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Low type-2 immune effectors modulate atopic diseases' protective role in pancreatic cancer risk

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Abstract

Studies reported that atopic individuals exhibit a 36% reduced risk of developing pancreatic ductal adenocarcinoma (PDAC); however, the underlying molecular mechanisms remain unclear. This study examines the specific role of type-2 immune response in the atopy–PDAC inverse association. To endotype atopic conditions using type-2 immune effectors (i.e., eosinophils and immunoglobulin-E[IgE]) and investigate their protective effect against PDAC risk, IgE levels were measured in 688 PDAC cases and 558 controls from the PanGenEU case–control study. 'IgE-sensitization' was defined as having >100 kU/L total IgE with lab-tested sensitization to ≥1 food- or aeroallergens. Atopic conditions were determined using the European Community Respiratory Health Survey questionnaire. The UK Biobank cohort's 544 PDAC cases and 92,038 nested controls were categorized based on a threshold of 0.15×10^9 eosinophil cells/L plus self-reported atopy. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated using multivariable logistic regression. Restricted cubic splines were applied to examine the nonlinear relationship between type-2 immune effectors and PDAC risk. PDAC risk was not linearly associated with type-2 immune effectors levels. Compared to low IgE-sensitized non-atopic individuals, the low IgE-sensitized atopic population had significantly reduced PDAC risk (OR = 0.56, 95% CI: 0.35–0.84). Similar trends were observed among atopic

Abbreviations: BMI, body mass index; CI, confidence interval; GWAS, Genome-Wide Association Studies; ICD, International Classification of Diseases; IgE, immunoglobulin E; OR, odds ratio; PDAC, pancreatic ductal adenocarcinoma; s-IgE, specific immunoglobulin E; SNP, single nucleotide polymorphism; t-IgE, total immunoglobulin E; Th1, type 1 helper T-cell; Th2, type 2 helper T-cell; Th17, type 17 helper T-cell; UKB, UK Biobank; WHO, World Health Organization.

Jiangchuan He and Bilal Alashkar Alhamwe equally contributed.

PanGenEU investigators are listed in Appendix S1.

We disclose that the preliminary results of this paper were presented in a poster form at the 55th European Pancreatic Club (EPC) in 2023.

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individuals with low eosinophil counts (OR = 0.67, 95% CI: 0.47–0.95). Atopic conditions were inversely associated with PDAC risk, particularly among those with low levels of type-2 immune effectors. This indicates the protective effect of atopy against PDAC risk is modulated by low type-2 immune response.

KEYWORDS

allergy, asthma, blood eosinophils, pancreatic cancer, serum IgE, type-2 immunity

What's New?

Pancreatic ductal adenocarcinoma (PDAC) risk is inversely related to atopic diseases, such as asthma, rhinitis, and eczema. Relationships between immune factors and PDAC etiology, however, remain undefined. Here, the authors examined atopic disease and PDAC risk in terms of relationships with type-2 immune effectors, including IgE. Analyses show that PDAC risk among atopic individuals is associated with total IgE levels and blood eosinophil counts in a non-linear pattern. Notably, PDAC risk was reduced among atopic individuals with low type-2 immune responses. The findings cast light on the influence of immune states on PDAC, with possible implications for future treatment strategies.

1 | INTRODUCTION

The incidence of pancreatic cancer has been increasing, particularly among high-income countries[1,2] and it is projected to become the second leading cause of cancer-related mortality in the US by 2040.[3] Pancreatic ductal adenocarcinoma (PDAC) constitutes over 90% of pancreatic cancer cases.[4] The majority of PDAC cases are diagnosed at advanced stages due to delayed diagnosis and the aggressive nature of this malignancy. Despite extensive research efforts, the five-year overall survival rate of PDAC remains below 10% given the tumor's limited response to treatments.[2] The etiology and carcinogenic mechanisms of PDAC are not as well understood as compared to other malignancies, thus hampering the development of effective prevention and treatment strategies. Well-established risk factors include older age, cigarette smoking, obesity, type-2 diabetes mellitus, chronic pancreatitis, excessive alcohol consumption, and A^+/B^+ blood groups.[5–7] At the genetic susceptibility level, up to 40 variants have been identified as associated with PDAC risk by genome-wide association studies (GWAS).[8] A recent European-based GWAS expanded the list, revealing 53 novel SNPs and four chromatin interaction regions in 17 additional loci.[9]

Studies have reported an inverse association between PDAC risk and atopic diseases, such as asthma, rhinitis, and eczema. A meta-analysis comprising 14 case–control and cohort studies discovered a significantly reduced PDAC risk among individuals with a history of allergies, reporting an odds ratio (OR) of 0.83 (95% confidence interval, CI, 0.68–0.80).[10] A recent extensive European-based case–control study involving 1297 PDAC cases and 1024 controls further supported these findings, indicating asthma and rhinitis individuals are associated with a 36% (95% CI 0.47–0.88) and 34% (95% CI 0.52–0.83) reduced PDAC risk, respectively.[11] A complementary meta-analysis of 10 studies further confirmed the reduced PDAC risk among the atopic population, whereas no association was found among people with eczema, possibly due to misclassification with other skin conditions.[11]

The relationship between the immune system and human cancer etiology remains complex and incompletely understood. The "chronic inflammation hypothesis" suggests that persistent local inflammation induces continuous immune stimulation, oxidative tissue damage, suppressor gene mutation, ultimately promoting cancer development.[12,13] On the other hand, the "immunosurveillance hypothesis" proposes that allergic individuals have an upregulated immune system that recognizes tumor neoantigens and eliminates dysregulated cells at their early stages, resulting in reduced cancer risk.[14–16]

Atopic conditions have complex phenotypes, thus presenting challenges for experts in classifying them. Conventional classifications of allergy and asthma are based on temporality (e.g., early-, late-onset) or phenotypes (e.g., atopic, non-atopic) in favor of clinical diagnosis and therapeutic approaches but lack precision at the molecular level.[17–19] Recently, endotyping atopic diseases (Th2-low or Th2-high) based on the presence of Th2 effectors (e.g., IgE, macrophages, mast cells, eosinophils) is of increasing interest compared to other mechanisms involving Th1 and Th17 effectors.[18,20] These type-2 immunity cells coexist and regulate immune responses through various cytokine pathways.[21–23] In this study, we applied serum total IgE (t-IgE) levels, a broad panel of food- and aeroallergen-specific IgE (s-IgE) levels, and blood eosinophil counts to endotype asthma and rhinitis, aiming to investigate the atopic-Th2 distinct association with PDAC risk.

2 | METHODS

2.1 | Data sources and study population

The PanGenEU study is a comprehensive European multicentric case–control study on PDAC; it was conducted between 2009–2014 and

2016–2018. The study recruited PDAC cases and controls from 28 centers across six countries (Spain, Italy, Germany, the United Kingdom, Ireland, and Sweden). Eligible PDAC cases included individuals aged >18 with a diagnosis of PDAC (ICD10: C25) confirmed through medical and pathological records reviewed by clinicians. Controls comprised patients admitted to participating hospitals or medical centres with diagnoses unrelated to recognized PDAC risk factors.[6,7] A total of 2500 PDAC cases and 1550 hospital-based controls were enrolled, with a response rate of 86.3% for cases and 77.8% for controls.[7] In this study, we focused on 1246 PanGenEU participants from Spain (688 cases and 558 controls) who had serum samples for IgE available for determination.

UK Biobank (UKB) cohort study was additionally applied to explore the relationship between atopic conditions, blood eosinophil counts, and PDAC risk. Given UKB's open cohort nature and extensive recruitment window, we extracted and reorganized the data into a nested case–control design to facilitate the analysis, as its reliability has been well-proven.[24,25] Only incident PDAC cases were considered; therefore, PDAC cases diagnosed before their enrolment in the UKB cohort were excluded. To ensure consistency with the PanGenEU study, selected UKB individuals were Caucasians with the same ICD9/10 coding system as PanGenEU. Given the relatively limited PDAC case number compared to eligible controls (544 vs. 92,038) from the UKB, matching was meticulously performed to ensure a balanced case–control distribution (R package: MatchIt) based on age, sex, healthcare center, and genetic profiles at a 1:4 PDAC case to control ratio, with a caliper of 0.02 to guarantee robust statistical power. Ultimately, 2720 individuals, including 544 PDAC cases, were selected for subsequent analysis.

2.2 | Variables

Sociodemographic, lifestyle, past exposures, and biosample information from both studies were collected and analyzed. In the PanGenEU study, information on asthma and rhinitis status was acquired through face-to-face interviews, utilizing a standardized and validated questionnaire developed by the European Community Respiratory Health Survey.[11,26] Covariates included sex (female/male), age (continuous), body mass index 2 years before diagnosis (<25/25 to 30/>30), diabetes (no/yes), smoking status (never/former/current smoker), autoimmune disease status (no/any), asthma medication usage (no/yes), corticosteroid systemic medication (no/yes), and family history of PDAC (no/yes) (Table S1). For the UKB study, similar covariates to PanGenEU were extracted, with BMI being assessed at baseline enrollment in the cohort (Table S2).

2.3 | IgE and eosinophil measurement

In the PanGenEU study, measurements of t-IgE and s-IgE levels in patient serum samples were performed by the ImmunoCAP™ (Thermo Fisher Scientific) test platform. This sandwich assay reports results in kilounits per liter (kU/L), calibrated against the WHO standard for IgE. Two premixed assays (sx1 and fx5), including 14 allergen extracts, were used to measure s-IgE antibodies against aeroallergens and food allergens. The sx1 mix contained eight aeroallergen extracts (*Artemisia vulgaris*, *Betula verrucosa*, *Cladosporium herbarum*, *Dermatophagoides pteronyssinus*, dog dander, cat epithelium, *Phleum pratense*, and cultivated rye). The fx5 mix comprised six food allergen extracts (cod, egg, peanut, lactose, soya, wheat flour). If the assay result was positive, antibodies against each allergen were measured to define the specific allergen sensitization. The threshold for positivity was set at 0.34 kU/L.[27] For the UKB study, each individual's eosinophil count was measured at the baseline enrolment following the protocol developed by the UKB team.[28]

2.4 | Statistical analysis

In the PanGenEU study, missing data were imputed using a random forest model (R package: missForest) under the assumption of data missing at random. Predictors for imputation included age, sex, medical center, smoking status, diabetes, and obesity.[29] The imputation was conducted with 100 trees with no maximum iterations. Assessment of the final imputation indicated a concordance mean between imputed and real data >90%, with out-of-bag errors <0.35, affirming a good imputation.[7] Restricted cubic spline models (R package splines2) were applied to evaluate the non-linear association between PDAC risk and type-2 immune effectors (i.e., t-IgE levels and eosinophil counts). Two knots at 100 and 300 kU/L t-IgE levels and one knot at 0.15×10^9 cells/L for eosinophil count were applied. Furthermore, smoothing parameters in the spline models were additionally introduced. Cut-off points for t-IgE and eosinophils were set at 100 kU/L and 0.15×10^9 cells/L, respectively, following clinical guidelines and established scientific literature.[30–35] To focus on the true population of interest while ruling out t-IgE outliers possibly resulting from seasonal change or infections, PanGenEU subjects were categorized as 'high IgE-sensitization' if their t-IgE level exceeded 100 kU/L and were tested to be sensitized to at least one food- or aeroallergen.

Unconditional logistic regression models were employed to estimate ORs and 95% CIs. Initially, the models were adjusted for sociodemographic and lifestyle factors mentioned above (model 1). Subsequently, additional adjustment was made to include autoimmune disease and corticosteroid medication (model 2). In the subgroup analysis for asthma, rhinitis was controlled as a confounder in model 2, and vice versa for the rhinitis subgroup analysis. For the PanGenEU study, the reference group consisted of individuals who were non-atopic and low t-IgE-sensitized, whereas for UKB it comprised non-atopic individuals with low eosinophil counts. The model did not include asthma medication to avoid over-adjustment due to its high collinearity with asthma conditions ($R = 0.74$). The statistical significance

threshold was set at $p < 0.05$, and all analyses were performed using the R statistical package (V.3.3.0).

3 | RESULTS

3.1 | Population characteristics

Among the 1246 PanGenEU study participants, 688 (55.2%) were diagnosed with PDAC. The proportion of males was slightly higher at 57.1% in both case and control groups. The average age of the study population was 66 years (SD: 12.5) (Table S1). Significant differences were observed in current smokers: 28.4% of cases vs. 21.7% of controls (p-value = 0.018). Similarly, a larger proportion of cases (30.5%) vs. controls (17.0%) reported being diabetic (p-value = 5.07×10^{-8}). Furthermore, family history of PDAC was found to be more prevalent in the case group (7.0% vs. 3.4%). On the other hand, 6.8% of controls vs. 3.9% of cases were treated with corticosteroids (p-value = 0.038) (Table S1). The UKB nested case–control study ($N = 2720$) comprised 544 PDAC cases. Baseline characteristics, including age, sex, smoking, and diabetes status, were distributed similarly to the PanGenEU population (Table S2). BMI at enrollment in the cohort was directly associated with PDAC risk (p-value = 0.024).

3.2 | Atopic conditions are inversely associated with PDAC risk

The prevalence rates of atopic conditions in the PanGenEU Spanish subset were consistent with prior studies conducted among the European population.[36–39] As displayed in Table 1A, over 20% of subjects reported asthma or rhinitis. Notably, individuals with asthma exhibited a significantly lower frequency of PDAC compared to those without asthma (7.3% vs. 11.4%, OR = 0.62, 95% CI 0.42–0.91). A similar reduced risk was observed among the 193 individuals with rhinitis (12.6% vs. 19.3%, OR = 0.60, 95% CI 0.44–0.82), aligned with prior evidence indicating a protective effect against PDAC within the atopic population.[11] Among 111 subjects with asthma, 39 (35.1%) also reported rhinitis, and 44 (39.6%) of them did not require medication; further investigation revealed that these individuals received asthma scores ≤1, indicating mild or minimal asthma symptoms at baseline (results not shown).

TABLE 1A Association between atopic conditions characteristics and pancreatic ductal adenocarcinoma (PDAC) risk in PanGenEU case–control study ($N = 1246$).

	No. (%)				
Characteristics	Total ($N = 1246$)	Case ($n = 688$)	Control ($n = 558$)	p-value	Odds ratio[a] (95% CI)
Asthma or rhinitis					
No	953 (78.2)	555 (82.7)	398 (72.8)	3.83×10^{-5}	ref
Yes	265 (21.8)	116 (17.3)	149 (27.2)		0.57 (0.43–0.76)
Missing	28	17	11		
Asthma					
No	1104 (90.9)	620 (92.7)	484 (88.6)	0.020	ref
Yes	111 (9.1)	49 (7.3)	62 (11.4)		0.64 (0.43–0.92)
Missing	31	19	12		
Asthma score					
0	920 (77.3)	531 (81.2)	389 (72.6)	3.59×10^{-4}	ref
1	196 (16.5)	96 (14.7)	100 (18.7)		0.66 (0.48–0.91)
≥2	74 (6.22)	27 (4.13)	47 (8.77)		0.38 (0.23–0.63)
Missing	56	34	22		
Rhinitis					
No	1041 (84.4)	595 (87.4)	446 (80.7)	0.004	ref
Yes	193 (15.6)	86 (12.6)	107 (19.3)		0.64 (0.46–0.86)
Missing	12	7	5		
Asthma medication					
No	1148 (95.0)	646 (97.0)	502 (92.4)	5.37×10^{-4}	ref
Yes	61 (5.0)	20 (3.0)	41 (7.6)		0.34 (0.19–0.60)
Missing	37	22	15		

[a]Model adjusted for sex, age, smoking status, medical center, body mass index, autoimmune disease status, corticosteroid use, diabetes status, and family history of PDAC.

Within the UKB study, 669 subjects (24.6%) were recorded as having atopic conditions. Notably, a lower number of individuals ($N = 67$, 2.5%) reported being diagnosed with asthma, as the UKB only includes doctor diagnoses rather than self-reported conditions. This suggests that the diagnosed individuals likely experienced more severe symptoms which may require medication, aligning with the observed stronger protective effect (OR = 0.32, 95% CI 0.13–0.79). Individuals with rhinitis constituted nearly a quarter of the UKB study population, and they were less likely to develop PDAC than the non-rhinitis group (OR = 0.75, 95% CI 0.60–0.95) (Table 1B).

3.3 | Type-2 effectors are associated with atopic conditions in both PanGenEU and UKB

As anticipated, the distribution of t-IgE levels among PanGenEU study subjects was skewed (Figure 1A). Individuals with asthma or rhinitis displayed significantly elevated t-IgE levels (Figure 1B.1,B.2). In the UKB study, where 24.6% of subjects reported atopic conditions, density plots in Figure 1B.3,B.4 revealed a significant increase in blood eosinophils among individuals with asthma or rhinitis, further supporting previous scientific reports.[40,41]

TABLE 1B Association between atopic conditions characteristics and pancreatic ductal adenocarcinoma (PDAC) risk in the UK Biobank study (nested case–control) ($N = 2720$).

	No. (%)				
Characteristics	**Total ($N = 2720$)**	**Case ($n = 544$)**	**Control ($n = 2176$)**	***p*-value**	**Odds ratio[a] (95% CI)**
Asthma or rhinitis					
No	2051 (75.4)	435 (80.0)	1616 (74.3)	6.82×10^{-4}	ref
Yes	669 (24.6)	109 (20.0)	560 (25.7)		0.72 (0.57–0.91)
Asthma					
No	2653 (97.5)	539 (99.1)	2114 (97.2)	1.51×10^{-3}	ref
Yes	67 (2.5)	5 (0.9)	62 (2.8)		0.32 (0.13–0.79)
Rhinitis					
No	2079 (76.4)	437 (80.3)	1642 (75.5)	1.92×10^{-3}	ref
Yes	641 (23.6)	107 (19.7)	534 (24.5)		0.75 (0.60–0.95)

[a]Models adjusted for sex, age, smoking status, diabetes status, body mass index, family history of cancer, and PC1–3.

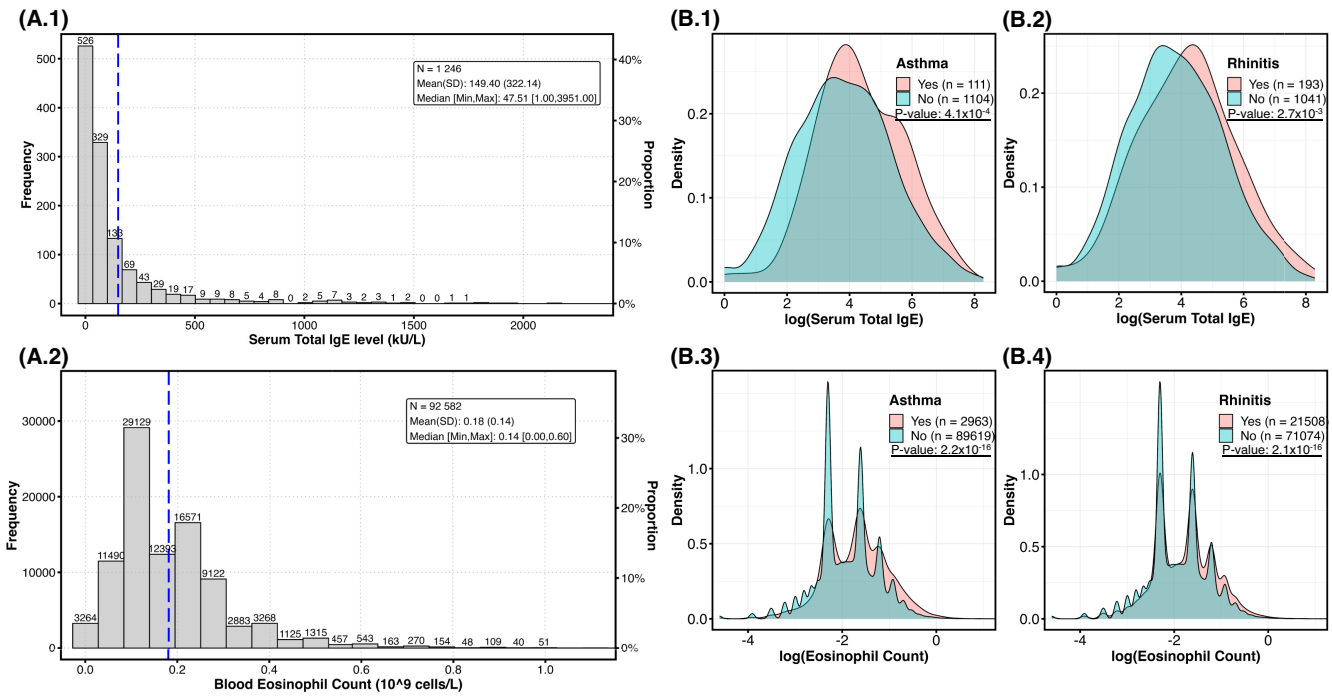

FIGURE 1 Distribution of serum total IgE (Panel A.1) and blood eosinophils (Panel A.2) and stratified by asthma and rhinitis status for PanGenEU (Panels B.1 and B.2, respectively) and UK Biobank (Panels B.3 and B.4, respectively) participants.

TABLE 2 Serum levels of total IgE and blood eosinophil count distribution by pancreatic ductal adenocarcinoma (PDAC) status in PanGenEU ($N = 1246$) and UK Biobank study ($N = 2720$).

	No. (%)				
Characteristics	**Total ($N = 1246$)**	**Case ($n = 688$)**	**Control ($n = 558$)**	***p*-value**	**Odds ratio[a] (95% CI)**
Serum total IgE levels				0.22	1.06 (0.96–1.16)
Mean (SD)	149.4 (322.0)	153.2 (335.17)	144.7 (305.52)		
Median [Min, Max]	47.5 [1.0, 3951.0]	48.0 [1.0, 3951.0]	47.0 [1.0, 3054.0]		
	No. (%)				
Characteristics	**Total ($N = 2720$)**	**Case ($n = 544$)**	**Control ($n = 2176$)**	***p*-value**	**Odds ratio[a] (95% CI)**
Eosinophil (count)				0.031	1.62 (1.03–2.39)
Mean (SD)	0.18 (0.14)	0.19 (0.16)	0.18 (0.14)		
Median [Min, Max]	0.14 [0.00, 6.60]	0.16 [0, 1.30]	0.14 [0, 6.60]		

Note: Unit: 10^9 cells/L.
[a]Models adjusted for sex, age, smoking status, diabetes status, body mass index, family history of cancer, and PC1–3.

3.4 | Type-2 effectors are inversely associated with PDAC risk among atopic subjects

Globally, t-IgE was not associated with PDAC risk, while eosinophil count showed a direct association (OR = 1.62, 95% CI 1.03–2.39) (Table 2). Fourteen food- and aeroallergen s-IgEs were examined individually, none of which revealed associations with PDAC risk (Figure S1).

Interestingly, restricted cubic spline models showed non-linear relationships between Type-2 effectors and PDAC risk only among the atopic subjects (Figure 2A, $n = 265$); with PDAC risk initially increasing at a t-IgE level of 30 kU/L and then declining to the lowest risk at 100 kU/L (OR = 0.7, $p = 0.01$). Subsequently, a positive dose–response relationship emerged at levels >300 kU/L, albeit non-significant. Among non-atopic individuals (Figure 2B, $n = 953$), the relationship was almost linear and non-significant. Table 3A showed that atopic low IgE-sensitized subjects experienced a 45% reduced PDAC risk (OR = 0.55, 95% CI 0.38–0.79) compared to non-atopic low IgE-sensitized individuals. Additional adjustment for autoimmune disease and corticosteroid usage yielded similar results. Notably, the risk of PDAC among the atopic high IgE-sensitized subjects was less reduced and non-significant. Conversely, the reduced risk was not evident among non-atopic individuals, regardless of their IgE levels (Figure 2B, Table 3A).

The restricted cubic splines (Figure 2C) show that individuals with rhinitis experienced an initial rise in PDAC risk at 15 kU/L of t-IgE, followed by a drop to the lowest risk at 100 kU/L (OR = 0.6) There was no association between t-IgE levels and PDAC risk among those subjects without rhinitis (Figure 2D). The fully adjusted logistic model revealed a 38% reduced risk of PDAC (OR = 0.62, 95% CI 0.40–0.96) among individuals with rhinitis and low IgE sensitization compared to their non-rhinitis counterparts (Table 3A). A non-significant linear relationship with PDAC risk was observed for both asthmatic and non-asthmatic subjects (Figure 2E,F, respectively), despite the asthmatics low IgE sensitization having a 44% lower risk of PDAC (OR = 0.56, 95% CI 0.31–0.96) compared to their non-asthmatic counterparts. Other endotypes with IgE sensitization did not exhibit such an association (Table 3A).

Eosinophils count >0.4 × 10^9 cell/L was positively associated with PDAC risk among non-atopic individuals (Figure 2H). However, no statistically significant association was found in the atopic group (Figure 2G). Compared to the non-atopic groups, atopic individuals with eosinophil counts <0.15 x 10^9 cells/L had a 33% decreased PDAC risk (OR = 0.67, 95% CI 0.47–0.95) (Table 3B).

4 | DISCUSSION

Existing scientific evidence consistently demonstrates an inverse association between atopic conditions and cancer development, except for lung cancer, of which the risk is increased among asthma patients.[35,42,43] Our findings not only consolidate previous conclusions about the inverse atopy–PDAC association but also extend the concept by suggesting that the protective effect is driven by a low type-2 immune response.

Our study uniquely employed major type-2 immune effectors, including serum t-IgE, s-IgEs, and blood eosinophils, to precisely endotype atopy within our populations. This novel approach enabled us to examine each atopic endotype individually. Following clinical guidelines and existing literature, we defined 'High IgE-sensitization' as t-IgE >100 kU/L combined with at least one positive s-IgE. This refined definition targets our population of interest while excluding IgE outliers caused by factors unrelated to atopy (i.e., parasites). Using this definition, we observed a nearly 45% reduction in PDAC risk among asthmatic individuals with low IgE-sensitization or low eosinophil counts in comparison to their non-asthmatic counterparts. A similar protective pattern was observed within the rhinitis population.

Our finding suggests the reduced PDAC risk among the atopic population is primarily influenced by low type-2 immune effectors.

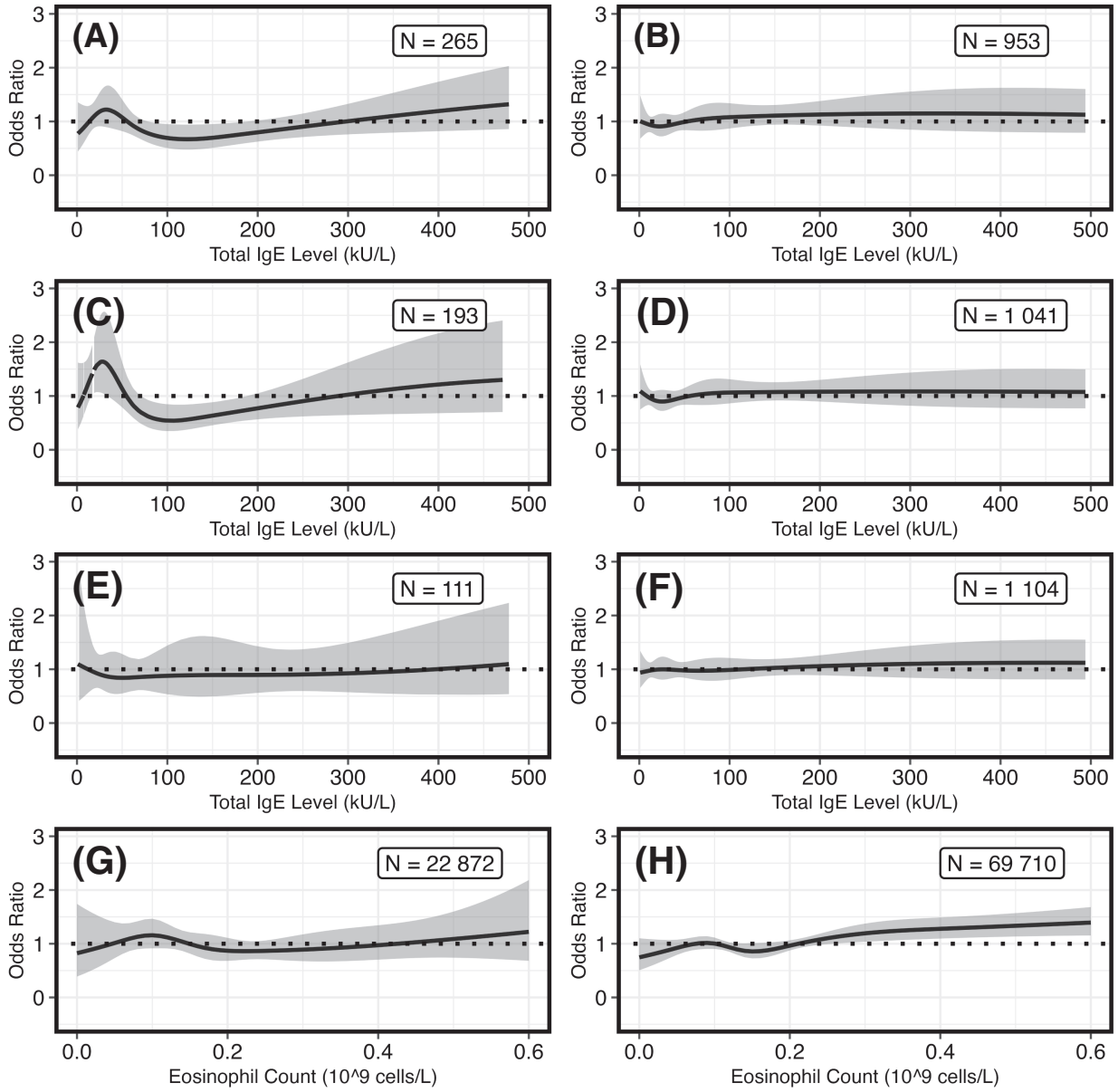

FIGURE 2 Non-linear relationships between total IgE levels (PanGenEU) and eosinophil counts (UKB) and the risk of PC depicted by restricted cubic splines and stratified by the atopic condition. (A) PanGenEU population with either asthma or rhinitis; (B) PanGenEU population with no asthma nor rhinitis; (C) PanGenEU population with rhinitis; (D) PanGenEU population without rhinitis; (E) PanGenEU population with asthma; (F) PanGenEU population with rhinitis; (G) UK Biobank population with either asthma or rhinitis; (H) UK Biobank population with no asthma nor rhinitis. Models were adjusted for sex, age, smoking status, medical center, diabetes status, body mass index, autoimmune disease status, corticosteroid use, and family history of PDAC for the PanGenEU-derived models; and for sex, age, smoking status, medical center, diabetes status, body mass index, family history of cancer, and PC1–3, for the UKB-derived models.

The protective effect may involve type-1 immunity, also known as cellular immunity, or type-17 immunity. Previous studies have highlighted the role of the type-1 immune response in tumor eradication.[44] A recent review demonstrated that a high T-helper 1 to T-helper 2 cell ratio enhances cancer immunity, leading to better cancer prognosis.[45] Furthermore, Chandra et al. observed that the gut epithelial IL-17 receptor may influence tumor development via microbial regulation,[46] while allergic conditions could enhance the IL-17/IL-17RA pathway, leading to reduced gut dysbiosis and a decreased risk of PDAC. Our study identified a significant increase in PDAC risk at a t-IgE level of 30kU/L. Subsequent analyses ruled out the possibility that this elevated risk was due to a limited sample size. Recent publications suggest that ultra-low type-2 immune cells may promote tumor development.[47,48] Examination of 14 IgEs targeting food and aeroallergen among the PanGenEU population exhibited no individual associations with PDAC risk (Figure S1). This lack of association is likely due to very few individuals meeting the sensitization threshold of 0.34 kU/L.

TABLE 3A Odds ratios (ORs) with 95% confidence intervals (CIs) for the association between pancreatic ductal adenocarcinoma (PDAC) risk and asthma or rhinitis status stratified by the IgE-sensitization status[a] ($N = 1246$) in the PanGenEU study.

	No. (%)		Odds ratio (95% CI)	
Characteristics	**Case ($n = 688$)**	**Control ($n = 558$)**	**Model 1 (a)**	**Model 2 (b)**
Asthma or rhinitis				
No asthma or rhinitis and low IgE-sensitization	392 (57.0)	284 (50.9)	1	1
No asthma or rhinitis and high IgE-sensitization	180 (26.2)	125 (22.4)	1.03 (0.78–1.37)	1.02 (0.76–1.36)
Asthma or rhinitis and low IgE-sensitization	59 (8.6)	83 (14.9)	**0.55 (0.38–0.79)**	**0.56 (0.35–0.84)**
Asthma or rhinitis and high IgE-sensitization	57 (85.3)	66 (11.8)	0.64 (0.42–1.03)	0.65 (0.41–1.05)
Rhinitis status				
No rhinitis and low IgE-sensitization	399 (59.2)	306 (54.8)	1	1
No rhinitis and high IgE-sensitization	195 (28.3)	145 (26.0)	1.00 (0.76–1.30)	1.02 (0.78–1.35)
Rhinitis and low IgE-sensitization	44 (6.4)	59 (10.6)	**0.62 (0.40–0.94)**	**0.62 (0.40–0.95)**
Rhinitis and high IgE-sensitization	42 (6.1)	48 (8.6)	0.67 (0.43–1.04)	0.76 (0.48–1.21)
Asthma status				
No asthma and low IgE-sensitization	430 (62.5)	335 (60.0)	1	1
No asthma and high IgE-sensitization	209 (30.4)	161 (28.9)	0.98 (0.75–1.27)	1.01 (0.78–1.40)
Asthma and low IgE-sensitization	22 (3.2)	33 (5.9)	**0.53 (0.29–0.93)**	**0.56 (0.31–0.96)**
Asthma and high IgE-sensitization	27 (3.9)	29 (5.2)	0.75 (0.40–1.23)	0.78 (0.44–1.40)

Note: (a) Model 1: adjusted for sex, age, smoking status, medical center, alcohol status, body mass index. (b) Model 2: Model 1 + additionally adjusted for autoimmune diseases status, corticosteroid usage, and atopic condition. Significant estimates are highlighted in bold.
[a]High IgE-sensitization: total IgE > 100 kU/L and with at least one sensitization to food or aeroallergen-specific IgEs.

TABLE 3B Odds ratios (ORs) with 95% confidence intervals (CIs) for the association between pancreatic ductal adenocarcinoma (PDAC) risk and asthma or rhinitis status stratified by blood eosinophil level cut-off point: 0.15 x 10^9 cells/L ($N = 2720$).

	No. (%)		Odds ratio (95% CI)	
Characteristics	**Case ($n = 544$)**	**Control ($n = 2176$)**	**Model 1 (a)**	**Model 2 (b)**
Asthma or rhinitis				
No asthma or rhinitis low eosinophil	216 (39.7)	843 (38.7)	1	1
No asthma or rhinitis high eosinophil	219 (40.3)	773 (35.5)	1.11 (0.90–1.37)	1.09 (0.88–1.40)
Asthma or rhinitis low eosinophil	44 (8.1)	252 (11.6)	**0.68 (0.47–0.96)**	**0.67 (0.47–0.95)**
Asthma or rhinitis high eosinophil	65 (11.9)	308 (14.2)	0.82 (0.60–1.11)	0.82 (0.60–1.10)

Note: (a) Model 1: raw model. (b) Model 2: models adjusted for sex, age, smoking status, diabetes status, body mass index, family history of cancer, and PC1–3. Significant estimates are highlighted in bold.

Our findings align with other studies suggesting that high IgE levels and eosinophil infiltration might be unfavorable for cancer development. The binding of allergens to IgE receptors on immune cells can interfere with their capacity to eliminate tumor cells, thereby suppressing the immune response against the tumor.[42] Moreover, studies have reported adverse effects of eosinophil infiltration in the context of cancer.[49,50] On the other hand, the unfavorable effect of type-2 immune effectors could be explained by the cytokines secreted by these cells, which potentially stimulate tumor progression.[48] A review on allergy and the risk of glioma suggested that type-2 cytokines (e.g., IL-4, IL-10) have tumor-promoting features and overexpression of Th2-associated genes corresponding to Th2 cell infiltration in glioblastoma is linked to worse prognosis.[23] These insights highlight the unique molecular pathways influenced by various immune responses, which have significant implications for advancing personalized medicine in cancer care.

The following are limitations of our study. The PanGenEU study relied on self-reported atopic conditions, introducing potential reporting and recall bias. Nevertheless, utilizing validated questionnaires from the European Community Respiratory Health Survey and involving trained professionals ensured overall study quality. Additionally, the prevalence rate of asthma (9.1%) and rhinitis (25.6%) among the PanGenEU population aligns with published Spanish studies, ensuring credibility.[37,51] The UKB study had fewer asthmatic individuals as they were asked for a medical asthma diagnosis, indicating these individuals had medical treatment-required endotypes. Consistent with our previous work, severe asthma patients exhibited a stronger PDAC risk reduction, although the effects of medication were only partially

controlled in our models to avoid overadjustment.[11] Sensitivity analyses using a larger UKB sub-cohort ($N = 92,582$) confirmed that the matching was well-performed, as the distribution of exposure and other sociodemographic and medical factors among the complete cohort was similar to our selected study population (Tables S2 and S3). The PanGenEU case–control design is subject to reverse causality bias, meaning PDAC might influence serum IgE. However, given that PDAC primarily occurs among the elderly while atopic diseases typically develop early in life, the likelihood of a reverse effect is very low. Notably, the cohort design of UKB precludes this bias, as blood eosinophils were measured at the study enrollment in 2006, preceding PDAC diagnoses. Moreover, neither UKB nor PanGenEU studies had detailed records on medication use. This limitation will be addressed in our future PanGen-Asthma study by collecting comprehensive medication use from participants. Certain subgroup analyses had limited statistical power due to stratification. Nonetheless, the consistency of our findings with prior research underscores the robustness of our study results.

Several strengths of our study should be highlighted. Firstly, our results are consistently supported by two large independent population groups, the PanGenEU study and the UKB cohort, in which we performed separate statistical analyses. This consistent alignment suggests excellent generalizability of our findings. Parallel analyses of PDAC risk in relation to sex, age, diabetes, and cigarette smoking yielded uniform outcomes from both studies and are similar to those reported in the literature, suggesting strong both internal and external validity. Furthermore, the study benefited from a large sample size including detailed information on serum biomarkers. The thresholds of both Th-2 effectors closely aligned with those reported by other studies, indicating a great representation of the general population in our study. The substantial number of PDAC cases together with comprehensive coverage of each participant's socioeconomic, lifestyle, and health-related factors enabled exhaustive analyses with minimized residual confounding effects and robust statistical power. In addition, we took a novel statistical approach to explore the non-linear relationship between type-2 immune effectors and PDAC risk. Identifying these non-linear risk patterns indicates a delicate balance between immune cells and cancer development, contributing valuable insights to the field.

Arguably, the incidence of allergies and asthma is rising, potentially reducing the number of PDAC cases in the population. However, the etiology of PDAC is multifactorial, influenced by environmental factors and host susceptibility, including immune and metabolic states. The complex relationship among these elements complicates our understanding of the intricate pathophysiology of this malignancy compared to other cancers. Other established risk factors, such as diabetes and obesity, are increasing, especially among younger individuals, thereby yielding an increase in PDAC risk. This complex interplay among all these elements requires further exploration to clarify the roles of various factors in the allergy–PDAC pathway. Future investigations should incorporate a broader range of biomarkers for atopy endotyping. In addition, longitudinal data collection is recommended to track changes in biomarker levels among patients over time. Our findings shed light on this intricate allergy–PDAC relationship by indicating the protective effect is mediated by a low type 2 immune response. This paves the way for further exploration of the underlying mechanisms related to PDAC and atopy and expands the possibility of applying tailored preventive and therapeutic interventions considering individual immune profiles. By doing so, we can optimize cancer treatment strategies and improve patient outcomes.

AUTHOR CONTRIBUTIONS

Jiangchuan He: Methodology; investigation; validation; data curation; software; writing – original draft; writing – review and editing; visualization; formal analysis. **Bilal Alashkar Alhamwe:** Methodology; investigation; validation; writing – review and editing; writing – original draft; resources. **Sergio Sabroso:** Methodology; software; data curation; validation; investigation; formal analysis; visualization; writing – review and editing. **Alfredo Carrato:** Investigation; resources. **Manuel Hidalgo:** Investigation; resources. **Xavier Molero:** Investigation; resources. **Mar Iglesias:** Investigation; resources. **José Perea:** Investigation; resources. **Antoni Farré:** Investigation; resources. **Adonina Tardón:** Investigation; resources. **Enrique Dominguez-Muñoz:** Investigation; resources. **Victor Barberà:** Investigation; resources. **Luís Muñoz-Bellvís:** Investigation; resources. **Matthias Löhr:** Investigation; resources. **William Greenhalf:** Investigation; resources. **Michael O'Rorke:** Investigation; resources. **Thomas Gress:** Investigation; writing – review and editing; resources. **Tatjana Crnogorac-Jurcevic:** Investigation; resources; writing – review and editing. **Auba Gayà:** Investigation; validation; resources; writing – review and editing. **Alberto Langtry:** Investigation; formal analysis; validation; writing – review and editing. **Jörg Kleeff:** Investigation; resources. **Rita Lawlor:** Investigation; resources. **Francisco X. Real:** Investigation; resources; methodology; validation; data curation; writing – review and editing. **Harald Renz:** Methodology; validation; resources; writing – review and editing; conceptualization; writing – original draft; investigation. **Núria Malats:** Supervision; project administration; conceptualization; methodology; investigation; validation; funding acquisition; visualization; resources; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The None.

DATA AVAILABILITY STATEMENT

This work has been conducted using the UK Biobank Resource under Application Number 94757 and The PanGenEU cohort. The UK Biobank is an open-access resource, and bona fide researchers can apply to use the UK Biobank dataset by registering and applying at http://ukbiobank.ac.uk/register-apply/. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

PanGen EU case–control Study: ethical approvals from Institutional Review Boards and written informed consent were obtained from all participating centers and individuals (HIP CI-CEI PI 09_2022-v2). UK Biobank cohort: all participants' informed consents were collected by the UKB team, and this study has been approved by the UKB administration (Project approval ID: 94757).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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