# Sex biases in cancer and autoimmune disease incidence are correlated across human tissues

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Keywords: Cancer incidence, autoimmune disease incidence, sex bias, mitochondria

## Abstract

Cancer occurs more frequently in men while autoimmune diseases (AIDs) occur more frequently in women. To explore whether these sex biases have a common basis, we collected 170 AID incidence studies from many countries for tissues that have both a cancer type and an AID that arise from that tissue. Analyzing a total of 182 country-specific, tissue-matched cancer-AID incidence rate sex bias data pairs, we find that the sex biases observed in the incidence of AIDs and cancers that occur in the same tissue are correlated across human tissues. Among key factors that have been previously associated with sex bias in either AID or cancer incidence, we find that the sex bias in the expression of the 37 genes encoded in the mitochondrial genome and the expression of a few immune pathways stand out as common key factors whose levels across human tissues are strongly associated with these incidence rate sex biases.

## Main Text

Both autoimmune diseases (AIDs) and cancers have notably sex-biased incidence rates. Most AIDs occur more often in women[1,2], and most cancers occur more often in men[3-5]. Given these observations, we asked whether the sex biases observed in the incidence of AIDs and cancers that occur in the same tissue are correlated *across* human tissues. This question is of fundamental interest, since an affirmative answer may suggest that there are shared underlying factors.

To study this question, we performed an extensive literature search for sex-specific incidence data for AIDs. We considered only population-based studies that use clinical inclusion criteria and have at least 25 cases for a given disease. Additionally, we considered only AIDs with a focal primary tissue (e.g., we included ulcerative colitis but excluded Crohn's disease), for which we could find incidence data for at least 3 countries. We excluded sex-specific tissues. For each study, we calculated the *incidence rate sex bias (IRSB)* as $\text{bias}_{\text{MALE/FEMALE}} = \log_2(\text{rate}_{\text{MALE}}/\text{rate}_{\text{FEMALE}})$, so that zero indicates no bias, a positive value indicates a higher incidence rate in males (termed a "male bias") and a negative value indicates a higher incidence rate in females (similarly termed a "female bias"). Most AID studies provided sex-specific incidence rates or their ratios. For the remaining studies, depending on the data available, we calculated the sex-specific incidence rate as $\text{rate}_{\text{SEX}} = \text{cases}_{\text{SEX}}/\text{population}_{\text{SEX}}$ or the (relative)

$rate_{SEX}$ as $cases_{SEX}/cases_{TOTAL}$ (Supplementary Methods). When multiple studies were available for an AID in a country, that country's AID incidence rate sex bias was determined as the arithmetic mean incidence rate ratio. Overall, surveying 170 published studies, we calculated 135 country-specific AID incidence rate sex bias data points for 17 AIDs across 29 countries (**Table S1**, e.g., the mean incidence rate sex bias for Type 1 diabetes in Spain is one such data point).

To calculate cancer incidence rates, we collected data from national cancer registries (whether aggregated in international databases such as GLOBOCAN[6] or reported in individual registries). We calculated the annual sex-specific incidence rates using annual case and population counts and used the mean annual sex-specific incidence rate to calculate the cancer incidence rate sex bias for each cancer in each country. To compute the correlation between AIDs and cancer incidence rate sex biases across tissues, we grouped AIDs with matched cancers occurring in the same tissue in the same country (**Table S2**). For example, for the UK, we paired thyroid AID data points for Hashimoto's hypothyroidism and Graves' hyperthyroidism with cancer data points for thyroid carcinoma and thyroid sarcoma, resulting in 4 possible thyroid cancer-AID pairs. The country-specific AID incidence rate sex bias data points were matched to the country-specific cancer incidence rate sex bias data points, yielding a total of 182 country-specific, tissue-matched cancer-AID incidence rate sex bias data pairs (**Table S3**).

First, to get a view of tissue-matched cancer and AID IRSB across tissues we computed the mean IRSBs across countries, yielding global IRSB values for 17 AIDs and 17 cancer types across 12 human tissues, comprising a total of 24 cancer-AID data pairs. As expected, most AID incidence rates are female-biased (a negative sex-bias score), while most cancer incidence rates are male-biased (a positive sex-bias score) (**Figure 1A**). **Figure 1B** presents the correlation of the incidence sex bias of these disorders across human tissues, summed up across all countries surveyed. Notably, we find an overall positive correlation (Pearson correlation $r=0.47$ with 1-sided t-test $p=0.0099$, Spearman correlation $r=0.42$, $p=0.021$). Repeating this analysis using various levels of cancer type classification shows a consistent and robust correlation (**Figures S1-2, Table S4**). Second, studying this correlation in a country-specific manner for the four countries with at least 18 AID-cancer data pairs, we find a country-specific significant correlation for Sweden, while

the correlations for Denmark, the UK and the USA have $p > 0.05$ but are quite close to this threshold, showing a consistent trend for each country (**Figure 1C**).

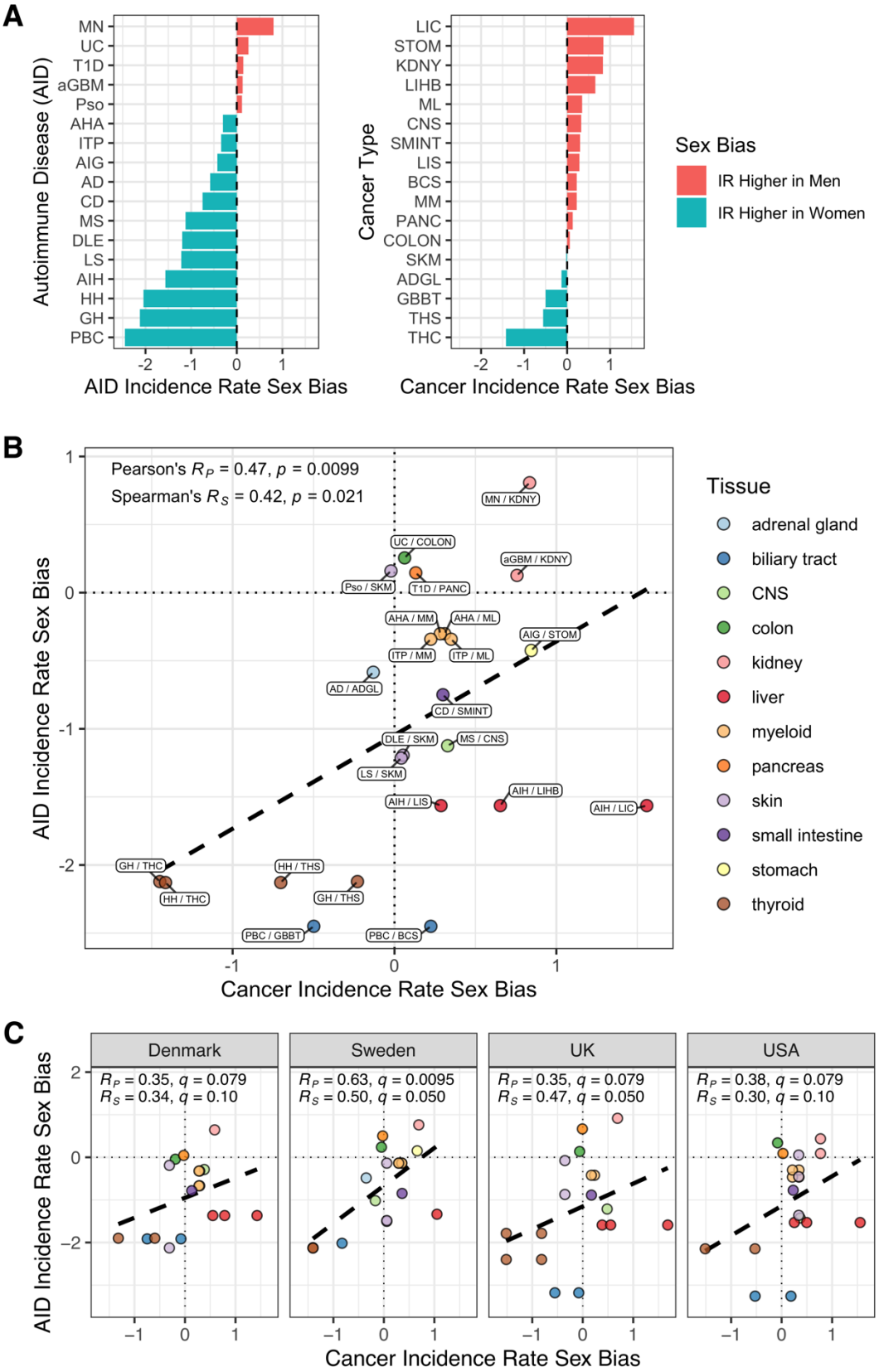
A
Autoimmune Disease (AID)
MN
UC
T1D
aGBM
Pso
AHA
ITP
AIG
AD
CD
MS
DLE
LS
AIH
HH
GH
PBC
AID Incidence Rate Sex Bias
Cancer Type
LIC
STOM
KDNY
LIHB
ML
CNS
SMINT
LIS
BCS
MM
PANC
COLON
SKM
ADGL
GBBT
THS
THC
Cancer Incidence Rate Sex Bias
Sex Bias
IR Higher in Men
IR Higher in Women
B
Pearson's $R_P$ = 0.47, $p$ = 0.0099
Spearman's $R_S$ = 0.42, $p$ = 0.021
AID Incidence Rate Sex Bias
Cancer Incidence Rate Sex Bias
Tissue
adrenal gland
biliary tract
CNS
colon
kidney
liver
myeloid
pancreas
skin
small intestine
stomach
thyroid
C
Denmark
Sweden
UK
USA
$R_P$ = 0.35, $q$ = 0.079
$R_S$ = 0.34, $q$ = 0.10
$R_P$ = 0.63, $q$ = 0.0095
$R_S$ = 0.50, $q$ = 0.050
$R_P$ = 0.35, $q$ = 0.079
$R_S$ = 0.47, $q$ = 0.050
$R_P$ = 0.38, $q$ = 0.079
$R_S$ = 0.30, $q$ = 0.10
AID Incidence Rate Sex Bias
Cancer Incidence Rate Sex Bias

***Figure 1. Incidence rate sex biases for cancers and AIDs are positively correlated across tissues of origin. (A)*** *Incidence rate sex bias (X-axis) for 17 AIDs and 17 cancer types (Y-axis). Positive sex bias (red) indicates higher incidence rate in men; negative sex bias (blue) indicates higher incidence rate in women.* ***(B,C)*** *Tissue-matched incidence rate sex biases for cancers (X-axis) and for autoimmune diseases (Y-axis) are displayed across different tissues of origin (circle color indicates the tissue). Positive values in each of the axes indicate male bias; negative values indicate female bias. The dashed line is the linear regression line. Statistics in the top left corner include the Pearson's product-moment correlation r-value ($R_p$) and a 1-sided t-test p-value; and the Spearman's rank correlation coefficient value ($R_s$) and a 1-sided t-test p-value. For country-level tests, p-values were corrected for multiple testing using the Benjamini-Hochberg method to produce q-values.* ***(B)*** *Across-population averages, with the cancer-AID pairs labeled.* ***(C)*** *Population-level data for the four countries with the largest numbers of data pairs (at least 18 out of 24 cancer-AID pairs), maintaining the tissue color labels used in the top panel (USA, 20 pairs; Denmark, Sweden, & UK, each 18 pairs).* ***AIDs****: AD, Addison's disease; aGBM, anti-glomerular basement membrane nephritis; AHA, Autoimmune hemolytic anemia; AIG, Autoimmune gastritis; AIH, Autoimmune hepatitis; CD, Celiac disease; DLE, Discoid lupus erythematosus; GH, Graves' hyperthyroidism; HH, Hashimoto's hypothyroidism; ITP, Immune thrombocytopenic purpura; LS, Localized scleroderma; MN, primary autoimmune membranous nephritis; MS, Multiple sclerosis; PBC, Primary biliary cholangitis; Pso, Psoriasis; T1D, Type 1 diabetes; UC, Ulcerative colitis.* ***Cancers****: ADGL, adrenal gland cancer; BCS, liver (biliary) cholangiosarcoma; COLON, colon cancer; CNS, central nervous system cancer; GBBT, gallbladder & biliary tract cancer; KDNY, kidney cancer; LIC, liver carcinoma; LIHB, liver hepatoblastoma; LIS, liver sarcoma; ML, myeloid leukemia (acute and chronic); MM, multiple myeloma; PANC, pancreatic cancer; SKM, skin melanoma; SMINT, small intestine cancer; STOM, stomach cancer; THC, thyroid carcinoma; THS, thyroid sarcoma.*

Observing this correlation, we next asked if we could identify factors that might jointly modulate both the incidence rate sex bias observed in cancer and in AID across human tissues. We conducted both an unbiased general investigation but while doing so, kept also a hypothesis-driven approach in mind; we specifically examined four major factors that have been previously associated in the literature with the incidence rates of cancers and AIDs and/or their incidence rate

sex biases. Those include (1) inflammatory or immune activity in the tissue[7,8]; (2) expression of immune checkpoint genes[9,10]; (3) the extent of X-chromosome inactivation[11,12]; and finally, (4) mitochondrial activity[13,14] and mitochondrial DNA copy number[15,16].

We began by systematically charting the landscape of gene sets whose sex-biased enrichment in normal tissues is associated with IRSB in cancers and AIDs. We analyzed gene expression data from non-diseased tissue samples from GTEx v8[17], for tissues in which both cancer and AID arise; GTEx data were available for 10 of the 12 tissues we studied above (**Table S2**). First, (1) for each gene in each tissue we calculated the *expression sex bias (ESB)* as the MALE/FEMALE bias = $\log2(TPM_{MALE}/TPM_{FEMALE})$, where $TPM_{MALE}$ or $TMP_{FEMALE}$ denote the average gene expression in TPM (transcripts-per-million) for male or female samples of the tissue. (2) Second, we computed the correlation of the expression sex bias of each gene with AID or cancer IRSBs, or with the aggregation of both (**Supplementary Methods**; we abbreviate these correlations as $corr_{ESB/IRSB}$). (3) Finally, for each of these three phenotypes, we ranked all the genes by the $corr_{ESB/IRSB}$ values and performed a gene set enrichment analysis (GSEA)[18,19] to identify gene sets and pathways that were either significantly positively or negatively associated with IRSB (Supplementary Methods). In total, this analysis covered 7763 gene sets, including gene ontology biological process sets and chromosome-location based sets from MSigDB[20], three X-chromosome gene sets (fully escape X-inactivation, variably escape X-inactivation, and pseudoautosomal region)[21], and finally, the sets of nuclear- and mitochondrial-genome genes encoding proteins that localize to the mitochondria[22].

**Figure 2** shows the top positively and negatively $corr_{ESB/IRSB}$ enriched sets with $p \leq 10^{-3}$ after multiple hypothesis test correction for AID (positive, Panel A; negative Panel B), cancer (positive, Panel C; negative Panel D), and their joint aggregate enrichment (positive, Panel E, negative, Panel F). Strikingly, the top enriched gene set (highest normalized enrichment score, NES) in *all* three phenotypes is the set of 37 genes encoded on the mitochondrial genome, including many genes with high $corr_{ESB/IRSB}$ values. In contrast, while the (much larger) set of all genes encoding proteins that localize to the mitochondria is significantly enriched for cancer IRSB, it is not significantly enriched for AID IRSB, where it is only ranked 3632 out of 6413 negatively enriched gene sets. Several immune-related gene sets also show high and significant $corr_{ESB/IRSB}$

enrichments in accordance with one of our initial hypotheses (**Figure 2**), but the three different X chromosome gene sets studied in light of another one of our original hypotheses are not significantly enriched in $corr_{ESB/IRSB}$ values.

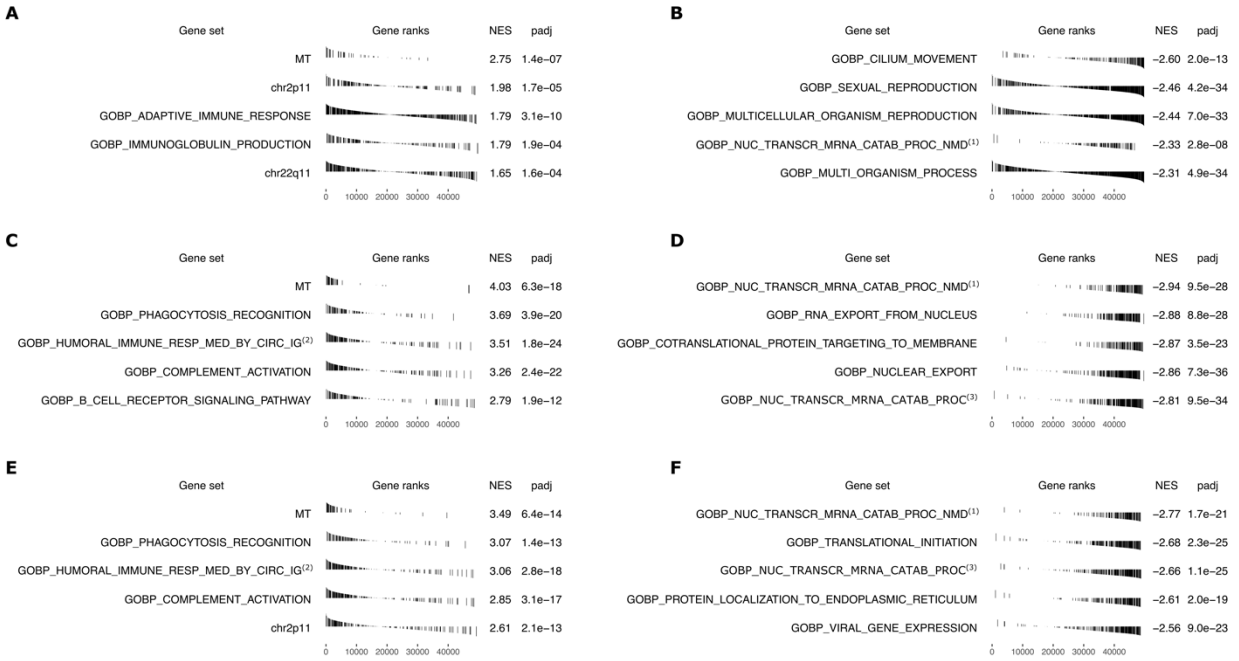


***Figure 2. GSEA results for correlations of gene expression sex bias with IRSB.*** *Top 5 positively and negatively enriched gene sets, with adjusted $p \leq 10^{-3}$, for AIDs (positive, **A**; negative, **B**), cancers (positive, **C**; negative, **D**), and AIDs and cancers jointly (positive, **E**; negative, **F**). For each gene set the plot shows: (**Gene set**) name;(**Gene ranks**) bar plot of $corr_{ESB/IRSB}$ values ordered from highest at the left to lowest at the right (bars for genes in the gene set are black); (**NES**) normalized enrichment score; and (**padj**) Benjamini-Hochberg corrected p-value.* ***Abbreviated gene set names:*** *(1) GOBP Nuclear transcribed mRNA catabolic process nonsense-mediated decay; (2) GOBP Humoral immune response mediated by circulating immunoglobulin; (3) GOBP Nuclear transcribed mRNA catabolic process.*

To obtain a clearer visualization of the emerging findings described above, we turned to compute the correlation across tissues between their levels in each normal tissue and the IRSBs of cancers or AIDs (**Figure 3**). To this end, we summarized the expression of the genes composing a given gene set in a normal GTEx tissue by computing their geometric mean, giving us a single

activity summary value. As expected from the results of the unbiased analysis presented above, we did not observe a significant correlation between cancer or AID incidence rate sex bias and the expression of key immune checkpoint genes (CTLA4, PD-1, or PD-L1, **Figure S4**), or the extent of X-chromosome inactivation (quantified by the expression of XIST lncRNA[23], **Figure S5**). We also do not find such significant consistent correlations for the top immune gene sets found via the unbiased analysis (previously shown in **Figure 2**). However, we do find strong correlations between these summary values for the mitochondrial gene set, which was ranked highest in **Figure 2** (gene set "MT"): Remarkably, we find that the sex bias of mtRNA expression in GTEx tissues is positively correlated both with AID incidence rate sex bias (r=0.57, p=0.017) and with cancer incidence rate sex bias (r=0.64, p=0.0095) (**Figures 3A** and **3B**; the correlations between mtRNA expression and cancer and AID incidence rates for each of the sexes individually are provided in **Figure S6**). These findings are in line with previous reports linking mitochondrial activity[13,14] and mtDNA copy number[15,16] with higher AID and cancer risk.

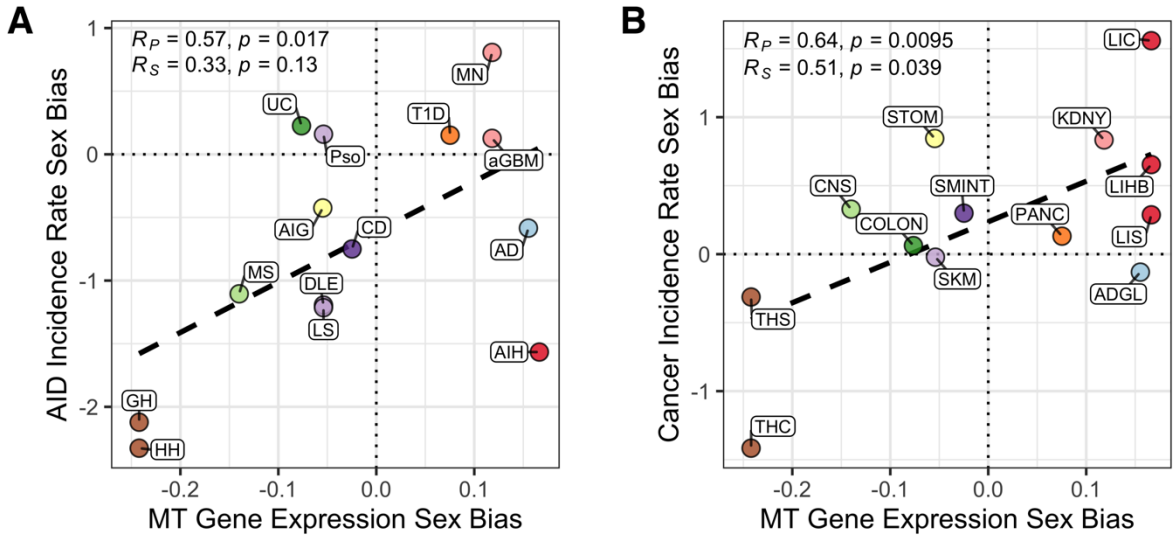


***Figure 3. Mitochondrial gene expression is a strong correlate of sex biases in incidence rate of autoimmune diseases and cancer types across tissues.*** *The correlation between expression ratio of mitochondrial gene expression in male vs female tissues (X-axis) with the incidence rate sex biases of* ***(A)*** *autoimmune diseases (Y-axis) and* ***(B)*** *cancer types (Y-axis) across human tissues (circle color indicates the tissue).* ***AIDs****: AD, Addison's disease; aGBM, anti-glomerular basement membrane nephritis; AIG, Autoimmune gastritis; AIH, Autoimmune hepatitis; CD,*

*Celiac disease; DLE, Discoid lupus erythematosus; GH, Graves' hyperthyroidism; HH, Hashimoto's hypothyroidism; LS, Localized scleroderma; MN, primary autoimmune membranous nephritis; MS, Multiple sclerosis; Pso, Psoriasis; T1D, Type 1 diabetes; UC, Ulcerative colitis.* ***Cancers****: ADGL, adrenal gland cancer; CNS, central nervous system cancer; COLON, colon cancer; KDNY, kidney cancer; LIC, liver carcinoma; LIHB, liver hepatoblastoma; LIS, liver sarcoma; PANC, pancreatic cancer; SMINT, small intestine cancer; SKM, skin melanoma; STOM, stomach cancer; THC, thyroid carcinoma; THS, thyroid sarcoma.*

The correlative findings between mitochondrial expression and cancer and AID IRSBs across human tissues are surprising, giving rise to two further fundamental questions. First, what relevant biological mechanisms may be associated with sex differences in mitochondrial functioning? The strongest potential candidate may be estrogen signaling, which has been shown to regulate at least four mitochondrial functions relevant to health and disease[24], including, (1) biogenesis of mitochondria, whose levels differ across sexes and tissues[25], (2) T cell metabolism (including mitochondrial activity measured by Seahorse assays) and T-cell survival (estimated by retention of inner membrane potential)[26], (3) unfolded protein response[27] (mediated partly via mitochondrial superoxide dismutase[28]), and (4) generation of reactive oxygen species (ROS)[29]. Second, how might sex differences in mitochondria modulate the sex-biased incidence observed in cancers and AIDs? One possible mechanism is through differences in ROS production: Increased mitochondrial ROS generation has been associated with both the initiation and intensification of autoimmunity in several organ-specific AIDs[13] and with cancer initiation and progression[14]. Furthermore, alterations in mtDNA copy number have been associated with increased risk of lymphoma and breast cancer,[15] and somatic mtDNA mutations producing mutated peptides may trigger autoimmunity[16].

Our analyses have a few limitations that should be acknowledged, and we list three main ones. First, the majority of our AID-cancer data pairs are from European countries (111 of 182 [61%]), which might introduce geographic, ethnic, or social biases. Second, factors beyond biological drivers, such as sex differences in the propensity to seek medical care or reporting of specific diseases, are not characterized in the datasets studied. However, disease-specific potential effects may be somewhat mitigated given the opposite tendency of sex biases for AIDs and cancers

and our study of tissue-specific correlations. Third, although much of the incidence rate data is age-standardized, we could not take additional steps to account for age-related incidence rate differences due to small sample sizes.

As in humans, sex differences have been reported in animal studies of diseases, which has prompted us to search the literature and survey previous studies of sex bias in disease incidence in rodent models of cancers and AIDs. We focused on studies of sex difference in spontaneous and/or autochthonous carcinogenesis by either carcinogen treatment or genetic engineering, excluding transplantation of syngeneic animals which do not model disease development (representative examples are listed in **Tables S6-7** for cancer and AIDs respectively.) **Table S6** lists our cancer incidence findings, where the sex bias was higher in colon, liver, kidney, pancreas, and stomach, and higher in females in the thyroid, consistent with the human reports. Interestingly, for colon, liver, kidney, pancreas, and thyroid, the sex bias disappeared or was reduced when the animals were subjected to castration/ovariectomy or hormone treatment, suggesting that the differences in these organs are likely to be driven by sex hormones. There are fewer AID rodent models, so we searched specifically for studies allowing for direct comparisons to the human data (**Table S7**). The AID sex bias reported is however generally higher in males than in females, in difference from the human findings, but the higher male bias observed in kidney, colon, pancreas, and skin compared to the thyroid is maintained. Again, castration and testosterone treatment suggested that occurrence of inflammation in the kidney and thyroid could be biased to male and female animals, respectively.

In summary, we find a surprising overall positive correlation between cancer and AID incidence rate sex biases across many different human tissues. Among key factors that have been previously associated with sex bias in either AID or cancer incidence, we find that mitochondrial gene expression sex bias and the expression of a few immune pathways stand out as key factors whose levels across human tissues is quite strongly associated with these incidence rate sex biases. Our findings thus call for further mechanistic studies on the role of mitochondrial and immune gene expression in determining cancer and AID incidence and their incidence rates sex bias.

## Acknowledgments

This research was supported in part by the Intramural Research Program of the NIH, NCI. This work utilized the computational resources of the NIH HPC Biowulf cluster (http://hpc.nih.gov).

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