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Sex-based differences in toxicity of immunotherapy cancer treatment: A systematic review and narrative synthesis

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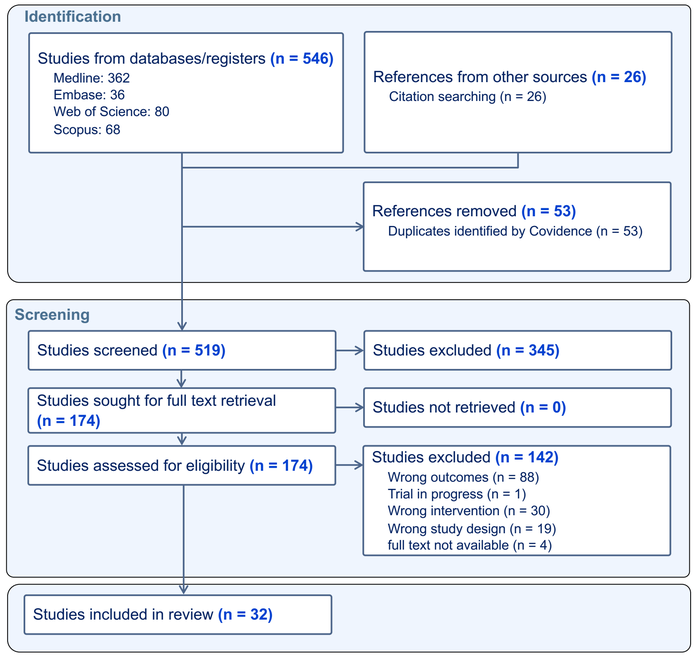
BACKGROUND

- Evidence supports complex sex-based differences in the innate and adaptive immune systems, which could account for observed differences in immunotherapy efficacy.
- However, less is known about how **toxicities** and **adverse events** may differ between males and females receiving immunotherapy for cancer.
- **We present a systematic review and narrative synthesis of the existing literature on sex-based differences in immune checkpoint inhibitor (ICI) toxicity for cancer patients, with potential implications for guiding future research and clinical practice.**

METHODS

- Systematic review of the following databases: Medline, Embase, Web of Science, Scopus
  - Covidence used to organize and complete screening and data extraction
  - Inclusion/Exclusion criteria, PRISMA below:

Inclusion Criteria	Exclusion Criteria
Studies that provide ICI toxicity/irAE data in adults receiving ICI cancer treatment, **stratified by biological sex**	Studies that do **not** provide ICI toxicity/irAE data in adults receiving ICI cancer treatment, stratified by biological sex
RCTs, retrospective or prospective cohort or case-control studies, systematic reviews with meta-analysis	Narrative literature reviews



RESULTS

Table 1. Included studies that reported a statistically significant difference in irAE incidence between male and female patients

Study	Study Design	Amount of Patients	Types of cancer included in study	Types of immune checkpoint inhibitors included in study	irAEs included in analysis	Difference in irAE incidence between males and females	
						Overall (if reported)	Specific irAE categories (if reported)
Studies that report or estimate a higher irAE incidence in female patients primarily							
Miceli 2023	Prospective Cohort Study	204 (118M, 86F)	NSCLC, melanoma, head & neck, CRC, urogenital	Anti-PD-1, Anti-PD-L1, Anti-CTLA-4	All irAEs	F > M for irAEs overall	F > M for endocrine and hepatic irAEs
Cortellini 2019	Retrospective Cohort Study	559 (379M, 180F)	NSCLC	Anti-PD-1	All irAEs	F > M for irAEs overall	N/A
Morganstein 2017	Retrospective Cohort Study	190 (M/F not reported)	Melanoma	Anti-PD-1, Anti-CTLA-4	Thyroid irAEs only	N/A	F > M for all thyroid irAEs
Yamauchi 2019	Retrospective Cohort Study	200 (134M, 66F)	NSCLC, melanoma, "other"	Anti-PD-1	Thyroid irAEs only	N/A	F > M for overt thyroid irAEs
Zhai 2019	Case-control Study	6,260 irAE case reports (3,428M, 2,095F)	Not reported	Anti-PD-1, Anti-PD-L1, Anti-CTLA-4	Endocrine irAEs only	N/A	F > M for hypothyroidism and hyperthyroidism reports (not true incidence data given case-control study)
Unger 2022	Systematic Review of Published Trial Data	2,319 (1476M, 843F) in immunotherapy analysis	Melanoma, NSCLC, genitourinary	Anti-PD-1, Anti-PD-L1, Anti-CTLA-4	All irAEs	F > M for irAEs overall	F > M for GI, mood, sleep, hematologic/BM, cardiovascular, endocrine, metabolic, neurological irAEs
Duma 2019	Retrospective Cohort Study	476 (259M, 217F)	Melanoma, NSCLC	Anti-PD-1	All irAEs	F > M for irAEs overall	F > M for endocrinopathies and arthralgias in melanoma and NSCLC F > M for pneumonitis in NSCLC M > F for dermatologic irAEs in melanoma and NSCLC
Muir 2021	Retrospective Cohort Study	1,246 (824M, 422F)	Melanoma	Anti-PD-1, Anti-PD-L1, Anti-CTLA-4	Thyroid irAEs only	N/A	F > M for thyroid irAEs
Sangahvi 2021	Retrospective Cohort Study	448 (254M, 194F)	Melanoma	Anti-PD-1	All irAEs	F > M for Grade 2 irAEs	N/A
Studies that report or estimate a higher irAE incidence in male patients primarily							
Kartolo 2018	Retrospective Cohort Study	78 (48M, 30F)	Melanoma, NSCLC, RCC	Anti-PD-1, Anti-CTLA-4	All irAEs	M > F for irAEs overall	M > F for dermatologic irAEs
Uhara 2022	Retrospective Cohort Study	2,008 (1,030M, 978F)	Melanoma	Anti-PD-1	All irAEs	M ~ F for irAEs overall	M > F for interstitial lung disease irAE
Faje 2014	Retrospective Cohort Study	154 (M/F not reported)	Melanoma	Anti-CTLA-4	Hypophysitis	N/A	M > F for hypophysitis irAE
Chen 2022	Case-control Study	30,342 irAE case reports (19,245M, 11,097F)	Melanoma, NSCLC, "other"	Anti-PD-1, Anti-PD-L1, Anti-CTLA-4	All irAEs	N/A	M > F for lung, renal, cardiovascular, nervous system, MSK, dermatologic, and hepatitis irAEs (not true incidence data given case-control study)
Yamaguchi 2021	Retrospective Cohort Study	188 (133M, 55F)	NSCLC, head & neck, gastric	Anti-PD-1	Pneumonitis	N/A	M > F for pneumonitis irAE

Figure 1. Types of Included Studies

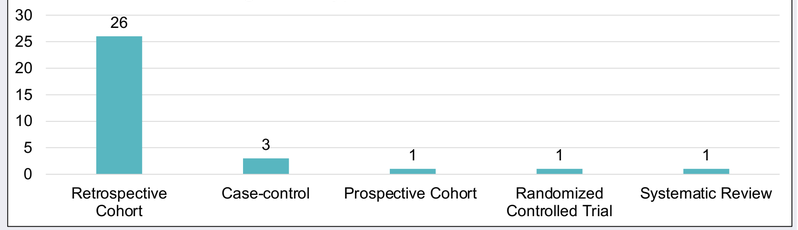
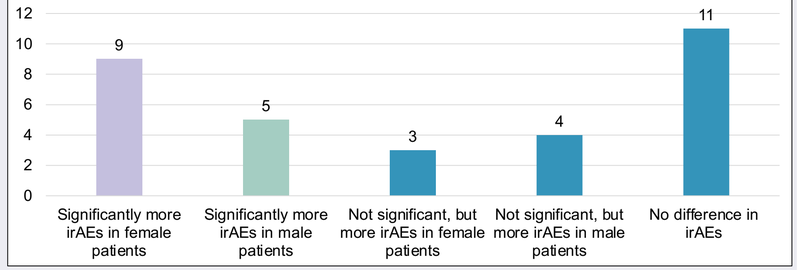


Figure 2. Number of included studies with each reported or estimated outcome



DISCUSSION

- **Our results indicate a pattern of sex-based dimorphisms in immune-related adverse events in cancer ICI therapy.**
- **In general, more studies in our sample tend to report a higher incidence of irAEs in females than in male patients.**
  - **Female patients tend to consistently have higher rates of endocrine irAEs.**
  - **Male patients tend to have higher rates of dermatologic irAEs and hypophysitis.**
- **Our data also indicate some conflicting results between male and female irAE incidence, including for the same ICI and cancer types, emphasizing the need for further study.**
- **More prospective data is needed to better understand these potential differences, and how cancer type and ICI class may play a role.**

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