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PRELIMINARY PHARMACOVIGILANCE INSIGHTS INTO SEX- AND TUMOR-SPECIFIC IMMUNE-RELATED ADVERSE EVENTS WITH IMMUNE-CHECKPOINT INHIBITORS

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ABSTRACT – ***Objective:*** Pembrolizumab has transformed the treatment of multiple solid tumors, but immune-related adverse events (irAEs) remain clinically relevant. Whether toxicity patterns differ according to biological sex and tumor histology is incompletely characterized in real-world pharmacovigilance data.

Materials and Methods: Individual Case Safety Reports associated with pembrolizumab monotherapy were extracted from EudraVigilance in March 2026. The analysis was restricted to reports with a reporting date between 1 January 2025 and 31 December 2025. irAEs were grouped into nine Medical Dictionary for Regulatory Activities System Organ Classes (MedDRA SOCs). Associations with sex and common tumor histologies (at least 100 reports per histology) were assessed using chi-square tests and Cramér's V. Rare histologies (10–99 reports) were explored using Fisher's exact tests. A Bonferroni-adjusted significance threshold of $p < 0.0056$ was used for the nine SOC comparisons.

Results: The overall cohort included 8,488 reports. Sex was specified in 7,991 cases: 4,159 females (52.1%) and 3,832 males (47.9%). The histology analysis included 6,482 cases across 14 common tumor types. Seven of nine SOCs were associated with tumor histology after multiplicity correction. Endocrine toxicity showed the strongest association ($\chi^2 = 202.6$; Cramér's V = 0.177), ranging from 27.7% in breast cancer to 10.1% in head and neck cancer. Respiratory toxicity was highest in bladder cancer (20.7%) and lowest in cervical cancer (2.4%; $\chi^2 = 144.4$; V = 0.149). Immune system disorders were most frequent in non-small cell lung cancer (19.3%; $\chi^2 = 52.8$; V = 0.090), cardiac disorders in melanoma (19.4%; $\chi^2 = 72.6$; V = 0.106), and gastrointestinal disorders in cervical cancer (25.1%; $\chi^2 = 32.3$; V = 0.071). Overall toxicity burden did not differ by sex ($p = 0.110$); however, females had more endocrine (18.4% *vs.* 12.4%) and hematologic/lymphatic disorders (13.4% *vs.* 9.5%), whereas males had more respiratory (12.4% *vs.* 7.0%) and cardiac disorders (13.9% *vs.* 11.5%). All four sex-associated differences met the adjusted threshold.

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Exploratory rare-histology analyses identified high rates of multisystem irAEs in brain tumors (84.6%; OR 6.58, 95% CI 1.46–29.71; $p = 0.009$) and sarcoma (71.4%; OR 2.99, 95% CI 1.16–7.72; $p = 0.026$), although these findings did not meet the Bonferroni-adjusted threshold. Conclusions: Pembrolizumab-associated irAE reporting patterns differed by sex and tumor histology. These findings are hypothesis-generating and may inform risk-adapted vigilance, but they require validation in denominator-based clinical cohorts with adjustment for confounding and treatment exposure.

KEYWORDS: Pembrolizumab, Immune-related adverse events, EudraVigilance, Pharmacovigilance, Sex differences, Tumor histology.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have changed the therapeutic landscape of solid tumors by restoring antitumor T-cell activity and overcoming tumor-induced immune suppression[1-3]. Pembrolizumab is a humanized IgG4 monoclonal antibody targeting programmed cell death protein 1 (PD-1) and is widely used across multiple solid tumors and biomarker-defined tumor-agnostic indications[4-6]. In addition to immune-mediated toxicity, ICIs may also produce atypical response patterns, including pseudoprogression and hyperprogression, which may complicate the distinction between disease progression and treatment-related toxicity[7]. The same immune activation that underpins efficacy can disrupt peripheral tolerance and cause immune-related adverse events (irAEs), which may affect virtually any organ, show delayed onset, persist after treatment discontinuation, and occasionally become life-threatening. Their pathogenesis is multifactorial and may involve autoreactive T cells and B cells, autoantibodies, inflammatory cytokines, host genetic factors, and the intestinal microbiota[8,9]. Both biological sex and tumor histology have been proposed as potential modifiers of the incidence and organ-specific distribution of irAEs. Females generally mount stronger adaptive and humoral immune responses and have a higher background prevalence of autoimmune disorders, likely reflecting the combined influence of sex hormones, X-linked immune genes, and sex-specific regulation of innate and adaptive immunity[10]. Tumor histology may influence toxicity through differences in immune infiltration, PD-L1 expression, tissue-specific antigenicity, oncogenic signaling, prior treatment exposure, and baseline organ vulnerability. Indeed, systematic analyses have shown that the incidence and spectrum of irAEs vary according to both the immune checkpoint inhibitor class and the underlying tumor type[11]. Nevertheless, most available evidence derives from selected clinical-trial populations or single-tumor cohorts, limiting the generalizability of current risk estimates to real-world populations[12]. Large spontaneous-reporting databases can complement trial evidence by detecting safety signals across heterogeneous real-world populations. This study therefore evaluated associations between biological sex, tumor histology, and the organ-system distribution of irAEs reported with pembrolizumab monotherapy in EudraVigilance, with the aim of generating hypotheses for personalized toxicity surveillance.

MATERIALS AND METHODS

Study Design and Data Source

This retrospective pharmacovigilance study used EudraVigilance, the European system for the collection and analysis of suspected adverse drug reaction reports. Data were extracted during March 2026. The database was queried using the active substance term “pembrolizumab,” and the analysis included Individual Case Safety Reports (ICSRs) received by EudraVigilance between 1 January 2025 and 31 December 2025. For the purposes of this study, pembrolizumab monotherapy was operationally defined at the report level as pembrolizumab being the only antineoplastic medicinal product recorded in the ICSR. Reports containing any additional antineoplastic agent, including cytotoxic chemotherapy, targeted therapy, endocrine anticancer therapy, or another immune checkpoint inhibitor, were excluded. Non-antineoplastic concomitant medications were permitted and did not constitute an exclusion criterion. Thus, pembrolizumab was not required to be the only medicinal product reported, but it had to be the only anticancer treatment documented in the ICSR. This database-based criterion was applied to reduce potential confounding from combination anticancer treatment[13]. However, because treatment classification relied on the medicinal products documented in spontaneous reports, the absence of

another antineoplastic agent in an ICSR cannot be considered definitive confirmation that no other anticancer treatment was administered. EudraVigilance contains information on suspected medicinal products, reported adverse reactions, patient characteristics, and, when available, the underlying therapeutic indication. Because EudraVigilance is a spontaneous-reporting system, the unit of analysis was the safety report rather than a prospectively followed patient with a known treatment denominator.

Study Population

The overall pembrolizumab-monotherapy cohort comprised 8,488 ICSRs. For the sex analysis, 497 reports with unspecified sex were excluded, leaving 7,991 evaluable reports: 4,159 females and 3,832 males. For the histology analysis, tumor types were stratified according to report frequency. Fourteen common histologies, each represented by at least 100 reports, contributed 6,482 cases to the primary analysis. Histologies represented by 10–99 reports were considered rare and analyzed separately (Table 1).

Table 1. Study population and analytic cohorts.

Population	n	Definition
Overall cohort	8,488	All EudraVigilance ICSRs for pembrolizumab monotherapy included in the analysis
Sex-evaluable cohort	7,991	Reports with specified sex
Female	4,159 (52.1%)	Sex specified as female
Male	3,832 (47.9%)	Sex specified as male
Sex unspecified	497 (5.9%)	Excluded from sex-stratified analyses
Common-histology cohort	6,482	Fourteen tumor types with at least 100 reports each
Rare histologies	10–99 per histology	Exploratory individual comparisons with the overall cohort

ICSR, Individual Case Safety Report.

Adverse-Event Classification

Reported irAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and grouped at the System Organ Class (SOC) level. Nine clinically relevant SOCs were analyzed: endocrine disorders; respiratory, thoracic and mediastinal disorders; immune system disorders; cardiac disorders; gastrointestinal disorders; blood and lymphatic system disorders; hepatobiliary disorders; skin and subcutaneous tissue disorders; and musculoskeletal and connective tissue disorders. A multisystem irAE pattern was defined as involvement of at least two SOCs within the same report.

Statistical Analysis

Associations between sex and each SOC, and between common tumor histology and each SOC, were assessed using chi-square contingency analyses. Effect size was summarized using Cramér's V, which ranges from 0 to 1. Rare histologies were compared individually with the overall pembrolizumab-monotherapy cohort using Fisher's exact test, with odds ratios (ORs) and 95% confidence intervals (CIs). To account for nine SOC comparisons, the Bonferroni-adjusted significance threshold was $p < 0.0056$. Rare-histology findings with p-values above this threshold were interpreted as exploratory signals rather than multiplicity-adjusted statistically significant associations.

Ethics and Reporting Considerations

The analysis used anonymized, aggregated pharmacovigilance data and did not involve direct patient contact or access to identifiable clinical records. Results were interpreted as reporting associations and not as incidence estimates or proof of causality.

RESULTS

Cohort Characteristics

The overall cohort included 8,488 pembrolizumab-monotherapy reports. Sex was available for 7,991 reports, comprising 4,159 females (52.1%) and 3,832 males (47.9%). The common-histology analysis included 6,482 reports across 14 tumor types.

Tumor Histology and Organ-Specific Toxicity Patterns

After Bonferroni correction, seven of the nine SOCs were significantly associated with tumor histology, indicating that the organ-system distribution of reported irAEs varied across tumor types. The strongest association was observed for endocrine disorders ($\chi^2 = 202.6$; Cramér's V = 0.177) (Table 2).

Table 2. Principal tumor histology-associated toxicity patterns.

SOC/toxicity domain	Highest-reporting histology	Highest rate	Lowest-reporting histologys	Lowest rate	χ^2	Cramér's V
Endocrine disorders	Breast cancer	27.7%	Head and neck cancer	10.1%	202.6	177
Respiratory, thoracic and mediastinal disorders	Bladder cancer	20.7%	Cervical cancer	2.4%	144.4	149
Immune system disorders	NSCLC	19.3%	Not reported in source thesis	—	52.8	90
Cardiac disorders	Melanoma	19.4%	Not reported in source thesis	—	72.6	106
Gastrointestinal disorders	Cervical cancer	25.1%	Not reported in source thesis	—	32.3	71

All displayed common-histology associations met the Bonferroni-adjusted threshold of $p < 0.0056$. Rates denote the proportion of reports containing at least one event in the specified SOC. NSCLC, non-small cell lung cancer; SOC, System Organ Class.

Breast cancer had the highest endocrine-event rate (27.7%), whereas head and neck cancer had the lowest (10.1%). Bladder cancer had the highest respiratory-event rate (20.7%), compared with 2.4% in cervical cancer. Immune system disorders were most frequent in NSCLC (19.3%). Melanoma had the highest cardiac-event rate (19.4%), and cervical cancer had the highest gastrointestinal-event rate (25.1%).

Rare Histologies and Multisystem irAEs

Among rare histologies, brain tumors and sarcoma showed elevated proportions of reports involving at least two SOCs. Because the corresponding *p*-values were 0.009 and 0.026, respectively, these signals did not meet the prespecified Bonferroni-adjusted threshold and should be considered exploratory (Table 3).

Table 3. Exploratory multisystem irAE signals in rare histologies.

Rare histology	Reports with multisystem irAEs	OR *vs.* overall cohort	95% CI	*p*-value	Multiplicity-adjusted interpretation
Brain tumors	84.6%	6.58	1.46–29.71	9	Exploratory; not significant at $p < 0.0056$
Sarcoma	71.4%	2.99	1.16–7.72	26	Exploratory; not significant at $p < 0.0056$

Multisystem irAEs were defined as involvement of at least two SOCs. CI, confidence interval; OR, odds ratio.

Sex-Associated Toxicity Patterns

Sex was not associated with the overall burden of reported toxicity (p = 0.110). However, four of nine SOCs differed significantly between females and males after Bonferroni correction. Females had higher rates of endocrine and blood/lymphatic disorders, whereas males had higher rates of respiratory and cardiac disorders (Table 4).

Table 4. Sex-associated differences in reported irAEs.

SOC/toxicity domain	Female	Male	Direction	*p*-value	Cramér's V
Endocrine disorders	18.4%	12.4%	Higher in females	<0.001	83
Respiratory, thoracic and mediastinal disorders	7.0%	12.4%	Higher in males	<0.001	93
Blood and lymphatic system disorders	13.4%	9.5%	Higher in females	<0.001	61
Cardiac disorders	11.5%	13.9%	Higher in males	1	36

All four comparisons met the Bonferroni-adjusted threshold of $p < 0.0056$. Percentages refer to the proportion of sex-specified reports containing at least one event in the specified SOC.

The largest sex-associated effect was observed for respiratory disorders (V = 0.093), followed by endocrine disorders (V = 0.083), although all effect sizes were small. These findings indicate qualitative differences in the distribution of reported toxicities rather than a difference in total toxicity burden.

DISCUSSION

In this large EudraVigilance analysis of 8,488 pembrolizumab-monotherapy reports, both tumor histology and biological sex were associated with distinct organ-specific irAE reporting patterns. Seven of nine SOCs differed across common tumor histologies. Sex did not affect the overall toxicity burden, but it was associated with four organ-system categories. These readily available clinical variables may therefore help define hypotheses for more individualized toxicity surveillance. Endocrine disorders showed the strongest histology association and were most frequently reported in breast cancer. The parallel female predominance in endocrine events is consistent with established sex differences in autoimmunity and with the high frequency of thyroid dysfunction among ICI-associated endocrinopathies[8]. However, because breast cancer is predominantly female, the histology and sex effects cannot be disentangled without multivariable analysis. Treatment line, menopausal status, endocrine therapy, baseline thyroid disease, and reporting practices may also contribute. Respiratory disorders were most frequently reported in bladder cancer and were more common in males. A possible explanation is shared tobacco exposure and chronic pulmonary comorbidity in older urothelial-cancer populations. Nevertheless, spontaneous-reporting data cannot establish whether baseline lung disease, prior therapy, sex distribution, or differential surveillance explains the association. Cardiac disorders showed the highest reporting proportion in melanoma and were modestly more frequent in males. ICI-associated myocarditis is uncommon but clinically important because severe cases can be rapidly fatal[8]. However, the observed melanoma-associated reporting pattern should not be interpreted as evidence of a higher incidence of cardiotoxicity. The association may have been influenced by the absolute number of reported events, stimulated reporting, treatment duration, prior or incompletely documented exposure to combination immunotherapy, age, baseline cardiovascular disease, demographic differences, and variability in clinical surveillance, none of which could be adequately assessed in the present dataset. Translational evidence suggests that intensified checkpoint blockade may promote cardiotoxic immune activation, although this evidence primarily supports the biological plausibility of cardiac toxicity rather than a melanoma-specific excess risk[14]. Accordingly, the present findings should be regarded as hypothesis-generating reporting signals rather than direct estimates of myocarditis incidence or comparative cardiotoxicity. From a clinical perspective, given the potentially severe and rapidly evolving nature of ICI-associated cardiac toxicity, the observed reporting

signal may support careful cardiovascular assessment within a multidisciplinary cardio-oncology framework integrating baseline cardiovascular risk, symptoms, electrocardiography, cardiac biomarkers, and imaging[15]. Emerging biomarkers reflecting early immune–metabolic myocardial stress, including heart-type fatty acid-binding protein, may provide additional information, although their clinical utility in ICI-treated patients requires prospective validation[16,17]. Cervical cancer showed the highest rate of gastrointestinal disorders. Persistent human papillomavirus (HPV) infection and mucosal immune dysregulation provide a biologically plausible hypothesis, but this result is novel and requires independent confirmation. Other explanations include prior pelvic radiotherapy, baseline gastrointestinal symptoms, and differential attribution of treatment-related events. The sex analysis is consistent with the broader observation that females have stronger humoral and adaptive immune responses and greater susceptibility to several autoimmune diseases[10]. Higher endocrine and hematologic reporting in females may reflect this predisposition. Conversely, higher respiratory and cardiac reporting in males may partly reflect the sex distribution of tumor types, smoking exposure, cardiovascular comorbidity, and treatment history. The small Cramér's V values indicate that sex alone has limited discriminatory ability and should not be used as a stand-alone predictor.

Microbiota, Concomitant Medications, and Multidimensional Predictors

Beyond sex and tumor histology, several host-, tumor-, and treatment-related factors may contribute to the heterogeneous safety profile of pembrolizumab. Among these, the gut microbiota has emerged as a key regulator of systemic immune homeostasis and of the clinical effects of immune checkpoint inhibition[18-20]. Microbial composition and function can influence antigen presentation, T-cell activation, cytokine production, and the balance between effector and regulatory immune responses. Microbiota-derived metabolites may also modulate the activity of ICIs by affecting antitumor T-cell responses[21]. Dysbiosis may therefore affect not only antitumor efficacy but also susceptibility to immune-mediated toxicity. Indeed, baseline gut microbial profiles have been associated with the development of immune checkpoint inhibitor-related colitis and other irAEs, although the available evidence remains preliminary and is largely derived from melanoma cohorts treated with different checkpoint inhibitors[22,23]. Microbial metabolites and environmental or pharmacological modifiers of the microbiome may interact with tumor biology and host immunity, although these relationships remain incompletely characterized. Concomitant medications are clinically relevant modifiers of the microbiota-immune axis. Antibiotic exposure has been associated with poorer survival outcomes in patients receiving ICIs, supporting the hypothesis that antibiotic-induced dysbiosis may disrupt the immune conditions required for an effective antitumor response[24]. Proton pump inhibitors (PPIs) use has likewise been associated with unfavorable progression-free and overall survival during immune checkpoint inhibitor therapy, potentially through alterations in gastrointestinal microbial composition, although residual confounding by comorbidity and treatment indication cannot be excluded[25]. Whether these agents also modify the incidence, severity, or organ distribution of irAEs remains uncertain and could not be evaluated in the present analysis. Importantly, microbiome-related determinants of efficacy should not automatically be assumed to predict toxicity in the same direction. Microbial configurations that favor immune activation and therapeutic response might, in some patients, also lower the threshold for immune-mediated tissue injury, whereas other microbial functions may promote immune regulation and protect against selected irAEs. The relationship among microbiota, efficacy, and toxicity is therefore likely to be non-linear, context-dependent, and organ-specific. Prospective studies integrating serial microbiome assessment with detailed irAE phenotyping are needed to clarify whether microbial signatures can support clinically useful risk stratification. Tumor-intrinsic and circulating biomarkers may further contribute to the observed heterogeneity. PD-L1 expression, microsatellite instability, mismatch-repair deficiency, tumor mutational burden, genomic alterations, inflammatory indices, circulating immune-cell subsets, cytokines, and circulating tumor-derived biomarkers capture different components of tumor immunogenicity and host immune competence. High tumor mutational burden may increase neoantigen availability, but its prognostic and predictive significance is context-dependent and can be modified by the underlying molecular background[26]. Similarly, the predictive value of individual biomarkers varies substantially across tumor types, as illustrated by the integration of mismatch-repair status, microsatellite instability, *POLE* alterations, PD-L1 expression, and other immune-related markers in endometrial cancer[27]. No single biomarker currently captures the complex interaction among tumor biology, host immunity, microbiota, concomitant

medications, efficacy, and toxicity. Taken together, these considerations suggest that the associations identified in this study should not be interpreted as being determined by sex or histology alone. Rather, these variables may function as readily measurable proxies for a broader biological framework that includes tumor immunogenicity, hormonal and genetic factors, comorbidities, prior treatments, concomitant medications, and microbiome composition. Future studies linking pharmacovigilance records with molecular, clinical, pharmacological, and microbiome-related data may enable multidimensional models capable of predicting both pembrolizumab efficacy and toxicity.

Strengths and Limitations

A major strength of this study is the large, European, real-world pharmacovigilance cohort, which enabled simultaneous evaluation of multiple tumor histologies and organ systems. Restriction to reports in which pembrolizumab was the only documented antineoplastic medicinal product reduced, but did not eliminate, confounding from concomitant anticancer treatment, as concomitant therapies may be incompletely reported in spontaneous-reporting databases. The use of standardized MedDRA SOC coding and multiplicity correction improved analytical consistency. The study also has important limitations. First, spontaneous-reporting databases are subject to under-reporting, stimulated reporting, notoriety bias, duplicate reports, incomplete clinical information, and variable diagnostic certainty. Second, the number of exposed patients is unknown; therefore, reporting proportions cannot be interpreted as incidence or comparative risk. Third, residual confounding by age, comorbidities, smoking, tumor stage, prior therapies, treatment duration, geographic region, and reporting source could not be addressed. Fourth, SOC-level grouping is broad and may combine clinically heterogeneous events. Fifth, the analysis did not establish temporal relationships, rechallenge outcomes, event severity, or causality. Sixth, the sex and histology analyses were unadjusted, so observed associations may reflect differences in case mix. Finally, rare-histology findings were based on small samples and did not remain significant under the prespecified multiplicity threshold. In addition, EudraVigilance does not provide sufficiently complete and standardized information on antibiotic or proton pump inhibitor exposure, dietary patterns, microbiome composition, PD-L1 status, tumor mutational burden, microsatellite instability, circulating biomarkers, or germline and somatic genomic factors. These potentially important prognostic and predictive variables could therefore neither be incorporated into adjusted models nor evaluated as effect modifiers of irAE reporting.

CONCLUSIONS

In EudraVigilance reports associated with pembrolizumab monotherapy, the organ-system distribution of irAEs varied by tumor histology and biological sex. Females had higher reporting proportions of endocrine and blood/lymphatic disorders, whereas males had higher proportions of respiratory and cardiac disorders. Breast cancer, bladder cancer, melanoma, and cervical cancer showed the highest reporting rates for endocrine, respiratory, cardiac, and gastrointestinal disorders, respectively. These findings are clinically plausible but remain hypothesis-generating. Prospective or registry-based studies with treatment denominators, validated diagnoses, exposure data, and multivariable adjustment are required before sex- or histology-specific monitoring strategies can be formally recommended.

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Authors' Contributions:
Conceptualization, G.C. (Giuliana Ciappina), F.B. and G.D.M.; methodology, F.B., S.P. and G.D.M.; validation, S.P., F.B. and G.D.M.; formal analysis, S.P. and M.D. (Marco Donato); investigation, G.C. (Giuliana Ciappina), S.P., F.B., M.D. (Marco Donato), F.D.L., C.I., E.M., P.C., M.D. (Maria Demana), D.M., S.F., C.S., G.C. (Giuseppe Corsaro), A.C., A.P. and G.D.M.; resources, G.C. (Giuliana Ciappina), S.P., F.B., M.D. (Marco Donato), C.I., G.C. (Giuseppe Corsaro) and G.D.M.; data curation, G.C. (Giuliana Ciappina), S.P., F.B., M.D. (Marco Donato) and G.D.M.; writing—original draft preparation, G.C. (Giuliana Ciappina), F.B. and G.D.M.; writing—review and editing, G.C. (Giuliana Ciappina), S.P., F.B., M.D. (Marco Donato), F.D.L., C.I., E.M., P.C., M.D. (Maria Demana), D.M., S.F., C.S., G.C. (Giuseppe Corsaro), A.C., A.P. and G.D.M.; visualization, G.C. (Giuliana Ciappina), F.B. and G.D.M.; supervision, G.C. (Giuliana Ciappina); project administration, G.C. (Giuliana Ciappina), F.B. and G.D.M. All authors have read and agreed to the published version of the manuscript.

Data Availability:

All data the authors extracted from the European Medicines Agency (EMA) pharmacovigilance database called EudraVigilance are publicly available at: www.adrreports.eu (accessed in March 2026).

Conflicts of Interest:

The authors declare no conflict of interest.

Ethics Approval and Informed Consent:

This study was based on a retrospective analysis of de-identified pharmacovigilance reports and did not involve direct patient recruitment, clinical interventions, or access to identifiable personal data. Therefore, Ethics Committee approval and informed consent were not required. Data were accessed and analyzed in accordance with the applicable data access and confidentiality requirements.

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