Hypothesis/Commentary

Consortia in Cancer Epidemiology: Lessons from InterLymph

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Since the middle of 20th century, epidemiology has been successfully elucidating the causes of human cancer and offering effective approaches to cancer prevention and control (1). In recent decades, substantial resources have been devoted to cancer epidemiologic studies without producing the expected yield of new results. The etiology of several important human cancers, such as prostate cancer, brain cancer, and lymphoma, remains largely unexplained, and entire areas of research, such as the search for genetic susceptibility variants with low or medium penetrance, have yielded very limited results (2).

Different approaches have been proposed to overcome the limitations of current cancer epidemiologic research, including the establishment of new studies of very large size (3). An alternative approach takes advantage of existing investigations by forming collaborative consortia; sharing raw data, biological samples, and other resources; and doing original data meta-analyses and, in some cases, prospectively pooling new data in combined analyses. One successful example of this approach is the combined reanalysis of hormonal factors and breast cancer carried out in more than 50 studies (4). In recent decades, consortia of molecular epidemiologic studies have been initiated; nonexhaustive lists are available from the National Cancer Institute website[5] and the HugeNet Network of Networks initiative (5). Epidemiologists should be encouraged to form and participate in such initiatives.

In 2000, we and other investigators who had recently completed case-control studies of lymphoma formed the International Lymphoma Epidemiology Consortium (InterLymph).[6] Its main objective, when established, was to create a structure that would facilitate near real-time pooling of data from most case-control studies of lymphoma that were in progress or had been recently completed. This approach would, in turn, increase statistical power for the study of lymphoma subtypes, rare exposures, and interactions between risk factors, both genetic and environmental. Although the main emphasis of the collaboration is epidemiology, InterLymph has expanded to include geneticists, pathologists, immunologists, clinicians, and other researchers. Indeed, virtually all recent large-scale epidemiologic studies of lymphoma belong to InterLymph.

Lymphoma offered a natural opportunity for such work because of the moderately low lifetime incidence (less common than breast or prostate cancers, for example), the striking diversity of subtypes, and the need for large numbers when studying common genetic variants. The 6-year experience we have gained in the coordination of InterLymph offers us the opportunity to discuss some general issues in the establishment and coordination of cancer epidemiology consortia.

A semiformal consortium like InterLymph represents a novel approach to promoting collaboration among a multidisciplinary group of investigators to (*a*) develop novel investigations that would not or could not be carried out by any existing single group of investigators (e.g., substantial size study of a very rare subtype, a genetic epidemiologic study of families, a very large study that examines gene-environment interactions); (*b*) provide a definitive result on an important risk factor for which findings have been inconsistent; and (*c*) mentor and encourage less experienced investigators to launch new studies in unusual or special populations (in the case of lymphoma, a coordinated series of studies in Asian populations).

InterLymph was formed out of informal discussions and sharing of protocols, questionnaires, and preliminary results among investigators involved in lymphoma epidemiology, including molecular and genetic epidemiology. The initial core of investigators quickly expanded to include colleagues from other disciplines and centers. A major characteristic of the consortium has been its effort to be inclusive. Potential members have been identified by review of recent articles and through personal contacts. Criteria for membership include only available data or biological materials and accepting some simple guidelines for collaboration (Appendix A). Almost all research groups invited to participate in the consortium have accepted and have been active in it. The organization of the consortium into working groups active in specific areas of lymphoma epidemiology has allowed the rapid identification and conduct of collaborative projects. The initial list of four working groups was quickly expanded to the eight listed in Table 1. Although most working groups aim to carry out pooled analyses, either based on independently collected data or done in a coordinated fashion, the pathology group has developed an epidemiologically oriented classification of lymphomas, based on a simplification of the recent WHO classification (6), to guide future epidemiologic work on lymphoma subtypes.[7] The consortium is coordinated by an executive committee; interactions between working groups occur in annual meetings and interactions within working groups also occur in teleconferences between meetings.

New pooled analysis projects are mainly elaborated within the working groups and are submitted to participating investigators on a project-by-project basis. In other words, acceptance of one project does not imply commitment to participate in any other project. Individual researchers can also propose a new idea for collaboration, which has to be approved by the executive committee before it is submitted to the other consortium members. Table 2 lists completed and published collaborative projects conducted within InterLymph; a dozen more projects are either ongoing or being planned. They are examples of the added value of the

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[5] http://epi.grants.cancer.gov/Consortia/ (accessed 25 July 2006).
[6] http://epi.grants.cancer.gov/InterLymph/ (accessed 25 July 2006).
[7] Morton et al., in preparation.

Table 1. Active InterLymph working groups and coordinators

Working Group	Coordinator	Institution, country
Diet and behavioral factors	James Cerhan	Mayo Clinic College of Medicine, United States
Family studies	Susan Slager	Mayo Clinic College of Medicine, United States
Genotyping	Christine Skibola	University of California at Berkeley, United States
Immunology	Wendy Cozen	University of Southern California, United States
Infections	Andrew Grulich	University of New South Wales, Australia
Occupation	Paolo Boffetta	IARC, France
Pathology	Martha Linet	National Cancer Institute, United States
Sunlight	Anne Kricker	University of Sydney, Australia

collaboration. The two reports on the role of tobacco smoking and alcohol drinking on the risk of non-Hodgkin's lymphoma (7, 8) have shed light on a controversial area of lymphoma epidemiology. The coordinated analysis of 12 immunologically related polymorphisms (9) resulted in an association with a variant in the *TNFα* gene (8). In all these cases, the large number of cases included in the pooled collaborative analysis facilitated the assessment of risks of specific subtypes of lymphoma and provided strong evidence of heterogeneity in the etiology of different B-cell lymphoma types.

In addition to joint publications, the consortium has been an effective tool for collaboration in a number of methodologic fields, including the development of an epidemiologic approach to the classification of lymphoma subtypes, the definition of new strategies to assessing immune dysfunction within the framework of epidemiologic studies, and the combination of genotyping results. The development of a policy for publication of joint results, which would satisfy the participants, is an important ingredient for the success of a consortium. The approach of InterLymph has been towards the inclusion of several names from each participating group; the long lists of authors have not been an obstacle to the publication of the joint articles.

Consortia operate with many different funding models. InterLymph does not offer collective funding for projects but does try to cover the costs of meetings and some conference calls. This infrastructural support has been funded mainly by the U.S. National Cancer Institute and the IARC, with additional funding from the Leukaemia Research Fund in the United Kingdom and the U.S. NIH Office of Rare Diseases. Individual projects have been supported from various sources, including small grants.

Management of noncollaborative behavior has been an important aspect of InterLymph. Most collaborative projects within the consortium require sharing novel ideas and preliminary results: this can result in use, or the perception of use, of confidential information for personal rather than collective benefit. Explicit guidelines have been developed in an endeavor to discourage consortium members from such behavior (Appendix A). Perceived infringements have been reported to the Executive Committee, which has reviewed and clarified the issues with all concerned parties.

Although InterLymph has been established as a collaboration of independently established studies, it has also quickly become a reference for new investigations in the field of lymphoma epidemiology. Access to detailed instruments and procedures used in ongoing studies has brought the adoption of more comparable methods in new studies; this in turn will facilitate future collaborative projects. Participation in InterLymph has also been considered as a strength in grant applications. A particularly important aspect of the consortium has been the attention given to promoting participation of young investigators. Publications from consortia involving a large number of partners entail low visibility of individual authors, including, in particular, students and junior scientists; this potential limitation has been turned into an opportunity for young investigators to promote novel projects based on shared resources.

The greatest challenge of InterLymph has been to overcome the reluctance of individual investigators to share data, biological samples, and ideas. Whereas bilateral collaborations are relatively common in cancer epidemiology, projects based on large-scale partnerships require a higher level of commitment if intellectual property rights on the primary resources for research are to be shared. This commitment is unlikely without great confidence that what is gained from the collaboration will be greater than what might be lost through joining it. In the experience of InterLymph, secondary analyses that make use of data that have already been reported, in full or sometimes in part (7, 8), have been perceived as less challenging than the sharing of unpublished material for original publications (9). Lymphoma epidemiology might be particularly suitable for a consortium-based approach because of the complex biology and etiology of this group of neoplasms (10), which begs large-scale and interdisciplinary collaborations.

Scientific research consists of a balance of competition and collaboration (11). As in any mature scientific discipline, important advances in cancer epidemiology have benefited from this combination. In recent years, epidemiologists have realized that a higher degree of collaboration is needed to overcome the difficulties inherent in the investigation of risk factors characterized by low potency, complex circumstances of exposure, and interactions.

The concept of the consortium has shown potential strength in its very nature of offering a forum for collaborative projects. We see this approach as a complement and not as an alternative to individual investigator-initiated studies to generate and test novel hypotheses. Whereas individual studies offer a more flexible mechanism to explore new hypotheses and alternative methods of exposure measurement, consortium provides a means, often the only means, to test existing and new hypotheses with adequate power; to replicate in a coordinated fashion results of individual studies; and to explore how an overall effect may differ within smaller populations.

Table 2. Completed collaborative projects within InterLymph

Project	*N* cases/controls	Principal investigator	Reference
Pooled analysis of tobacco smoking	6,594/8,892	Lindsay Morton	(7)
Pooled analysis of alcohol drinking	6,492/8,683	Lindsay Morton	(8)
Coordinated genotyping of 12 immunology-related polymorphisms	3,586/4,018	Nathaniel Rothman	(9)

Appendix A. Guidelines for the InterLymph Collaboration, Adopted by InterLymph Members on 27 March 2004

(a) Definition. InterLymph is a consortium of scientists involved in lymphoma research. Although originally organized among principal investigators of epidemiologic case-control studies of lymphoma, InterLymph is open to researchers from other disciplines relevant to lymphoma and, in particular, lymphoma etiology, and to investigators involved in other types of epidemiologic studies.

(b) Membership. InterLymph members are epidemiologists involved in lymphoma studies and scientists with expertise in domains relevant to lymphoma. Members are expected to bring to the consortium their expertise, ideas, and resources, including results, raw data, and biological samples. Membership is effective upon notification to and confirmation of acceptance by the executive group. Active participation in at least one working group is a requirement for maintaining membership.

(c) Organization. InterLymph is organized in working groups that promote collaborative projects in specific areas of lymphoma research. Each working group selects one or more coordinators. Participation in all working groups is open to all InterLymph members. Coordinators should inform all InterLymph members of the activities of the respective working group.

(d) Executive Group. A small executive group is elected each year, either during a general meeting of InterLymph or by e-mail. Members of the executive group serve for a maximum of 3 years. The executive is responsible for the maintenance of an updated list of members, the overall coordination of the collaboration, the communication among working groups, the organization of general meetings, and the coordination of grant applications. It also provides assistance to the participants when needed (e.g., by supporting a grant application at the national or international level). It will make decisions on matters relating to InterLymph, when appropriate, with or without first consulting with members. All its decisions will be transmitted immediately to the members.

(e) Resources. InterLymph has no specific resources. Institutions participating in the collaboration are encouraged to provide a minimal amount of resources (e.g., by contributing to the coordination of working groups). Working groups are expected to obtain grants to fund specific projects. The executive group can raise ad hoc funds to support coordination and meetings either independently or in collaboration with working groups or individual members.

(f) Sharing of Results, Data, and Samples. Participation in working groups implies the willingness to share results, raw data, and biological samples in collaborative projects. However, for each project, a specific written agreement has to be obtained from participating members. Refusal to participate in a project does not compromise the possibility of participating in other projects. In general, ownership of data and biological materials shared within InterLymph projects remains with the original investigator; however, working groups can decide a different policy for specific projects provided that this decision is made before data or biological materials are committed or that members are free at the time of decision to withdraw their data and material.

(g) Respect for the Intellectual Property and Fairness in Collaboration. InterLymph members should not seek to take unfair advantage of other members by improper use of original ideas, data, information, or results shared within the consortium. Should such a case occur, adversely affected member(s) should inform the executive group, which will decide on the action to be taken, including the possibility of expulsion of the offending member(s).

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