Overview

The scope of the research carried out by the Genetic and Molecular Epidemiology Group (GMEG) ranges from the identification of aetiological agents and genetic pathways to the translation of the findings into the clinical and public health domains, focusing on bladder, pancreatic, and breast cancers.

We employ a wide variety of biomarkers, including omics data, to better characterise exposures, genetic susceptibility patterns, and cancer outcomes. While omics data provide a unique opportunity in this regard, their integration with non-omics data poses important challenges, and GMEG explores this methodological field in epidemiologic studies.

The strategic goals of the Group are to:

→ Identify non-genetic and genetic factors, as well as their interactions, associated with cancer development and progression, and with its molecular/omics subphenotypes.

→ Develop and apply statistical/informatics tools to model the risk and course of patients with cancer by integrating epidemiological and clinical data with omics information.

→ Assess clinical and public health strategies for cancer control using newly developed biomarkers and algorithms.

“Epidemiological studies aim to analyse the causal relationship between an exposure and an outcome. We have applied causal inference approaches to assess bias generated by factors that may distort the real effect of the exposure.”
In 2023, GMEG contributed to the pancreatic cancer (PC) field by undertaking a study that showed that PDAC tumours of women are more sensitive to gemcitabine-based neoadjuvant chemoradiotherapy (nCRT), resulting in longer survival after resection compared with men. The tumour microenvironment (TME) of women contained fewer pro-tumoural macrophages after nCRT, highlighting the importance of considering sex disparities for PDAC treatment. GMEG also contributed to showing that GATA4 and GATA6 cooperated to maintain the classical phenotype. Reduced expression of both proteins in tumours was associated with the worst patient survival. GATA4 and GATA6 expression was significantly decreased in metastases and negatively correlated with basal markers. On bladder cancer (BC), GMEG conducted a study to characterise the muscle-invasive bladder cancer (MIBC) microenvironment by analysing the tumour-infiltrating B and T cell repertoire according to the taxonomic molecular subtypes. We used RNAseq data from 396 MIBC samples included in TCGA. We found different patterns of tumour-infiltrating immune variants for bladder cancer, summing up 24 independent BC clonally expanded than the Luminal subtypes (FIGURE 1).

We found that smoking and nCRT contribute to bladder tumorigenesis through distinct molecular mechanisms involving different FGFR3 and PIK3CA mutations. Finally, we identified a predictive signature for response to neoadjuvant chemotherapy in BC patients that integrates the expression of 3 genes with clinicopathological characteristics and taxonomic subtypes.

Methodological contributions

We further applied causal inference approaches such as mediation analysis (CMA), which consider the mediation effect of a third variable, and proposed an extension of CMA, combining it with Mendelian randomisation (MRinCMA) to address the limitations resulting from fitting strong assumptions on confounding bias (FIGURE 2). We applied the new approach to analyse the causal effect of obesity and diabetes on pancreatic cancer, considering each factor as potential mediator. By applying MRinCMA, we did not find any evidence of causality of obesity or diabetes on pancreatic cancer. With this new methodology, researchers would be able to address CMA hypotheses by appropriately accounting for the confounding bias assumption, regardless of the conditions used in their studies in different settings. Furthermore, we performed a benchmarking analysis of 5 tools for microse sequence detection using transcriptionomics data (Kraaken2, MetaPhlAn2, PathSeq, DRAC, and Pandora). To this end, we built a synthetic database mimicking real-world structure with tuned conditions accounting for microse species prevalence, base calling quality, and sequence length. Results from this study supported the use of Kranke2 for routine microbiome profiling based on its competitive sensitivity and runtime performance. Nonetheless, we strongly endure to complement it by combining with MetaPhlAn2 for thorough taxonomic analyses.

Translational activities

GMEG actively supports several clinical trials on immunotherapy in BC at the methodological level. We continue to support the Spanish Familial Pancreatic Registry (PanGen-PAM) and the European Registry of PC (Pancer38) under the umbrella of Pancreatic Cancer Europe (PCE). We chair the Spanish Alliance for Pancreatic Cancer Research (ALIPANC) to accelerate the translation of research results into the clinical and public health domains. We lead the Research WorkStream of the PCE multistakeholder platform, and we have advanced in increasing awareness about PC. We also contributed to the European Alliance for Personalised Medicine (EAFPM) series of expert interviews to ascertain the current state of the uptake of advanced molecular diagnostics/NGS for quick and efficient genetic profiles of tumour cells across member states.

**PUBLICATIONS**


**AWARDS AND RECOGNITION**