A multi-center international hospital-based case-control study of lymphoma in Asia (AsiaLymph)

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Summary

The contribution of environmental, occupational, and genetic factors to lymphoma risk has generated a series of novel findings in studies of Caucasians. However, none of the chemical associations have been conclusively established and the identification of the key, functional alleles in gene regions associated with risk of NHL requires further elucidation. Further, the ability to follow-up, confirm, and extend these observations is limited by the low prevalence and limited range of several important chemical exposures and the high to complete linkage disequilibrium among key candidate genetic loci in Western populations. To optimize the ability to build on and clarify these findings, it is necessary to investigate populations that differ from Caucasians in both exposure patterns and underlying genetic structure. A multidisciplinary case-control study of lymphoma in Asia provides an opportunity to replicate and extend recent and novel observations made in studies among Caucasians in a population that is distinctly different with regard to patterns of key risk factors, including range of exposures, prevalence of exposures, correlations between exposures, and variation in gene regions of particular interest. Thus, a hospital-based case-control study of lymphoma in Eastern Asia (i.e., AsiaLymph) of 3,300 cases and 3,300 controls to be enrolled over a three-year period will be conducted. The major postulated risk factors for evaluation in this study are chemical exposures (i.e., organochlorines, trichloroethylene, and benzene) and genetic susceptibility. Other factors potentially related to NHL, such as viral infections, UV exposure, medical conditions, and other lifestyle factors will also be explored. A particularly noteworthy aspect of AsiaLymph is central pathology review with immunophenotyping by one of the world's leading lymphoma pathologists, which will enable accurate analysis of findings by molecular and histologic subtypes. AsiaLymph represents the optimal next step in the DCEG lymphoma portfolio. AsiaLymph should confirm and extend previous findings, and yield novel insights into the causes of lymphoma in both Asia and the West.

Background and Rationale

Important leads have emerged from studies focused on the etiology of lymphoma, particularly those that include novel observations on the role of chemical exposures in the environmental and occupational setting and genetic susceptibility. These studies include the NCI-SEER non-Hodgkin Lymphoma (NHL) case-control study (Wang et al. 2006; De Roos et al. 2005; Colt et al. 2005; Colt et al. 2009; Stewart 2009; Purdue et al. 2010), a case-control study of NHL among women in Connecticut (Lan et al. 2006), a case-control study of NHL in New South Wales, Australia (Purdue et al. 2007), InterLymph pooled genetic studies (Rothman et al. 2006; Conde et al. 2010; Skibola et al. 2009), and studies of organochlorines in the US and Europe (De Roos et al. 2005; Engel et al. 2007; Rothman et al. 1997). This body of research suggests that organochlorines, trichloroethylene (TCE), and benzene may be associated with risk of lymphoma and that benzene and TCE have immunotoxic properties (Stewart 2009; Lan et al. 2004; Lan 2009), that genetic variation in certain loci involved in immunologic regulation (e.g., *TNF/LTA*, *IL10*, and *IL4*) may contribute to risk of lymphoma, and that interactions between these chemicals and genes may exist (Lan et al. 2004; Colt et al. 2009; Wang et al. 2007). However, none of these chemical or genetic associations have been conclusively established, and the underlying biologic plausibility, including identification of critical functional alleles in genetic studies, requires further elucidation. At the same time, there is a growing appreciation of the critical need for high quality pathology review in etiologic studies of lymphoma, as evidence is increasing that some risk factors may be highly specific to one or more subtypes of lymphoma (Morton et al. 2008). A multidisciplinary case-control study of lymphoma in Asia is timely because it will provide an opportunity to replicate and extend recent and novel observations made in studies among Caucasians in a population that is distinctly different with regard to patterns of key risk factors.

Lymphoma in Asia

Although NHL rates historically have been lower in Asia than in the West, there is evidence that rates have been rising in recent decades in Shanghai and Singapore (Jin et al. 1999; Chia et al. 2001). For example, in Shanghai between 1972-1973 and 1993-1994, NHL rates rose 33% in males and 66% in females, while there was a small drop in incidence rates for leukemia in both sexes. Overall, there was an 11% and 13% decline in the incidence rates of all cancers for males and females, respectively, during this time period (Jin et al. 1999). The distribution of NHL histologic subtypes also differs in Asians and Caucasians. Although diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype in both Asians and Caucasians, rates of follicular lymphoma are substantially lower in Asians, whereas rates of T-cell lymphomas, particularly nasal type NK/T-cell lymphomas, are substantially higher in Asians (Au and Lo 2005; Ng et al. 1986; Gross et al. 2008; Kadin et al. 1983). As a consequence, this study provides a unique opportunity to replicate and extend key findings observed in Caucasians for histologies with characteristics shared by both populations as well as to rigorously study the epidemiology of those tumors that appear to be more common in Asia than in Western populations.

Organochlorines

Organochlorine compounds (OCs) are chemicals comprised of joined carbon and chlorine atoms, and account for several classes of chemicals including dioxin, polychlorinated biphenyls (PCBs), and pentachlorophenols (PCPs). OCs are primarily synthetic chemicals that were first introduced in the 1940's, and have been widely used as insulators and pesticides. OCs are relatively long-lasting, and can enter the environment through pesticide application, disposal of contaminated waste in landfills, and releases from manufacturing facilities that produce these chemicals (Centers for Disease Control, 2010). OCs have been suggested to be associated with a number of health concerns, including thyroid, metabolic, and reproductive disorders, in addition to several cancers, although results have been inconsistent (Toft et al. 2004; Langer 2010; Longnecker et. al. 1997; Gallagher et al. 2010; Purdue et al. 2009). While most OCs are banned, some are still being used in developing countries (e.g., DDT), and remain important environmental contaminants in the West.

A series of studies, many led by DCEG investigators over the last 12 years, have reported associations between NHL and plasma levels of several OCs, including DDT (rated by IARC as Group 2B, a possible carcinogen), PCBs (Group 2A, a probable carcinogen), and chlordane (Group 2B, a possible carcinogen), but it is not clear which class of compounds or specific congeners is primarily driving the association due in part to moderate to high correlation between them (Colt et al. 2005; De Roos et al. 2005; Engel et al. 2007; Rothman et al. 1997; Spinelli et al. 2007). In addition, only one study (the NCI-SEER study) has examined the relationship between plasma levels of more potent dioxin-like OCs and NHL, reporting associations for co-planar PCBs and dibenzofurans. At the same time, even though seven milliliters of plasma from each subject were used in that analysis, the most potent dioxin compounds could not be measured because they are present at very low levels (De Roos et al. 2005). Further, no epidemiologic study to date has been able to evaluate this finding because of the large volume of plasma required. Overall, the literature suggests that one or more components of OCs measured in blood, or some factor associated with OCs that has yet to be identified, are causally related to risk of NHL, but the specific compounds have not been identified with confidence. It is thus important to disentangle the different specific OCs and associated factors to further our understanding of the role of environmental exposures in lymphomagenesis. Such efforts will also have important public health implications with regard to current use of DDT in developing countries and the need to carry out environmental clean-up of sites contaminated by OCs in the West [e.g., the Hudson River (Environmental Protection Agency, 2008)].

There are several advantages to studying OCs and lymphoma in Asia including much higher plasma levels and a wider range of several OCs (e.g., DDE, the major DDT metabolite) than in the West, differences in correlation among certain compounds, and substantial differences in plasma levels between countries in Asia due to different industrialization histories and pesticide use patterns (e.g., higher DDE and lower PCB levels in China vs. lower DDE and higher levels of other OCs in Taiwan) (Hsu et al. 2009; Lee et al. 2007; Gammon et al. 2002; Stellman et al. 1998). As a consequence, the higher levels and wider range of exposure for several chemicals, the weaker overall correlation pattern between certain compounds, and the availability of a large plasma sample from study subjects to measure potent dioxin-like and dioxin chemicals will provide us with a unique opportunity to assess chemical-specific OC associations with NHL, which will complement previous and ongoing efforts to study these associations in the West.

Trichloroethylene (TCE)

TCE, a chlorinated solvent used in several industries primarily for metal degreasing, is one of the most important ground water contaminants in the US, and has been studied in cohort and case-control studies in the West. TCE is commonly found in ground water, and has been estimated to be present in about one-third of municipal water supplies in the United States (Jollow et al. 2009). While most water supplies are thought to have a relatively small concentration of TCE (i.e., parts per trillion or billion), samples taken from areas near direct contamination sites may have concentrations on the order of several hundred parts per million (ppm) (Jollow et al. 2009). The carcinogenicity of TCE has been well studied with generally inconsistent results, although there is some suggestion that occupational rather than environmental exposures may be most relevant (Raaschou-Nielsen et al. 2003; Jollow et al. 2009). Cohort and case-control studies (including NCI-SEER) with extensive exposure assessment have generally observed associations with NHL, typically at relatively high estimated levels of exposure (Raaschou-Nielsen et al. 2003; Scott and Chiu 2006; Stewart 2009; Wartenberg et al. 2000; Purdue et al. 2010). Despite the research carried out to date, a connection between TCE and lymphoma has still not been established. It is currently rated by IARC as a probable carcinogen (Group 2A).

It is not feasible to conduct new cohort studies of TCE in the West or Asia due to current instability of the industrial workforce. Case-control studies of NHL in the US and Europe have been hampered by the low prevalence of exposure in these populations and the fact that most occupational exposures occurred in the distant past, as occupational use of TCE has been reduced and several manufacturing processes that use TCE have moved to developing countries (Mandel et al. 2006). In addition, collective interpretations of the various studies have been difficult due to differing exposure assessment methodologies and lack of evidence concerning exposure response trends (Mandel et al. 2006). In contrast, due to the extensive use of TCE in Asia, a higher proportion of the population is exposed, and there is a wide range of exposure levels. Whereas less than 1% of women in the NCI-SEER case-control study were ever exposed to TCE, approximately 7% of women in the Shanghai Women's Health Study have been exposed, with half of these exposures continuing beyond 1990. A case-control study of lymphoma in Asia would take advantage of the higher prevalence of exposure and the opportunity to link to extensive TCE databases in Asia (e.g., Shanghai CDC database; Guangdong Poison Control Center database). AsiaLymph would also benefit from the use of refined questionnaire workplace modules developed by DCEG investigators to capture chlorinated solvent exposures.

Benzene

Benzene is a ubiquitous occupational and environmental contaminant worldwide, and is used for many applications including pesticides, detergents, and dyes, as well as in the rubber manufacturing process. Although an established leukemogen, there is substantial controversy about its lymphomagenic potential. Both cohort and case-control studies have been somewhat inconsistent (Orsi et al. 2010; Vlaanderen et al. 2010; Cocco et al. 2010, Alexander et al. 2010). There has been some suggestion that this inconsistency may be in part due to the etiological heterogeneity of lymphoma subtypes, as occupational benzene exposure has been shown to be associated with some NHL subtypes but not others (Cocco et al. 2010). A recent meta-analysis of

the association between benzene exposure and lymphoid neoplasms found a moderately increased, though not significant, risk of NHL with increasing study quality in workers occupationally exposed to benzene, and acknowledged that the effects of benzene on overall NHL may be attenuated due to the inclusion of specific NHL subtypes that are not associated with benzene exposure (Vlaanderen et al. 2010).

Although DCEG has studied hematopoietic malignancies in a large cohort of Chinese workers with detailed benzene exposure data spanning a 50-year period, the number of NHL cases is limited (i.e., there are ~ 20 benzene-exposed cases with a high probability of being NHL). Because the follow-up period was 1972-1999, almost half of the exposed cases have no specific molecular or histologic information and only nine cases have pathology material for re-review; this lack of biospecimens is the bane of retrospective cohort studies. As such, we have limited power to study the benzene association with NHL and cannot evaluate histology-specific effects. The lack of histologic information and our inability to obtain material from the majority of cases for independent confirmation has raised concerns about our reported benzene-NHL association from the cohort study (Hayes et al. 1997). AsiaLymph will complement the NCI-China CDC benzene cohort study, as the case-control investigation would have substantial power to detect an association between occupational exposure to benzene with confirmed cases of lymphoma (e.g., we would expect ~180 NHL cases with a high probability of exposure to benzene, assuming a prevalence of 3% among controls and an OR of 2.0), would be able to analyze benzene effects on lymphoma by subtype, and would take advantage of the extensive benzene databases we have accumulated on workplace exposures in China.

Environmental exposures to industrial emissions

Environmental pollution has been suspected as a cause of NHL based on findings from occupational studies and increasing incidence in industrialized countries over the past 50 years. Industries of particular interest include petroleum processing (for potential solvent releases) and pulp and paper mills, municipal waste incinerators, and other combustion facilities (for dioxin releases). Studies of NHL in Western countries have found increased risk associated with residential proximity to specific industrial facilities, especially pulp and paper (Linos et al. 1991; Johnson et al. 2003; Ramis et al. 2009), copper smelters (Johnson et al. 2003), and petroleum processing plants (De Roos et al. 2009; Linos et al. 1991). Residence near municipal solid waste incinerators, a major source of dioxin emissions, has been associated with increased risk of NHL in several European studies (Porta et al. 2009). In the NCI-SEER NHL study, we linked residential histories to a nationwide database of dioxin-emitting facilities and observed increased risk associated with residence near cement kilns and hazardous waste incinerators (Pronk et al. submitted). China has undergone rapid industrialization over the past 30 years with little control of industrial emissions until recently (Zhang et al. 2010). In AsiaLymph, we are collecting detailed residential addresses, which will allow us to geocode and map residences over most of participants' lifetimes and to link this information to data on incinerators to estimate environmental dioxin exposure. Most of the study population resides in highly industrialized areas, thus providing an excellent opportunity to follow up on these suggestive findings from Western studies.

Genetic Susceptibility

Lymphomas show significant familial aggregation in the population indicating that genes are likely to play a role in susceptibility. Candidate gene studies have consistently identified SNPs in the pro-inflammatory cytokine, *TNF*, to be associated with NHL, particularly with DLBCL (Rothman et al. 2006; Fernberg et al. 2010). Genes in other pathways such as DNA repair, oxidative stress, and innate immunity have also been shown to be associated with NHL (Shen et al. 2010; Wang et al. 2006; Hosgood et al. 2011). A major limitation of the *TNF* results, however, has been the inability to distinguish the *TNF* association from neighboring human leukocyte antigen (*HLA)* alleles, which are in linkage disequilibrium (LD) with *TNF*. Caucasian populations carry the 8.1 ancestral haplotype (AH) that includes the *TNF* -308A allele (*HLA*-A1-B8-*TNF*-308A-DR3-DQ2) (Candore et al. 2002); virtually all individuals with *HLA*-A*01-B*08-DR*03 have a variant *TNF* allele (GA or AA). Interestingly, the 8.1 AH is implicated in the risk of numerous autoimmune conditions, including those associated with NHL (e.g., systemic lupus erythematosus, Sjogren's syndrome) (Candore et al. 2002; Jacob et al. 1990; Newton et al. 2004) and is also associated with higher *TNF* activity and increased production of autoantibodies. It therefore remains unknown whether the association reported for *TNF* G-308A is due to or independent from *HLA* alleles and/or haplotypes.

A large-scale evaluation of genes associated with lymphoma in Asian populations that parallels efforts being conducted in Caucasian populations [e.g., currently a genome-wide association study (GWAS)] would be particularly informative because of Asian population genetic differences in patterns of LD and local haplotype structure (Lan et al. 2007). For example, definitive delineation between *TNF* G-308A and DLBCL could be achieved in Asian populations where the 8.1 ancestral haplotype does not exist. Among Asians, further delineation from other ancestral haplotypes, notably, 58.1, which includes *HLA*-A33, -B58, *TNF*-308A, and -DR3, could also be evaluated (Price et al. 2003). Another example follows from the report by Lan et al. of striking differences between Chinese and Caucasian populations in genotype and haplotype frequencies of polymorphisms in *IL4* and *IL10* (Lan et al. 2007), which have been associated with NHL among Caucasians (Rothman et al. 2006). To demonstrate the same associations in Asians would add substantial evidence to the causality of these specific SNPs in lymphoma etiology. The study of Asian populations also would allow for identification of novel susceptibility genes.

Viral exposures

Several aspects of lymphoma epidemiology in Asia support the importance of studying potential infectious etiologies for these tumors including the higher incidence of certain types of T-cell lymphomas than in Western countries that are known or likely to be virally-related and the higher prevalence of exposure to certain viruses such as Hepatitis B (Aoki et al. 2008; Aozasa et al. 2008; Du et al. 2009; Kadin et al. 1983). For example, the profound excess incidence of nasal NK/T-cell lymphoma, a uniformly EBV-positive tumor, suggests the existence of important co-factors related to host control of EBV that may be unique to Asian populations (Kadin et al. 1983). Some cases of other histologic types are also EBV-positive, which may be more frequent in T-cell than B-cell derived tumors. An intriguing parallel is nasopharyngeal carcinoma, another uniformly EBV-positive tumor occurring in excess among Asians. Both NK/T-cell lymphoma and nasopharyngeal carcinoma exhibit EBV latency pattern II, characterized by expression of

EBV-encoded RNA (EBER), latent membrane proteins, and EBV nuclear antigen-1, but not other EBNAs. We will screen all collected tumor samples by EBER *in situ* hybridization to identify the EBV-positive lymphomas. Risk factors including demographic, environmental, and genetic characteristics for NK/T-cell lymphoma and for other EBV-positive lymphomas will be compared and contrasted to the risk factors for EBV-negative lymphomas in case-case and case-control comparisons. This will be the most extensive study of EBV positivity and lymphoma carried out to date in an epidemiologic study.

NK/T-cell lymphoma represents a putative EBV-related disorder (Aozasa et al. 2008). We will be collecting an unprecedented number of these tumors for molecular pathologic analysis. In collaboration with our basic science colleagues, we will use microarray-based global gene expression analysis and whole transcriptome deep cDNA sequencing to investigate EBV-specific as well as host genome pathways for this tumor. These studies have the potential to identify proto-oncogene-activating mutations, altered expression of known microRNAs, and/or heretofore uncharacterized NK lymphoma-specific small non-coding RNAs that are dysregulated in NK lymphomagenesis. Results from these collective studies would lead to the identification of candidate lymphoma genes causally involved in NK lymphoma tumor initiation and/or progression.

As noted, Asians as compared to Western populations have a higher incidence of certain types of T-cell lymphoma (Aoki et al. 2008). The difference is due in part to endemic HTLV-I in southern Japan, but suggests possible involvement in other regions by a second directly transforming agent. This study will generate a large collection of tumors with uniform processing and histologic interpretation. We will select one or more histologic subtypes that appear particularly in excess relative to Western populations. These tumors will be analyzed for evidence of oncogenic viral infections that could explain the excess incidence. We will use high-throughput sequencing of whole genome and whole transcriptome tumor samples followed by digital subtraction analysis to search for non-human sequences other than EBV, including known infections as well as potential novel agents.

Finally, chronic hepatic inflammation caused by hepatitis B (HBV) or hepatitis C viral (HCV) infection has been implicated as a potential risk factor for NHL. The evidence for HCV infection is somewhat more suggestive, although the associated histologic sub-types have not been consistent between studies (Dal and Franceschi 2006). Evidence for HBV is more mixed, with both null (Anderson et al. 2008) and positive associations (Chen et al. 2008; Engels et al. 2010). A NHL study in East Asia, with its relatively high prevalence of HBV infection in particular (Du et al. 2009), provides a valuable opportunity to examine potential important etiologic associations. Accordingly, cases and controls will be screened for Hepatitis B and C exposure and chronic infection. With centralized pathologic review with extensive immunophenotyping, we will have greater precision for examining the associated subtypes and the magnitude of association for each infection. Risk factor analyses for viral-positive cases as well as for histologies with high attributable risk will provide important additional insight into the role of these viruses in lymphomagenesis.

Early life exposures

Emerging evidence suggests that childhood and adolescent exposures in conjunction with genetic makeup may be important in the etiology of NHL. Environmental exposures early in life are important triggers in the development of the adult immune system. The relationship between the development of atopic conditions and surrogates of early-life exposures to infection such as sibship size, childhood crowding, and daycare attendance is well established (Strachan, 1989; 2000). The explanation, termed the 'hygiene hypothesis', suggests that delayed exposure to infection leads to subsequent development of atopic conditions via a persistent Th2-dominant immune response or another immune mechanism (Willis-Karp et al. 2001). A recent pooled analysis of 13 case-control studies by the Interlymph consortium (Vadjic et al. 2009) showed significant reductions in B-cell NHL risk among those having at least one atopic condition over their lifetime. The changing social and economic conditions in China, which have resulted in reduced family size and migration from the rural countryside to large urban areas, are likely to provide a broad range in early life exposures to infections. In addition to collecting information about allergies, asthma, and other atopic conditions, we will assess childhood crowding, family size, and early life contact with animals, surrogates of early life infection that have not been extensively evaluated in Asian populations. To date, no large case-control studies have evaluated this hypothesis by histologic type of NHL.

UV Radiation Exposure

Epidemiologic findings generally suggest that exposure to solar ultraviolet radiation (UV) may be associated with a reduced risk of NHL (Armstrong et al. 2007). Increasing ambient UV levels (or, as a proxy, decreasing latitude) have been associated with decreasing NHL incidence or mortality rates in the United States and some parts of Europe (Hartge et al. 1996; Freedman et al. 1997; Grant 2003; Hu et al. 2004), although conflicting ecologic findings have also been reported (McMichael et al. 1996; Bentham 1996; Langford et al. 1998). Several case-control studies from Australia, Europe, and the U.S. have also observed decreasing risks of NHL with increasing self-reported lifetime sun exposure (Hughes et al. 2004; Smedby et al. 2005; Hartge et al. 2006; Weihkopf et al. 2007; Petridou et al. 2007; Soni et al. 2007).Thus far, the existing epidemiologic evidence regarding sun exposure and NHL involves studies conducted in Western, predominantly Caucasian, populations. Replication of these findings in other populations, with potentially different lifestyle correlates of time spent outdoors, would strengthen the inference that the sun exposure-NHL association is real and not attributable to confounding. An inverse association between sun exposure and NHL was observed in a recent small case-control study from Singapore, but more evidence from Asian and other populations are needed (Wong et al. 2010). In Asialymph, we will perform a detailed assessment of past UV exposure, incorporating both self-reported estimates of usual time spent outdoors at different periods of life and satellite-derived estimates of intensity of UV irradiance linked to subjects' lifetime places of residence using the Total Ozone Mapping Spectrometer (TOMS) database (http://toms.gsfc.nasa.gov). AsiaLymph will be particularly well suited for investigating sun exposure effects given the wide variability in intensity of UV irradiance expected across study centers, owing to the broad range of latitudes [from 39º N (Tianjin, China) to 22º N (Hong Kong)].

Other Potential Risk Factors

In addition to the postulated risk factors described above, the AsiaLymph study will enable the evaluation of other suspected and/or novel hypotheses that may contribute to lymphoma risk, including diet, alcohol and smoking habits, sleep quality and duration, dental health, and alternative medicine practices. Specifically, studies conducted in Caucasian populations have suggested that a high intake of certain fruits and vegetables, and possibly fish, may lower the risk of NHL, while high consumption of red meat and some dairy products may increase risk, though the relationships are inconclusive (Skibola et al. 2007). Similarly, studies of the association between smoking and NHL have been equivocal, with some suggesting that smoking may increase the risk of follicular lymphoma specifically or that certain types of tobacco may modify risk (Morton et al. 2005; Stagnaro et al. 2004). Given the increasing prevalence of this exposure in parts of Asia, we will also have an opportunity to evaluate patterns of smoking habits which have been understudied in the Asian population. Consumption of alcohol, particularly red wine, may decrease the risk of NHL, though further exploration is needed (Morton et al. 2005; Briggs et al. 2002). Detailed evaluation of these risk factors will clarify this relationship and extend findings to the Asian population. Given the strong relationship between lymphoma and immune status, we have postulated that sleep quality and duration and prior practice of acupuncture, which is thought to have some immunostimulatory properties, may influence lymphoma risk. Circadian rhythm disruption, part of which is influenced by sleeping patterns, has emerged as a potential risk factor for several cancers, including lymphoma, where night-shift workers may have an increased risk of NHL (Lahti et al. 2008; Davis et al. 2006). Finally, a recent report has suggested that dental health may be associated with NHL risk (Michaud et al. 2008). Our large sample size will enable us to adequately explore this and other novel hypotheses.

Identification of Study Centers

Our goal has been to have enough study centers and public hospitals to be able to enroll 3,300 lymphoma cases and 3,300 controls in three years; to have a number of centers with a high prevalence of exposure to occupational compounds of interest; to have adequate variation in exposure patterns for particular environmental exposures; and, to the extent possible, to carry out the study in centers and regions where NCI personnel have successfully carried out research previously to be able to take advantage of existing infrastructure and experience.

Centers were considered for inclusion in AsiaLymph based initially on NCI study personnel's familiarity with a particular site, additional information provided by lymphoma and hematological pathologists and clinicians that we have come to know during the course of our research in Asia, and a literature search to identify investigators who had carried out descriptive or analytic studies of NHL previously.

Additional issues taken into account were as follows:

1) Availability of local industrial hygienists and occupational health personnel to work with us on the exposure assessment effort;
2) Availability of local epidemiologists in each center;
3) Availability of high quality lymphoma pathologists in a given hospital;

4) Willingness to collaborate with other hospitals in a given center;
5) Willingness to collaborate with NCI on a large, multi-centered effort that required shipment of blood samples to NCI, and shipment of tumor samples to Hong Kong for central pathology review and to NCI for molecular analyses.

Objectives

The primary scientific objectives of the study are to evaluate the etiology of lymphoma in Asia. The main focus of the study is on chemical exposures, viral exposures, and genetic susceptibility, with central pathology review to characterize effects by histologic subtype. The study will be the largest molecular epidemiology study of lymphoma ever carried out anywhere in the world, and will offer substantial scientific contributions to the literature.

Specific primary goals are as follows:

1) Investigate the role of environmental exposure to organochlorines and occupational exposure to TCE, benzene, and other chemical solvents as well as other potential occupational exposures;
2) Investigate the role of family history, high-prior candidate genetic variants (e.g., *TNF/LTA* locus), and emerging findings from genome-wide association studies of lymphoma in Caucasians, and to use state-of-the-art genomics to study genetic variants that may be unique to risk of lymphoma in Asia;
3) Investigate the etiologic role of EBV, Hepatitis B and Hepatitis C; evaluate potential novel viral agents in T-cell lymphoma and carry out studies to understand pathogenetic mechanisms of NK/T-cell lymphoma;
4) Study other potential determinants of lymphoma including medical conditions, UV exposure, and other lifestyle factors;
5) Determine the influence of risk factors for lymphoma overall and by histologic subtype determined by central pathology review.

Study Design and Methods

Study Design

A hospital-based case-control study design will be used for AsiaLymph. A total of 3,300 incident cases of lymphoma and 3,300 hospital-based controls will be enrolled over a three-year study period in Hong Kong, Mainland China, and Taiwan.

All subjects will be directly interviewed. To maximize DNA resources, a buccal cell and blood sample will be collected from all subjects. Case and control identification and interview methods are based on methods used in previous DCEG hospital-based case-control studies.

There will be a study center in Hong Kong, Taiwan, Chengdu, and Tianjin, and an overall study coordinating center in Hong Kong (Figure 1). A pathology center has also been established in Hong Kong. Study logs and questionnaires will be designed for web-based data transmission and biologic samples will be shipped to the NCI every three months. Receipt will be logged and tracked using the Biological and Environmental Sample Tracking (BEST) System, developed by Westat, Inc. Study progress reports will be generated weekly using the Study Management System (SMS) and will be transmitted weekly to the NCI.

Case Selection and Enrollment

Eligible cases will be Chinese patients at a participating hospital (Figure 1) who are between 18 and 79 years of age at the time of initial diagnosis and admitted or treated for incident diagnoses of any lymphoid neoplasm including all NHL and Hodgkin disease. Although it is important to understand the etiology of lymphoma in children as well, this undertaking would require additional hospitals, instruments, expertise, and funding that are not currently available to our research team. Adults over the age of 80 are generally among the sickest patients in the hospital and often have multiple comorbidities, which may preclude their participation in an interview of this length. Cases will be permanent residents of the general geographic region that is served by the hospital at the time of diagnosis. Specifically, they must have lived in this general geographic region for at least 15 years at some time in the past. Cases will include chronic lymphocytic leukemia/small lymphocytic lymphoma, Waldenström macroglobulinemia, plasmacytoma, multiple myeloma, aggressive NK cell leukemia, and cutaneous lymphomas. Cases with a previous diagnosis of lymphoma are ineligible.

An incident case will be defined as a case enrolled into the study within 12 weeks after the date of diagnosis of a lymphoid neoplasm. Ideally, a case will be enrolled, interviewed, and provide a blood and buccal cell sample at the time of diagnosis and before receiving any type of therapy. A rapid case ascertainment system will be established for case identification in participating hospitals. In each hospital, new cases will be identified within 48 hours of diagnosis to study personnel. Arrangements will be made with hospital staff (particularly in the oncology and radiology departments) so that all newly diagnosed cases are quickly reported to the study staff. In addition, daily admission logs will be reviewed by study staff to identify cases. The interviewer will approach the patient within 48 hours of the patient being diagnosed with lymphoma, explain the study to them, and then ask questions determining their permanent residence in the current geographic region and if they have a previous history of a lymphoid neoplasm. If the patient is eligible for the study, based on answers to these questions, and agrees

to participate, they will be asked to sign the case informed consent form, which includes willingness to be interviewed, to provide access to medical records, to provide a buccal cell and blood sample, and to allow a portion of previously collected pathology material to be made available for additional laboratory studies. The minimum requirement for enrollment in the study is providing consent to participate in the interview or to provide either a blood or buccal cell sample. Subjects who consent to one or more of these items will be enrolled**.** The interviewer will then carry out the interview in private.

Given that this is a hospital-based case-control study and all effort must be made to enroll subjects while they are still in the hospital, it will be necessary to approach potential subjects within the first 48 hours of diagnosis. Study staff will be trained specifically on how to approach patients that have just been diagnosed with a serious illness, using approaches and experiences from past studies that the study investigators have been involved in. Study staff will work in close coordination with the treating physicians in order to assess the emotional state of the potential subject and to identify an opportune time to conduct the eligibility screening. Further, conducting the eligibility screening in a private setting will allow the interviewer to better establish rapport with subjects and answer any questions or concerns that may arise.

If a case is missed from enrollment during the initial visit to the hospital, the case will be approached at the next scheduled follow-up visit to the hospital. A case referred from a non-study hospital/clinic to a study hospital will be eligible for inclusion into the study if they come from the general geographic region served by the study hospital, if they are enrolled at the study hospital within 12 weeks of diagnosis, and are otherwise eligible for the study based on the same criteria used for patients initially seen at a study hospital. In addition, at a minimum. the diagnostic slide and preferably additional unstained slides (see Pathology Review), as well as relevant parts of the hospital record and pathology report plus other diagnostic tests, need to be obtained.

Scanned medical records will be used to obtain information related to the confirmation of the diagnosis. In addition, treatment information and health status will be obtained from the scanned medical records in the future for cases who continue to be cared for by physicians at study hospitals. This information will be used in future studies of the determinants of survival.

Control Selection and Enrollment

Controls will be enrolled from Chinese patients seen at the participating hospitals. Controls will be individually matched to cases by hospital, age at date of diagnosis/admission (+/-5 years), sex, and date of enrollment (within 3 months). Further, all cases and controls must live in the same general geographic region served by the hospital and have lived in this region at least 15 years at some time in the past.

Controls will be drawn from patients seen at the same hospital for diseases/conditions that are unlikely to be associated with risk factors under study, such as injuries and selected diseases of the circulatory, digestive, genitourinary, and central nervous system (see Appendix A). Each potential control disease has the same general referral pattern as lymphoma cases to avoid bias. Patients with a history of any lymphoma, including acute lymphoblastic lymphoma, multiple

myeloma, chronic lymphocytic leukemia, Hodgkin lymphoma, and NHL will not be eligible to serve as controls.

The interviewer in each hospital will randomly select one of the five disease categories from which to draw a given potential control patient for a specific case. The interviewer will then identify potential controls from admissions records with a disease from one of the five disease categories who could be a match to a given case on age and sex, randomly select one control patient from the list of potential matched controls, and approach the potential control patient, explain the study, and obtain information to determine if the patient is eligible (i.e., residence in the current geographic region for at least 15 years in the past and no prior history of a lymphoid neoplasm). If the patient is eligible, and if the patient agrees to participate, they will be asked to sign the control informed consent form, which includes willingness to be interviewed, to provide access to medical records, and to provide a buccal cell and blood sample. As with cases, controls who provide consent to participate in the interview or to provide either a blood or buccal cell sample will be enrolled. The interviewer will then carry out the interview in a private setting. If the patient is not eligible, or the patient is eligible but does not consent to participate in the study, then the interviewer will randomly select another potential control from the list of potential matched controls. No more than ~15% of controls enrolled in any hospital can have one type of control disease.

Participation Rates

Based on the relatively high participation rates we have had in various types of studies in Asia, we expect to have a participation rate between 70%-85%. We will spend a substantial amount of time during training on approaches to enhance patient participation and refusal conversion. Further, we will closely follow case capture rates and case and control participation rates and identify hospitals and interviewers that are low outliers and re-train as needed.

Interview

Both cases and controls will be interviewed within 48 hours after they are identified. A computer assisted personal interview (CAPI) in the local language will ascertain occupational, family, medical, and residential histories. Specific exposure modules in the CAPI will be triggered in response to certain combinations of industry and job title for certain types of occupational solvents (e.g., benzene, OCs, TCE). For each residence, we will ascertain the primary source of drinking water at the home and obtain an accurate address for geocoding to allow for future assessment of environmental exposures. Additional questions focus on other lymphoma hypotheses that have been developed by DCEG investigators and include history of autoimmune conditions and allergies, height and weight, reproductive and breastfeeding history (to model lifetime organochlorine body burden for women), hair dye use, sunlight exposure, sleep duration/quality, diet and alcohol intake, childhood crowding, and contact with animals, as well as variables used to adjust for socioeconomic status (e.g., education level, household income). It is estimated that the interview will take on average approximately 60-75 minutes.

The CAPI has been developed by NCI investigators and the coordinating center in Hong Kong. The CAPI will trigger occupational exposure assessment modules in the OccIDEAS system. OccIDEAS is a system designed specifically to assess occupational exposures using more detailed, exposure-oriented job and industry questionnaires. OccIDEAS will implement modules

developed by NCI to ask questions about work tasks with the potential for chlorinated solvent and benzene exposure. A key feature of the OccIDEAS system is the ability to program exposure decision rules based on the patterns of responses to one or more questions, which can provide automated exposure assessments.

Biological Sample Collection

We plan to obtain a blood sample if at all possible when blood is being collected from subjects for clinical care, so that an additional phlebotomy is not needed. The specific time that blood is usually collected for clinical purposes may vary across the study hospitals, and therefore the study staff will work closely with the clinical care team at each facility to identify consented subjects and coordinate blood collection whenever possible. For example, in hospitals that typically collect blood for clinical care in the early morning, study staff would inform the clinical nurses of consented subjects from the previous day who have not yet provided biologic samples so that extra blood is drawn for research purposes at the time of collection. A 27ml blood sample will be collected from each study subject. To the extent possible, blood samples will be collected prior to initiation of therapy. The samples will be collected in EDTA vacutainers (3 tubes with 9ml each). The samples will need to be transported to the processing laboratory within 4 hours and processed, which will include standard low speed centrifugation, vortexing, and aliquotting into 1ml plasma aliquots and the remaining blood fraction into 3.4ml aliquots. Aliquots will then be stored at either -20ºC short-term for up to one week and then stored at -80ºC, or stored at -80ºC immediately after aliquotting. Information about biologic sample collection, processing, aliquotting, and storage will be entered directly into a web-based information system as soon as samples are processed. Standardized procedures and training will be provided to each processing lab. The processed samples will be shipped to the study center and subsequently the NCI biorepository, where they will be stored at -80ºC. Some hospitals may wish to retain up to one-third of blood samples to carry out research. In these instances, the remaining two-thirds of each type of blood sample will be shipped to the NCI biorepository.

A buccal cell sample will be collected and used as an additional source of DNA. Buccal cells will be collected from cases and controls by swishing water in the mouth for about a minute. Isopropanol will be added to the sample, which will then be centrifuged, the supernatant removed, and cells frozen. The pellet will be stored at -20ºC, and samples will subsequently be shipped to the study center followed by the NCI Repository and stored at -80ºC.

Tumor tissues will be collected where possible. For each case, 25 unstained 5 micron sections on HistoBond slides will be made and shipped to the study pathology center. Since the various pathology laboratories do not favor sending out paraffin blocks (due to the duty to keep safe custody of the blocks), unstained paraffin sections will be sent for pathology review instead (10% buffered formalin). Each participating center will be supplied with HistoBond glass slides. The 25 unstained sections will be cut and mounted on the HistoBond slides (slides are labeled with the original pathology number, with the unique project number beneath it, and a label with the specimen identifier and barcode for tracking in BEST). Two 20µm-thick sections will also be cut and placed in two separate eppendorfs for molecular studies. These will be sent to the hospital coordinator and delivered to central storage. Tissue slides will be stored at 4ºC. In addition, the pathology report and all relevant diagnostic tests will be scanned (e.g., flow cytometry, molecular studies or cytogenetic studies) and transmitted.

Study Subject Compensation

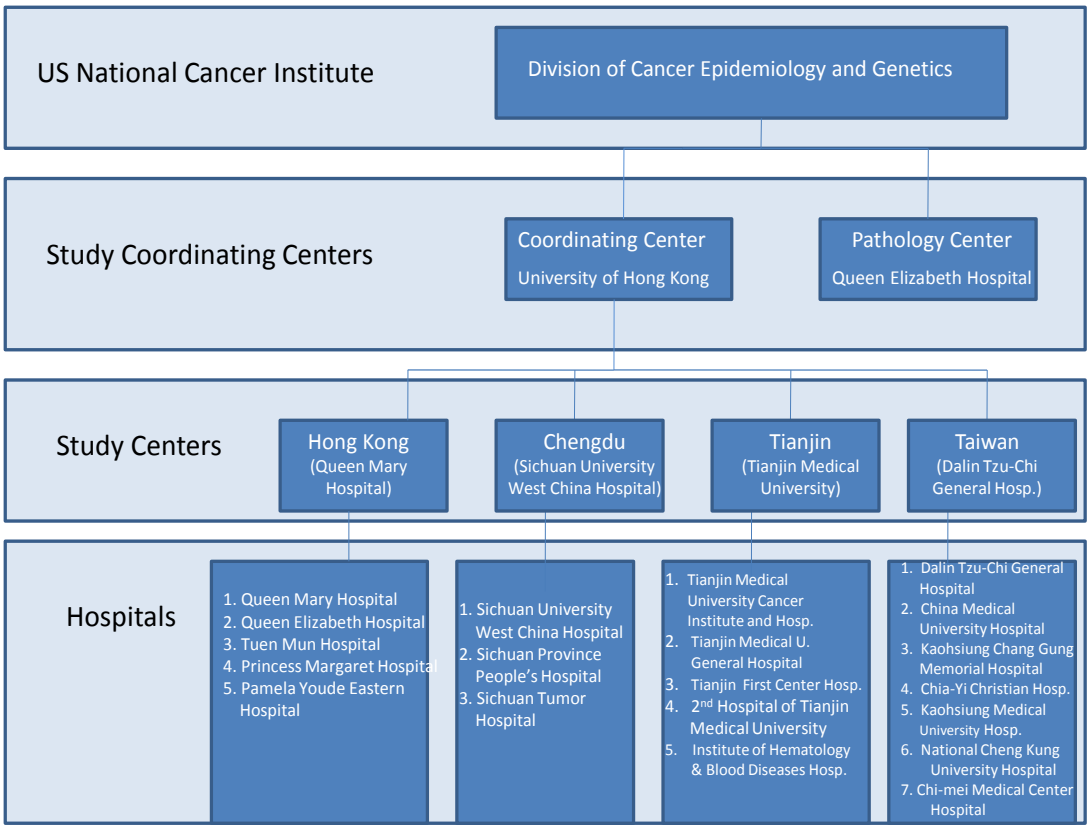
Study participants will be compensated about $22.50 for completing the interview and donating a buccal sample and a blood sample. It is estimated that approximately 2 hours will be required for the initial contact, the consent procedure, the interview and the collection of buccal cell and blood samples. The time for the interview will range on average between 60-75 minutes.

Study Organization

The U.S. National Cancer Institute is funding this collaborative, hospital-based case-control study of lymphoid neoplasms in four centers in Eastern Asia: Hong Kong, Chengdu, Tianjin, and Taiwan (Figure 1). The NCI study PIs are Drs. Qing Lan and Nathaniel Rothman. The study will enroll 3,300 cases and 3,300 controls over a three-year period, from approximately March, 2012 to February, 2015.

The AsiaLymph Coordinating Center Co-PIs, located at the University of Hong Kong, are Drs. T.H. Lam and Dennis Ip. Dr. Lam is a leading epidemiologist in this region with extensive experience conducting international studies in Asia and Dr. Ip has experience conducting epidemiologic studies in Hong Kong. In addition, Dr. John K.C. Chan will be leading the pathology component of the study. He is one of the leading lymphoma pathologists in the world who has contributed to the World Health Organization classification scheme of lymphoma histology. Leaders for the Hong Kong, Chengdu, Taiwan, and Tianjin centers are Drs. Y.L. Kwong, Caigang Xu, Y.C. Su, and Kexin Chen, respectively, who have experience conducting multi-hospital studies. Dr. Roel Vermeulen is the study Co-PI for occupational and environmental exposure assessment and is one of the leading industrial hygienists in the field, with extensive research experience in Asia.

Figure 1: Overview of the AsiaLymph study organization.



Study Coordinating Center: The overall study coordination in Asia will be by the School of Public Health, University of Hong Kong (Dr. T.H. Lam). Dr. Jun Xu will assist Dr. Lam with the field management of all aspects of the study. The Coordinating Center will manage the activities of the four study centers (Hong Kong, Chengdu, Tianjin, and Taiwan), all participating hospitals, and will coordinate the activities of the study pathology center. Investigators will maintain regular contact with each center and hospital, carry out training and re-training as necessary, receive enrollment data, questionnaires, biologic sample specimen information, and hospital records. They will make regular visits to each center and participating hospital to carry out site-visits and monitor quality control and coordinate shipments of biologic samples.

In addition to coordinating all aspects of the study, the coordinating center staff will be responsible for implementing a computer assisted personal interview (CAPI), which will ascertain occupational, family, and residential histories. The coordinating center will also be responsible for purchasing tablet PCs.

Study Pathology Center: The pathology component of the study will be coordinated by the Pathology Department, Queen Elizabeth Hospital, Hong Kong (Dr. John K.C. Chan). Investigators there will receive all pathology samples, pathology reports, and relevant medical records and tests and organize and carry out central pathology review (see Pathology Review

section). They will also maintain a sample biorepository that will be used to carry out additional analyses.

Center Organization: The study centers will consist of one site in each region that will coordinate and support all aspects of the AsiaLymph study in the hospitals in each respective region. These centers include Queen Mary Hospital, University of Hong Kong (Hong Kong), the West China (Huaxi) Hospital of Sichuan University (Chengdu), Tianjin Medical University (Tianjin) and Dalin Tsu-Chi General Hospital (Taiwan) (Figure 1).

There will be one center study manager in each study center who will be responsible for all parts of the study taking place in their center including distribution of supplies and programmed laptops, funding reimbursement to hospitals and physicians for study subject enrollment, coordination of biologic sample storage and shipment to the processing laboratory (Pathology Review Center and/or NCI), coordination of interview data and biological sample collection, maintaining quality control oversight, and other related tasks at each hospital. Further, the center study manager will hire and train interviewers on all tasks for each hospital in his/her region. The center study manager will maintain regular contact with each study hospital in their region, and will conduct monthly site-visits at each hospital.

In addition, the center study manager will utilize the SMS and BEST system to review study progress and monitor quality control oversight measures from each hospital. This includes routinely collecting and reviewing enrollment data, questionnaires, information on samples, and hospital records to ensure complete case and control identification. The center study manager will meet with NCI Investigators every three months as planned by the Study Coordinating Center, and will send monthly reports to the NCI on recruitment, diagnosis, pathology, staff changes, protocol violations if applicable, and quality control measures. The quality control report will include the number of cases and controls enrolled, participation rates, status of the sample shipments, and the completeness of enrollment data, questionnaires, biologic sample specimen information, and hospital records for enrolled subjects. The study center will coordinate shipments of blood and buccal samples to the NCI every 3 months (overnight shipping with tracking). Similarly, it will coordinate shipments of pathology specimens to the study pathology center every 3 months (overnight shipping with tracking). Specimens will be tracked via the specimen tracking system provided by the NCI.

Hospital Organization: Each interviewer will have full responsibility for all aspects of the study that pertain to each case and control that they enroll. This includes subject enrollment and interviewing, determining eligibility and documenting consent, collecting and scanning medical records, preparing and shipping pathology materials, coordinating blood and buccal cell collection, processing, and shipment, documenting all study outcomes and activities in the SMS and BEST systems, reporting to the center study coordinator, and other related tasks. All medical records will be scanned and uploaded into the SMS. Each participating hospital will have high-speed internet access. Each hospital additionally will host monthly site visits by the study center manager and meetings with the study coordinating center staff.

Biological Sample Tracking

BEST will track the status of the cases, controls and samples, including the unique project number. Before shipment of the slides, the details of the shipment will be entered and scanned into the system. Cases will be shipped in batches approximately every 2-3 months to the study pathology center at the Department of Pathology, Queen Elizabeth Hospital, Hong Kong.

For cases with limited material, the best opportunity of getting unstained sections for this project is at the time the diagnostic immunohistochemical stains are ordered (with the expectation that most cases of lymphoma will be enrolled in the study). Depending on the size of the tissue, 5-12 additional unstained sections besides those required for the in-house immunohistochemical staining will be cut. The left-over unstained sections will then be shipped out for central pathology review (the pathology center may request the pathologist to bring along original immunostained slides to the consensus conference for review if the available unstained sections are inadequate for full immunophenotyping). For cases with no more tissue in paraffin blocks, original slides and immunostains will not be shipped out, but will be brought to the consensus conference by the participating pathologist of the city. Since leukemia, Waldenstrom macroglobulinemia, and multiple myeloma cases usually have limited pathology material, 5-12 unstained sections on coated slides taken from marrow biopsies will be made and shipped like other cases. Reports (including flow cytometry, cytogenetics, etc.) will be scanned and original slides/smears will be brought to the consensus conference for review.

Pathology Review

Evidence increasingly supports both commonality and heterogeneity in the etiology of lymphoid neoplasms. It is therefore essential that an epidemiologic study of lymphoid neoplasms achieve high quality diagnostic specificity in identifying disease subtypes. Classification of lymphoid neoplasms has evolved rapidly in recent decades. In 2001, the World Health Organization (WHO) introduced a new classification that was adopted worldwide and represents the current gold standard for classifying all hematopoietic neoplasms (Jaffe et al. 2004; Swerdlow 2009). The WHO classification distinguishes approximately 45 lymphoid neoplasm subtypes based on morphologic, phenotypic, genotypic, immunologic and clinical features, the relative importance of which depends on the specific subtype. WHO subtypes are ideally assigned by an expert hematopathologist after review of diagnostic material and additional clinical and laboratory test results (The Non-Hodgkin's Lymphoma Classification Project, 1997; Jaffe E 2009; Clarke et al. 2004). Because of variability in the laboratory testing undertaken, additional immunophenotyping is often required in order to achieve high confidence in the diagnosis (Turner et al. 2004).

Based on the importance of accurately identifying lymphoid neoplasms and classifying disease subtypes, the proposed study will conduct centralized pathology review for all cases using the gold-standard WHO classification. The pathology review will take place in Hong Kong, led by Dr. John Chan and in collaboration with Dr. Dennis Weisenburger, both internationally-recognized expert hematopathologists. For each case, a minimum of 25 x 5-micron unstained slides and diagnostic slides (e.g., hematoxylin and eosin-stained slides) if unstained slides are not available will be sent from each study center to Dr. Chan, accompanied by copies of pathology reports and laboratory tests. The cases (25 unstained sections and printed shipment report for

each case) will be shipped in batches to the pathology review center at the Department of Pathology, Queen Elizabeth Hospital, Hong Kong. Specimens will be packed carefully to avoid breakage of the slides. Specifically, after air drying and briefly baking, slides will be thoroughly dried and cooled and all slides of individual cases will be tightly wrapped in paper towels. Adhesive tape with be affixed to the surface, where the unique project number will be written. These rigid "glass blocks" will be tightly stacked and sealed in a card box containing cushion material, and the box will be shaken to ensure no sound is produced (i.e. no dead spaces). Each center will be supplied with the name of a Courier and the customer number for shipment. For the hospitals in Hong Kong, shipments will be delivered through the internal mail system of the Hospital Authority.

Dr. Chan's laboratory will review the diagnostic materials and accompanying reports, and conduct additional immunophenotyping as necessary to assign the WHO disease subtype. We plan to form a pathology review group with representation from each study center that would meet two times per year during the duration of the study to review pathology material from the 3,300 cases that will be enrolled into the study over a three-year period.

A consensus conference will be held at Queen Elizabeth Hospital in Hong Kong, and all cases will be reviewed by a panel of experienced pathologists with a consensus diagnosis (full agreement in classification by ≥3 of 4 experts) being reached for each case. The 2008 WHO Lymphoma Classification categories will be used. Unclassifiable cases will not be forced into existing categories, but will be designated "unclassifiable" with notes on why a WHO subtype cannot be assigned. On completion of the project, these cases will be re-reviewed to determine if new entities can be recognized from this group. At the time of pathology review, molecular subtypes of key entities will be classified according to current methods (e.g., identification of DLBCLs by cell of origin).

It is envisioned that each consensus conference will review about 500 cases, and the first one of six is projected to be in December, 2012. Logistically, Dr. Dennis Weisenburger and Dr. B. Nathwani, in addition to a panel of pathologists from participating institutions, will review the sorted slides. Since the usual capacity of a pathologist is 50 cases per day, the cases will be divided into two separate sets (250 cases per set), to be examined by two separate panels of pathologists. Cases lacking consensus will be examined by both panels under multihead microscope at the end of the day. During review of the cases, additional immunostains can be requested if necessary to aid in diagnosis/classification, and these will become available the next day. For cases pending further workup, these will be reviewed at the next round. Additional cases to be reviewed at the consensus conference include original slides (H&E and immunostains) of cases for which unstained sections are not available, and original slides (H&E and immunostains) of cases with limited available unstained sections. Original slides and all related reports for leukemia and myeloma cases will be reviewed by two hematopathologists in Hong Kong. Since each panel should consist of 4 pathologists, a consensus conference theoretically will require the participation of 8 pathologists (2 panels, with 4 pathologists each). To economize on the number of invited pathologists, all cases will be reviewed by Dr. John Chan beforehand, and the diagnosis/classification will count towards one of the diagnoses for consensus purposes. Thus, only 6 invited pathologists (2 panels, 3 pathologists each) will be required each time.

Slides not required for WHO subtype classification will be stored in boxes at 4ºC for future molecular studies. Examples of such studies include evaluation of protein expression, chromosomal translocations, viruses such as Epstein-Barr virus, and tumor DNA to investigate somatic alterations. Archiving of tumor tissue specimens will also enable the study to take advantage of the rapidly-improving technology for formalin-fixed, paraffin-embedded tissues (e.g., gene expression and microRNA profiling), thus allowing us to be responsive if it is appropriate to newly developed technology at the time the study has completed recruitment. Initially, 50% of tissue samples from each case will be shipped to NCI and the remaining will be stored at Queen Elizabeth Hospital. Additional samples will be shipped to NCI depending on future assay needs.

Linking Occupational Histories with Occupational Exposure Databases

Occupational histories and data from solvent modules will be reviewed by DCEG and local industrial hygienists in each of the study centers, and linked with TCE and benzene exposure databases in Eastern Asia to obtain estimates of TCE and benzene exposure for each job, industry, and region. For example, the Shanghai CDC occupational exposure database contains measurements of TCE beginning in 1963 and benzene measurements since the 1950s from many types of workplaces and is generalizable to factory conditions in China during this period. Further, the NCI-China CDC benzene cohort study also has an extensive database of benzene measurements from many factories in 12 cities going back to the 1950s.

We will extract exposure data from several sources into a single exposure database. Experience of such an effort has been obtained in several DCEG projects, including the Shanghai Women's Health Study, the NCI-China CDC benzene cohort study, and the NCI-SEER NHL study. We will also use multi-level modeling of the exposure data where one can extrapolate information of job related exposures across regions and countries, while still accounting for regional differences. A similar approach has been followed in the ongoing NCI-China CDC benzene cohort study. Exposure modeling of the benzene data indicated that there are regional differences in exposures but that the relative ranking of jobs remains largely the same across the different regions. These and other analyses show that routinely collected exposure data from different regions can be used in a statistical framework which allows extrapolation of data across time and geographic regions based on observed similarities in the exposure data (Dosemeci et al., 1997).

Besides the quantitative data, we will also use targeted job and industry questionnaire modules to focus on a few specific exposures (e.g. benzene, TCE). The subject-specific information obtained in these modules will further aid in the determination of how to extrapolate exposure levels across countries and to allow differences in exposure estimates for jobs within a single region/time period.

Quality control

The study team has had extensive experience conducting multi-center studies in Asia over many years. For example, it has studied lymphoma in 12 centers in the NCI-China CDC benzene cohort study in Mainland China over the past 24 years where subjects speak Mandarin and/or Cantonese. The study team also has members who worked extensively on the multi-center hospital-based DCEG Brain Cancer study in the United States and the NCI Spanish Bladder

Cancer study, carried out in 5 regions and 18 hospitals in Spain. The study team has used the experience acquired from these previous investigations to design the quality control component of AsiaLymph.

We will have experienced personnel on site in Asia who will work with us to coordinate and manage the study. Dr. T.H. Lam and Dr. Dennis Ip will be the lead epidemiologists at the coordinating center in Hong Kong. We have recruited Dr. Jun Xu to manage the study from Hong Kong and to have responsibility in Asia for all aspects of quality control. He has experience conducting epidemiologic studies in China and after a one year stay at NCI from early 2010- early 2011 to receive additional training, he is now in Hong Kong as the study manager of AsiaLymph at Hong Kong University. He will make regular visits to each center and hospital (once every 3 months) throughout the 3-year course of the study to provide oversight. NCI staff will make site-visits to all centers and each hospital every 6 months in coordination with staff at the study coordinating center in Hong Kong.

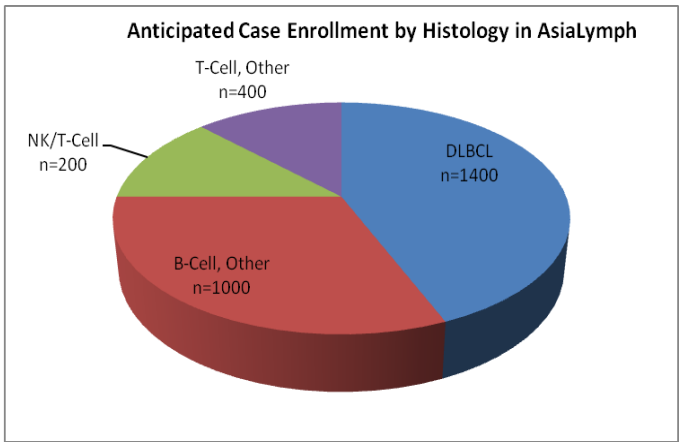
In addition to the oversight of the study in Asia, the NCI study Co-PIs will review the study status on a weekly basis, including review of enrollment reports generated from the SMS (described below) in Hong Kong, review of questionnaires for completeness and quality, and review of biological sample collection, processing, and storage. OEEB investigators will also have a weekly phone call with the coordinating center.

A SMS with online access has been developed by Hong Kong University under the direction of the NCI and will be used to monitor the study progress. Specifically, the SMS will track subject enrollment, interview and hospital record status, biospecimen and tumor tissue collection status, and other key data as described in the protocol. The SMS will be available to study staff at the Study Centers for data input and reporting, and to NCI investigators to monitor study progress. The SMS will generate regular reports to the NCI pertaining to the number of cases and controls enrolled, participation rates, the status of sample shipments, and the completeness of the enrollment data and questionnaires. In addition, hospital records and information on biologic specimens will be uploaded into the SMS.

Anticipated Distribution of Enrolled Cases

Distribution of lymphoma types expected: Of the 3,300 lymphoma cases we will enroll into AsiaLymph, we anticipate enrolling 3,000 NHL cases. Most of the remaining 300 cases will be multiple myeloma cases. Among the NHL cases, we expect 1,400 DLBCL cases and 600 total T-cell lymphomas (of which approximately 200 will be NK/T-cell). The expected distribution of cases is shown in Figure 2.

Figure 2. Anticipated NHL case enrollment in AsiaLymph



Biological Sample Analysis

Biomarker measurements: The major classes of biomarkers that will be measured in AsiaLymph include plasma markers of long-term exposure to organochlorines and hepatitis B and C infection and active viral replication, DNA-based markers of genetic susceptibility and tumor markers at the DNA, mRNA, and protein level.

A total of 12 ml of plasma will be analyzed for PCBs, DDT and its metabolites, chlordane metabolites, and at no additional cost other pesticides routinely measured in blood samples, and selected co-planar PCBs, dibenzofurans, and dioxins on a subgroup of study subjects, after pilot testing of samples from controls in each study center. The primary approach we are using to assess environmental exposure to PCBs, DDT, other pesticides, and dibenzofurans is biological monitoring because the primary route of environmental exposures in the general population is through dietary contamination, which cannot be reliably estimated by other methods. We reported statistically significant findings for several key organochlorine compounds in a study of 100 cases and 100 controls in the NCI-SEER NHL study (De Roos et al. 2005). We have conservatively budgeted for analyzing samples from 150 cases and 150 controls in AsiaLymph. In addition, the subgroup for organochlorine analysis will be limited to cases with pre-treatment blood samples, to controls who similarly have not undergone treatment that can potentially cause local or systemic toxicity or inflammatory responses, and to both cases and controls that have not undergone recent weight loss for any reason.

Viral Assays: Screening hepatitis B and C assays are routinely carried out at some centers and will be made available to us at no cost for case-control analysis (on approximately 1,200 cases and 1,200 controls). We plan on testing the remaining unscreened samples for antibodies to hepatitis B core antigen and hepatitis C at minimal cost in Asia. Importantly, antibody positivity stably indicates viral exposure, with equal reliability in cases and controls, and is unlikely to be affected by disease. All positive samples will then be analyzed for hepatitis B surface antigen and hepatitis C RNA, respectively, which generally measure chronic replication. These assays also can potentially become positive from reactivation due to waning immunologic competence in some lymphomas. Positive results with the latter assays would be suggestive but would need

to be confirmed in the future when prospective cohort specimens become available. On the other hand, null results with hepatitis B surface antigen and hepatitis C RNA would be informative in this well-powered study and unlikely to be affected by disease status. Sortable lymphocytes from cryopreserved blood samples will be used for PCR-based analyses of integrated/episomal viral genomes.

Genetic Studies: DNA will be extracted for all study subjects and analyzed for a series of germ-line association analyses. Initially, we will attempt to replicate the candidate gene and other GWAS findings from Caucasian populations in our sample of Asian cases and controls. We may also include a specialized chip to assay a large number of variants in the HLA region. Any functional variants identified in previous studies will be a high priority to replicate in this population with a sample size of this magnitude. Finally, a separate application for a genome-wide scan using the best and most cost-efficient technology will be made in FY15/16 in order to identify novel variants for NHL in Asian populations.

Tumor Sample Analyses

All tumor samples will be re-stained by hematoxylin and eosin and immunophenotyped at Queen Elizabeth Hospital. Special diagnostic stains (immunohistochemical and in-situ hybridization) will be performed including basic panel plus additional stains depending on the individual case, with a sequential strategy to preserve the maximum number of slides for molecular assays. Remaining slides will be wrapped in aluminum foil, and stored according to the unique project number in -80^{o}C refrigerator to preserve antigenicity. All tumor samples will be screened for EBV-encoded RNA (EBER) by in situ hybridization to identify the EBV-positive lymphomas. For all cases of Burkitt lymphoma or suspected Burkitt lymphoma, FISH will be conducted to detect *MYC* break-apart and *MYC-IGH*. For all other cases, FISH will be performed only when required (i.e. *BCL2* break-apart, *BCL6* break-apart, *CCND1* break-apart).

Special studies will be carried out for lymphoma subtypes of interest, and may include the following, depending on number of cases and availability of pathology samples and resources:

- NK/T-cell studies: Whole transcriptome deep cDNA sequencing will investigate EBV-specific as well as host genome pathways for NK/T-cell lymphomas.
- T cell tumors: For one or more T-cell tumors that appear to be at excess relative to rates in the West, we will use high-throughput sequencing of whole genome and whole transcriptome tumor samples followed by digital subtraction analysis to search for non-human sequences other than EBV, including known infections as well as potential novel agents.
- CLL/SLL: Additional DNA-based studies will be determined.
- Multiple myeloma cases: Collection of unstained bone marrow biopsies will allow characterization of the tumor microenvironment.

Additional studies (immunohistochemical/ FISH) can be performed on this superb collection of cases as unstained sections will be available, including tissue microarray block production which will be considered in the future.

Data Analysis and Power

Statistical Analysis: All study data will be compiled and cleaned at Hong Kong University under the direction of study investigators. Analytic files will be analyzed by DCEG scientists. Since lymphoma comprises a group of related yet heterogeneous diseases, each characterized by the malignant transformation of lymphoid cells but with distinctive morphologic, immunophenotypic, genetic, and clinical features, we will analyze risks by lymphoma subtype as well as larger subgroups.

For analyses by subtype, odds ratios (ORs) and 95% confidence intervals (CIs) will be derived for each risk factor from polytomous unconditional logistic regression models. P values for the linear trend will be computed for continuous variables and using ordinal variables. To evaluate heterogeneity among lymphoma subtypes, we will use 2 statistical approaches. First, we will conduct a homogeneity test in the polytomous model, testing the null hypothesis that the regression coefficient for each risk factor was the same for all subtypes. Values of P less than .05 will be considered to provide evidence of heterogeneity. The test for homogeneity has the greatest power to detect risk differences when the risks for the subtypes all vary slightly from one another. Second, we will analyze all possible case-case pairwise comparisons using dichotomous logistic regression models (Morton et al. 2008). We will test the null hypothesis that the particular risk factor does not discriminate between the 2 disease groups modeled. To account for the pairwise analysis, we will apply a Bonferroni correction. In contrast to the test for homogeneity, the pairwise analysis has the greatest power to detect risk differences when the risk for one disease group is distinct from the other(s). For risk factors with more than 2 categories, we will use the ordinal variable for the homogeneity test and pairwise analysis. Analyses will also be conducted for larger lymphoma subgroups including NHL and B-cell lymphomas using unconditional logistic regression models in order to utilize all controls, adjusting for the matching factors. We will also conduct analyses for all lymphoma cases and controls using conditional logistic regression. For genetic analyses, standard methods will be used to test the effect of each SNP. We will also use a new powerful and flexible subset-based approach to the combined analysis of heterogeneous traits, which is an approach that agnostically explores subsets of the traits to identify the strongest association signal and then evaluates the significance of the detected association using efficient adjustment for multiple correlated tests involved (N. Chatterjee, personal communication).

Initial analyses will be conducted for lifestyle risk factors, occupational exposures, environmental exposures, viral exposures, and genetic main effects. Exploratory gene-environment interaction analyses will also be conducted. We will also conduct genetic pathway analysis to evaluate whether the set of genes in a well-defined pathway (e.g., Th1/Th2 pathway) are associated with the disease risk. This type of analysis is particularly helpful in situations when the pathway is enriched with multiple SNPs with small effects. All models will be adjusted for sex, age, study center, and date of enrollment (the control matching factors) and education. Additional potential confounders will be selected based on initial analyses of the study data set and through identification of well-established risk factors in the literature.

Power Analysis: For a dichotomous exposure variable with a prevalence of 2%, we will have 80% power (two-sided alpha = 0.05) to detect ORs of 1.40, 1.51 and 1.72 for all NHL, DLBCL,

and total T-cell lymphomas, respectively, using all 3,300 controls in a logistic regression model (Table 1). For an exposure variable with a prevalence of 3%, we will have 80% power to detect ORs of 1.32, 1.41, and 1.58 for each of these case groups, respectively. For risk factors with high prevalence of exposure, we will have adequate power to detect lower odds ratios.

For studies of genetic polymorphisms, we will have 80% power to detect an OR of 1.2 per allele (from an additive genetic model) for minor allele frequencies (MAFs) of 8%, 13.5%, and 36% for all NHL, DLBCL, and total T-cell cases, respectively (Table 2). We will be able to detect an OR of 1.3 per allele for MAFs of 3.5%, 5.5% and 11.5% for these categories, respectively.

Table 1. Power table according to exposure prevalence

Exposure Prevalence	NHL Subtype	Odds Ratio	Power
2%	NHL	1.40	80%
	DLBCL	1.51	80%
	Total T-Cell	1.72	80%
3%	NHL	1.32	80%
	DLBCL	1.41	80%
	Total T-Cell	1.58	80%
5%	NHL	1.25	80%
	DLBCL	1.32	80%
	Total T-Cell	1.45	80%
10%	NHL	1.18	80%
	DLBCL	1.23	80%
	Total T-Cell	1.32	80%

Table 2. Power table according to minor allele frequency (MAF)

Odds Ratio per Allele	NHL Subtype	MAF	Power
1.2	NHL	8%	80%
	DLBCL	13.5%	80%
	Total T-Cell	36%	80%
1.3	NHL	3.5%	80%
	DLBCL	5.5%	80%
	Total T-Cell	11.5%	80%
1.4	NHL	2%	80%
	DLBCL	3.5%	80%
	Total T-Cell	6.5%	80%
1.5	NHL	2.5%	80%
	DLBCL	2%	80%
	Total T-Cell	4%	80%

Personnel

Co-Principal Investigators

Qing Lan (OEEB), Nathaniel Rothman (OEEB): Overall study conduct and primary responsibility for occupational, environmental, and genetic components

Lead Investigators

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Martha Linet, Alina Brenner (REB): Study design
Charles Rabkin (IIB): Viral studies
Mark Purdue (OEEB): Occupational solvent exposures
Lynn Goldin, Neil Caporaso (GEB): Family history, CLL studies
Stephen Chanock (CGF, LTG): Genomics
John Chan (Queen Elizabeth Hospital): Pathology
Roel Vermeulen (Utrecht Univ.), Melissa Friesen (OEEB): Occupational exposure assessment
Mary Ward (OEEB): Environmental exposure assessment
Sholom Wacholder, Kai Yu (BB): Study design and statistical analysis
H. Dean Hosgood and Wei Hu (OEEB): Field training, quality control, and study management
Xu Jun (Univ. of Hong Kong): Field study management in Asia

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Human Subjects Protection

Briefly, a trained hospital interviewer will identify eligible cases and controls and approach the patient to discuss the study. The interviewer will make it clear to the patient, in a non-coercive environment, that participation in this study is strictly voluntary and their healthcare will in no way be affected regardless of study participation. All information received through the eligibility and consenting processes will be kept secure to the extent permitted by law regardless of study participation. If the patient agrees to participate, informed consent will be requested after a full explanation of the benefits and hazards of participation in the study. Written consent will be obtained for each of the components of the study: (1) access to medical records and pathology material, (2) interview, (3) buccal cell and blood sample collection. The patient can give consent to some or all of these components. Upon consenting, trained staff will administer the interview and collect the biological samples. All study documents with personal identifiers will be kept securely at the study center. All interview responses and other study documents will be kept secure to the extent permitted by law. The National Identifying Number of each subject will be collected in the CAPI as this information is typically collected in the hospital setting. This number along with other personally identifiable information will be kept secure to the extent permitted by law. Data collected on study computers will be password protected and encrypted, with access limited to qualified and trained members of the study staff. Each hospital will have a designated area where study records and equipment will be securely stored (i.e. a locked room or filing cabinet). All data from the CAPI that is uploaded into the SMS will be encrypted and uploaded and stored using securely and password protected servers. All patient identifiers in the CAPI, including the National Identifying Number and address of the subject, will be removed by the coordinating center before the data is sent to the NCI. Information will be kept at the coordinating center for quality control purposes, but no other investigators will have access to data including patient identifiers.

All data from the CAPI will be uploaded to the SMS on a daily basis. Medical records that are scanned and uploaded into the SMS will first be masked by study staff using labels to cover all personally identifiable information in the records. Study staff will work with each hospital to evaluate the format of the medical records and to identify all locations within the records where identifying information might be found. This will assist in the proper training of the person responsible for the masking procedure by study investigators, with oversight from the study manager in each hospital.

All biological samples will contain study ID numbers only, and all samples sent from the NCI biorepository to laboratories for analysis will be characterized by identifier numbers only (i.e. no patient information). Biological sample analytic results will be sent to the NCI for addition to the study database. There will be no personal identifiers in data analysis files prepared by the study coordinating center for study investigators. Finally, no individual results will be presented in publications or other reports. All procedures for this study will be conducted according to the recommendations of the World Medical Association Declaration of Helsinki for human study subject protection. At any time during the study, subjects who wish to discontinue their participation in the study may do so, and further may request to withdraw consent for use of any collected data, including medical records. The name and contact information for the relevant authority at each hospital is provided on each of the consent forms.

A Federal-Wide Assurance will be established with each study center, whose IRB will review the study. The protocol will also be reviewed by the NCI SSIRB and IRBs from collaborating hospitals (or will be under the umbrella of the study center IRB).

All original questionnaire responses, other study documents and medical record abstraction data with personal identifiers will be kept securely at the study coordinating center. All biological samples sent from the NCI biorepository to laboratories for analysis will be characterized by identifier numbers only. Biological sample analytic results will be sent to for addition to the study database. All personal identifiers will be stripped from data analysis files prepared by the study coordinating center for study investigators. Finally, no individual results will be presented in publications or other reports.

Recruitment

Subjects will be recruited by study interviewers in each participating hospital. The interviewer will identify eligible cases from daily admission records and other sources and approach the patient to discuss the study and then, if the patient agrees to participate, carry out informed consent. There will be consent for access to medical records and pathology material, interview, buccal cell and blood sample collection. In addition, cases will be consented for follow-up of medical treatment and clinical status.

The interviewer will identify potential eligible controls based on age, and reasons for admission from selected Departments as described previously. They will approach each potential control, briefly explain the study, and then, if the patient agrees to participate, carry out informed consent. There will be consent for access to medical records, interview, buccal cell and blood sample collection.

Informed Consent: Informed consent will be requested, in the local Chinese dialect, after a full explanation of the benefits and hazards of participation.

Potential benefits and risks: No direct benefits to the participants are expected from this study except the satisfaction of contributing to the scientific understanding of etiology of lymphoma. The research involves no more than minimal risk to subjects from venous phlebotomy which will be carried out by local medical or nursing staff. No physical harm is expected from the collection of buccal cells. No other risks are expected from participating in this study. Participation is voluntary.

Compensation: Subjects will be compensated $22.50 for time and effort spent in this study. It is estimated that 2 hours will be required from each subject.

Communication of study results: Pathologists will be notified of the final lymphoma classification. In cases where the central pathology review differs from the initial hospital pathology diagnosis, the hospital pathologist who did the initial review will be informed of the consensus diagnosis by the chair of the central pathology review group. We do not plan to provide individual results to study subjects or their physicians because the assays are for research only and have uncertain clinical relevance. The laboratory results will be used to understand the

etiology of lymphoma in humans. The research laboratories will use state-of-the art methods that can be duplicated, but most of the protocols will not be used or approved for clinical settings. Individual requests for study data will be honored, as required by law. The risks to study subjects are minimal. The study results could help us to understand the etiology of lymphoma in this population and elsewhere.

Appendix A: Eligible control diseases

Controls will be drawn from multiple non-malignant disease categories that have not been linked to risk factors under study and are not known or suspected to have an immunological, infectious, and/or inflammatory etiology.

I. Injuries

a. Fractures

800. Fracture of vault of skull 800.0-800.9
801. Fracture of base of skull 801.0-801.9
802. Fracture of face bones 802.0 Nasal bones, closed
802. Fracture of face bones 802.1 Nasal bones, open
802. Fracture of face bones 802.2 Mandible, closed
802. Fracture of face bones 802.3 Mandible, open
802. Fracture of face bones 802.4 Malar and maxillary bones, closed
802. Fracture of face bones 802.5 Malar and maxillary bones, open
802. Fracture of face bones 802.6 Orbital floor (blow-out), closed
802. Fracture of face bones 802.7 Orbital floor (blow-out), open
802. Fracture of face bones 802.8 Other facial bones, closed
802. Fracture of face bones 802.9 Other facial bones, open
803. Other and unqualified skull fractures 803.0-803.9
804. Multiple fractures involving skull or face with other bones 804.0-804.9
805. Fracture of vertebral column without mention of spinal cord injury 805.0-805.9
806. Fracture of vertebral column with spinal cord injury 806.0-806.9
807. Fracture of rib(s), sternum, larynx, and trachea 807.4 Flail chest
807. Fracture of rib(s), sternum, larynx, and trachea 807.5 Larynx and trachea, closed
807. Fracture of rib(s), sternum, larynx, and trachea 807.6 Larynx and trachea, open
808. Fracture of pelvis 808.0-808.9
820. Fracture of femur 820.0-820.9
821. Fracture of other and unspecified parts of femur 821.0-821.3

b. Injury to blood vessels

900. Carotid artery 900.1 Internal jugular vein
900. Carotid artery 900.8 Other specified blood vessels of head and neck
900. Carotid artery 900.9 Unspecified blood vessel of head and neck
901. Injury to blood vessels of thorax 901.0-901.9
902. Injury to blood vessels of abdomen and pelvis 902.0-902.9

c. Other internal injuries

860. Traumatic pneumothorax and hemothorax
861. Injury to heart and lung

862. Injury to other and unspecified intrathoracic organs
863. Injury to gastrointestinal tract
864. Injury to liver
865. Injury to spleen
866. Injury to kidney
867. Injury to pelvic organs
868. Injury to other intra-abdominal organs
925-929, Crushing
940-949, Burns
950-957, Injury to nerves and spinal cord
930-939 Injury to foreign bodies

II. Disease of the circulatory system

a. Hypertensive disease

401. Hypertensive disease 401.0 Malignant

b. Ischemic heart disease

410. Acute myocardial infarction 410.0 Of anterolateral wall
410. Acute myocardial infarction 410.1 Of other anterior wall
410. Acute myocardial infarction 410.2 Of inferolateral wall
410. Acute myocardial infarction 410.3 Of inferoposterior wall
410. Acute myocardial infarction 410.4 Of other inferior wall
410. Acute myocardial infarction 410.5 Of other lateral wall
410. Acute myocardial infarction 410.6 True posterior wall infarction
410. Acute myocardial infarction 410.7 Subendocardial infarction
410. Acute myocardial infarction 410.8 Of other specified sites
411. Other acute and subacute forms of ischemic heart disease 411.0 Post myocardial infarction syndrome
411. Other acute and subacute forms of ischemic heart disease 411.1 Intermediate coronary syndrome
411. Other acute and subacute forms of ischemic heart disease 411.81 Acute coronary occlusion without myocardial infarction

c. Diseases of pulmonary circulation

415. Acute pulmonary heart disease 415.0 Acute cor pulmonale
415. Acute pulmonary heart disease 415.1 Pulmonary embolism and infarction
417. Other diseases of pulmonary circulation 417.0 Arteriovenous fistula of pulmonary vessels
417 Other diseases of pulmonary circulation 417.1 Aneurysm of pulmonary artery

d. Cerebrovascular disease

430. Subarachnoid hemorrhage

431. Intracerebral hemorrhage
432. Other and unspecified intracranial hemorrhage 432.0 Nontraumatic extradural hemorrhage
432. Other and unspecified intracranial hemorrhage 432.1 Subdural hemorrhage
432. Other and unspecified intracranial hemorrhage 432.9 Unspecified intracranial hemorrhage
433.0 - Occlusion and stenosis of precerebral arteries 433.0 Basilar artery
433.0 - Occlusion and stenosis of precerebral arteries 433.1 Carotid artery
433.0 - Occlusion and stenosis of precerebral arteries 433.2 Vertebral artery
433.0 - Occlusion and stenosis of precerebral arteries 433.3 Multiple and bilateral
433.0 - Occlusion and stenosis of precerebral arteries 433.8 Other specified precerebral artery
434.0 Occlusion of cerebral arteries 434.0 Cerebral thrombosis
434.0 Occlusion of cerebral arteries 434.1 Cerebral embolism
434.0 Occlusion of cerebral arteries 434.9 Cerebral artery occlusion, unspecified

e. Other symptomatic heart disease

428.0 Congestive heart failure, unspecified
428.1 Left heart failure
426.6 Other heart block
427.3 Atrial fibrillation and flutter
427.0 Paroxysmal supraventricular tachycardia

III. Disease of the digestive system

a. Hernia of abdominal cavity

550. Inguinal hernia 550.0 Inguinal hernia, with gangrene
550. Inguinal hernia 550.1 Inguinal hernia, with obstruction, without mention of gangrene
550. Inguinal hernia 550.9 Inguinal hernia, without mention of obstruction or gangrene
551. Other hernia of abdominal cavity, with gangrene 551.0 Femoral hernia with gangrene
551. Other hernia of abdominal cavity, with gangrene 551.1 Umbilical hernia with gangrene
551. Other hernia of abdominal cavity, with gangrene 551.2 Ventral hernia with gangrene
551. Other hernia of abdominal cavity, with gangrene 551.3 Diaphragmatic hernia with gangrene
551. Other hernia of abdominal cavity, with gangrene 551.8 Hernia of other specified sites, with gangrene
551. Other hernia of abdominal cavity, with gangrene 551.9 Hernia of unspecified site, with gangrene
552. Other hernia of abdominal cavity, with obstruction, but without mention of gangrene 552.0 Femoral hernia with obstruction
552. Other hernia of abdominal cavity, with obstruction, but without mention of gangrene 552.1 Umbilical hernia with obstruction
552. Other hernia of abdominal cavity, with obstruction, but without mention of gangrene 552.2 Ventral hernia with obstruction

552. Other hernia of abdominal cavity, with obstruction, but without mention of gangrene 552.3 Diaphragmatic hernia with obstruction
552. Other hernia of abdominal cavity, with obstruction, but without mention of gangrene 552.8 Hernia of other specified sites, with obstruction
552. Other hernia of abdominal cavity, with obstruction, but without mention of gangrene 552.9 Hernia of unspecified site, with obstruction
553. Other hernia of abdominal cavity without mention of obstruction or gangrene 553.0 Femoral hernia
553. Other hernia of abdominal cavity without mention of obstruction or gangrene 553.1 Umbilical hernia
553. Other hernia of abdominal cavity without mention of obstruction or gangrene 553.2 Ventral hernia
553. Other hernia of abdominal cavity without mention of obstruction or gangrene 553.3 Diaphragmatic hernia
553. Other hernia of abdominal cavity without mention of obstruction or gangrene 553.8 Hernia of other specified sites
553. Other hernia of abdominal cavity without mention of obstruction or gangrene 553.9 Hernia of unspecified site

b. Other diseases of intestines and peritoneum

562. Diverticula of intestine
562. Diverticula of intestine 562.0 Small intestine
562. Diverticula of intestine 562.01 Diverticulitis of small intestine (without mention of hemorrhage
562. Diverticula of intestine 562.02 Diverticulosis of small intestine with hemorrhage
562. Diverticula of intestine 562.03 Diverticulitis of small intestine with hemorrhage
562. Diverticula of intestine 562.1 Colon
562. Diverticula of intestine 562.11 Diverticulitis of colon without mention of hemorrhage
562. Diverticula of intestine 562.12 Diverticulosis of colon with hemorrhage
562. Diverticula of intestine 562.13 Diverticulitis of colon with hemorrhage
569. Other disorders of intestine 569.1 Rectal prolapse
569. Other disorders of intestine 569.2 Stenosis of rectum and anus
569. Other disorders of intestine 569.3 Hemorrhage of rectum and anus

c. Cholelithiasis

574.2 Calculus of gallbladder without mention of cholecystitis
574.5 Calculus of bile duct without mention of cholecystitis
574.9 Calculus of gallbladder and bile duct without cholecystitis

IV. Diseases of genitourinary system

a. Other diseases of urinary system

591. Hydronephrosis
592. Calculus of kidney and ureter 592.0 Calculus of kidney
592. Calculus of kidney and ureter 592.1 Calculus of ureter

592. Calculus of kidney and ureter 592.9 Urinary calculus, unspecified
593. Other disorders of kidney and ureter 593.2 Cyst of kidney, acquired
593. Other disorders of kidney and ureter 593.3 Stricture or kinking of ureter
593. Other disorders of kidney and ureter 593.4 Other ureteric obstruction
593. Other disorders of kidney and ureter 593.5 Hydroureter
594. Calculus of lower urinary tract 594.0 Calculus in diverticulum of bladder
594. Calculus of lower urinary tract 594.1 Other calculus in bladder
594. Calculus of lower urinary tract 594.2 Calculus in urethra
594. Calculus of lower urinary tract 594.8 Other lower urinary tract calculus
594. Calculus of lower urinary tract 594.9 Calculus of lower urinary tract, unspecified
599. Other disorders of urethra and urinary tract 599.1 Urethral fistula
599. Other disorders of urethra and urinary tract 599.2 Urethral diverticulum
599. Other disorders of urethra and urinary tract 599.4 Urethral false passage
599. Other disorders of urethra and urinary tract 599.5 Prolapsed urethral mucosa
599. Other disorders of urethra and urinary tract 599.6 Urinary obstruction

b. Hydrocele

603.0 Encysted hydrocele
603.8 Other specified types of hydrocele
603.9 Hydrocele, unspecified

V. Diseases of the central nervous system and sense organs

a. Other disorders of the central nervous system and sense organs

342. Hemiplegia and hemiparesis 342.0 Flaccid hemiplegia
342. Hemiplegia and hemiparesis 342.1 Spastic hemiplegia
342. Hemiplegia and hemiparesis 342.8 Other specified hemiplegia
342. Hemiplegia and hemiparesis 342.9 Hemiplegia, unspecified
344. Other paralytic syndromes 344.0 Quadriplegia and quadriparesis
344. Other paralytic syndromes 344.1 Paraplegia
344. Other paralytic syndromes 344.2 Diplegia of upper limbs
344. Other paralytic syndromes 344.4 Monoplegia of upper limb
344. Other paralytic syndromes 344.6 Cauda equina syndrome
345. Epilepsy and recurrent seizures 345.0 Generalized nonconvulsive epilepsy
345. Epilepsy and recurrent seizures 345.1 Generalized convulsive epilepsy
345. Epilepsy and recurrent seizures 345.2 Petit mal status
345. Epilepsy and recurrent seizures 345.3 Grand mal status
345. Epilepsy and recurrent seizures 345.4 Localization-related (focal) (partial) epilepsy and epileptic syndromes with complex partial seizures
345. Epilepsy and recurrent seizures 345.5 Localization-related (focal) (partial) epilepsy and epileptic syndromes with simple partial seizures
345. Epilepsy and recurrent seizures 345.6 Infantile spasms
345. Epilepsy and recurrent seizures 345.7 Epilepsia partialis continua

345. Epilepsy and recurrent seizures 345.8 Other forms of epilepsy and recurrent seizures
345. Epilepsy and recurrent seizures 345.9 Epilepsy, unspecified
348. Other conditions of brain 348.0 Cerebral cysts
348. Other conditions of brain 348.2 Benign intracranial hypertension
722. Displacement of intervertebral disk 722.0 Displacement of cervical intervertebral disc without myelopathy
722. Displacement of intervertebral disk 722.1 Displacement of thoracic or lumbar intervertebral disc without myelopathy
722. Displacement of intervertebral disk 722.2 Displacement of intervertebral disc, site unspecified, without myelopathy

b. Eye diseases

366. Cataract 366.0 Infantile, juvenile, and presenile cataract
366. Cataract 366.1 Senile cataract
366. Cataract 366.2 Traumatic cataract
366. Cataract 366.5 After-cataract
365. Glaucoma 365.1 Open-angle glaucoma
365. Glaucoma 365.2 Primary angle-closure glaucoma
361. Retinal detachments and defects 361.0 Retinal detachment with retinal defect
361. Retinal detachments and defects 361.00 Retinal detachment with retinal defect, unspecified
361. Retinal detachments and defects 361.01 Recent detachment, partial, with single defect
361. Retinal detachments and defects 361.03 Recent detachment, partial, with giant tear
361. Retinal detachments and defects 361.04 Recent detachment, partial, with retinal dialysis
361. Retinal detachments and defects 361.05 Recent detachment, total or subtotal
377. Disorders of optic nerve and visual pathways 377.0 Papilledema
377. Disorders of optic nerve and visual pathways 377.1 Optic atrophy
377. Disorders of optic nerve and visual pathways 377.2 Other disorders of optic disc
377. Disorders of optic nerve and visual pathways 377.4 Other disorders of optic nerve
377. Disorders of optic nerve and visual pathways 377.5 Disorders of optic chiasm
377. Disorders of optic nerve and visual pathways 377.6 Disorders of other visual pathways
377. Disorders of optic nerve and visual pathways 377.7 Disorders of visual cortex

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