



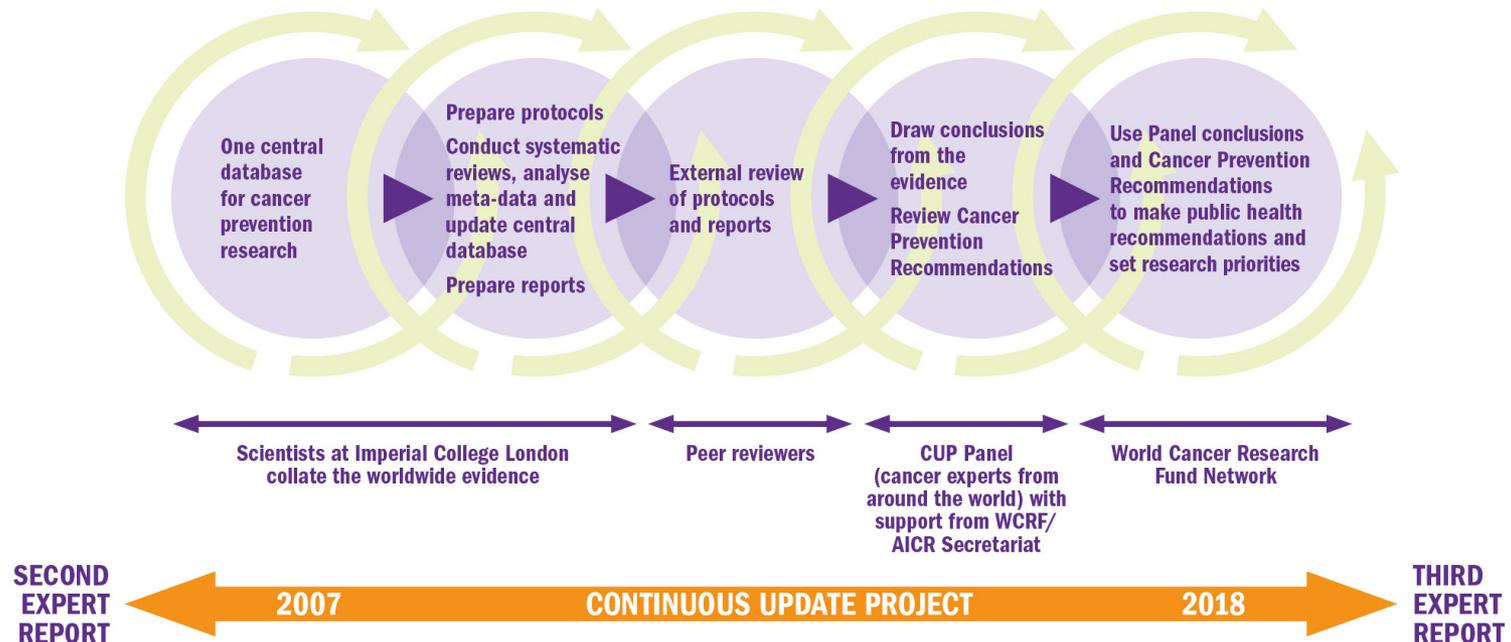
The Continuous Update Project

Kostas Tsilidis, PhD, co-PI of CUP



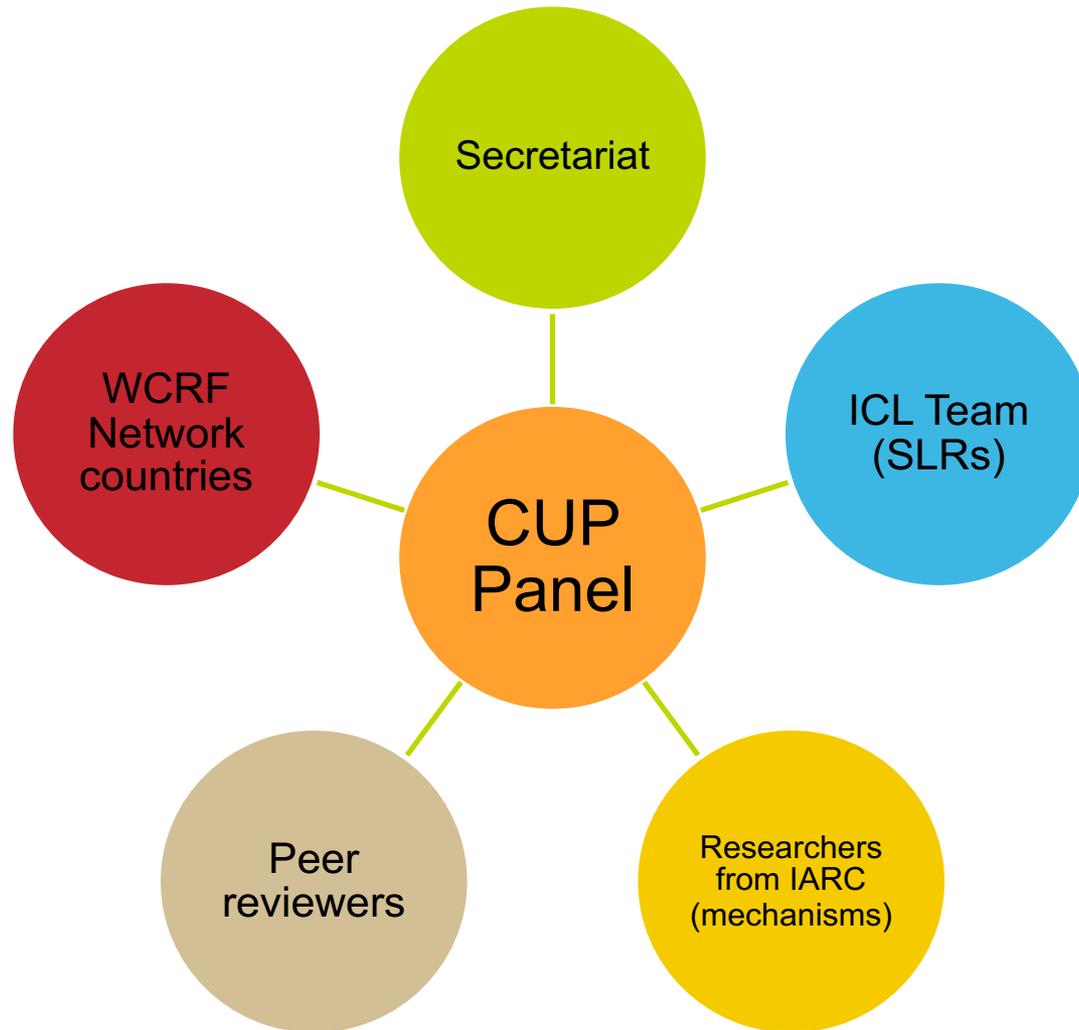
Introduction to the Continuous Update Project (CUP)

- Rigorous, systematic and ongoing programme
- Trusted, authoritative scientific resource
- Provides the most up-to-date information on reducing cancer risk

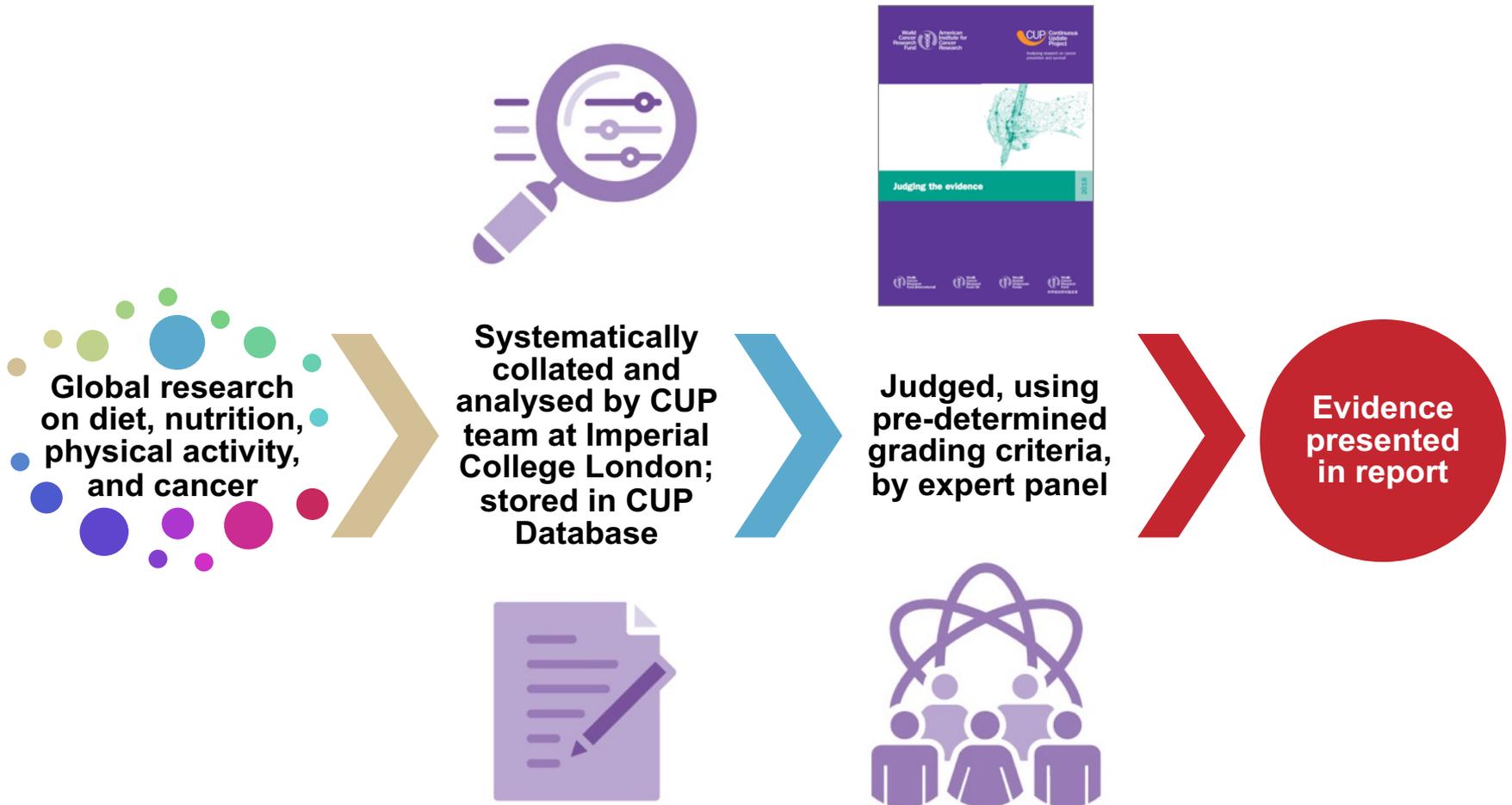


© World Cancer Research Fund International dietandcancerreport.org

Who is involved in the CUP?



Summary of the CUP process

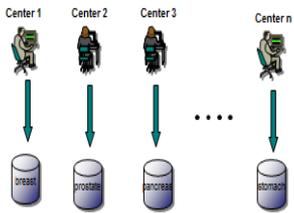


The systematic process of the CUP

Internal quality control: guidelines, standardisation, double checks

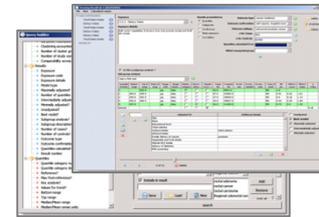
External quality control: Peer reviewers, CUP Expert Panel

Research team



Global research

CUP application



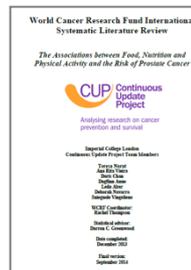
CUP database



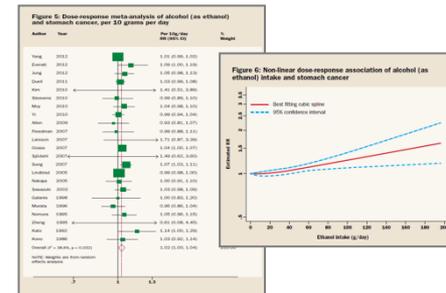
CUP Expert Panel



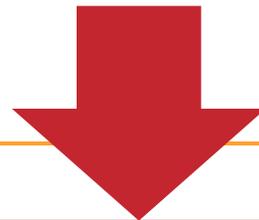
Findings



Data synthesis and analysis



CUP publications



The evidence is judged using grading criteria

Evidence Matrix		Decreases risk	Increases risk
Strong evidence	Convincing	Basis for Recommendations	
	Very Likely		
Limited evidence	Limited - suggestive		
	Limited – no conclusion		
Strong evidence	Substantial effect on risk unlikely		

Pre-determined criteria for grading the evidence:

- Design and number of studies
- Quality of exposure and outcome assessment
- Exclusion of chance, bias or confounding
- Heterogeneity within and between study types
- Biological gradient (dose-response)
- Evidence of mechanisms
- Size of effect

Obesity and cancer risk associations supported by convincing evidence

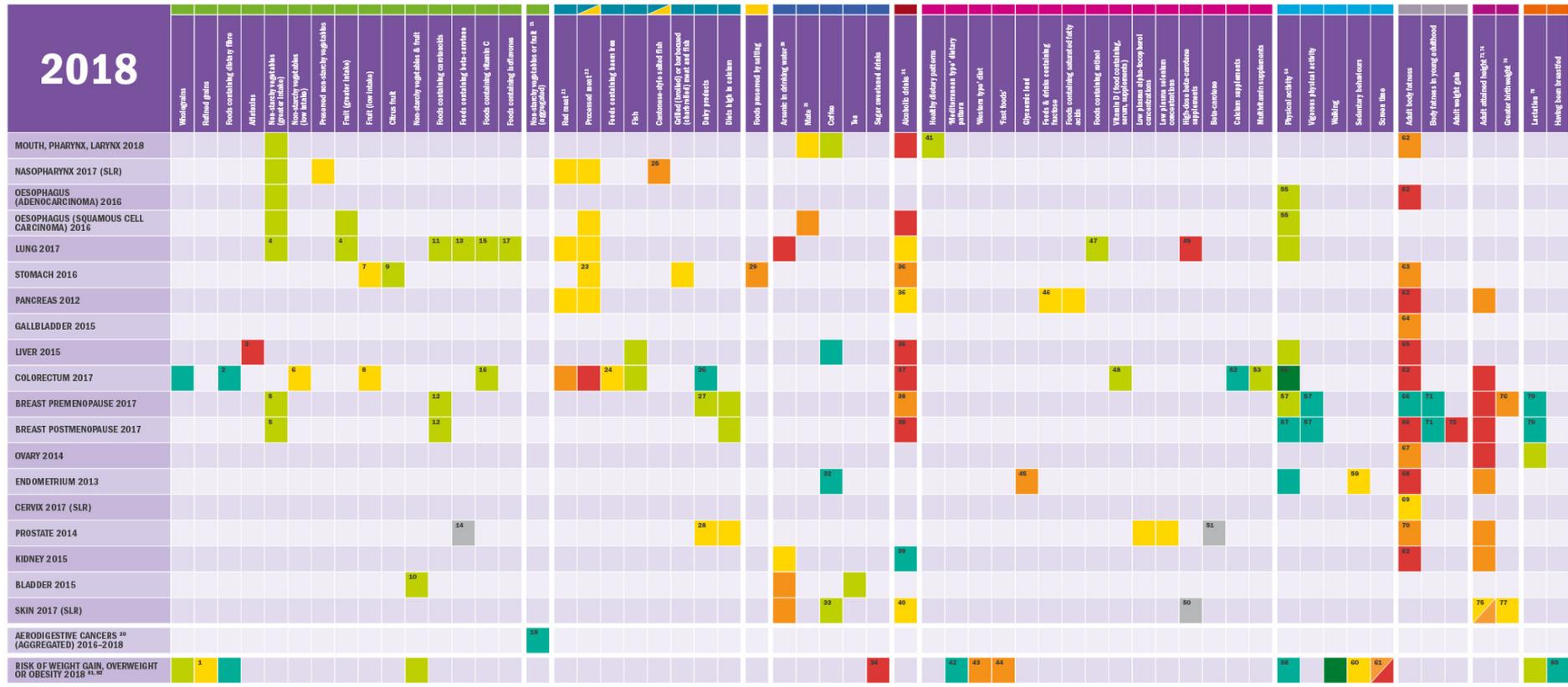
Cancers	IARC <small>(Lauby-Secretan B, et al. NEJM 2016)</small>	WCRF <small>(www.wcrf.org)</small>	Umbrella review <small>(Kyrgiou M, et al. BMJ 2017)</small>
Oesophagus (adenoCA)	✓	✓	✓
Endometrium	✓	✓	✓
Gastric cardia	✓	Probably	✓
Liver	✓	✓	Highly suggestive
Pancreas	✓	✓	✓
Kidney (renal cell)	✓	✓	✓
Meningioma	✓	Not assessed	Weak
Multiple myeloma	✓	Not assessed	✓
Colon & rectum	✓	✓	✓
Gallbladder	✓	Probably	✓
Breast (postmenopausal)	✓	✓	✓
Ovary	✓	Probably	✓
Thyroid	✓	Not assessed	Highly suggestive

Conclusions in the 'convincing' category

- **Strong association and unlikely to change in future**
- **No unexplained heterogeneity**
- **At least two independent cohorts**
- **Good quality studies that account for error**
- **Dose response**
- **Robust evidence from laboratory studies**



Findings: Summary of conclusions



Conclusions Key

- Dark Green: Convincing decreases risk
- Light Green: Probable decreases risk
- Yellow-Green: Limited - suggestive decreases risk
- Dark Red: Convincing increases risk
- Light Red: Probable increases risk
- Yellow-Red: Limited - suggestive increases risk
- Grey: Substantial effect on risk unlikely

Exposure Group Key

- Green: Wholegrains, vegetables and fruit
- Teal: Meat, fish and dairy products
- Yellow: Preservation and processing of foods
- Blue: Non-alcoholic drinks
- Red: Alcoholic drinks
- Pink: Other dietary exposures
- Light Blue: Physical activity
- Grey: Body fatness and weight gain
- Purple: Height and birthweight
- Orange: Lactation/having been breastfed

Abbreviation: SLR, systematic literature review.

dietandcancerreport.org

© 2018 World Cancer Research Fund International. All rights reserved

Interactive matrix

Lifestyle Risk Factors for Cancer



Cancer Prevention Recommendations 2018

Be a healthy weight

Keep your weight within the healthy range and avoid weight gain in adult life

Be physically active

Be physically active as part of everyday life – walk more and sit less

Eat a diet rich in wholegrains, vegetables, fruit and beans

Make wholegrains, vegetables, fruit, and pulses (legumes) such as beans and lentils a major part of your usual daily diet

Limit consumption of 'fast foods' and other processed foods high in fat, starches or sugars

Limiting these foods helps control calorie intake and maintain a healthy weight

Limit consumption of red and processed meat

Eat no more than moderate amounts of red meat, such as beef, pork and lamb. Eat little, if any, processed meat

Limit consumption of sugar sweetened drinks

Drink mostly water and unsweetened drinks

Limit alcohol consumption

For cancer prevention, it's best not to drink alcohol

Do not use supplements for cancer prevention

Aim to meet nutritional needs through diet alone

For mothers: breastfeed your baby, if you can

Breastfeeding is good for both mother and baby

After a cancer diagnosis: follow our Recommendations, if you can

Check with your health professional what is right for you

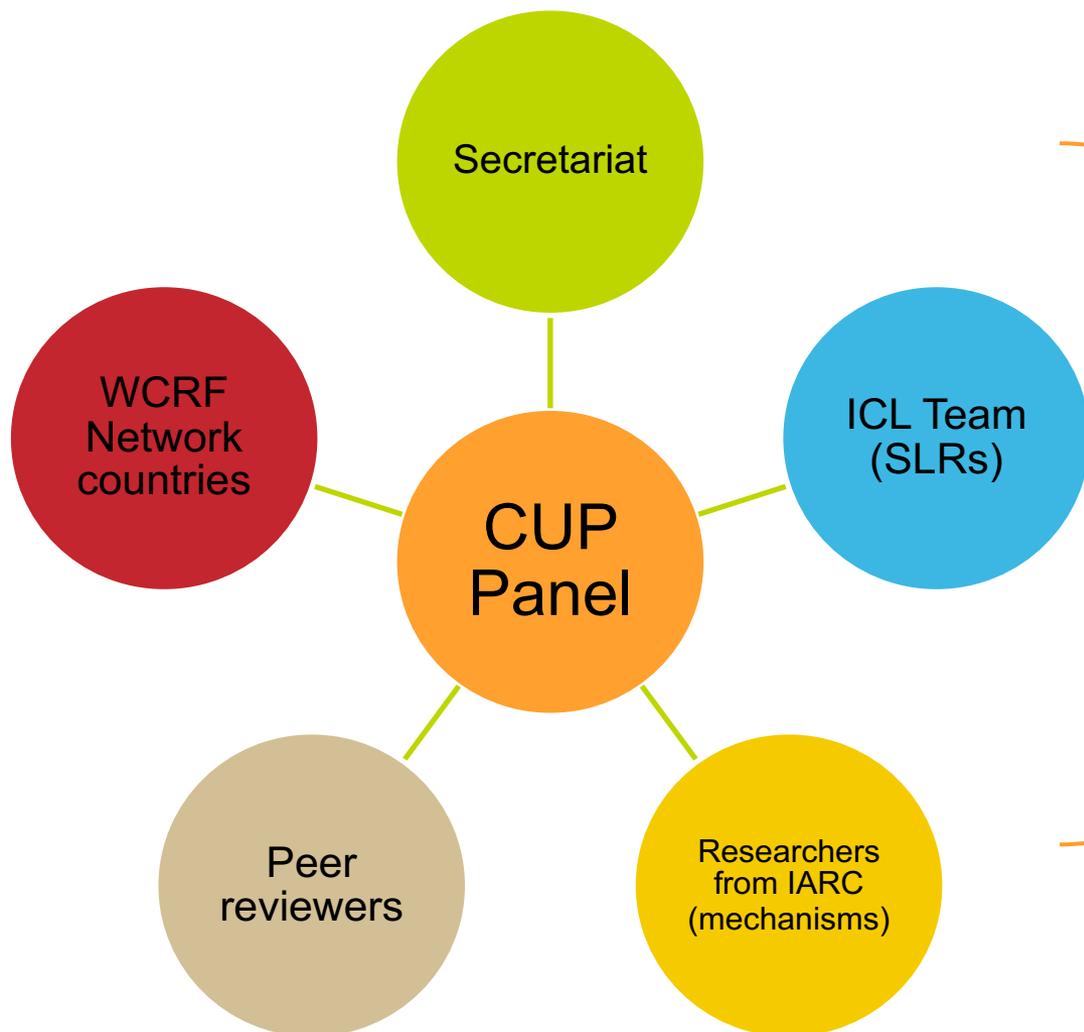
Not smoking and avoiding other exposure to tobacco and excess sun are also important in reducing cancer risk.

Following these Recommendations is likely to reduce intakes of salt, saturated and trans fats, which together will help prevent other non-communicable diseases.

The CUP 2.0

- **Evidence search and synthesis process** – reviewing the robust process by which we conduct our work.
- **Outcomes after a cancer diagnosis** – furthering our understanding of nutrition and lifestyle during and after cancer.
- **Childhood cancers** – outlining how the WCRF network can investigate how diet, nutrition and physical activity affect survival from childhood cancers.
- **Cancer subtypes** – understanding how different factors affect different subtypes of cancer.
- **Dietary and lifestyle patterns** – gaining a better understanding of how patterns of eating and behaviour affect cancer risk.
- **Life course** – understanding how diet, nutrition and physical activity across the whole life span link to cancer.
- **Biological data** – digging deeper into key biological mechanisms that underpin the associations we observe.
- **Systems approach** – creating a framework to better understand the cancer process at multiple levels.

Acknowledgements



Dr Doris Chan



Dr Teresa Norat
(PI until 2019)



Dr Dagfinn
Aune



Dr George
Markozannes



Dr Nerea
Becerra Tomas



Margarita
Cariolou



Katia
Balducci



Rita
Vieira



**International Guideline
Harmonization Group**

for Late Effects of Childhood Cancer

Leveraging International Multidisciplinary Expertise to Improve Childhood Cancer Survivor Outcomes

Melissa M. Hudson, MD
Director, Survivorship Division
St. Jude Children's Research Hospital

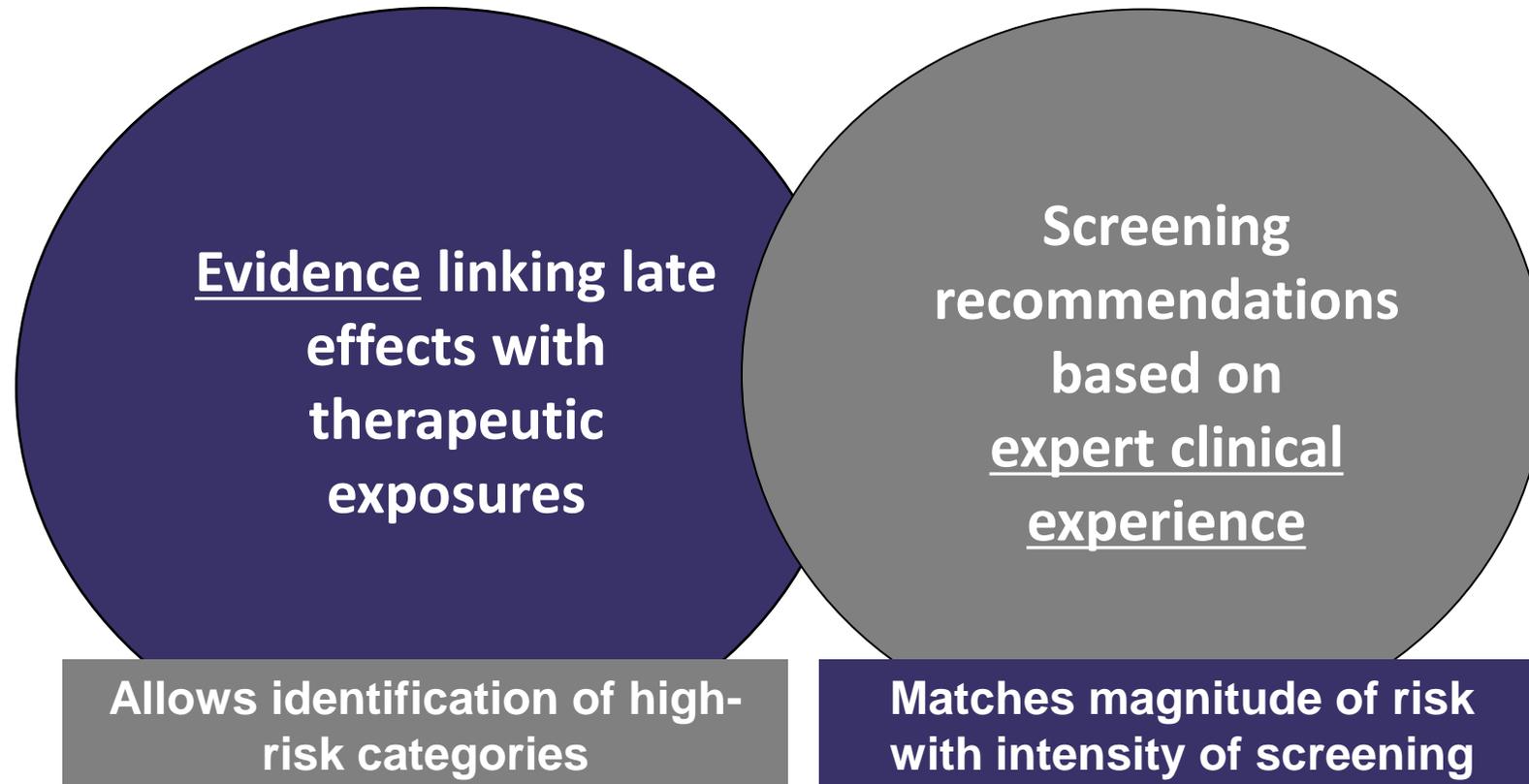
Why we need long-term follow-up guidelines?

- Most children, adolescents and young adults diagnosed with cancer will become long-term survivors.
- Cancer and its treatment predispose to excess morbidity that increases risk of early mortality.
- Late effects research provides data to anticipate treatment-related health risks.
- Health screening/surveillance provides opportunity for prevention, early detection, and interventions that may preserve health.
- Survivors and providers need guidance to be proactive about cancer-related health risks.

Challenges with pediatric follow-up guidelines

- Survivors of childhood cancer comprise a relatively small population.
 - Estimated 500,000 in U.S.
- Pediatric cancer includes heterogeneous subtypes managed with diverse therapeutic strategies and associated with variable health risks.
- The prevalence of many late effects is relatively low.
 - Therapy has been modified/risk-stratified to reduce risk, particularly of life-threatening toxicities.
- Many health events present years from diagnosis and completion of therapy when survivors have been discharged from follow-up care.
- Implementation of randomized clinical surveillance trials is often not feasible.

Guideline Design



***Evidence-Based Guidelines for Childhood Cancer Survivors:
A Hybrid Model***

Long-term follow-up guidelines

Scottish Intercollegiate Guidelines Network

76 Long term follow up of survivors of childhood cancer
A national clinical guideline

- 1 Introduction 1
- 2 Long term follow up 4
- 3 Growth problems 7
- 4 Problems with puberty and reproduction 11
- 5 Cardiac problems 14
- 6 Thyroid dysfunction 16
- 7 Cognitive and psychosocial outcomes 18
- 8 Patient issues 30
- 9 Research, implementation and audit 22
- 10 Development of the guideline 24
- Abbreviations 27
- References 28

January 2004

COPIES OF ALL SIGN GUIDELINES ARE AVAILABLE BY CALLING 0131 247 3664 OR ONLINE AT WWW.SIGN.AC.UK

THEMATIC BASED LONG TERM FOLLOW UP
(2010-2011, 2012-2013)

Practice Statement

UNITED KINGDOM CHILDREN'S CANCER STUDY GROUP
SAFE EFFICACY GROUP

© 2011

18. Where there is a risk of harm to the patient, the clinician should consider the following:

19. Where there is a risk of harm to the patient, the clinician should consider the following:

20. Where there is a risk of harm to the patient, the clinician should consider the following:

Supported by an educational grant from Novartis

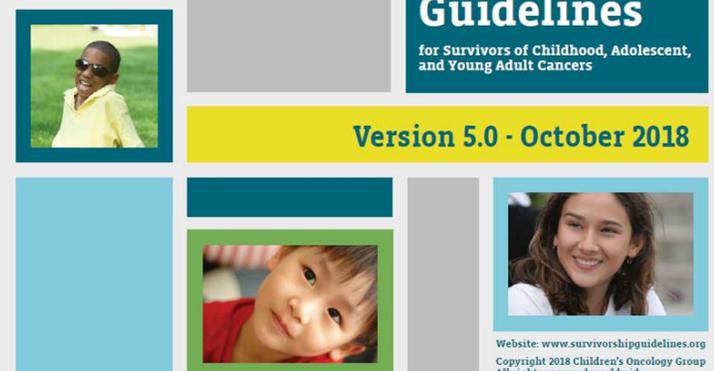


CHILDREN'S ONCOLOGY GROUP
The world's childhood cancer experts

Long-Term Follow-Up Guidelines
for Survivors of Childhood, Adolescent, and Young Adult Cancers

Version 5.0 - October 2018

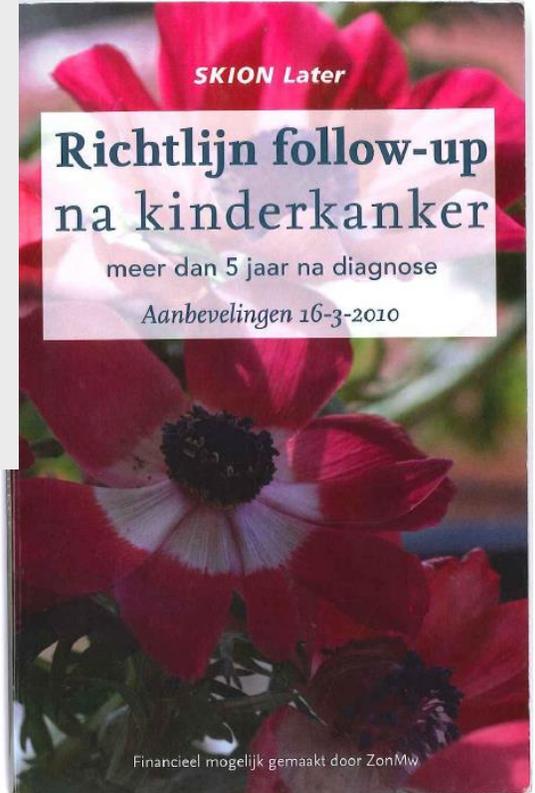
Website: www-survivorshipguidelines.org
Copyright 2018 Children's Oncology Group
All rights reserved worldwide



SKION Later

Richtlijn follow-up na kinderkanker
meer dan 5 jaar na diagnose
Aanbevelingen 16-3-2010

Financieel mogelijk gemaakt door ZonMw



Benefits of Collaboration

Optimize use of expertise

- Pediatric/radiation oncology
- Pediatric/medical subspecialties
- Late effects
- Systematic reviews/meta-analysis
- Clinical epidemiology
- Guideline methodology

Harmonize national guidelines

- Reduce duplication of effort
- Establish standards of survivorship care
- Improve quality of survivorship
- Identify research agenda
- Enhance research opportunities

International Late Effects of Childhood Cancer Guideline Harmonization Group

Initiated in 2010 by

National guideline groups

Cochrane Childhood Cancer Group

In partnership with the PanCareSurFup Consortium



Goal

Establish a common vision and integrated strategy for the surveillance of late effects in childhood, adolescent, and young adult cancer survivors

International Late Effects of Childhood Cancer Guideline Harmonization Group

Established core group

Chaired by Melissa Hudson and Leontien Kremer

Dynamic guideline groups

~ 300 experts involved

Resources

Handbook and methodology paper

Website: www.ighg.org

Guideline development

KNOWLEDGE



RECOMMENDATION

Harmonization process

Standardized guideline development method

Step 1 Determine concordances and discordances

Step 2 Formulate clinical questions

Step 3 Identify available evidence by systematic literature searches

Step 4 Summarize and grade evidence

Step 5 Formulate and grade recommendations

For the evidence & recommendation key issues that need to be addressed

WHO?

Who needs surveillance?

WHEN?

At what age or time from exposure should surveillance be initiated and terminated?

HOW OFTEN?

At what frequency should surveillance be performed?

HOW?

What surveillance modality should be used?

ACTIONS?

What should be done when abnormalities are identified?

Harmonization Methods

- Evidence-based methods
 - Institute of Medicine’s Developing Trustworthy Guidelines
 - Appraisal of Guidelines for Research & Evaluation
- Evaluation of quality of evidence
 - American Heart Association’s “Applying Classification of Recommendations and Level of Evidence”
 - Grading of Recommendations Assessment Development and Evaluation (GRADE) criteria

Grading system

Grade of recommendation	I Strong recommendation to do	IIa Moderate recommendation to do	IIb Weak recommendation to do	III Recommendation not to do
Conclusions of evidence	Benefits >>> risk & burdens	Benefits >> risk & burdens	Benefits >= risks & burdens	No benefit / Potentially harm
A High level of evidence Consistent evidence from well performed and high quality studies or systematic reviews (low risk of bias, direct, consistent, precise)	Strong recommendation based on high level of evidence	Moderate recommendation based on high level of evidence	Weak recommendation based on high level of evidence	Recommendation based on high level of evidence
B Moderate /Low level of evidence Evidence from studies or systematic reviews with few important limitations	Strong recommendation based on moderate/ low level of evidence	Moderate recommendation based on moderate/ low level of evidence	Weak recommendation based on moderate/ low level of evidence	Recommendation based on moderate/ low level of evidence
C Very low level of evidence Evidence from studies with serious flaws. Only expert opinion, or standards of care	Strong recommendation based on expert opinion	Moderate recommendation based on very low level of evidence Diverging expert opinions	Weak recommendation based on very low level of evidence Diverging expert opinions	Recommendation based on very low level of evidence Expert opinion

Recommendations

STRONG recommendation “*is recommended*”

MODERATE recommendation “*is reasonable*”

WEAK recommendation “*may be reasonable*”

NOT TO DO recommendation “*is not recommended*”

IGHG Publications

- Methodology (Pediatr Blood Cancer 2013)
- Breast cancer (Lancet Oncol 2013, J Clin Oncol 2020)
- Cardiomyopathy (Lancet Oncol 2015)
- Premature ovarian insufficiency (J Clin Oncol 2016)
- Fertility preservation review (Cancer 2016)
- Male gonadotoxicity (Lancet Oncol 2017)
- Thyroid cancer (Cancer Treat Rev 2018)
- Ototoxicity (Lancet Oncol 2019)
- Meningioma surveillance practices (J Neuro-Oncol 2020)
- Cancer-related fatigue (J Cancer Surviv 2020)
- Obstetrical care (Am J Obstet Gynecol, 2020)
- COVID-19 survivorship statement (Pediatr Blood Cancer, 2020)
- Fertility preservation series (female, male, ethics) (Lancet Oncol, in press)
- Meningioma screening (Lancet Oncol, in press)

IGHG COVID-19 Working Group

COVID-19 Guidance for childhood, adolescent, young adult survivors

- Definition of survivor: diagnosis < 25 years, \geq 1 year off therapy
- “.....collaborative approach that utilized methods that balanced the paucity of information regarding the incidence and clinical course of COVID-19 in CAYA cancer survivors with the rapidly emerging need for guidance within the survivorship community and beyond.”

Methods

- Review of local/national health authorities' recommendations for general population
- Systematic review of COVID-19 outcomes (hospitalization, mechanical ventilation, ICU admission, death)
- Translation of findings to survivorship care

- Organized through collaboration of individuals from North America, Europe, Asia, and Oceania
- Available in 11 languages at www.ighg.org
- Disseminated through PanCare, SIOP, ASPHO, other national cooperative groups and institutions
- Focuses on precautions for survivors with health conditions associated with severe course of COVID-19 in general population
- Addresses interventions for reducing exposure/ infection and staying emotionally healthy
- Emphasizes adherence to national/local guidelines

Who

is at

higher risk?



Based on medical information about COVID-19 in the general population, cancer survivors with the specific health conditions below may have a higher risk for a severe course of COVID-19, especially if they have more than one of these conditions.

In addition to these comorbid conditions, a more severe course has been observed in older individuals, especially those 60 years of age or older, which may be because older individuals are more likely to have the chronic health conditions listed in the table. Individuals with conditions and/or use of drugs that affect immune system function may also be at risk for a more severe course of COVID-19 because of their overall higher risk of infection.

Conditions ¹ most frequently identified by national health services and WHO to increase risk for a severe course of COVID-19	Examples of cancer treatment-related conditions that may increase a childhood, adolescent and young adult cancer survivor's risk for a severe course of COVID-19
Heart disease, including but not limited to: <ul style="list-style-type: none"> • Heart failure requiring medication • History of myocardial infarction (heart attack) 	Heart disease, including but not limited to: <ul style="list-style-type: none"> • Cardiomyopathy (heart muscle disease) following anthracycline therapy • Coronary artery disease following chest radiation
Chronic lung disorders, including but not limited to: <ul style="list-style-type: none"> • Chronic obstructive pulmonary disease (COPD) • Severe asthma • Any lung disease causing chronic shortness of breath, difficulty breathing or requiring oxygen therapy 	Chronic lung disorders, including but not limited to: <ul style="list-style-type: none"> • Lung fibrosis (scarring) following bleomycin or chest radiation • Chronic lung disease after bone marrow transplant
Diabetes	Diabetes following radiation to abdomen or pancreas
Conditions and/or use of drugs that affect immune system function, including but not limited to: <ul style="list-style-type: none"> • Anticancer treatment • Organ transplantation • Immune disorders 	Conditions and/or use of drugs that affect immune system function, including but not limited to: <ul style="list-style-type: none"> • Ongoing treatment for a new or recurrent cancer • History of organ transplant because of cancer or damage from cancer treatment (for heart, kidney or liver) • Chronic graft versus host disease

IGHG COVID-19 Working Group

Long-Term Follow-Up Provider Survey

- Describe LTFU care services offered
- Describe how COVID-19 has affected care
- Evaluate personal impact of COVID-19
- Evaluate anticipated impact on future survivorship care
- Describe novel strategies that have facilitated care during COVID-19

Region	Institutions Contacted (n)	Institutions Responded (n)	%
Europe	121	95	79
Asia	50	45	90
North America	34	24	71
Central/South America	14	10	71
Australia	8	4	50
Total	226	178	79

37 countries, 5 continents, 226 clinics contacted.

Current activities

Manuscript draft/under review

- Pituitary deficiencies
- Coronary artery disease
- Bone mineral density deficit
- Education & employment
- Mental health

In process

- Pulmonary toxicity
- Metabolic syndrome
- Renal toxicity
- Hepatotoxicity
- Neurocognitive deficits
- Thyroid dysfunction
- Gastrointestinal neoplasms
- Cardiomyopathy update

Proposed

- Dexrazoxane cardioprotection
- Growth hormone use/safety
- Asplenia/Hyposplenia
- HPV vaccination

Summary

- IGHG provides an infrastructure to facilitate global collaboration to define and update standards of survivorship care.
- The IGHG methodology involves a multidisciplinary collaboration, an evidence-based approach, and transparency in deriving and rating the strength of recommendations.
- IGHG activities aim to improve survivorship outcomes by facilitating early detection of late effects and timely initiation of interventions to preserve health and optimize survivor quality of life.
- IGHG efforts also identify priority research objectives to address knowledge gaps in survivorship care.

Thank you for your attention!



**International Guideline
Harmonization Group**
for Late Effects of Childhood Cancer

www.ighg.org