Final Project Group 11

(1) Background: What is the investigators' question(s) and why did they investigate this.

Question: What are the profiles of cancer risk associated with immune-mediated diseases?

Importance: This research highlights the importance of immune regulation and its relation and direct impact with carcinogenesis.

Why did they investigate this? Despite this, the research also notes that the cancer risk profiles associated with immune-mediated diseases need further characterization.

Objective: The purpose behind this research study was to assess the prospective association of 48 immune-mediated diseases with the risk of total and individual cancers and the prospective association of organ-specific immune-mediated diseases with the risk of local and extralocal cancers.

(2) Methods: How was data collected and who were the subjects?

Data was collected through a number of methods.

Design/ Setting/ Participants: This prospective cohort study used data from the UK Biobank cohort study on adults aged 37 to 73 years who were recruited at 22 assessment centers throughout the UK between January 1, 2006, and December 31, 2010, with follow-up through February 28, 2019.

Accountability was upheld throughout the study because all participants were registered with the UK National Health Service. To gauge the demographic of their population, all participants were asked to complete a self-administered touchscreen questionnaire on sociodemographic characteristics, lifestyle exposures, medical history, and medication use and underwent physical measurements. This information was carefully stored by The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10). All participants provided written informed consent. Those who withdrew their consent were excluded from the study. In order to meet the confidentiality standard, all participants were

de-identified for this study, and the study was approved by the UK Biobank.Furthering their stance on ethics, the UK Biobank also received ethical approval from the UK National Health Service, National Research Ethics Service North West, the National Information Governance Board for Health and Social Care in England and Wales, and the Community Health Index Advisory Group in Scotland. In addition to this, an independent ethics and governance council was formed to oversee its continued adherence to the ethics and governance framework.

Methods: Hazard Ratios (HRs) and 95% Confidence Intervals (CIs)

These were the two methods used to calculate total and individual cancers.

(1) Ascertainment of Immune-Mediated Diseases

A total of 48 immune-mediated diseases and compared cancer risk between individuals with and without any of these diseases were identified.

- In efforts to narrow down the analysis of individual immune-mediated diseases, the study focused on 27 diseases that affected at least 100 affected individuals and at least 10 cancer cases among the affected individuals.
- Among the diseases, the study focused primarily on 12 organ-specific diseases for their associations with local or extralocal cancer that was diagnosed in at least 1 participant.
- This study also required that the immune-mediated disease diagnosis be present at least 12 months before the cancer diagnosis.

(2) Method: multivariable hazard ratios (HRs)

- The association of immune-mediated diseases with risk of cancer was assessed with multivariable hazard ratios (HRs).
    - Model 1 was adjusted for age at recruitment, sex, and ethnicity.

(3) Method: 95% CIs

- The study also used 95% CIs after adjusting for various potential confounders using time-varying Cox proportional hazards regression.
    - Model 2 was further adjusted for a set of a priori determined cancer risk factors that may be associated with immune-mediated diseases, including socioeconomic status (Townsend deprivation score), educational level,

total physical activity, body mass index (BMI), waist-to-hip ratio, height, smoking status and intensity, alcohol use, consumption of processed meat and oily fish, family history of cancer, and regular use of aspirin and vitamin supplements.

This study used time-varying Cox proportional hazards regression with age as the time scale.

(4) Method: Heterogeneity

- in the associations of organ-specific immune-mediated diseases with local and extralocal cancers was assessed using the contrast test method.

(5) Method: Measuring accuracy of the study

- To account for multiple testing, we performed Bonferroni correction for the primary analysis on the associations of the 27 individual immune-mediated diseases with total cancer risk and considered $\alpha = .05/27 = .002$ as statistically significant. SAS software, version 9.4 (SAS Institute Inc) was used for all analyses. All statistical tests were 2-sided.

Important: This study did not conduct the correction for secondary analyses on individual cancers, which were considered exploratory, and interpreted the results with caution.

(3) Description of the data: summarize the outcome measures of the study.

Results:

(1) Statistical analysis

All participants were followed up from the date of recruitment until that of cancer diagnosis, death, loss to follow-up, or the end of the study period (February 28, 2019), whichever occurred first.

- This was not a completely accurate study, out of all of the participants, 1253 participants were lost to follow-up, and thus, 99.7% completed the study.

- For this study, the exposure group consisted of individuals with either prevalent immune-mediated diseases reported at baseline enrollment or incident diseases reported during follow-up.
- In this study, incident cases were those that were considered to have no immune-mediated disease until the date of the first reported diagnosis during follow-up.

(2) Characteristics of the Study Population

A total of 478 753 participants (mean [SD] age, 56.4 [8.1] years; 54% female) were assessed in this cohort study. Most participants were White (95%), and 61 496 (13%) had at least 1 immune-mediated disease (Table 1). Compared with participants without immune-mediated diseases, participants with immune-mediated diseases were more likely to have lower socioeconomic status, higher BMI, and lower physical activity; smoke; consume processed meat and vitamins; and use aspirin. They were less likely to have a college or university education and to consume alcohol (Table 1).

(3) Any Immune-Mediated Diseases and Risk of Total Cancer

During a total of 4 600 460 person-years and a median of 10.0 (IQR, 9.2-10.7) years of follow-up, we documented 2834 cases of cancer in participants with immune-mediated diseases and 26 817 cases in those without immune-mediated diseases. Overall, immune-mediated diseases were associated with total cancer risk after multivariable adjustment (model 2: HR, 1.08; 95% CI, 1.04-1.12) (Figure 1).

(4) Individual Immune-Mediated Diseases and Risk of Total Cancer

Ulcerative colitis was significantly associated with an increased risk of total cancer, with a multivariable-adjusted HR of 1.33 (95% CI, 1.17-1.51). Asthma (HR, 1.06; 95% CI, 1.01-1.12) and primary biliary cholangitis (HR, 1.74; 95% CI, 1.10-2.76) were associated with an increased risk of total cancer (Figure 1).

(5) Any Immune-Mediated Disease and Risk of Individual Cancers

For individual cancers, participants with any immune-mediated disease were at higher risk of developing lung cancer (multivariable-adjusted HR, 1.36; 95% CI, 1.20-1.53),

lymphoma (multivariable-adjusted HR, 1.49; 95% CI, 1.26-1.75), and liver cancer (HR, 1.75; 95% CI, 1.30-2.36) (Figure 2).

(6) Organ-Specific Immune-Mediated Diseases and Risk of Local and Extralocal Cancers

Five of the organ-specific immune-mediated diseases were significantly associated with the increased risk of local cancers, but not extralocal cancers:

asthma with lower airway cancer (HR, 1.34; 95% CI, 1.14-1.56)

celiac disease with small intestine cancer (HR, 6.89; 95% CI, 2.18-21.75)

idiopathic thrombocytopenic purpura with hematologic cancer (HR, 6.94; 95% CI, 3.94-12.25)

primary biliary cholangitis with hepatobiliary cancer (HR, 42.12; 95% CI, 20.76-85.44)

autoimmune hepatitis with hepatobiliary cancer (HR, 21.26; 95% CI, 6.79-66.61) ($P < .001$ for all comparisons; $P < .002$ for heterogeneity).

Contrasting these results, ulcerative colitis was significantly associated with higher risk of colorectal cancer and extra colorectal cancer, with a stronger association for:

- colorectal (HR, 1.73; 95% CI, 1.26-2.39)
- than extra colorectal cancer (HR, 1.30; 95% CI, 1.13-1.49) (Table 2).

(7) Individual Immune-Mediated Diseases and Risk of Individual Cancers

Figure 3 shows the results for the site-specific analysis associating individual immune-mediated diseases with individual cancers.

- Seven immune-mediated diseases were significantly associated with an increased risk of cancer in the involved organs.
    - asthma with lung cancer (HR, 1.34; 95% CI, 1.14-1.57)
    - celiac disease with small intestine cancer (HR, 6.89; 95% CI, 2.18-21.75).

The HRs ranged from 1.34 (95% CI, 1.14-1.57) to 62.42 (95% CI, 29.14-133.74) ($P < .002$).

- 2 associations with cancers in the involved organs were found for:
    - sicca syndrome with small intestine (HR, 8.49; 95% CI, 1.18-61.32)
    - mouth cancers (HR, 13.59; 95% CI, 1.86-99.09)
    - Guillain-Barré syndrome with soft tissue cancer (HR, 11.17; 95% CI, 1.56-79.80).

Thirteen immune-mediated diseases were associated with an increased risk of cancer in the near or distant organs or different systems.

Among these results, 2 were associated with increased risk of cancer in the near organs:

- (Crohn disease with liver cancer [HR, 4.01; 95% CI, 1.65-9.72]
- ulcerative colitis with liver cancer [HR, 2.59; 95% CI, 1.15-5.81])

Among these results, 2 were associated with cancer in the distant organs:

- autoimmune hepatitis with tongue cancer [HR, 27.65; 95% CI, 3.82-199.91]
- esophageal cancer [HR, 9.28; 95% CI, 1.31-65.94]
- ulcerative colitis with tongue cancer [HR, 3.49; 95% CI, 1.29-9.43].

Among these results, Twelve immune-mediated diseases were associated with cancers in different systems:

- idiopathic thrombocytopenic purpura with liver cancer (HR, 11.96; 95% CI, 3.82-37.42)
- bullous disorders with laryngeal cancer (HR, 26.23; 95% CI, 3.62-190.15)
- Graves disease or autoimmune thyroiditis with soft tissue cancer (HR, 9.19; 95% CI, 2.93-28.81)
- ulcerative colitis with prostate cancer (HR, 1.45; 95% CI, 1.13-1.85).

Among all cancers, lymphoma demonstrated an extensive association with immune-mediated diseases.

- The HR ranged from 2.01 (95% CI, 1.34-3.01) for rheumatoid arthritis
- The HR ranged to 7.72 (95% CI, 3.67-16.23) for idiopathic thrombocytopenic purpura.

Among these results rheumatoid arthritis was associated with an increased risk of:

- lung cancer (HR, 1.71; 95% CI, 1.28-2.28)
- lymphoma (HR, 2.01; 95% CI, 1.34-3.01)

However, rheumatoid arthritis was associated with a decreased risk of:

- Prostate cancer (HR, 0.62; 95% CI, 0.41-0.94)
- Breast cancer (HR, 0.64; 95% CI, 0.46-0.89)

Among the results, Necrotizing vasculopathies as a systemic disease was significantly associated with an increased risk of multiple myeloma (HR, 7.98; 95% CI, 2.97-21.43).

Among these results, Type 1 diabetes was associated with an increased risk of:

- Liver cancer (HR, 2.82; 95% CI, 1.43-5.56)
- Esophageal cancer (HR, 2.13; 95% CI, 1.13-4.02)
- Tonsil cancer (HR, 3.57; 95% CI, 1.11-11.46)

However, it was seen that there was a decrease in prostate cancer (HR, 0.67; 95% CI, 0.46-0.97).

(4) Clearly State the Null and Alternative Hypotheses.

Null hypothesis: This study will work to determine whether cancer risk is associated with immune-mediated diseases.

Alternative hypothesis: It is safe to assume that cancer risk is not associated with immune-mediated diseases.

(5) Results: Describe the hypothesis tests used in the paper and provide the results (e.g. standard error, statistic, C.I., p-value). Explain why the investigators rejected or failed to reject the null hypothesis. Explain what your results mean in simple words to the general public.

The investigators of this study failed to reject the null hypothesis because the findings of this study indicate that any immune-mediated disease was associated with a modestly increased risk of total cancer after adjusting for common cancer risk factors. To our knowledge, the current

study represents the first comprehensive effort to dissect various individual immune-mediated diseases associated with cancer risk. We found that ulcerative colitis, asthma, and primary biliary cholangitis were associated with an increased risk of total cancer. Prior studies also support the findings of this study, e.g., (footnotes, 16-18) a national cohort study(16) in Sweden found an association of asthma with a 19% increased risk of total cancer. Ulcerative colitis was associated with a 40% higher risk of total cancer, mainly colorectal and hepatobiliary cancers.(17) Patients with primary biliary cholangitis had double the risk of total cancer and approximately 40 times higher risk of hepatobiliary cancer.(18)

This study identified 7 immune-mediated diseases that were significantly associated with increased risk of cancer in the involved organs. These findings suggest an important role of a local carcinogenic effect of immune dysregulation.

(6) Conclusion: Interpret the results of the paper; describe any limitations; provide a summary conclusion of the work

Strength: The major strengths of this study include the prospective cohort design, large sample size, and comprehensive organ-specific assessment. In addition, we adjusted for a variety of lifestyle risk factors that may have confounded the association of immune-mediated disease and cancer risk.

Limitations:

(1) The medications for treatment of immune-mediated diseases were self-reported by participants at recruitment only.There is no detailed data on dose or duration information were collected, thus precluding a detailed analysis of these medications. However, in line with our sensitivity analysis results, medications for immune-mediated diseases have not been associated with cancer risk and thus are unlikely to have had a substantial confounding effect on our results.
(2) The number of cancer cases was small for some rare immune-mediated diseases.
(3) Despite our use of Bonferroni correction for multiple testing, chance findings could not be ruled out.
(4) The ascertainment of immune-mediated diseases was based on inpatient records only. We may have missed some diagnoses made in the outpatient setting. However, our reported

prevalence of immune-mediated disease appeared to be consistent with those in other studies in Western countries.2,3 In addition, given the prospective design, any misclassification in the exposure status is likely to have biased the associations toward the null.

(5) The cohort was relatively young, with a limited number of cases of rare cancers, thus reducing the power to identify associations, particularly for metastatic cancers.

(6) The cohort participants are predominantly White, and the findings may not be generalizable to other racial and ethnic groups.

Conclusion: In this cohort study, immune-mediated diseases were associated with an increased risk of total cancer. Organ-specific immune-mediated diseases had stronger associations with risk of local cancers than extralocal cancers. The associations for individual immune-mediated diseases were largely organ specific but were also observed for some cancers in the near and distant organs or different systems. Our findings support the role of local and systemic immunoregulation in cancer development