Substitution of red meat with legumes and risk of primary liver cancer in 126,744 UK Biobank participants: a prospective cohort study

Purpose: Primary liver cancer is on the rise worldwide, partially due to poor diets and sedentary lifestyles. Shifting to more plant-based diets may lower the risk. We aimed to estimate the effect of replacing unprocessed red meat, processed red meat and total red meat with legumes on primary liver cancer in a free-living population. Methods: We analyzed data from 126,744 UK Biobank participants who completed 2 24-hour diet recall questionnaires. Baseline characteristics were collected from the initial assessment visit. Information on liver cancer diagnoses was collected via external linkage to inpatient hospital episodes or central cancer registries. Cox proportional hazards regression models were used to estimate substitution of 15g/day of legumes with 15/day of total red meat, unprocessed red meat and processed red meat on liver cancer risk, using the leave-one-out food substitution model. Results: During a median follow-up time of 11.3 years, 173 participants developed liver cancer. In the fully adjusted models, no association was observed when substituting 15/day of legumes with total red meat (HR: 0.98 (95% CI 0.93-1.04)), unprocessed red meat (HR: 0.97 (95% CI 0.91-1.03)) or processed red meat (HR: 1.02 (95% CI 0.93-1.13)). Conclusion: Overall, little evidence of an association between replacing red meat with legumes and liver cancer was observed. Further research in larger study populations with longer follow-up time is warranted.

# 1 Background

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world and the third leading cause of cancer-related death with viral hepatitis being the leading risk factor (Massarweh and El-Serag 2017). In low-infection populations, modifiable risk factors, such as dietary habits, may play an increasing role in HCC pathogenesis as non-alcoholic fatty liver disease (NAFLD) has become the leading cause of liver cirrhosis (Zobair M. Younossi et al. 2016; Zobair M. Younossi et al. 2019) that may in turn progress to HCC. A western dietary pattern high in fats and red meats and concurrently low in fruits, vegetables, and whole grains is associated with NAFLD progression (Guo et al. 2022). The prevalence of NAFLD-related HCC cases is an increasing global problem [7], and it is estimated that prevalent cases of NAFLD-related HCC in the US will increase by 146%, from 10,100 to 24,900 cases, while incident NAFLD-related HCC cases will increase by 137%, from 5,160 to 12,240 cases, in 2030 (Estes et al. 2017).

The second most common primary liver cancer is the intrahepatic cholangiocarcinoma (ICC) (Khan, Tavolari, and Brandi 2019). While HCC emerges from the liver parenchyma, ICC emerges from the bile duct. Despite being a relatively rare cancer, ICC is characterized by its aggressivity, late diagnosis and poor survival (Kirstein and Vogel 2016). It is estimated that the incidence of ICC is on the rise worldwide (Bergquist and Seth 2015). Recent meta-analyses have shown a significant adverse association between NAFLD and ICC (Wongjarupong et al. 2017; Corrao, Natoli, and Argano 2020).

The impact of specific food groups on liver cancer risk is not well known. Observational studies suggest that intake of coffee, vegetables and whole grains may lower HCC risk (W. Zhang et al. 2013; Yang et al. 2014; X. Liu et al. 2021; Bhurwal et al. 2020). The protective properties of these foods are proposedly due to their content of dietary fibers and polyphenols, which are also defining components of legumes. The health benefits of legumes extend to improved glycemic control and hypotensive and anticarcinogenic properties with obsevered inverse associations with cardiovascular disease and colorectal cancer (Viguiliouk et al. 2019; Jin and Je 2022). Two large prospective cohort studies found some evidence of inverse associations between legume consumption and risk of HCC (W. Zhang et al. 2013; X. Liu et al. 2021). However, replacement foods were not specified in these studies, which fails to reflect that an increase in intake of one food is at the expense of a concomitantly decreased intake of another food. Studies on substituting plant protein for animal protein are important as we need to eat less animal-based foods and more plants to lower the climate impact of our diet (UN, n.d.). Although previous research has investigated substitution of animal-based proteins with plant-based proteins in relations to NAFLD (S. Zhang et al. 2022), research on substituting meats with legumes in relation to risk of HCC and ICC is sparse. This leaves a substantial gap in our current knowledge on the beneficial effects on primary liver cancer from substituting red meat with legumes.

The main aim of this study was to estimate the effect of replacing unprocessed red meat, processed red meat and total red meat with legumes on primary liver cancer in a free-living population.

# 2 Research Design and Methods

## 2.1 Study population

The UK Biobank, a population-based prospective cohort, was initiated in 2006. (Sudlow et al. 2015) During 2006-2010, more than 500,000 participants, aged 40-69, were recruited and visited designated assessment centres across the UK. Participants provided information about age, sex, sociodemographic factors (education, Townsend deprivation index, living alone) and lifestyle factors (smoking, alcohol consumption, physical activity) via touch screen questionnaires and computer-assisted interviews. Anthropometric data (waist circumference) were collected via physical measurements (UK Biobank 2011).

## 2.2 Dietary assessment

A web-based 24-hour dietary recall was administered at the end of the initial assessment visit for the last 70,000 recruited participants (UK Biobank 2024a). From February 2011 to April 2012, 320,000 participants who had provided an e-mail address were invited on four separate occasions to complete the 24-hour dietary recall, the Oxford WebQ, of which 210,947 participants completed at least one. The Oxford WebQ covered 206 food items and 32 beverage items commonly consumed in the UK. Intakes were reported in standard units of measurements, e.g., servings, cups, slices, etc. with intake categories ranging from 0 to 3+ units (Piernas et al. 2021). The Oxford WebQ has been validated against interviewer-based 24-hour dietary recalls and biomarkers (B. Liu et al. 2011; Greenwood et al. 2019).

Researchers defined 79 food groups and 14 beverage groups from the Oxford WebQ using the UK National Diet and Nutrition Survey categories (Piernas et al. 2021). These food and beverage groups were used when defining the food groups used in the substitution analyses (Table ). Legumes were defined as dietary pulses, baked beans, tofu-based products, peas, hummus, soy drinks, and soy-based desserts and yogurt. Red meat intake was defined as intake of beef, pork, lamb, or other meat, including offal. Processed red meat intake was defined as sausages, bacon (with and without fat), ham, or liver pate. Other food groups included were animal-based foods, unhealthy plant-based foods, healthy plant-based foods, and alcoholic beverages (Table ). Animal-based and healthy and unhealthy plant-based food foods were grouped based on plant-based diet indices from previous studies (A. S. Thompson et al. 2023; Heianza et al. 2021; Satija et al. 2017, 2016).

As a single 24-hour dietary recall does not assess habitual dietary intake and variation in diet over time at an individual level (F. E. Thompson and Subar 2013; Gurinović et al. 2017), only participants who completed two or more Oxford WebQs were eligible for inclusion in this study.

## 2.3 Liver cancer assessment

Liver cancer was defined according to ICD-10 diagnosis codes C22.0 for Hepatocellular carcinoma (HCC) or C22.1 for Intrahepatic cholangiocarcinoma (ICC) and ICD-9 diagnosis codes 1550 Malignant neoplasm of liver, primary or 1551 Malignant neoplasm of intrahepatic bile ducts. Incident and prevalent cases of liver cancer and corresponding diagnosis dates were obtained via external linkage to central cancer registries or hospital inpatient episodes (UK Biobank 2024b, 2023).

## 2.4 Assessment of confounders

Confounders were defined *a priori* from a review of the background literature and illustrated using directed acyclic graphs (Figure ). The following confounding variables were selected: age at baseline (years, continuous), sex (male, female), educational level (high: College or University degree, intermediate: A levels/AS levels, O levels/GCSEs, or equivalent, low: none of the previous mentioned), Townsend Deprivation Index (continuous), Living alone (yes, no), waist circumference (cm, continuous), physical activity (above/below the 2017 UK Physical activity guidelines of 150 minutes of moderate activity per week or 75 minutes of vigorous activity, or unknown), smoking (pack years as a proportion of lifespan exposed to smoking, continous), and alcohol intake (g/day, continuous). All confounders except age were selected from the initial assessment visit before the start of follow-up.

## 2.5 The substitution model

The substitution analyses were conducted by by modelling replacement of an equal mass of meat with legumes. The portion size of the substitution was set to 15 g of legumes for 15 g of red meat to ensure that substitutions were below the mean intake of any of the substituted food groups in the cohort. The substitutions were modeled using the leave-one-out-approach in which variables for every food group along with a variable for total food intake are included, except the food group that are to be substituted (Ibsen et al. 2021). To estimate substitution of 15 g of all red meats (red and processed) with 15 g of legumes, the following model was defined:

When substituting only unprocessed red meat with legumes, processed red meat was added to the model:

When substituting only processed red meat with legumes, red meat was added to the model:

The performance of the leave-one-out model when modeling equal mass substitutions has been validated against simulated data (Tomova, Gilthorpe, and Tennant 2022).

## 2.6 Statistical analysis

Multivariable-adjusted Cox proportional hazards regression models were used to estimate hazard ratios (HR) with corresponding 95% confidence intervals (CI) with age as the underlying timescale. Participants were followed from the date of their last completed Oxford WebQ until the occurrence of the event of interest or due to right censoring, whichever came first. Participants were right censored in the event of death, loss to follow-up, or administrative end of follow-up (October 31, 2022). Two levels of adjustments were added to the substitution model. Model 1 was minimally adjusted for age (as the underlying timescale), total weight of food and beverage intake, and all other food groups to fit the substitution model. Model 2 was further adjusted for sex, educational level, Townsend Deprivation Index, living alone, physical activity, smoking, alcohol intake, and waist circumference.

In secondary analyses, each cancer type was analysed separately to evaluate if the pooling of HCC and ICC as one outcome in the main analysis was justified. Furthermore, to estimate the association of legume intake with liver cancer regardless of other dietary components, legume consumers (divided into quartiles) were compared to non-consumers.

To evaluate the robustness of the main analyses, sensitivity analyses were performed on subsamples of participants by excluding those with high alcohol intake (exclusion of the upper decile of alcohol intake (g/day) by sex), implausible energy intake (exclusion of participants below the 2.5th percentile and above the 97.5th percentile of energy intake (kJ/day) by sex), any liver disease before baseline, any type of cancer before baseline, and fewer than 3 completed Oxford WebQs. As neither the central cancer registries nor the hospital inpatient registries were complete, liver cancer diagnoses retrieved from death registries, which were more up-to-date, were included in a sensitivity analysis to test for outcome misclassification. Lastly, one of our causal assumptions was that anthropometry confounded the causal relationship between replacing red meat with legumes and liver cancer; however, strong arguments exist giving support to anthropometry being a mediator between diet and health outcomes. Thus, to test for erroneously conditioning on a potential mediator, waist circumference was removed in a sensitivity analysis. Sensitivity analyses were modeled as the fully adjusted models in the main analyses.

All analyses were conducted in R (version 4.1.1) with a significance level of 5 %.

# 3 Results

After excluding participants with liver cancer before baseline, participants lost to follow-up before baseline, and participants with errors in dietary data, 126,744 participants who had completed two or more Oxford WebQs remained (Figure ).

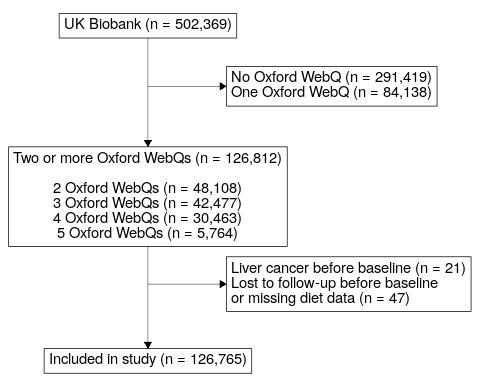


Figure 3.1: Flowchart of included participants. Missing diet data were merged with loss to follow-up before baseline due to n being less than 5. It should be noted that not all UK Biobank participants were invited to complete an Oxfords WebQ. Only the last 70,000 participants to visit an assessment center were asked to complete an Oxford WebQ at the end of their visit. Further Oxford WebQs were sent to ~320,000 participants who provied an e-mail adress.

During a median follow-up time of 11.3 years, 173 participants developed liver cancer. Participants who developed liver cancer were older at baseline, were more likely to be male, have a higher waist circumference, be less physically active, and fewer had never smoked, compared to all included participants (Table ).

Mean daily energy and total food intakes as well as daily intake of all specified food groups in grams are presented in Table .

No evidence of associations was found for substituting 15 g/day of legumes with 15 g/day of total red meat, unprocessed red meat, or processed red meat and risk of primary liver cancer in Model 1 (Table : total red meat: HR: 0.98, 95% CI: 0.93-1.04; unprocessed red meat: HR: 0.97, 95% CI: 0.91-1.03; processed red meat: HR: 1.02, 95% CI: 0.93-1.13). The estimated associations changed minimally with further adjustments. There was weak evidence of an association between replacement of processed red meat with legumes ( HR: 1.09, 95% CI: 0.98-1.20; Table ).

In secondary analyses, when analyzing the associations between replacement of red meat with legumes and HCC or ICC separately, weak evidence of a higher risk of HCC was observed (Table , total red meat: HR: 1.06, 95% CI: 0.97-1.16; unprocessed red meat: HR: 1.05, 95% CI: 0.96-1.15; processed red meat: HR: 1.09, 95% CI: 0.95-1.26). This was opposite for replacement of total red meat and unprocessed red meat and ICC (total red meat: HR: 0.97, 95% CI: 0.90-1.05; unprocessed red meat: HR: 0.95, 95% CI: 0.87-1.03) but not for processed red meat ( HR: 1.07, 95% CI: 0.93- 1.22, Table Table ). The magnitude or direction of associations were not significantly different across strata of liver cancer types.

In the adjusted non-substitution analysis, only the first quartile of legume intake (mean intake 6.3 grams/day) was associated with a lower risk of liver cancer, compared to no intake (HR: 0.59, 95% CI: 0.35-0.98); no associations were observed for quartiles 2, 3 or 4 compared to no intake (Table ).

In sensitivity analyses, excluding participants based on high alcohol intake, implausible energy intake, any liver disease or cancer before baseline, or fewer than 3 completed Oxford WebQs did not alter the estimates appreciably. Similar results were also found when including death registries as a source of liver cancer cases and when excluding waist circumference from the fully adjusted analysis (Table ).

# 4 Discussion

Contrary to our hypothesis, in this study we found little evidence of an association between replacing 15g/day of red or processed meat with legumes on risk of primary liver cancer. The estimates were robust to our sensitivity analyses. When investigating liver cancer types separately, replacing total red meat and unprocessed red meat with legumes showed some weak evidence of an inverse association with ICC. Our results for legume intake without specified substitutions did not show a clear pattern of association.

This study had some limitations. First, none of the registries used to determine a diagnosis of liver cancer were complete or up-to-date at the time of analysis (UK Biobank 2024b). Data from external providers, such as the NHS England, NHS Central Register or National Records of Scotland, were estimated to be mostly complete by the UK Biobank at various dates, ranging from 31 December 2016 for cancer data from Wales to 31 October 2022 for hospital inpatient data from England (UK Biobank 2023). This could introduce misclassification of the outcome, as individuals with liver cancer may not be identified as cases. However, the estimates were robust in a sensitivity analysis that included death registries as an additional source of liver cancer diagnoses to accommodate missing outcome events. Incorrectly classifying non-cases as cases would lead to attenuation of our results, but this is unlikely due to register linkage. Second, the relatively low number of events limited our ability to adjust for confounding factors. Excessive adjustment parameters per event can compromise the validity of the multivariable Cox regression model, potentially causing biased estimates. To ensure statistical validity, we aimed for at least 10 events per variable in the main analysis by limiting the number of adjustment levels, using fewer and broader food groups, and fewer levels for categorical covariates. This approach was guided by our *a priori* causal assumptions. Although this method helped maintain statistical validity, it may have increased residual confounding by diluting the importance of specific food groups. Additionally, risk factors that we could not adjust for, such as aflatoxin B1, a known liver carcinogen, may have contributed to residual confounding. Third, by specifying that the dietary exposure was collected on at least two occasions, our study population suffered considerable attrition. This is unlikely to be completely at random, and most likely resulted in a study population with greater focus on their dietary habits. For example, the mean intake of processed meat was low in our study population. If a diet consisting of higher intakes of healthier plant-based foods is associated with lower liver cancer incidence, our study population may be at lower risk overall, thus reducing the power of our study to detect an association.

Information on dietary intake was collected using self-reported 24-hour diet recall questionnaires. Strengths of this study are the prospective longitudinal design, which establish temporality between the diet exposure and liver cancer outcome, and the large sample size, which enabled analyses of a rare cancer. Though health registries may have been only partially up to date, using registries almost eliminates selection bias due to loss to follow-up. Estimates were robust to exclusion of participants with fewer than three completed Oxford WebQs, indicating that at least two 24-hour diet recall measurements were sufficient to estimate diet over time. Further, our specified substitution analyses have some strengths in contrast to traditional methods in nutritional epidemiology through examining the effect of consuming a food or nutrient while holding all other foods constant. The substitution is easily interpretable and reflects the implications that an increased intake of a food is at the expense a decreased intake of other foods. In that sense, the food substitution model mimics some aspects of a randomized controlled design.

Contrary to our hypothesis, replacing processed red meat with legumes was associated with a non-significant increase in risk of primary liver cancer, with a greater effect size compared to unprocessed red meat. This pattern persisted across all sensitivity analyses. However, the estimates for processed red meat were labeled with less confidence, partly due to the low median intake. These findings align with recent analyses from the UK Biobank, which indicated that unprocessed red meat intake was associated with a non-significant increase in liver cancer risk, with a greater effect size than processed meat (both white and red meat) (Knuppel et al. 2020). This supports the notion that processed meat may not be associated with liver cancer risk in this population.

The literature on food substitutions, particularly in relation to liver cancer, is sparse. Accordingly, we also conducted an analysis of legume intake without specifying food substitutions. However, a recent meta-anlysis of observational studies found a non-linear dose-response relationship between legume intake and liver cancer risk, with a protective effect observed between intakes of 8 g/day to 40 g/day (K. Liu et al. 2023). This somewhat contrasts with our findings where any increase above 6.3 g/day of legumes was not associated with a decreased risk of liver cancer, compared to no legume intake. A recent meta-analysis of observational studies showed no association between red or processed meat intake and HCC (Di et al. 2023).

# 5 Conclusion

Supplementary table

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