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
Who is involved in the CUP?

- Secretariat
- ICL Team (SLRs)
- WCRF Network countries
- CUP Panel
- Peer reviewers
- Researchers from IARC (mechanisms)
Summary of the CUP process

Global research on diet, nutrition, physical activity, and cancer → Systematically collated and analysed by CUP team at Imperial College London; stored in CUP Database → Judged, using pre-determined grading criteria, by expert panel → Evidence presented in report
The systematic process of the CUP

**Internal quality control:** guidelines, standardisation, double checks

**External quality control:** Peer reviewers, CUP Expert Panel

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**Research team**

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**Global research**

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**CUP application**

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**CUP database**

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**CUP Expert Panel**

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**Findings**

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**Data synthesis and analysis**

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The evidence is judged using grading criteria

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

<table>
<thead>
<tr>
<th>Evidence Matrix</th>
<th>Decreases risk</th>
<th>Increases risk</th>
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<tbody>
<tr>
<td><strong>Strong evidence</strong></td>
<td></td>
<td></td>
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<tr>
<td>Convincing</td>
<td>Basis for Recommendations</td>
<td></td>
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<tr>
<td>Very Likely</td>
<td></td>
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<tr>
<td><strong>Limited evidence</strong></td>
<td></td>
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<tr>
<td>Limited - suggestive</td>
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<tr>
<td>Limited – no conclusion</td>
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<tr>
<td><strong>Strong evidence</strong></td>
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<tr>
<td>Substantial effect on risk unlikely</td>
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Obesity and cancer risk associations supported by convincing evidence

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Oesophagus (adenocarcinoma)</td>
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<td></td>
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<tr>
<td>Endometrium</td>
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<td>Gastric cardia</td>
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<td>Liver</td>
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<tr>
<td>Pancreas</td>
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<tr>
<td>Kidney (renal cell)</td>
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<tr>
<td>Meningioma</td>
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<tr>
<td>Multiple myeloma</td>
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<tr>
<td>Colon &amp; rectum</td>
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<tr>
<td>Gallbladder</td>
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<tr>
<td>Breast (postmenopausal)</td>
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<tr>
<td>Ovary</td>
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<tr>
<td>Thyroid</td>
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</table>
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

<table>
<thead>
<tr>
<th>Year</th>
<th>Exposure</th>
<th>Conclusions</th>
<th>Evidence Quality</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>2018</td>
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</table>

### 2018 Studies
- Mouth, Pharynx, Larynx 2018
- Nasopharynx 2017 (SLR)
- Oropharynx (Adenoid cystic carcinoma) 2016
- Oropharynx (Squamous cell carcinoma) 2016
- Lung 2017
- Stomach 2016
- Pancreas 2016
- Gallbladder 2015
- Liver 2015
- Colon 2017
- Breast Premenopause 2017
- Breast Postmenopause 2017
- Ovarian 2014
- Endometrium 2015
- Cervix 2017 (SLR)
- Prostate 2014
- Kidney 2015
- Bladder 2016
- Skin 2017 (SLR)
- Aerobic/cutaneous cancers (aggregated) 2011-2016

### Conclusions Key
- **Conclusively decreases risk**
- **Probable decreases risk**
- **Limited - suggestive decreases risk**
- **Substantial effect on risk unlikely**

### Exposure Group Key
- **Grains, vegetables, and fruit**
- **Other dietary exposures**
- **Meat, fish, and dairy products**
- **Physical activity**
- **Preservation and processing of foods**
- **Body fatness and weight gain**
- **Non-alcoholic drinks**
- **Height and birthweight**
- **Alcoholic drinks**
- **Lactation having been breastfed**

**Abbreviation:** SLR, systematic literature review.
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

- Secretariat
- CUP Panel
- ICL Team (SLRs)
- WCRF Network countries
- Peer reviewers
- Researchers from IARC (mechanisms)

- 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
Leveraging International Multidisciplinary Expertise to Improve Childhood Cancer Survivor Outcomes

Melissa M. Hudson, MD
Director, Survivorship Division
St. Jude Children’s Research Hospital
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.
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.
Evidence-Based Guidelines for Childhood Cancer Survivors: A Hybrid Model

**Guideline Design**

- **Evidence linking late effects with therapeutic exposures**
  - Allows identification of high-risk categories

- **Screening recommendations based on expert clinical experience**
  - Matches magnitude of risk with intensity of screening
Long-term follow-up guidelines
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
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

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Conclusions of evidence</th>
<th>I</th>
<th>IIA</th>
<th>IIb</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A High level of evidence</strong></td>
<td>Consistent evidence from well performed and high quality studies or systematic reviews (low risk of bias, direct, consistent, precise)</td>
<td>Strong recommendation based on high level of evidence</td>
<td>Moderate recommendation based on high level of evidence</td>
<td>Weak recommendation based on high level of evidence</td>
<td>Recommendation based on high level of evidence</td>
</tr>
<tr>
<td><strong>B Moderate/Low level of evidence</strong></td>
<td>Evidence from studies or systematic reviews with few important limitations</td>
<td>Strong recommendation based on moderate/low level of evidence</td>
<td>Moderate recommendation based on moderate/low level of evidence</td>
<td>Weak recommendation based on moderate/low level of evidence</td>
<td>Recommendation based on moderate/low level of evidence</td>
</tr>
<tr>
<td><strong>C Very low level of evidence</strong></td>
<td>Evidence from studies with serious flaws. Only expert opinion, or standards of care</td>
<td>Strong recommendation based on expert opinion</td>
<td>Moderate recommendation based on very low level of evidence Diverging expert opinions</td>
<td>Weak recommendation based on very low level of evidence Diverging expert opinions</td>
<td>Recommendation based on very low level of evidence Expert opinion</td>
</tr>
</tbody>
</table>

- **I** Strong recommendation to do
- **IIa** Moderate recommendation to do
- **IIb** Weak recommendation to do
- **III** Recommendation not to do
- **Benefits >> risk & burdens**
- **Benefits >> risk & burdens**
- **Benefits >> risks & burdens**
- **No benefit / Potentially harm**
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)
- 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, ≥ 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.

<table>
<thead>
<tr>
<th>Conditions most frequently identified by national health services and WHO to increase risk for a severe course of COVID-19</th>
<th>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</th>
</tr>
</thead>
</table>
| Heart disease, including but not limited to:  
• Heart failure requiring medication  
• History of myocardial infarction (heart attack)  
| Heart disease, including but not limited to:  
• Cardiomyopathy (heart muscle disease) following anthracycline therapy  
• Coronary artery disease following chest radiation |
| Chronic lung disorders, including but not limited to:  
• 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:  
• 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:  
• Anticancer treatment  
• Organ transplantation  
• Immune disorders

Conditions and/or use of drugs that affect immune system function, including but not limited to:  
• 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

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

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
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!

www.ighg.org