International consortia in cancer epidemiology

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Scientific advancement is based on a balance between competition and collaboration (Hull, 1988).

Need for large-scale studies in cancer epidemiology

- Weak effects
- Low prevalence of exposures and genetic variants
- Assessment of interactions
- Heterogeneity of effects

Options for large-scale studies

- Meta-analysis
  - formal combination of published results
- Pooled analysis
  - original data obtained from investigators
- Multicentric studies
  - collection of data according to common protocol

Approaches to combine evidence

	Advantages	Disadvantages
Meta-analysis	Quantitative, cheap	Comparability of data, bias
Pooled analysis	Comparability of data, efficient	Bias
Multicentric study	Comparability of data	Complex, expensive

Cancer consortia

- Collaborative efforts of PI of studies conducted in different populations/countries according to a comparable protocol
- Open to other experts in the field

- Criterion for participation: willingness to share ideas, data, material

Domains of activity of consortia

- Sharing ideas, hypotheses, unpublished results
- Conducting pooled analyses on raw data
- Generating new data on existing material
- Conducting multicentric studies

Aims of cancer consortia

- To develop novel investigations that would not or could not be carried out by any existing single group
- To provide definitive results on issues for which findings have been inconsistent
- To mentor and encourage less experienced investigators

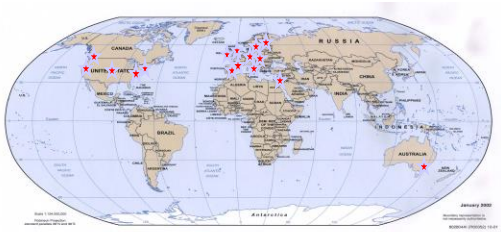
Examples of cancer consortia

- Cohort studies
  - NCI-sponsored cohorts
  - Asian cohorts (ACC)
- Genetic epidemiology
- Molecular epidemiology
  - lymphoma (InterLymph)
  - esophageal squamous cell carcinoma (ESC3)

InterLymph

- Aims: to share data and biological samples among studies in order to explore etiologicand me chanistic hypotheses that cannot be adequately addressed in individual studies.
- Working groups co-ordinate and conduct projects in specific areas.
- Approaches:
  - sharing instruments and resources (e.g., questionnaires)
  - pooling results of independent analyses
  - conducting pooled analyses of raw data
  - generating new data (e.g., genetic analyses)

Studies currently included in InterLymph



Population	*N cases*
Four US areas	600
SF Bay area	2,200
Nebraska	300
British Columbia	750
New South Wales	700
Six European areas	2,700
United Kingdom	800

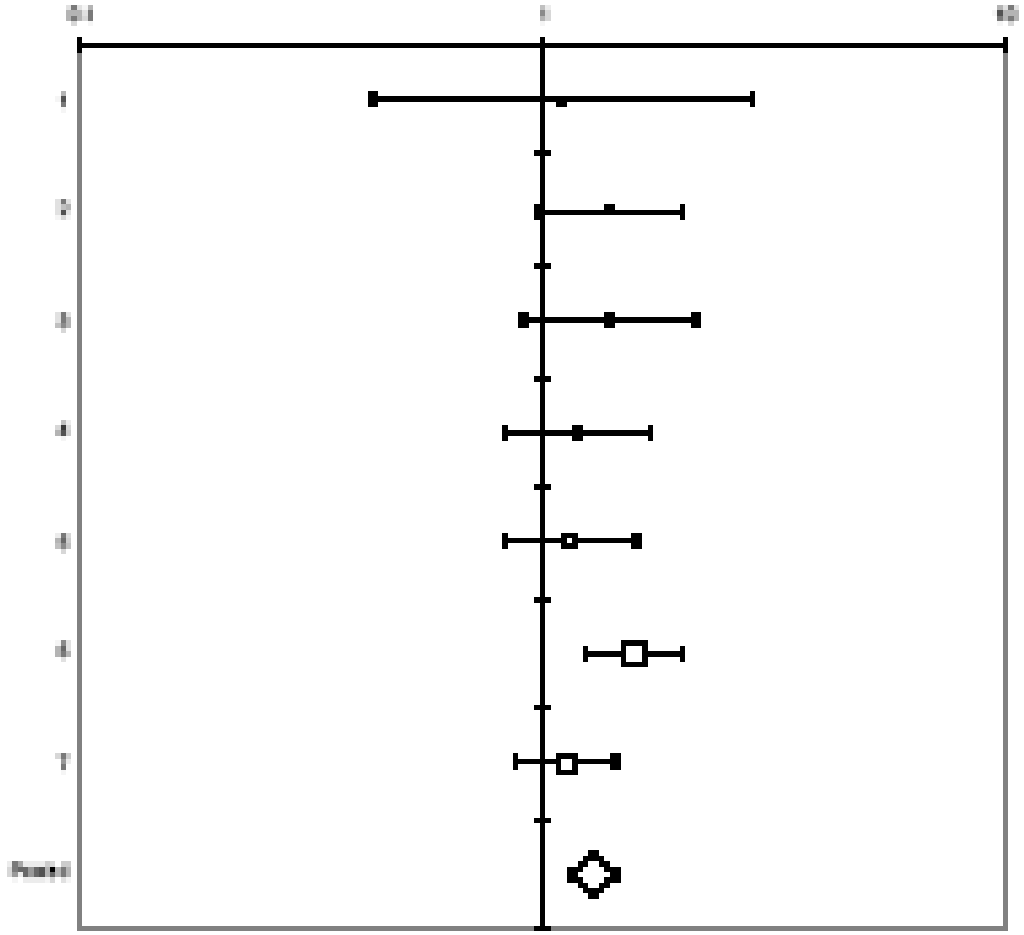
Collaborators

Australia A.E. Grulich, B.K. Armstrong
Canada R.P. Gallagher, J.J. Spinelli
Czech Republic L. Foretova
Finland M. Vornanen
France M. Maynadie, P. Boffetta, P. Brennan
Germany N. Becker, A. Nieters
Ireland D. Crowley, A. Staines
Israel G. Rennert
Italy P.L. Cocco, P. Vineis
Spain S. de Sanjose
UK G. Morgan, E. Roman
USA M.T. Smith, N. Mueller, W. Cozen, T.Z. Zheng, B. Chiu, D. Weisenburger, J.R. Cerhan, E.A. Holly, P. Hartge, M.S. Linet, N. Rothman

InterLymph - Completed projects

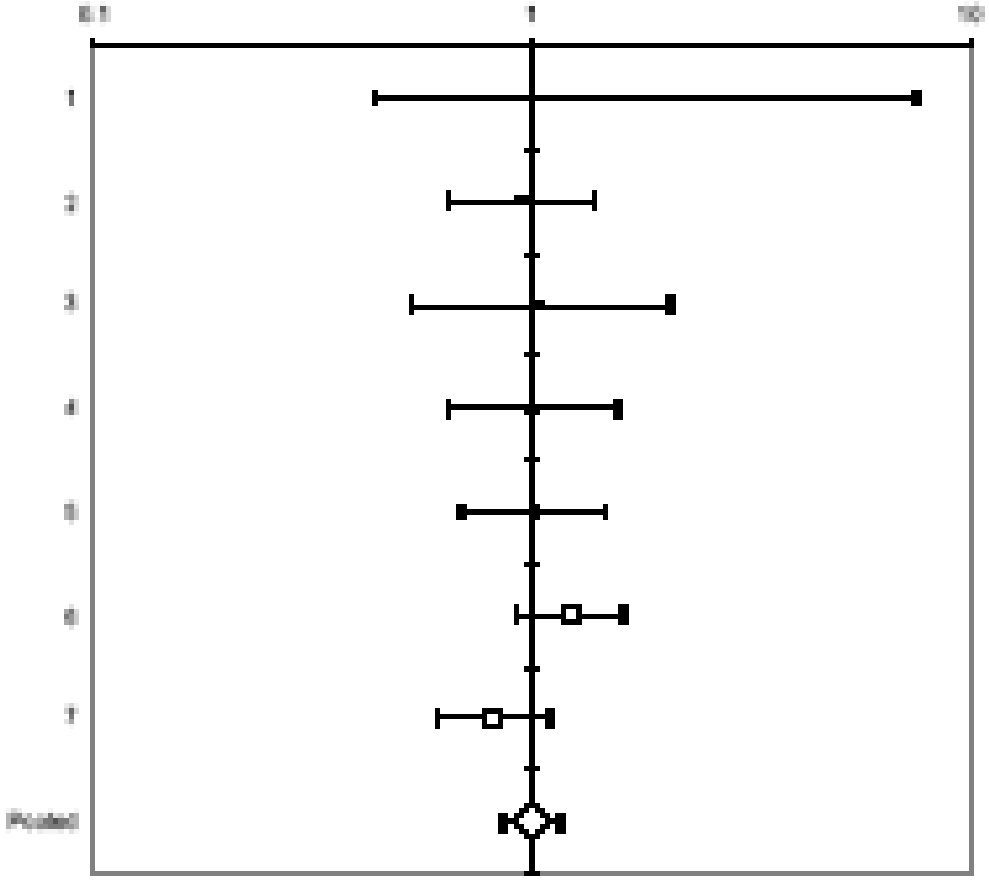
Project	*N ca/co*	*PI*
Pooled analysis of tobacco smoking	6594/8892	L. Morton
Pooled analysis of alcohol drinking	6492/8683	L. Morton
Coordinated genotyping of 12 immunology-related polymorphisms	3586/4018	N. Rothman

Study-specific and pooled odds ratio for TNF G-308A genotype
Diffuse large B-cell lymphoma
Preliminary results of InterLymph SNP analysis



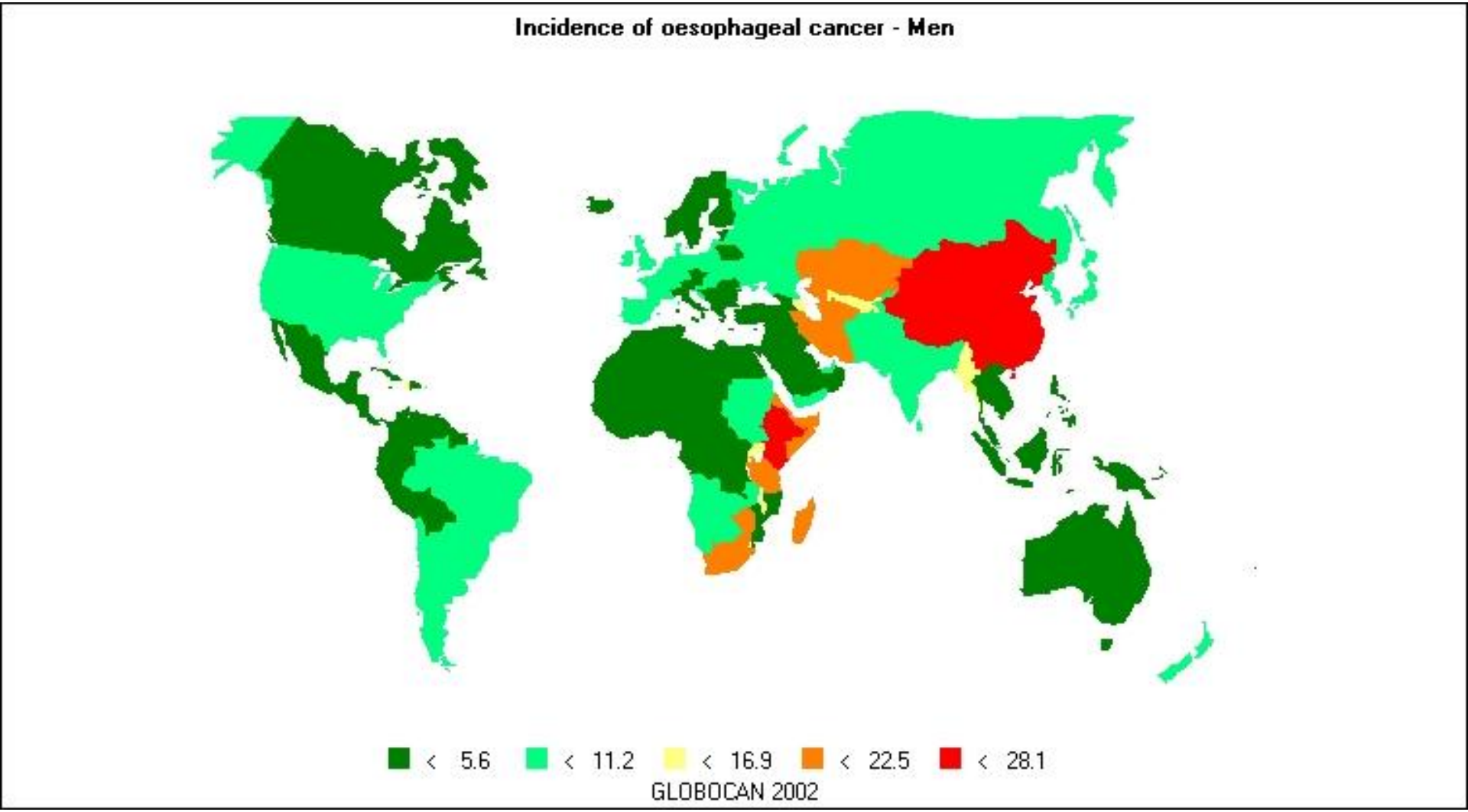
Rothman et al., 2006

Study-specific and pooled odds ratio for TNF G-308A genotype
Follicular lymphoma
Preliminary results of InterLymph SNP analysis



Rothman et al., 2006

Esophageal squamous cell carcinoma consortium ESC3



Features of esophageal squamous cell carcinoma epidemiology

- Several areas at high (and very high) risk
  - predominance of squamous cell carcinoma
  - variable men/women ratio
  - higher risk in the poor
- Common risk factors?
  - poor diet
  - groups of carcinogens (PAH, NA)
  - physical injury
- Population-specific risk factors

Risk factors of esophageal squamous cell carcinoma

- Europe, North America
  - tobacco smoking and alcohol drinking (80% AF)
  - rare medical conditions
  - low fruit and vegetable intake?
  - occupational exposure to PAH?
- Suspected risk factors in high-risk areas
  - low fruit and vegetables; low selenium
  - local smoking and chewing habits
  - hot beverage drinking
  - genetic susceptibility

Collaborative activities of ESC3

- Meetings, conferences
  - Exchange of results and ideas
- Pooled analyses of independent studies
  - Limited by heterogeneity of risk factors
- Collaborative studies
  - Patterns of molecular alterations
  - Surveys of risk factors in case series
  - Case-control and cohort studies

ESC3 - membership

- IARC, Lyon - Paolo Boffetta, Pierre Hainaut
- NCI, Bethesda - Christian Abnet, Sandy Dawsey
- TUMS, Tehran, Iran - Reza Malekzadeh
- CICAMS, Beijing, China - Yulin Qiao
- Glasgow University, UK - Kenneth McColl
- KI, Stockholm, Sweden - Olof Nyren
- MRC Cape Town, S. Africa - Iqbal Parker
- Eldoret U., Kenya - Diana Manya

On-going studies

- Linxian, China
  - dietary intervention
  - early detection
- Golestan, Iran
  - case-control and cohort study
- Transkei, S. Africa
  - case-control study
- Kenya
  - case-control study

ESC3 - Planned activities

- Patterns of TP53 mutations in high-risk populations
- Survey of risk factors in Central Asian countries
- Screening and intervention trials in high-risk populations

Side effects of cancer consortia

- Methodological developments
  - pathological classification in InterLymph
- Standard for future studies
- Support to individual studies
  - effect on local grant application

Issues in the coordination of cancer consortia

- Need to obtain support for infrastructure
- Definition of IP issues
  - publication policy
  - authorship rules
  - ownership of new results
- Management of non-collaborative behaviours

Challenges in cancer consortia

- To overcome the reluctance of individual investigators to share data, biological samples and ideas
  - high level of commitment
  - confidence that what is gained from the collaboration will be greater than what might be lost through joining it
  - secondary analyses less challenging than sharing of unpublished material

Conclusions

- Strength of consortia in their very nature of offering a forum for collaborative projects
- Complement rather than alternative to individual investigator-initiated studies to generate and test of novel hypotheses

Consortia vs. individual studies

- Individual studies
  - flexible mechanism to explore new hypotheses
  - development of novel methods
- Consortia
  - increased statistical power
  - coordinated replication of results
  - heterogeneity of effects