The exposome: a new concept to support research on causes and prevention

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Global cancer burden - marked increases

Assuming no change in underlying incidence

“We cannot treat our way out of the cancer problem”

A balanced and integrated approach to prevention and treatment is required.

## Major cancer risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco including environmental tobacco smoke</td>
<td></td>
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<tr>
<td>Alcohol</td>
<td></td>
</tr>
<tr>
<td>Physical inactivity, overweight and obesity</td>
<td></td>
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<tr>
<td>Unhealthy diet</td>
<td>Relatively limited understanding on how specific nutrients or dietary patterns affect cancer risk</td>
</tr>
<tr>
<td>Infections</td>
<td><em>HBV, HPV, H. pylori, HCV; vaccination; avoid contaminated injections</em></td>
</tr>
<tr>
<td>Radiation</td>
<td>UV light; ionising radiation; medical diagnostic, indoor radon</td>
</tr>
<tr>
<td>Environmental carcinogens</td>
<td>Naturally occurring (arsenic, aflatoxins); air pollution</td>
</tr>
<tr>
<td>Occupation</td>
<td>Risks of “exporting” at-risk occupational exposures</td>
</tr>
<tr>
<td>Reproductive factors and hormones</td>
<td>Allied to earlier age at menarche, later age at first live birth; fewer children; shorter duration of breast feeding</td>
</tr>
</tbody>
</table>

Adapted from Franceschi and Wild, Molec. Oncol., 7: 1-13, 2013
Preventable Exposures Associated With Human Cancers

Vincent James Cogliano, Robert Baan, Kurt Straif, Yann Grosse, Béatrice Lauby-Secrefat, Fatihai El Ghissassi, Véronique Bouvard, Lamia Benbrahim-Tallaa, Neela Guha, Crystal Freeman, Laurent Galichet, Christopher P. Wild

The IARC Monographs Volume 100: The known causes of human cancer by organ site

Section of the IARC Monographs (IMO)
International Agency for Research on Cancer

World Health Organization
Primary cancer prevention

• “One third of cancers are preventable – the most cost-effective response” (Action against Cancer: European Partnership)
• Higher estimates from Doll and Peto (1981) for USA; Parkin (2012) for UK
• But the majority (~90%) of cancers have an environmental or lifestyle cause, so the potential for prevention is much higher; “aetiology gap”
Cancers where aetiology is (largely) unknown

<table>
<thead>
<tr>
<th>Organ sites</th>
<th>Estimated annual no. new cases worldwide</th>
<th>Percent global cancer burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>1,100,000</td>
<td>7.9</td>
</tr>
<tr>
<td>Lymphoma and Leukemia</td>
<td>850,000</td>
<td>6.0</td>
</tr>
<tr>
<td>Kidney</td>
<td>340,000</td>
<td>2.4</td>
</tr>
<tr>
<td>Pancreas</td>
<td>340,000</td>
<td>2.4</td>
</tr>
<tr>
<td>Thyroid</td>
<td>300,000</td>
<td>2.1</td>
</tr>
<tr>
<td>Brain</td>
<td>260,000</td>
<td>1.8</td>
</tr>
<tr>
<td>Colorectal</td>
<td>1,400,000</td>
<td>9.7</td>
</tr>
</tbody>
</table>
Two-way Translational Cancer Research

Basic Science

Population
Causes and Prevention
Risk factors

Patient
Personalized treatment
Prognosis

Specific molecular alterations

Laboratory Methodologies
- genomics, transcriptomics, epigenomics, proteomics, metabolomics

Wild CP (2012) Int. J. Epidemiol, 41: 24-32
Laboratory science in population studies – five areas of promise

- Improved exposure assessment
- Contributing to biological plausibility
- Stratifying risks by tumour sub-group
- Evaluating interventions
- Hazard and risk assessment
Importance of environmental exposure assessment

- Most common chronic diseases have an environmental or lifestyle aetiology
- Currently exposure measurement is problematic in many areas, leading to misclassification
- Large prospective cohort studies (e.g. UK Biobank) are predicated on the availability of accurate exposure assessment
Complementing the genome with an “exposome”

All exposures throughout the lifetime of an individual from conception to death

*Uca Pugnax*, the male Fiddler Crab

- Wild CP (2012) Int. J. Epidemiol, 41: 24-32
Domains of the exposome

Internal
- metabolism, endogenous hormones, body morphology, physical activity, gut micro flora, inflammation, aging etc.

General external
- social capital, education, financial status, psychological stress, urban-rural environment, climate, etc

Specific external
- radiation, infectious agents, chemical contaminants and pollutants, diet, lifestyle factors (e.g. tobacco, alcohol), occupation, medical interventions, etc.

Wild CP (2012) Int. J. Epidemiol, 41: 24-32
Mechanism-based exposure biomarkers

- **First generation:**
  - *a focus on a classical mutagen – carcinogen model*
  - *examples are chemical metabolites, DNA and protein adducts, chromosomal alterations, somatic mutations*

- **Second generation:**
  - *global alterations in mRNA, protein or metabolite levels using omics technologies*
  - *epigenetic changes (promoter methylation, histone acetylation, microRNA)*
  - *pathway-specific omics approaches e.g. lipidomics*
Exposure – clues from transcriptomics

- 127 individuals (47 non-smokers, 58 “healthy” smokers, 22 smokers with COPD)
- Small airway epithelial cells collected by fiberoptic bronchoscopy with subsequent microarray analysis
- Generated a gene expression “index” for each individual using 375 smoking-responsive genes, which distinguished smokers and non-smokers but also “high” and “low” response among smokers

Tilley et al., PLoS ONE 6: July 2011
Gene expression in small airway epithelium of smokers and non-smokers

A: Probe sets comparing smokers and nonsmokers: Top right: higher expression in smokers; Top left: lower expression in smokers

B: Up-regulated in smokers >1; down-regulated in smokers <1 compared to nonsmokers

C: Expressed above average in red, below in blue; each row is one of 375 smoking-responsive genes

Tilley et al., PLoS ONE 6: July 2011
## Exposure – clues from transcriptomics

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Tissue</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acrylamide, dioxin</td>
<td>Cord blood</td>
<td>Hochstenbach et al., 2012</td>
</tr>
<tr>
<td>Arsenic</td>
<td>PBL, cord blood</td>
<td>Argos et al., 2006; Fry et al., 2007</td>
</tr>
<tr>
<td>Benzene</td>
<td>PMBC</td>
<td>Forrest et al., 2005; McHale et al., 2009; 2011</td>
</tr>
<tr>
<td>Dioxin</td>
<td>PBMC</td>
<td>McHale et al., 2007</td>
</tr>
<tr>
<td>Metal fumes</td>
<td>Whole blood</td>
<td>Wang et al., 2005</td>
</tr>
<tr>
<td>Diesel exhaust</td>
<td>PBMC</td>
<td>Peretz et al., 2007</td>
</tr>
<tr>
<td>Tobacco smoke</td>
<td>PMBC; airway epithelial cells</td>
<td>Lampe et al., 2004; van Leeuwen et al., 2007; Tilley et al., 2011; Wright et al., 2012; Hackett et al., 2012</td>
</tr>
</tbody>
</table>
Exposure – clues from methylomics

Methylation of specific gene promoter regions by:

- Tumour grade

Risk factor

Hernandez Vargas et al., PLoS One 2010
Exposure - clues from metabolomics

Urinary polyphenols in high and low consumers within the EPIC study

Edmans W, Scalbert A
IARC, unpublished
Exposure – clues from genomics

74 matched head and neck tumour and normal tissue; exome seq.

Stransky et al., Science 333: 1157-1160, 2011
Temporal application of exposure biomarkers in cancer epidemiology

- Peri-natal
- Adolescence
- Adult

- Birth cohort
- Adult cohort
- Case-control study

Timing of exposure measurement

- Carcinogen metabolites
- DNA/protein adducts
- Cytogenetic alterations
- Mutation spectra
- Antibodies
Activation of inflammation/NF-κB signalling in infants born to arsenic-exposed mothers

- 32 pregnant women in Thailand in high and low areas of arsenic exposure
- Toenail analysis of arsenic; cord blood for microarray gene expression
- Expression signatures highly predictive of prenatal arsenic exposure; genes related to stress, inflammation, metal exposure and apoptosis

Fry et al., PLoS Genetics, 3: 2180-2189, 2007
Laboratory science in population studies – what is promised?

- Improved exposure assessment
- Contributing to biological plausibility
- Stratifying risks by tumour sub-group
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- Hazard and risk assessment
Kinetics of N2-ethylidene-DNA adducts in the oral cavity after drinking alcohol

- Subjects consumed approx. 27 (d1), 39 (d2) or 51 (d3) g ethanol; provided oral mouthwash for DNA extraction
- Dose response with peak adduct after 4 hours; up to 100-fold above baseline
- Considerable interindividual variation

Volatile organic carcinogens and home cooking among Chinese women non-smokers

- Lung cancer in non-smoking Chinese women has been associated with Chinese-style wok cooking.
- Urinary biomarkers were compared in women who engaged in regular home cooking and those who did not.

Biomarkers of mercapturic acid metabolites pmol/mg creatinine but x10³ for benzene and x10 for 1,3-butadiene.

*Hecht et al., CEBP, 19: 1185-1192, 2010*
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Genomic and transcriptomic architecture of breast tumours

- Analysis of acquired somatic copy number aberrations and gene expression in 2,000 tumours
- Identified novel molecular sub-groups of breast cancers with distinct clinical outcomes
- Subgroup-specific gene networks associated with aberration hotspots
- A basis for stratified medicine (beyond Herceptin)
- But any implications for breast cancer aetiology?

Curtis et al., Nature 2012
Molecular subtypes of premenopausal breast cancer in Latin American Women

- Standardized protocol for clinical, pathological information and biological specimens
- Identification of specific endogenous (genetics and genomics) and exogenous factors (biological modifications, behavioral, dietary and cultural factors) with specific subtypes of premenopausal BC, identified based on molecular and pathological phenotypes
- Provide advanced training, development of the BC research community in Latin America, and influence the public health agenda regarding the management of BC

IARC PI: Dr Isabelle Romieu, Section of Nutrition and Metabolism, IARC
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International Agency for Research on Cancer
World Health Organization
Biomarkers and intervention studies – aflatoxin in subsistence farms in Guinea

20 Villages (10 intervention, 10 control), 30 subjects per village

Survey 1
Survey 2
Survey 3

Blood sample collection
Groundnut sample collection
Laboratory science in population studies – what is promised?

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New research continues to find additional human carcinogens & Use of mechanistic data to identify carcinogens is accelerating

Types of mechanistic upgrades

**Ethylene oxide**: Dose-related increase in the frequency of SCE, CA, and MN in lymphocytes of exposed workers.

DNA adducts and A:T→T:A transversions in TP53 identified **aristolochic acid** as the carcinogen in herbal remedies - environmental exposures: cereal fields in the Balkans where *Aristolochia* plants grow as weeds.

**Benzidine-based dyes**: Metabolism results in the release of free benzidine in humans and in all experimental animal species studied.
Conclusions

• The challenge of a rising cancer burden must be met by an integrated approach of prevention (including early detection) and treatment
• Recent advances in the molecular (epi)genetics of cancer and related tools offer exciting inter-disciplinary approaches to cancer prevention
• There are barriers to be overcome in relation to vision, inter-disciplinary working and resources to benefit from these opportunities