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Book of Abstracts

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Characterising pulmonary carcinoids through molecular analyses within the lungNENomics project

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Introduction

Pulmonary carcinoids are well differentiated low to intermediate grade lung neuroendocrine tumours (LNETs), that belong to the group of lung neuroendocrine neoplasms which also include highly aggressive lung neuroendocrine carcinomas (LNECs). Carcinoids are further divided into atypical and typical, based on mitotic count and presence of necrosis. Although pulmonary carcinoids show relatively good prognosis in comparison to carcinomas, metastatic disease and relapse do occur. In a previous study we introduced the concept of molecular groups of carcinoids: A1, A2, and B, which, importantly, contained a mixture of the two histological types. Additionally, we identified six tumours, termed supra-carcinoids, that displayed genuine carcinoid-like morphology, but had clinical and molecular characteristics of LNECs. The focus of our work is to better understand the biological and clinical characteristics of these molecular groups of carcinoids.

Methods

To address this aim we have designed the lungNENomics study, an international cohort of over 250 cases of pulmonary carcinoids, with clinical data and central pathology review, as well as whole-genome sequencing, RNA sequencing, DNA methylation array, and digital spatial profiling data. These data have been combined with previously published LNET data to perform integrative analysis using multi-omics factor analysis (MOFA), resulting in a molecular map of lung neuroendocrine neoplasms for exploration. To these data we applied the evolutionary theory of task specialisation (ParetoTI) to identify and characterise distinct archetypes, i.e. molecular subtypes, of LNETs.

Results

Multi-omics integration analysis of 319 carcinoids resulted in a molecular map forming a distinctive tetrahedron. ParetoTI theory identified four tumour archetypes within the tetrahedron, corresponding to the three previously reported molecular groups, and the fourth enriched for the aggressive supra-carcinoids. Each archetype was characterised by specific clinical, genomic, and microenvironmental features.

Conclusion

While progress has been made in recent years in the characterisation of pulmonary carcinoids, little is known about the underlying biology or developmental origins of these molecular groups, hampering efforts to identify predictive markers and suitable therapeutic options. The lungNENomics project aims to address these important questions, and will continue to improve the biological understanding of this exceedingly rare and understudied disease.

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Socioeconomic status and lung cancer incidence: An analysis of 19 prospective cohorts from 4 continents

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Background: In some settings, lung cancer incidence appears higher among disadvantaged groups. We analyzed the harmonized database of the Lung Cancer Cohort Consortium (LC3) to assess the relationship between socioeconomic status and lung cancer incidence across different world regions.
Methods: We analyzed 19 prospective cohorts from 16 countries in North America, Europe, Asia, and Australia. Separately for never or currently/formerly smoking participants, we estimated the association between educational level (as a proxy for socioeconomic status, modeled in 4 categories) and incident lung cancer using Cox proportional hazards models. Models were adjusted for age, sex, and where applicable, smoking duration, cigarettes per day, and time since cessation.
Results: Among 2.4 million participants, 58,785 developed lung cancer (median follow-up 12.6 years). Among current/former smoking participants, higher educational level was associated with decreased lung cancer incidence in nearly all cohorts. By world region, this association was similar for North America (HRpooled=0.88, 95%CI:0.87-0.89), Europe (HRpooled=0.89, 95%CI:0.88-0.91), and Asia (HRpooled=0.91, 95%CI:0.86-0.96), but attenuated in the Australian Melbourne Collaborative Cohort Study (HR=1.02, 95%CI:0.95-1.09). The association with education was strongest for squamous cell carcinoma and weakest for adenocarcinoma ($p<0.001$ separately in current and former smoking participants). Among never smoking participants, there was no statistically significant association between education and lung cancer incidence in any cohort (all p-trend>0.05), except for the US Southern Community Cohort Study (HR=0.75, 95%CI: 0.62-0.90).
Conclusion: Among cohort participants from 16 countries, higher socioeconomic status showed a strikingly consistent association with decreased risk of lung cancer among currently/formerly smoking individuals, but not never smoking individuals.

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Socioeconomic position and risk of cervical cancer in the Nordic countries: results from the Nordic Occupational Cancer Study (NOCCA)

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Background: The Nordic countries have benefited from steep declines in cervical cancer incidence rates, as a consequence of the implementation of nationwide screening programmes. However, it is not clear whether all social groups have equally benefited from these preventive services. We provided an assessment of the magnitude and temporal trends of cervical cancer incidence by socioeconomic position (SEP), as measured by occupational group, across four Nordic countries (Denmark, Norway, Finland, and Sweden) using population-based data from the Nordic Occupational Cancer Study (NOCCA).
Methods: We computed age-standardized incidence rates (ASRs) of cervical cancer per 100,000 person-years truncated at ages 50–69 years by SEP during 1961–2005. ASR ratios and differences for low_vs_high SEP levels we estimated. Using Poisson regression models, we estimated the relative risks (RRs) and corresponding 95% confidence intervals of cervical cancer for SEP levels in the Nordic countries separately and combined for the period 1991–2005.
Results: There was a general decline in the incidence rates of cervical cancer among all SEP groups. Rates were generally higher among lower SEP groups in all countries, with a social gradient consisting of a progressive increase in risk as SEP decreased. RRs for lowest vs highest SEP in the most recent period ranged from 1.33 in Sweden to 1.76 in Denmark and was 1.42 when the four selected Nordic countries were pooled together. The ASR difference decreased over time in all selected countries, ranging from 31.1/100.000 in Sweden to 4.6/100.000 in Denmark.
Discussion and Conclusion: Despite the general declining trends, socioeconomic inequalities in cervical cancer remained in the most recent study period, this suggesting that not all women benefited equally from screening. Low SEP women still carry the highest risks of the disease, everywhere in the Nordic countries. Efforts should be continued to ensure broad access to preventive services.

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Preventable and treatable avoidable cancer deaths in 185 countries for 34 cancer sites

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Introduction: Disparities in cancer-specific incidence, mortality, and survival exist worldwide. Avoidable deaths have recently been used to estimate the burden of disease and as a measure of the inequality between countries.
Methods: Five-year net survival estimates were obtained from the SURVCAN-3 project and from a review of the literature for 34 cancer sites. Survival estimates were then obtained using a regression model versus HDI level for 185 countries. Age-specific survival estimates were estimated using patterns seen in the available individual patient data. Attributable fractions for five major risk factors across all 34 cancer sites were included to estimate preventable avoidable deaths. We then estimated the risk factor preventable and treatable avoidable deaths for 2020 scaled to IARC's GLOBOCAN incidence estimates. Analysis was done by country, region, HDI, cancer site and globally.
Results: In total 3·1 million (34·1%) of cancer deaths are potentially risk factor preventable and 1·3 million (14·5%) treatable avoidable deaths. In total, 4·4 million (48·6%) cancer deaths are avoidable out of an estimated 9·1 million deaths through prevention and treatment improvements There are large disparities in the number and proportion of avoidable deaths globally. A significant proportion of avoidable deaths can be found across country income levels, but low- and middle-HDI countries are disproportionately affected, having large total proportions of avoidable deaths. The total proportion of avoidable deaths internationally range from 28·9% in Sweden to 70·6% in Uganda.
Discussion/ Conclusion: Our analysis provides a detailed mapping of global avoidable cancer death disparities in treatment and risk factor prevention and can be used to indicate where resources should be allocated. Prevention should be a priority, but as its impact can take decades, global efforts are also needed to address present screening and treatment inequalities

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Incidence of childhood cancer in Latin America and the Caribbean: coverage, patterns and time trends

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Introduction: Global childhood cancer control requires high-quality information, which is lacking particularly in low- and middle-income countries.
Methods: We described geographical variations in the period 2001-2010 and incidence trends over the period 1993-2012 in the populations under the age of 20 years of the countries in Latin America and the Caribbean (LAC) using the database of the third volume of the International Incidence of Childhood Cancer study containing comparable data. Age-specific incidence per million person-years (ASR) was calculated for population subgroups and age-standardised (WSR) using the world standard population.
Results: Overall, 36 744 unique cases were included in this study. The overall WSR in age 0-14 years was 132.6; the most frequent being leukaemia (WSR 48.7), CNS neoplasms (WSR 23.0), and lymphomas (WSR 16.6). The overall ASR in age 15-19 years was 152.3 with lymphoma ranking first (ASR 30.2). Incidence was higher in males than in females. Incidence was higher in South America compared with Central America and the Caribbean. Compared with combined global data, LAC had higher incidence of lymphomas and the other and unspecified tumours, and lower incidence of CNS neoplasms, neuroblastoma, renal tumours, soft tissue sarcomas, and carcinomas with other epithelial neoplasms. Overall incidence increased by 1.0% per year (95%CI: 0.6,1.3) over 1993-2012.
Conclusion: The observed patterns provide a baseline to assess the status and evolution of childhood cancer occurrence in the region. Population coverage with high-quality registries should increase to provide representative and timely data in support of childhood cancer control in LAC.

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Obesity and endometrial cancer: using proteomics to identify underlying mechanistic pathways

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Background
Obesity is a major risk factor for endometrial cancer (EC), but the underlying mechanisms are not well understood. Using proteomics and causal mediation analysis, we examined 155 circulating protein markers in 624 cases and 624 matched controls in a case-control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.
Methods
Anthropometric measures and blood samples were collected at cohort recruitment. Protein levels were measured in pre-diagnostic plasma samples using Proximity Extension Assay technology (Olink Bioscience AB, Sweden) and reported in Normalised Protein eXpression (NPX), which correlates to 2-fold increase in protein concentration. The body mass index (BMI)-protein associations were estimated among controls using multivariate linear regression. The protein-EC associations were estimated using conditional multivariate logistic regression including adjustment for BMI. For each protein associated with both BMI and EC, we decomposed the total effect of obesity [BMI ≥30kg/m2 vs <25kg/m2] on risk of EC into natural indirect effect (NIE) mediated by the protein and natural direct effect, and calculated the proportion mediated.
Results
IL6 [odds ratio (OR) per NPX = 1.32 (95% confidence interval (CI) = 1.05–1.65)], HGF [1.48 (1.06–2.07)], PIK3AP1 [1.22 (1.00–1.50)] and CLEC4G [1.52 (1.00–2.32)] were positively associated with risk of EC, and HSD11B1 [0.67 (0.49–0.91)], SCF [0.68 (0.49–0.94)], and CCL25 [0.80 (0.65–0.99)] were inversely associated with risk. Of these, IL6 [NIE OR = 1.19 (1.09–1.31); proportion mediated = 15%], HSD11B1 [1.25 (1.15–1.36); 19%], HGF [1.10 (1.03–1.18); 8%], and SCF [1.06 (1.00–1.11); 5%] could represent mediators of the effect of obesity on risk of EC [total OR = 3.17 (2.68–3.75)].
Conclusion
Protein markers related to inflammation (IL6, PIK3AP1, HGF), cortisol-cortisone conversion (HSD11B1), immunoregulation (CLEC4G, CCL25), and angiogenesis (HGF) could influence risk of EC. Some of these markers may represent pathways involved in mediating the effect of obesity on risk of EC, and may be potential targets for cancer prevention in women with obesity.

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Genetic susceptibility and fine-mapping of human leukocyte antigen loci in head and neck cancer

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Head and neck cancer (HNC) is the sixth most common cancer worldwide originating from oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx causing 444,347 deaths in 2020. Although alcohol, tobacco, and human papillomavirus (HPV) are major risk factors for HNC, only a small fraction of high-risk individuals developed HNC implying a crucial role of genetic susceptibility in the disease etiology.
In 2014, Genome-Wide Association Study (GWAS) was performed with 2,398 individuals with laryngeal squamous cell carcinoma cases and 2,804 cancer-free controls from Chinese populations, and identified a novel susceptibility loci in complex human leukocyte antigen (HLA), which plays crucial role in immune response. Subsequently, two separate GWASs has been conducted and consistently identified locus in HLA region in association with HNC. Recently, this signal of HLA region was confirmed to be specific to HPV(+) in oropharyngeal cancer suggesting the role of HLA variants in the immune pathogenesis. Despite these significant findings, it is important to note that imputed data for the HLA locus may pose challenges due to high level of linkage disequilibrium and polymorphism. Thus, fine-mapping studies for this region are essential to uncover the causal variants. Additionally, the limited sample size could potentially impede the ability to detect the association signal. Therefore, in this study, we are investigating the relationship between HNC and HLA loci using an advanced fine-mapping approach and a significantly larger dataset.
In this study, we collect samples from different studies of 19,749 HNC samples from oral cavity, oropharynx, hypopharynx, and larynx subsites, and 38,877 non-HNC control. The raw genotype data was filtered with stringent threshold to obtain only high-quality variants. HLA imputation was performed with Michigan HLA imputation server with recent multi-ethnic HLA imputation panel. Post-imputation QC was applied to obtain high-quality imputed variants. The associations between the variants and HNC were evaluated by adjusting for population structure, imputation batch and gender. Novel HLA loci associated with HNC are expected to be discovered in this study.

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Mutational signatures of ethanol and acetaldehyde in experimental models

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1- Introduction

Alcohol use is associated with cancer development at various anatomical sites including oral cavity, and is responsible for ~13% of all cancers worldwide. Despite strong epidemiological evidence, the mechanisms of ethanol carcinogenicity in the oral cavity remain unclear. Ethanol's main metabolite acetaldehyde (AcA) may play a crucial role in head and neck cancers by forming covalent DNA adducts that can be mutagenic and may contribute to cancer development. We hypothesized that the role of AcA in alcohol-related oral cancer is based on the formation of specific mutational signature(s) which can be identified in suitable experimental systems.

2- Methods

Using a multi-system experimental approach, we aimed to characterize the mutagenic modes of action of ethanol and AcA at the genome scale level. Firstly, we analyse oral tumour tissues derived from ethanol- and AcA-driven carcinogenesis studies in longitudinally exposed rats, by using whole genome-sequencing (WGS). The animal study is complemented by in vitro chronic AcA exposure of non-tumour hTERT-immortalized oral cell lines, followed by clonal expansion and WGS. Mutational signatures are identified in the genomes of the rat tumours and exposed cells, and are matched with the pre-mutagenic DNA lesions identified by LC-MS/MS DNA adductomic analysis of the cell exposure models.

3- Preliminary results

Oral squamous cell carcinomas collected from the cheeks of rats exposed to 10% ethanol in drinking water have been sequenced at genome scale. We observed mutation patterns (COSMIC signature SBS17) consistent with a possible role oxidative DNA damage processes linked to inflammation and cell keratinization. In the rat oral tumours analysed thus far, we have not detected the COSMIC signature SBS16 putatively linked to alcohol drinking.

4- Next steps

The in vivo findings are being extended to additional cancer sites, including the zymbal gland and forestomach, where ethanol/AcA exposure-associated tumour formation had been observed. The analysis of AcA exposure impact on the cell line genomes is underway and will be integrated with AcA-induced DNA adductome analyses.
We anticipate that this study will improve our understanding of the mechanisms by which ethanol and AcA induce the cancer formation, to ultimately support cancer prevention measures.

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The impact of suspected promoters on the clonal architecture of normal tissues from RCC patients

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Cancer is thought to result from the gradual accumulation of genetic mutations in a cell. Environmental and lifestyle exposures to mutagenic agents and endogenous processes may cause mutations in normal cells. Collections of these cells (clones) harbouring driver mutations can exist in different tissues without ever transforming into cancer. However, recent evidence suggest that non-mutagenic promoting stimuli can drive phenotypically normal clones toward malignant transformation.

In the case of renal cell cancer (RCC), high body-mass index (BMI), tobacco smoke and hypertension have been identified as factors associated with an increased risk to develop cancer, however, no evidence of a mutagenic effect of these factors has been found. PROMINENT will try to determine how specific risk factors and exposures influence the clonal architecture of normal tissues.

The International Agency for Research on Cancer (IARC) are unique for their large collection of normal human tissues from cancer patients. This collection includes nearly 1000 renal tissues from 11 countries, ranging from low to high RCC incidence. Accompanying these samples are detailed information on the individuals'lifestyles and exposures, including information on suspected promoters associated with higher RCC risk. IARC will select normal tissue samples from 100 RCC cases to be characterised using different genomic and spatial-omics methodologies. The Institute for Research in Biomedicine (IRB) will perform duplex sequencing utilising a panel of 9 known RCC driver genes. This analysis should accurately identify mutations in normal tissues and reveal their clonal architecture.

Preliminary results have revealed clones possessing mutations in the panel of 9 driver genes analysed. The sequencing of more cases will provide power to explore if different risk profiles based on the exposure to suspected promoters could have an impact on the clonal structure of normal renal tissues. Additionally, geographical trends could emerge to link clonal architecture to higher-risk regions and possible region-specific exposures. This could further elucidate the non-mutagenic factors promoting RCC onset in high incidence countries.

Through understanding the link between exogenous factors and RCC risk, the promoting stimulus causing malignant transformation could be identified, leading to tools to for the prevention of this cancer.

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The impact of opium use prevention on future cancer incidence in Iran

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Background and objectives: We undertook this study to estimate the number of cancer cases that could be prevented through decreasing the prevalence of opium use by 2035 in Iran, where 40% of the world opium is consumed.
Methods: The projection of the population attributable fraction (PAF) of cancers due to opium use was calculated using four data sources including (i) national cancer incidence, (ii) age- and gender-specific prevalence of opium use, (iii) relative risk of cancers associated with opium use, and (iv) annual percentage change in the incidence rates of cancers in Iran. Age-specific PAFs were estimated for males and females for overall cancers and for opium-related cancers using Levin's formula. Opium-related cancers were cancers in the lung, larynx, bladder, oesophagus, stomach, pancreas, and pharynx. The number of potentially preventable cancer cases in each opium prevalence scenario was calculated by subtracting the numbers of attributable cancers in each year of the study period based on current prevalence of opium use from the number of attributable cancers in the alternative scenarios in that specific year.
Results: We estimated until 2035 a total of 3,001,421 new cancer cases will be diagnosed in Iran, with 905,207 (30.1%) of these being opium-related cancers. With the continuation of the current prevalence of opium use (overall = 5.6%; among men = 10.0%; among women = 1.2%), using opium will lead to the development of 111,150 new cancer cases (3.9% of all cancers) by 2035. The proportion of preventable opium-related cancers was 12.7%. Reducing opium use prevalence by 50%, 30%, and 10% could potentially prevent 9,063, 28,218, and 49,096 of the total incident cancers by 2035. We estimate that reducing opium use prevalence will have the highest impact on preventing cancers of the larynx (34.0% of the total incident laryngeal cancers), bladder (20.2%) and lung (13.0%).
Conclusion: In this study for the first time, we quantified the burden of using opium, a newly identified carcinogen, on future cancer incidence. Our results highlight the significant benefits that can be achieved through effective cancer prevention policies targeting opium use in the Iranian population.

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Childhood brain tumours: a systematic review and meta-analysis of risk factors

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[Abstract suppressed at the request of the author]

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Associations of smokeless tobacco (snuff-use) with site-specific cancer risk in adult black South African women: findings from the Johannesburg Cancer Study

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INTRODUCTION: In South Africa, traditional and social practices influence the use of smokeless tobacco (SLT) products, particularly in women. SLT use is an established carcinogen, but few studies have been conducted in African populations with their specific exposure routes, ages and intensity. We investigated SLT use and the risk of site-specific cancers among women in Johannesburg, South Africa.

METHODS: Among the 15,703 adult black females diagnosed with cancer in the Johannesburg Cancer Study, we designed case-control studies across a range of cancer outcomes. We analysed risks of cancers previously found to have sufficient evidence of an association with SLT use according to the IARC monographs - namely lip oral cavity and pharynx (n=259), oesophagus (n=548) and pancreas (n=81) - and other cancers with insufficient association with SLT use (n>50). A constant control group (n=1,179) was used throughout, made up of patients with cancers that have limited or no association with SLT/tobacco. The relative risk of cancer due to snuff use was estimated form logistic models to give multivariate-adjusted odds ratios.

RESULTS:26% of females ever used snuff, with an average prevalence of 16% for women <40 years rising to 32% at ages 60+. Ever versus never snuff use was not clearly associated with cancer of the oesophagus (OR 1.13; 95%CI: 0.89 - 1.43), lip oral cavity and pharynx (OR 0.71 (0.49 - 1.03)) nor pancreatic cancer (OR 0.89 (0.52 - 1.49)). Ever snuff use was associated with an increased risk of cervical cancer (OR 1.17 (1.00 - 1.36), bone cancer (OR 1.97 (1.03 - 3.81)) and eye and adnexa cancer (OR 2.28 (1.18 - 4.40)).

CONCLUSION: Snuff use may increase the risk for specific cancers. Further confirmatory work with more detailed exposure timing, intensity and routes, is needed to ascertain the effects of snuff use on cancer risk with a particular focus on cervical, bone, eye and adnexa cancer.

Keywords: smokeless tobacco use, snuff use, cancer, South Africa, Johannesburg cancer study

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Perceptions towards the adoption of tobacco-related recommendations of the European Code Against Cancer (4th ed.) among the European Union population: a qualitative study.

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Background: Cancer is a major public health problem. Four million new cancer cases are diagnosed annually in Europe; of which, 40% could be prevented. The European Code Against Cancer (ECAC) is a health education tool aimed at raising awareness about evidence-based actions to prevent cancer. It reports 12 recommendations to reduce individuals'cancer risk. Our aim was to explore perceived barriers towards the adoption of cancer prevention actions recommended by the ECAC in 7 European Union (EU) countries (Croatia, France, Germany, Ireland, Poland, Portugal, Spain).
Methods: The COM-B model of behaviour change was used as a framework for the design and analysis of the study since it identifies factors (capability, opportunity, motivation) that need to be present for any behaviour to occur. We designed an exploratory research qualitative study by means of in-depth semi-structured interviews among adults with no previous cancer diagnose. Participants were selected using a quota sampling strategy according to sex, age and education level (18 profiles/country). Interviews were conducted in participants'native language by trained researchers. We conducted a thematic content analysis to identify common topics.
Preliminary results: Most participants were aware of all ECAC recommendations, except for radon; but did not know how to put them into practice nor where to find information. The main barriers to adopt lifestyle-related recommendations were having an addiction to quit smoking, lack of skills to be physically active or breastfeed (capability); lack of time to exercise or cook, lack of financial resources, cultural norms and peer pressure (opportunity). Barriers for other risk factors included lack of knowledge about work carcinogens or radon, lack of control of the exposure since it depends on others'diligence (e.g., employer) (capability). Finally, barriers to participate in vaccination and screening programs were personal beliefs (e.g., anti-vaccines movement) (capability), living in rural areas, and lack of quality and saturation level of national health system (opportunity).
Conclusions: Understanding how the ECAC recommendations are perceived by EU citizens and the barriers they encounter to take action to reduce their cancer risk is key to promote adoption of the recommendations and improve supportive societal structures to overcome these barriers.

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Antibodies against high-risk human papillomavirus proteins as markers for noncervical HPV-related cancers in a black South African population, according to HIV status.

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Human papillomavirus (HPV) proteins may elicit antibody responses in the process towards HPV-related malignancy. However, HPV seroepidemiology in noncervical HPV-related cancers remains poorly understood, particularly in populations with a high prevalence of human immunodeficiency virus (HIV). Antibodies against E6, E7 and L1 proteins of HPV16 and HPV18 were measured in sera of 535 cases of noncervical HPV-related cancers (anal (n=104), vulval (n=211), vaginal (n=49), penile (n=37) and oropharyngeal (n=134)) and 6,651 non-infection-related cancer controls, from the Johannesburg Cancer Study that recruited Black South African with newly diagnosed cancer between 1995 and 2016. Antibody response was evaluated using a glutathione S-transferase-based multiplex serology assay. Logistic and Poisson regression models were used to calculate adjusted odds ratios (aOR) and prevalence ratios (aPR) and 95% confidence intervals (CI) in cases versus controls. HPV16 E6 was strongly associated with noncervical HPV-related cancers: anal (females (aOR=11.50;95%CI:6.0-22.2), males (aOR=10.12;95%CI:4.9-20.8), vulval (aOR=11.69;95%CI:7.9-17.2), vaginal (aOR=10.26;95%CI:5.0-21), penile (aOR=18.95;95%CI:8.9-40), and oropharyngeal (females (aOR=8.95;95%CI:2.9-27.5), males (aOR=3.49;95%CI:1.8-7.0)) cancers. HPV16-E6 seropositivity ranged from 24.0% to 35.1% in anal, vulval, vaginal and penile cancer but was significantly lower (11.2%) in oropharyngeal cancer. After adjustment for HIV, prevalence of which increased from 22.2% in 1995-2005 to 54.1% in 2010-2016, HPV16 E6 seropositivity increased by period of diagnosis (aPR for 2010-2016 versus 1995-2006=1.84;95%CI:1.1-3.0). Assuming HPV16 E6 seroprevalence reflects HPV attributable fraction, the proportion of certain noncervical-HPV-related cancers caused by HPV is increasing over time in South Africa. This is expected to be driven by the increasing influence of HIV

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Modelling the Impact of Even Faster: HPV vaccination and HPV-based screening for rapid elimination of HPV infection

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[Abstract suppressed at the request of the author]

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A framework for evaluating the biologic pathways linking dietary patterns with colorectal cancer

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Introduction: Colorectal cancer (CRC) is a significant public health issue, both in terms of incidence and mortality. Lifestyle, particularly diet, is a crucial factor in the development of this cancer. The Global Cancer Update Programme (CUP Global) by World Cancer Research Fund International evaluates how diet, nutrition, physical activity, and body weight affect cancer risk and survival. Within CUP Global, we developed a framework for a systematic evaluation of the mechanistic evidence linking dietary patterns (DPs) with CRC.
Methods: To achieve this goal, our approach involved identifying intermediate phenotypes (IPs) between DPs and CRC to gain a better understanding of the biological processes that underpin the associations between these two components.
Preliminary Results: The designed framework applied a two-stage approach: first, using expert knowledge in combination with automated tools we identified a list of main potential biological processes and their associated IPs linking DPs to CRC. Second, we performed systematic literature reviews of human studies to evaluate the associations between DPs and IPs, and between IPs and CRC. If appropriate, specific questions may be answered by conducting additional literature reviews of experimental studies.
Next step: This project will produce a framework for a systematic evaluation of mechanistic research to support causal associations between DP and CRC.

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European commission initiative on cervical cancer (EC-CvC)

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Introduction:
The European Commission (EC) has supported the development of best practice guidelines and quality assurance benchmarks for cervical screening since 1993. These guidelines have contributed to improving coverage and quality of screening in Europe. However, guidelines need to be updated to address new screening methods, socio-demographic changes and growing inequalities in access to screening. In addition, a novel integrated and patient-centered quality assurance (QA) scheme will be included to ensure better care in key quality domains and covering primary, secondary, and tertiary prevention with a focus on their connection.

Methods:
The EC Initiative on Cervical Cancer (EC-CvC) follows a precise methodological framework for the integrated development of the European clinical practice guidelines and the cervical cancer QA scheme which is guided by Guidelines International Network standards.
A multidisciplinary team of experts will evaluate systematic reviews to establish a care pathway, map priority healthcare questions and identify quality aspects using visual maps and evidence tables. Healthcare questions will be rated, ranked and prioritised. Then each priority question will be investigated by systematic review, evaluated by a sub-group and the working group who will try to reach a guideline recommendation that is clear and based on scientific evidence of benefits; harms; patient preferences, equity and costs. The QA scheme will be developed in parallel with the incorporation of quality indicators, performance measures, and performance indicators integrated into guideline development.

Results:
The key outcomes of the EC-CvC are the development of the European clinical practice guidelines for cervical cancer prevention (from vaccination, to screening and treatment of pre-cancerous lesions), and a corresponding European QA scheme covering the entire care pathway including primary to tertiary prevention.

Conclusion:
Our goal is to help European countries achieve the Beating Cancer Plan and WHO targets while addressing existing inequalities in cancer distribution and evaluating the new methods for screening that are available. The EC-CvC aims to reduce incidence and morbidity from cervical cancer in Europe by providing evidence-based guidelines and quality standards for screening.

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Reconstructing patterns of human papillomavirus age-specific prevalence in Europe

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Introduction
Age-specific human papillomavirus (HPV) prevalence data are crucial for stakeholders to predict the future impact of public health policies. However, in the European Union (EU), the availability of this data is heterogenous across countries (and sometimes missing) therefore evaluating the impact of HPV vaccination or HPV-based screening can be challenging. This study reviewed type- and age-specific HPV prevalence data in the EU and identified clusters of countries sharing similar patterns to fill in the needed missing information on HPV prevalence.
Methods
Publications used for our analysis were selected in two steps. First, we systematically reviewed studies from 2009 to 2022 assessing type- and age- specific HPV prevalence in normal or general population, in EU countries. A second search, for countries without recent data, was conducted for papers published prior to 2009. The studies identified were then selected using a quality algorithm, assessing the sample population, and the availability of the aggregated age-prevalence data. Finally, model-based clustering methodology was applied to group countries with similar HPV16 trajectories (in 2 to 4 typical groups) accounting for statistical heterogeneity. The final cluster was selected according to BIC criteria (adequacy of data) and the epidemiological relevance of the clusters obtained.
Results
A total of 28 studies were included, representing 20 EU countries and 467 704 women. Overall, prevalence trajectories were similar across European countries. The optimal cluster selection produced 3 typical patterns which were mainly differentiated by varying HPV prevalence rates at age 20.
Conclusion
The findings of our study showed that the level of heterogeneity in the trajectories of age-specific HPV16 prevalence across Europe was limited: EU countries could be clustered into 3 mains categories based on their similar HPV age-specific prevalence trajectories differing mainly in magnitude. These trajectories can be used to model typical EU countries, and fill gaps for countries without HPV age-prevalence information using similar geographical or sexual behaviour data. Although good quality HPV type-specific prevalence surveys are crucial for informing cervical cancer control strategies, our results provide the missing information for EU countries to evaluate the impact of cancer prevention policies.

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Occupational exposure to heavy metals and welding fumes and testicular germ cell tumours risk in a French case-control study

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Introduction
Testicular cancer is the most frequent malignancy in young men in industrialized countries with an increasing incidence, and its aetiology remains largely unknown. An association with occupational exposure to heavy metals (HMs) and welding fumes (WFs) has been suggested in the literature but with inconsistent findings, most likely due to methodological exposure assessment limitations. We investigated the role of occupational HMs and WFs exposures on the risk of testicular germ cell tumours (TGCT) in the TESTIS study.

Methods
The French nationwide case-control study TESTIS was conducted between 2015 and 2018 among men aged 18-45 years old and included 454 cases and 670 controls frequency-matched on year of birth and hospital centre. Questionnaire-based data were collected regarding subjects'occupational histories. The INTEROCC job-exposure matrix was then applied to the subjects' jobs coded according to ISCO-68, to assign individual occupational exposure to five selected HMs (lead, iron, cadmium, chromium, nickel) and WFs. Odds ratios and 95% confidence intervals (OR [;]) were estimated using conditional logistic regression models adjusted for sibship size, being born from multiple pregnancies, personal history of testicular trauma, family history of TGCT, family history of cryptorchidism and exposure to solvents.

Results
The prevalence of occupational exposure to at least one of the HMs and WFs was 30.4% among cases and 24.6% among controls. Heavy metals co-occur largely in occupational settings; Cramer's V statistics showed correlations between 0.68 and 1.0. OR for ever being occupationally exposed to iron was (OR=1.57 [1.07 ; 2.30]), and for welding fumes (OR=1.54 [1.05 ; 2.27]), nickel (OR=1.56 [1.06 ; 2.28]), lead (OR=1.32 [0.93 ; 1.86]), cadmium (OR=1.28 [0.87 ; 1.88]) and chromium (OR=1.35 [0.91 ; 1.98]).

Conclusion
Due to the high correlation observed between HMs and WFs, it is difficult to identify which HM/WF or a combination of them is driving the positive associations seen. More experimental studies and alternative methodological approaches are mandatory to understand the mechanisms related to each specific metal and solvent exposure and testicular cancer development for prevention purposes.

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Head and neck cancer risk in relation to jobs held in a nationwide case-control study in Iran

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Background: Worldwide, head and neck cancers (HNC), including cancers of the oral cavity, oropharynx, hypopharynx, and larynx, accounted for more than 744,000 cancer cases in 2020. Tobacco and opium use, alcohol consumption, and human papillomavirus (HPV) infection have been identified as major risk factors for HNC cancer. In addition, several occupational exposures are known to increase the risk of some HNC cancers. There is evidence that some of the known carcinogens may increase the risk of HNC cancers in occupational settings, namely exposure to wood dust for sinonasal cancer, and exposure to asbestos and strong acid mists for laryngeal cancer. Although an association has been observed in some studies, a strong association cannot be ruled out due to the small sample size in most studies. Therefore, the current study may help to improve our understanding of the rule of occupational exposure in the risk of HNC.
Methods: We will use the IROPICAN nationwide hospital-based case-control study including 918 incident head and neck cancer cases and 3477 controls. We will assess the risk of HNC in relation to ever working in major International Standard Classification of Occupations (ISCO-68) groups and specific jobs that possibility increase the risk of HNC including textile dust, working in the rubber industry, metal working fluids, while controlling for individual potential confounders including cigarette smoking and opium consumption.
Next steps:
To investigate associations between occupations and HNC, odds ratios (ORs) and 95% confidence intervals (CIs) will be computed using unconditional logistic regression models. The models will be adjusted for tobacco, opium, and alcohol consumption.
Keywords: Occupational cancer, Head and Neck cancer, Exposure, Carcinogen, Iran

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Metabolic profile analyses of diets with different degrees of food processing (EPIC cohort)

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Introduction
Diets have shifted towards the consumption of processed food. The NOVA system classifies it into (1) minimally processed, (2) culinary ingredients, (3) processed foods (PF) and (4) ultra-processed foods (UPF). There is evidence that PF and UPF are related with disease outcomes (obesity, diabetes, cardiovascular disease, cancer), and mortality but the metabolic signatures according to the degrees of processing is unknown.
Methods
There were 1,367 cancer-free participants from nested case-control studies within the EPIC cohort with measurements of endogenous metabolites (N=129) and fatty acids (FA)(N=37). The metabolite data was processed following the pipeline developed at IARC. Then linear regression models were performed with the metabolites (dependent) and the NOVA groups (independent), adjusting for sex, age, fasting status, body mass index, waist circumference, alcohol intake, smoking status, and physical activity. The p values were corrected by the Benjamini Hochberg method. A PLS model was performed to confirm directionality.
Results
Most of the participants were women (60.2%), with a median age at enrolment of 55.6 ± 9.01 years, and many were overweight (44.6%) or obese (13.6%). After adjustments Proline and kynurenine were positively associated with PF. Phosphatidylcholine acyl-alkyl (PC ae) C32:2 and C38:0, PC diacyl (PC aa) C36:5, C38:6 and C42:6, serin, lysine asparagine, sphingomyelin C24:1 and eicosapentaenoic acid (EPA 20:5n-3) were negatively associated with UPF. Stearic acid, monounsaturated FA (fatty acid) 18:1n-5, gamma-linolenic acid docosatetraenoic acid, ruminant trans conjugated linoleic acid CLA, -Vaccenic acid and industrial trans (iTFA) elaidic acid were positively associated with UPF.
Conclusion
Our findings might highlight metabolic pathways related to health outcomes particularly because iTFAs and stearic acid, which are positively associated with UPF in our study, are related with increased risk with non-communicable diseases, and mortality. Also serine and asparagine, which were negatively associated with UPF in our findings, are inversely associated with obesity and positively associated with increased WCRF/AIRC score.

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Association of food processing and colorectal cancer risk in EPIC

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Introduction

Worldwide, more than 1.9 million new colorectal cancer cases and 935,000 deaths were estimated to occur in 2020, representing about one in 10 cancer cases and deaths. Previous studies found evidence of a positive association between the NOVA 4 consumption and colorectal cancer but few studied the association between the four Nova groups and the different anatomical subsites of CRC which constitutes the main aim of our study.

Methods

Setting and participants
450,111 participants recruited across 9 European countries and 6155 incident cases of CRC were detected. Dietary intakes were assessed using baseline food frequency questionnaires adapted to each country. Food items were classified into 4 groups (unprocessed foods, culinary ingredients, processed foods, and ultra-processed foods) according to the NOVA classification system.

Main outcome measures
Associations between ultra-processed food intake/ unprocessed food intake and risk of CRC/CRC subsites were assessed by multivariable Cox proportional hazard models stratified by age, centre and sex and adjusted for known risk factors.

Results
A 10% increase in the proportion of ultra-processed food was associated with 6% increase in the risk of overall CRC (p value=0.002) and 8% increase in the risk of colon cancer (p=0.001).
Strong associations were found for the processed food group (fourth quartile versus first quartile of consumption) with CRC (HR: 1.16(1.04-1.28;p=0.004) and CRC subtypes (HRcolon:1.23 (1.08-1.40); p=0.001; HRdistalcolon:1.28(1.06-1.56); p=0.010). We lost these associations when alcohol is removed from this food group.
In parallel, unprocessed food group was inversely associated with CRC (HR:0.93, 95%CI: 0.90–0.95) and all CRC subtypes.

Conclusion
These findings are in line with the recommendations that encourage the consumption of unprocessed/minimally processed food instead of ultra-processed food as potential way for reducing CRC risk. These results also support the strong evidence of the role of alcoholic beverages in increasing the risk of CRC. Further studies are needed to better understand the pathways in which food processing affects colorectal cancer risk.

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Association between pre-diagnostic circulating lipid metabolites and colorectal cancer risk: a nested case-control study in the European Prospective Investigation into Cancer and Nutrition (EPIC)

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Introduction
Lipids are involved in many metabolic processes that may be relevant for cancer development. However, the role of specific lipid metabolites on colorectal cancer risk is unclear.
Methods
In a case-control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC), we examined associations between pre-diagnostic circulating concentrations of 97 lipid metabolites (acylcarnitines, glycerophospholipids and sphingolipids) and colorectal cancer risk. Circulating lipids were measured using targeted mass spectrometry (Biocrates AbsoluteIDQ Kit) in 1,591 incident colorectal cancer cases and 1,591 matched controls. Multivariable conditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for associations between concentrations of individual lipid metabolites and metabolite patterns with colorectal cancer risk.
Results
Of the 97 assayed lipids, 24 were inversely associated (nominally at $p<0.05$) with colorectal cancer risk. Hydroxysphingomyelin (SM (OH)) C22:2 (ORper doubling 0.60, 95%CI 0.47-0.77) and phosphatidylcholine (PC) ae C34:3 (ORper doubling 0.71, 95%CI 0.59-0.87) remained associated after multiple comparisons correction. These associations were unaltered after excluding cases diagnosed <5 years after blood collection and were consistent according to sex, age at diagnosis, BMI, and colorectal subsite. Associations between metabolite patterns and colorectal cancer risk yielded a similar pattern of results, with inverse associations observed for one component including 26 phosphatidylcholines and all sphingolipids (OR per doubling0.93, 95% CI 0.88-0.99, $p=0.0162$) and weaker evidence of an inverse association with another component including 30 phosphatidylcholines (OR per doubling 0.95, 95% CI 0.90-1.00, $p=0.0529$).
Conclusion
Elevated pre-diagnostic circulating levels of SM (OH) C22:2 and PC ae C34:3 and lipid patterns including phosphatidylcholines and sphingolipids were associated with lower colorectal cancer risk. Additional studies are needed to confirm these novel associations and understand the role of lipid dysregulation in colorectal cancer development.

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A proteogenomic analysis of the adiposity colorectal cancer relationship identifies GREM1 as a probable mediator

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Adiposity is an established risk factor for colorectal cancer (CRC). However, the pathways underlying this relationship, and specifically the role of the circulating proteome, is unclear.

Utilizing two-sample Mendelian randomization and colocalization, based on summary data from large sex-combined and sex-specific genetic studies, we estimated the univariable (UV) associations between: (I) adiposity measures (body mass index, BMI; waist hip ratio, WHR) and overall and site-specific (colon, proximal colon, distal colon, and rectal) CRC risk, (II) adiposity measures and plasma proteins, and (III) adiposity-associated plasma proteins and CRC risk. We used multivariable MR (MVMR) to investigate the potential mediating role of adiposity- and CRC-related proteins in the adiposity-CRC association.

BMI and WHR were positively associated with CRC risk, with similar associations by anatomical tumour site. 6,591 adiposity-protein (2,628 unique proteins) and 33 protein-CRC (8 unique proteins) associations were identified using UVMR and colocalization. 1 protein, GREM1 was associated with BMI only and CRC outcomes in a manner that was consistent with a potential mediating role in sex-combined and female-specific analyses. In MVMR, adjusting the BMI-CRC association for GREM1, effect estimates were attenuated - suggestive of a potential mediating role - most strongly for the BMI-overall CRC association in women.

These results highlight the impact of adiposity on the plasma proteome and of adiposity-associated circulating proteins on the risk of CRC. Supported by evidence from cis-SNP UVMR and colocalization analyses, GREM1 was identified as a potential mediator of the BMI-CRC association, particularly in women, and warrants further experimental investigation.

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Changes of Lifestyle and Risk of Breast Cancer in Women of the European Prospective Investigation into Cancer and Nutrition (EPIC)

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Introduction

It has been postulated that adopting healthy behaviours such as limiting alcohol consumption, maintaining a healthy weight, engaging in regular physical activity, not smoking, and eating a healthy diet could reduce the risk of breast cancer. Within the EPIC cohort, we previously combined these five lifestyle factors, assessed at recruitment, into a single Healthy Lifestyle Index (HLI) and found that a reduction of 3% of breast cancer risk was associated with each unit increase in HLI. However, regarding the potential impact of changes in these behaviours on the risk of breast cancer, epidemiological data still remain scarce. The objective of the present study is to evaluate the association between lifestyle changes and breast cancer risk among women in the EPIC cohort.

Methods

Using questionnaire data, collected at baseline and follow-up, the HLI score was calculated by combining information on alcohol consumption, body mass index, physical activity, and smoking status. This score ranged from 0 (unfavorable lifestyle) to 16 (favorable lifestyle). Among 184,799 eligible participants, 4,922 cases of breast cancer were observed over a median duration of 7.05 years after the follow-up questionnaire. Cox proportional hazards models, using age as the time scale, were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for associations between changes in HLI and breast cancer risk. Associations between changes in each of the four components of the HLI, mutually adjusted, and breast cancer risk were also assessed.

Preliminary Results

Continuous and categorical HLI changes were not significantly associated with breast cancer risk. However, women experiencing an improvement of their BMI component (corresponding to a weight loss) were associated with a 5%lower risk of breast cancer (HR 0.95; 95% CI 0.91-0.99). In premenopausal women, a similar association between an improvement of the physical activity component and breast cancer risk was found (HR 0.92; 95% CI 0.86-0.98).

Next Steps

An analysis by breast cancer subtypes (estrogen receptor positive or negative, ER+/ER-) is currently on going. The latter is based on competitive risks, notably with the application of the Lunn and McNeil's approach.

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Career Panel and Q & A

Dr Melina Arnold, Population Health Insights Lead at Roche
Dr Ingrid Knarston, Scientific Writer at AbCellera
Dr Nmazuo Ozuah, Assistant Professor at Baylor College of Medicine
Dr Mathilde Touvier, Professor, Research Director at INSERM