four-fold in young adults [73,74]. Certain genetic variants in the human leukocyte antigen (HLA) region, which encodes key molecules involved in immune function, are also consistently associated with HL risk [75,76].

The importance of the HLA region in HL etiology has been confirmed by four genomewide association studies [77–80], which also identified other putative susceptibility loci in other regions and demonstrated evidence of heterogeneity by tumor EBV status [80]. Cigarette smoking is positively associated with risk of EBV-positive and mixed-cellularity HL [81], and obesity appears to increase HL risk [50], whereas alcohol consumption may be inversely associated [82] and sun exposure may decrease EBV-positive HL risk [83]. Otherwise, few HL risk factors have been confirmed across multiple studies [67–71].

MM incidence increases steadily with age after approximately 40 years [25]. Rates are higher in males than females and, in the United States, in blacks than whites, who in turn have higher rates than Asians and Pacific Islanders [28]. Besides these demographic characteristics and a family history of MM [84,85], and perhaps obesity, which appears to be associated with an approximately 20% increase in MM risk [86], virtually no risk factors for MM are well established [87–89].

Profound immune suppression in the context of HIV infection or organ transplantation has been shown in several studies to increase MM risk, albeit to a lesser extent than risk of NHL and HL [90]. Certain autoimmune diseases and infections other than HIV have been shown in some but not all studies to be linked to higher risk of