Opioid Cohort Consortium (OPICO)
to investigate the effects of regular opioid use on mortality
and on cancer development

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Outline

- Overview of the project and its aims
- Current status
- Progress made
- Feasibility study
- Plans for further funding
- Challenges and solutions
Global crisis of opioid use

- Thousands of deaths and billions in economic losses each year
- Long-term health consequences remain unknown
# Opioids Definition

- **Natural opioids (opiates):** opium and its natural derivatives
- **Semi-synthetic opioids:** synthesized in labs from natural opioids
- **Synthetic opioids:** synthesized in labs using the same chemical structures of natural opioids to mimic their effects

<table>
<thead>
<tr>
<th>Natural prescription opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine, Codeine, Thebaine, Powdered Opium, Opium syrup</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Semi-synthetic prescription opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzhydrocodone, Desomorphine, Diamorphine, Dihydromorphine, Dihydrocodeine, Etorphine, Ethylmorphine, Hydrocodone, Hydromorphone, Nalbuphine, Nalorphine, Nicomorphine, Oxycodone, Oxymorphone,</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Synthetic prescription opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfentanil, Alphaprodine, Alphacetylmethadol, Bezitramide, Buprenorphine, Butorphanol, Carfentanil, Dezocine, Dextromoramide, Dextropropoxyphene, Dihydroetorphine, Diphenoxylate, Dipipanone, DPDPE, Eluxadoline, Fentanyl, Ketobemidone, Levacetylmethadol, Levorphanol, Lofentanil, Meptazinol, Methadone, Methadyl acetate, Normethadone, Noscapine, Oliceridine, Papaveretum, Pentazocine, Pethidine (Meperidine), Piritramide, Phenazocine, Phenoperidine, Remifentanil, Sufentanil, Tapentadol, Thebaine, Tilidine, Tramadol</td>
</tr>
</tbody>
</table>
Scientific motivation

Opioids
used by 58 million (2018)

Opiates (mainly Opium)
used by 30 million (2018)

Human studies

2 Cohort
30 Case control

Association with at least 9 cancer types
Genotoxicity
Carcinogenic compounds

Experimental studies

Opioids
prescription opioids

Human studies

6 Registry data linkage

Association with several cancer types (lung, urogenital, liver)
Genotoxicity
Involvement in tumor initiation and progression

Experimental studies

Opium consumption classified by IARC Monographs into Group1 / Carcinogen to humans

Many limitations in the current evidence on opioid effects
Confounding effects and biases from linkage studies
No opioid use data in most cohorts
Limited number of opioid users in cohorts with opioid use data

Comprehensive consortium-based approach is needed
Overview of the Opioid Cohort Consortium (OPICO)

Grant support
- International Hundred K+ Cohort Consortium / Global Genomic Medicine Collaborative

Overarching aim
- To build a strong international resource for multidisciplinary scientific studies on the use of opioids and their long-term effects

Main exposure
- Use of natural opioids from questionnaire data
- Use of prescription opioids from medication questionnaire
- Use of prescription opioids from linkage to national medication dispensing records

Main outcomes
- Cancer analysis: diagnosis of any cancer type / digestive cancers / respiratory cancers / urinary tract cancers / brain cancer
- Mortality analysis: death from any cause / death from circulatory diseases / respiratory diseases / digestive diseases / cancer

Aims & Approach
- Organize data on opioid use from prospective cohorts
- Compile data on opioid use in cohorts through linkage to national records
- Assess the type, distribution, and extent of opioid use across diverse populations
- Determine the association of opioid use with cancer incidence and mortality
OPICO cohorts (n=1,266,247 participants)

- UK Biobank (n = 502,713)
- Constances cohort (n = 217,000)
- Generation Scotland (n = 24,000)
- Golestan (n = 50,045)
- Pars (n = 9,264)
- WHI (n = 93,676)
- PLCO (n = 58,895)
- EPIC (n = 100,000)
- PERSIAN (n = 172,894)
- 45 & UP (n = 37,760)
## Cohorts with medication data participating in OPICO

<table>
<thead>
<tr>
<th>Cohort Study</th>
<th>Participants (N)</th>
<th>Total opioid users N (%)</th>
<th>Medication data</th>
<th>Linkage source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Golestan cohort</td>
<td>50,045</td>
<td>8,519 (17.0%)</td>
<td>Questionnaire</td>
<td>N/A</td>
</tr>
<tr>
<td>PERSIAN cohort</td>
<td>172,894</td>
<td>21,557 (12.4%)</td>
<td>Questionnaire</td>
<td>N/A</td>
</tr>
<tr>
<td>45 and up cohort</td>
<td>37,760</td>
<td>8,603 (22.7%)</td>
<td>Linkage</td>
<td>PBS (Australia)</td>
</tr>
<tr>
<td>UK Biobank cohort</td>
<td>502,713</td>
<td>25,864 (5.1%)</td>
<td>Questionnaire</td>
<td>N/A</td>
</tr>
<tr>
<td>Scottish Family Health Study</td>
<td>24,000</td>
<td>2,082 (8.6%)</td>
<td>Linkage</td>
<td>SPI (Scotland)</td>
</tr>
<tr>
<td>Pars cohort</td>
<td>9,264</td>
<td>818 (8.8%)</td>
<td>Questionnaire</td>
<td>N/A</td>
</tr>
<tr>
<td>PLCO Cancer Screening Trial</td>
<td>58,895</td>
<td>25,187 (42.7%)</td>
<td>Linkage</td>
<td>Medicare (USA)</td>
</tr>
<tr>
<td>Women Health Initiative (WHI)</td>
<td>93,676</td>
<td>8,430 (8.9%, estimated)</td>
<td>Questionnaire</td>
<td>N/A</td>
</tr>
<tr>
<td>EPIC</td>
<td>100,000</td>
<td>4,000 (4%, estimated)</td>
<td>Linkage</td>
<td>Insurance Plan</td>
</tr>
<tr>
<td>CONSTANCES</td>
<td>217,000</td>
<td>8,680 (4%, estimated)</td>
<td>Linkage</td>
<td>CNDS (France)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1,266,247</strong></td>
<td><strong>113,740 (8.9%)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Progress since October 2020

• Ethical approval (IARC Ethics Committee, 4 Local Committees)
• Submitted formal applications for data use (7 of 10 cohorts)
• New cohorts joined the OPICO (2 cohorts)
• Harmonization protocols (in collaboration with 3 Pharmacoepidemiologists, 6 cohort representatives, 2 cancer epidemiologists, 2 clinicians, 1 statistician, 1 data manager)
Feasibility of compiling opioid use data in cohorts with linkage

Collaboration with:
• Cancer Council NSW, Australia (Prof. Canfell, Dr. Weber, Dr. Sarich)
• University of NSW Sydney (Prof. Pearson)

Australian 45 and Up Study
• Recruited 267,153 adults (2006 – 2009) / General population of NSW

Linked to the Pharmaceutical Benefits Scheme (PBS)
• Australia’s national drug subsidy program
Considerations when compiling opioid use data in cohorts with linkage (1)

Defining *time for estimating opioid exposure from linkage* records
- To be able to **harmonize** the linkage-based data with questionnaire-based data
- To **minimize the possible misclassifications** in defining the exposure
- Most questionnaire-based cohorts have info about lifelong opioids use
- Linkage-based cohorts only have info for a specific period of individual’s life span

**Time defined:** from 12 months before recruitment to 1 months after recruitment
Considerations when compiling opioid use data in cohorts with linkage (2)

Identification of the:

- policy of medication dispensing / subsidy program
- pricing of opioids at the time of cohort recruitment

Reasons:

- To minimize the possible misclassifications
- To identify the inclusion and exclusion criteria

Example from the Feasibility Study:

Australia → co-payment program for prescriptions
- different thresholds for ‘concessional beneficiaries’ vs. ‘general beneficiaries’

In 2008 (45 and up recruitment period):
- Co-payment for ‘concessional beneficiaries’ = $5.00
- Co-payment for ‘general beneficiaries’ = $31.30.
- Many opioid medications in Australia are priced $20 - $25
- These medications were not recorded in the linked national data source (PBS database) when dispensed to general beneficiaries.

- Only 37,760 participants who were concessional beneficiaries at recruitment were included

- We compiled opioid use for all included participants, of whom 8,603 (22.8%) were users of opioids
Plans for more funding support

- R01 grant application to the NIH – planned for early June
- Local funders (INCA in France, etc.)
Challenges and solutions

Challenge:
• Some included cohorts cannot send their linked data to IARC due to their national regulations for data protection and security

Solution:
• Using an additional distributed analysis model
• Analyze the data from these cohorts using the corresponding secure platform
• Perform meta-analyses using the aggregated outputs from these cohorts
Required data from cohorts to participate in OPICO

- **Use of opioids**
  - questionnaires
  - data linkage to national records

- **Outcomes at follow-up**
  - vital status
  - cause of death
  - diagnosis of cancer
  - type of cancer

- **Dates or equivalent follow-up times**

- **Demographics**
  - age
  - sex
  - ethnicity
  - socioeconomic indicator

- **Smoking cigarettes**

- **Alcohol intake**

- **Chronic health conditions**
  - Diabetes
  - Hypertension
  - inflammatory conditions

**IARC / Genomic Epidemiology Branch**

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Acknowledgement

International agency for Research on Cancer (France)
• Paul Brennan
• Hilary Robbins
• Pietro Ferrari

Tehran University of Medical Sciences (Iran)
• Reza Malekzadeh
• Hossein Poustchi

Morgan State University (USA)
• Farin Kamangar

National Cancer Institute (USA)
• Neal Freedman

Cancer Council Australia (Australia)
• Karen Canfell
• Marianne Weber
• Peter Sarich

The University of NSW Sydney (Australia)
• Sallie-Ann Pearson
• Louisa Degenhardt

University of Edinburgh (Scotland)
• Archie Campbell

Australian National University (Australia)
• Emily Banks

Fred Hutchinson Cancer Research Center (USA)
• Lesley Tinker

INSERM (France)
• Marcel Goldberg
• Sofiane Kab

Wake Forest University (USA)
• Chris Gillette
• Mara Vitolins

Sax Institute (Australia)
• Kerrin Bleicher