

1. TITLE OF PROPOSED RESEARCH PROJECT

A global consortium initiative on the association between dietary intake and the prevention of bladder cancer.

2. SUPERVISORY TEAM

Maurice Zeegers is professor of Complex Genetics & Epidemiology. He is ranked among the top5 bladder cancer epidemiologist worldwide. He serves as head of CAPHRI and the department of Complex Genetics. His main interest is in Cancer Epidemiology and Nutrition and Genetics.

Anke Wesselius is PostDoc in Epidemiology at UM and the study manager of BLEND. She leads the Evidence Based Nutrition team at the department of Complex Genetics. Her main interest is in Cancer Epidemiology.

3. PROJECT OUTLINE

Background

Our 2008 expert report for the World Health Organization, our 7 meta-analyses and the 2nd WCRF expert report all concluded that the accumulated evidence on the association between specific foods, nutrients, dietary patterns and the risk of bladder cancer is weak. This is surprising as diet is expected to play an important role in carcinogenesis because the bladder is an excretion organ. The most likely reason for this is that most previous studies have had insufficient sample size and thus lacked adequate statistical power for analyses on 1) individual food items instead of the more common but less detailed food groups, 2) for subgroup analyses and 3) for food-food interactions.

The majority of nutritional epidemiologic studies on bladder cancer followed the approach of assessing single food categories. This type of analysis has several limitations: 1) People do not eat isolated nutrients. 2) The variety of food items consumed could also influence disease risk. 3) There is a high level of interrelationships among nutrients, and 4) the effect of a single nutrient may be too small to detect when compared to the cumulative effects of multiple nutrients. The investigation of dietary patterns could solve this issue. To date, however, no study has done this.

Aim

The proposed research brings together the world's data on diet and bladder cancer. In a unique collaboration, researchers from across the world have agreed to share their nutritional data with over 30.000 participants including over 10.000 bladder cancer patients.

This PhD project aims to provide definite answers on which individual food products, nutrients, existing diets (both regionally and culturally defined) and adherence dietary recommendations (such as those from the WCRF) could influence bladder cancer risk. In addition, contemporary principle components and machine-learning algorithms will be used to identify novel explanatory dietary patterns. The results will be used to update existing dietary recommendations for the prevention of bladder cancer.

Study Recruitment

As a part of the USA National Cancer Institute Biomarker Bladder Cancer Consortium and with help of the International Bladder Cancer Network, literature searches and the professional network of the applicants, we have identified 26 case-control studies with at least 100 cases with bladder cancer. So far, 20 case-control studies (77%) from the USA, Canada, Belgium, the Netherlands, Germany, Sweden, Italy, France, the United Kingdom, Hungary, Romania, Slovakia, China and Japan have agreed to participate in the project and provide their data, 85% of which have already been transferred their data to us.

Harmonize the data (quality control, data cleaning, classification and composition)

All dietary information have been classified using the hierarchal Eurocode 2 food coding system which has been developed by the European Union. On its highest level, the Eurocode 2 describes common food categories such as fruit, vegetables, grain, dairy, meat and beverages. The system further provides the possibility enter information on three deeper levels of detail depending on the available data in each study. During the last harmonization phase new composite variables will be constructed. These include equalization in intake per week, transformations in grams or milliliters using national specific standard portions sizes for each food item, summarizing of component intake into higher order categories and linking each food item to nation specific food composition tables in order to calculate nutrient intakes.

Association with foods, nutrients and variety of dietary consumption

Associations will be calculated for both frequency and variety in dietary consumption. The latter will be investigated by calculating Diet Diversity Scores that count the total number of different food items eaten at least once per fortnight in the common food categories of the Eurocode 2. Odds ratios (OR) will be calculated using random effects logistic regression in which between-study heterogeneity will be estimated and taken

into account. Study design characteristics will be evaluated as potential sources of heterogeneity and incorporated in the regression model when needed. All analyses will be simultaneously adjusted for age, sex and smoking status, which is available in all studies. Potential residual confounding by smoking frequency and smoking duration will be investigated among those studies with available data. Subgroup analyses in these and the below-mentioned exploratory analyses will be performed by smoking status, tumour grade, tumour muscle-invasiveness, geographical region, sex and study design (cohort vs. case-control study).

An a-priori approach to dietary patterns

In addition to an in depth analyses of the association between the quantify and variety of foods and nutrients we will investigate the totality of dietary risk factors simultaneously in order to discover associations with expected and unexpected explanatory dietary patterns. In first instance, we will investigate the relationship between dietary patterns and bladder cancer by investigating the adherence to well known diets such as regionally defined diets (including the Mediterranean, Mesoamerican, oriental and “western type”) and culturally defined diets (including dietary patterns such as vegetarian/vegan diets, prudent diets, macrobiotic diets and diets of Seventh-day Adventists). Similarly, we will evaluate the adherence to dietary recommendations arising from large health organizations such as the World Health Organization (<http://www.who.int/nutrition>) and patient organizations. For this purpose, we will build indices as linear scales that incorporate selected components of the predefined diets. Each component will be divided into two or three categories and a score from 0 to 2 will be assigned to each of these categories. The total indices will then be computed by summing up the points for each component in which higher values indicate higher adherence to the diet and regressed against bladder cancer risk.

4. HOST ENVIRONMENT

The studentship will be embedded within the team of prof.dr. Maurice Zeegers. During the last decade Maurice and his team have built a strong research line on bladder cancer epidemiology with a specific emphasis on diet. This has led to over 70 publications on this topic. Although, the literature is still sparse, Maurice Zeegers and his team have concluded that some micronutrients in the diet such as vitamins C, E and selenium may play a preventive role in bladder carcinogenesis. They are currently pursuing this lead with two chemoprevention clinical trials and two case-control studies. Although other food products have been researched, so far the results remain inconclusive.