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Immune perturbation in arsenic-induced adverse health effects and cancers

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Chronic exposure to inorganic arsenic remains a global health concern and is strongly associated with cutaneous malignancies, pigmentation abnormalities, internal cancers, and a range of non-malignant outcomes. In addition to direct genotoxic stress and epigenetic remodeling, arsenic exerts broad immunomodulatory effects that shape disease initiation, persistence, and progression. In the skin, arsenic perturbs barrier integrity, antigen presentation, cytokine networks, and immune surveillance—features that may contribute to the multiplicity and recurrence that characterize arsenic-associated skin cancers. Emerging evidence also highlights the importance of exposure timing (particularly perinatal windows), co-exposures, and host susceptibility factors. This review synthesizes recent advances in: (i) exposure assessment (including noninvasive image-based estimation and biomarker interpretation in the context of diet), (ii) long-latency cancer risk and the population impact of water mitigation, (iii) keratinocyte stress and inflammatory signaling pathways that intersect with cutaneous immune dysregulation, (iv) perinatal metal exposure and allergic disease trajectories with immune profiling, and (v) genetic and epigenetic determinants of susceptibility (including polymorphisms influencing tissue remodeling and arsenic metabolism). We propose an updated framework in which arsenic-driven immune perturbation acts as a unifying axis linking exposure to cutaneous carcinogenesis, internal cancers, and allergic phenotypes, and we outline research gaps and translational opportunities for precision prevention.

KEYWORDS

arsenic, atopic dermatitis, exposure assessment, genetic susceptibility, immune dysregulation

Introduction

Arsenic is a common element in the Earth's crust and a pervasive environmental toxicant encountered through drinking water and diet [1]. It is also used in the semiconductor industry because of its unique electronic properties [2]. Human activities—including mining and smelting, well drilling, and fossil-fuel combustion—can increase arsenic exposure in communities and raise the risk of arsenic-related illnesses. Acute arsenic poisoning can cause abdominal cramping, diarrhea, arrhythmia, liver decompensation, seizures, brain edema, and death [3]. Historically, arsenic has been a notorious poison and has been implicated in deaths of prominent figures, including the Guangxu Emperor of the Qing dynasty of China [4]. Chronic arsenic poisoning remains a major public health issue because it increases the risk of multiple cancers, including those of the skin, bladder, and lung.

Tens of millions of people worldwide are at risk for chronic arsenic exposure, including populations in Bangladesh, India, Pakistan, Taiwan, Vietnam, Mexico, China, Argentina, Chile, and the United States [5]. In the skin, chronic arsenic exposure can lead to keratosis and pigmentation abnormalities, including variegated pigmentation and palmoplantar hyperkeratosis [6]. Chronic arsenic exposure is also associated with vascular diseases, including blackfoot disease—once endemic in Taiwan—as well as cardiovascular disease and stroke [7].

Despite its well-known adverse health effects, arsenic has been used medicinally. Fowler's solution was used for fever, headache, and tumors in the 17th century [8]. In the 19th century, Atoxyl (sodium arsanilate) was used to treat human trypanosomiasis (sleeping sickness) [9]. In 1910, Paul Ehrlich (Nobel Laureate, 1908) synthesized Salvarsan ("606"), a landmark treatment for syphilis [10]. Most of these uses were abandoned with the advent of antibiotics and other modern therapies. However, arsenic trioxide—approved by the FDA in 2003—remains a treatment option for acute promyelocytic leukemia because of its strong antiproliferative effects on leukemic cells. This leukemia-targeting activity underscores arsenic's potent effects on immune and hematopoietic cells. The fact that not all exposed individuals develop cancers or vascular disease suggests that arsenic-induced immune perturbation may contribute to inter-individual susceptibility.

The specific molecular targets of arsenic in biological tissues remain incompletely defined. One possibility is that arsenic's chemical similarity to other group 15 elements (e.g., nitrogen and phosphorus), which are essential components of proteins and nucleic acids, enables broad interactions with critical biomolecules. After entering the body, inorganic arsenic is metabolized through reduction/oxidation and methylation to produce arsenite [As(III)], arsenate [As(V)], monomethylarsonic acid (MMA), and dimethylarsinic acid (DMA) [11] (Figure 1).

We previously summarized key epidemiologic and mechanistic evidence linking arsenic carcinogenesis to immune dysfunction [12]. The World Health Organization (WHO) identifies drinking water as a major exposure route and recommends a guideline value of 10 μg/L for arsenic in drinking water [13]. These regulatory benchmarks draw heavily on large-scale longitudinal studies from Taiwan [14]. Importantly, arsenic exposure does not act solely through direct cellular toxicity; it can reshape innate and adaptive immune function, thereby altering tissue homeostasis, inflammatory tone, and tumor immune surveillance. Since our 2019 synthesis, our group has advanced the field with population-level evidence for reduced cancer burden after mitigation, improved approaches for exposure estimation, and new insights into host susceptibility across the life course.

Exposure analysis and sources: water, rice, and seafood

Drinking water and mitigation

Arsenic-contaminated artesian and well water has driven endemic arsenicosis, including characteristic skin manifestations and internal cancers. Drinking contaminated water remains the most important route of chronic inorganic arsenic exposure in many settings. Arsenic-associated skin cancers are distinguished from classical UV-related skin cancers by their multiplicity and their predilection for sun-spared skin. We reported that interactions between arsenic-induced keratinocyte apoptosis and UV exposure may help explain the relative rarity of arsenic-associated skin cancers in chronically sun-exposed skin [15]. Even after exposure reduction, cancer risk can persist for years to decades, consistent with arsenic's long natural history in carcinogenesis and immune remodeling. In Taiwan, water mitigation has been associated with a reduced burden of arsenic-related cancers, with substantial age-cohort effects—supporting primary prevention while underscoring the need for long-term surveillance in previously exposed populations [16]. Water mitigation remains one of the most important preventive measures against chronic arsenic poisoning worldwide.

Dietary sources and biomarker interpretation

When arsenic in drinking water is controlled, diet can become a major source of inorganic arsenic intake. Rice and rice-based products can contribute to inorganic arsenic exposure, and biomonitoring studies have linked rice consumption to higher urinary arsenic species reflective of inorganic exposure [17]. In addition to drinking-water guidelines, several

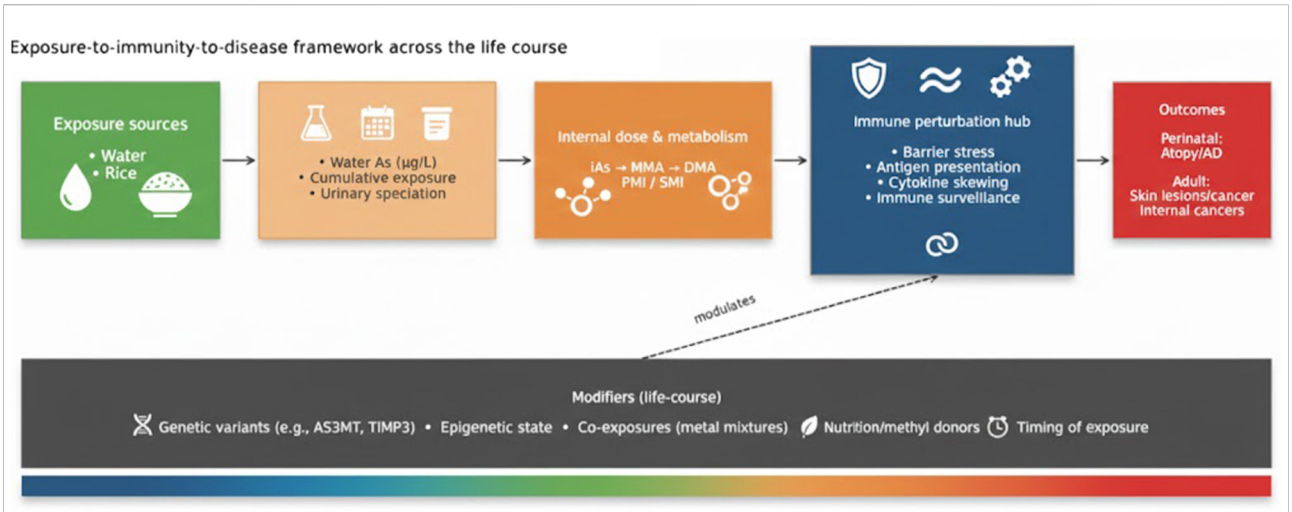

FIGURE 1
Exposure-to-immunity-to-disease framework across the life course. Flow schematic showing how exposure sources (water, rice, seafood) contribute to exposure metrics (water concentration, cumulative exposure, urinary speciation) and internal dose/metabolism (iAs -> MMA -> DMA; PMI/SMI). An immune perturbation hub (barrier stress, antigen presentation, cytokine networks, immune surveillance) links exposure to outcomes by timing: perinatal/early life (atopy and atopic dermatitis trajectories) and adulthood (cutaneous lesions and skin cancer; urothelial cancers). Modifiers include genetic variation (e.g., metabolism and tissue-response genes), epigenetic state, metal mixtures, and availability of nutritional methyl donors.

TABLE 1 Regulatory limits for inorganic arsenic in rice (µg/kg, ppb).

µg/kg (ppb)	EU	Taiwan	US	WHO
White/polished rice	150	200		200
Parboiled/husked rice	250	350		350
Infant/Children's food	100	100	100	

jurisdictions—including the European Union, Taiwan, and the United States—have established regulatory limits for inorganic arsenic in rice and rice-based products (Table 1). In general, husked (brown) rice tends to contain higher arsenic concentrations than polished (white) rice.

Seafood exposure complicates biomarker interpretation because most arsenic in seafood is organic rather than inorganic. In finfish and many shellfish, arsenic is primarily present as organic species (especially arsenobetaine), which are generally considered of low toxicity and are rapidly excreted. However, seafood consumption can increase urinary arsenobetaine and may elevate urinary dimethylarsinate (DMA), complicating the use of total urinary arsenic or DMA as proxies for inorganic arsenic exposure in seafood-consuming populations [18]. In children, urinary arsenic species vary with rice and seafood intake, underscoring the importance of dietary context when interpreting biomonitoring results [19]. Practical approaches include arsenic speciation where feasible and analytical strategies that account for arsenobetaine in epidemiologic studies [17]. Using urinary speciation, Liao et al. showed that people with a higher percentage of dimethylarsinic acid had a higher risk of developing hepatitis viral infection-related liver cancer than otherwise [20]. Hijiki, a type of seaweed, can contain high concentrations of inorganic arsenic; Park et al. from Korea reported that boiling hijiki at 90 °C and soaking it in a 2% NaCl solution reduces the intake of inorganic arsenic by consumers [21].

Biomonitoring and emerging tools

Urinary arsenic speciation provides a widely used metric of recent exposure and metabolism, enabling the derivation of methylation indices that approximate arsenic biotransformation capacity. In a long follow-up cohort from an arsenicosis-endemic area, low-to-moderate arsenic exposure was associated with urothelial tract cancers, with susceptibility signals concentrated among individuals with a lower primary methylation index or a higher secondary methylation index [22].

Arsenic exposure is sometimes approximated as water intake × years of use. Still, this metric does not capture exposure from other routes (e.g., diet, smoking, and inhalation) and may not reflect the true internal dose. As a result, exposure assessment often relies on biomarkers measured in tissues and fluids such as nails, hair, skin, blood, and urine. Because arsenic is rapidly cleared from the blood, blood arsenic is generally not a reliable biomarker of exposure [23]. In contrast, urinary arsenic is a relatively good indicator of internal dose and has been associated with several chronic health outcomes linked

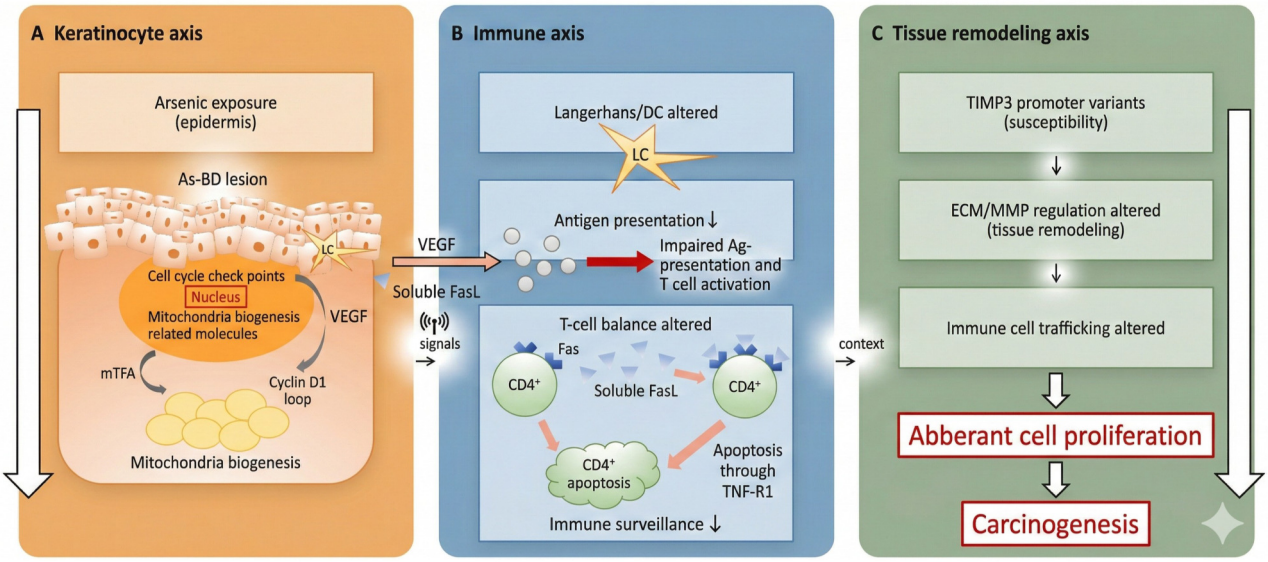

FIGURE 2
Cutaneous immune microenvironment in arsenic carcinogenesis. The progression of arsenic-induced Bowen's disease (As-BD) to cancer involves three interconnected axes: **(A)** Keratinocyte axis: Arsenic exposure induces intracellular dysfunction, including mitochondrial biogenesis and cell cycle disruption, prompting keratinocytes to secrete VEGF and soluble FasL. **(B)** Immune axis: These secreted signals suppress local immunity by impairing Langerhans cell antigen presentation and triggering $CD4^+$ T-cell apoptosis via Fas/TNF-R1 signaling pathways. **(C)** Tissue remodeling axis: The resulting immunosuppression, combined with host genetic susceptibilities (e.g., TIMP3 variants), drives ECM/MMP dysregulation, which may alter immune cell trafficking, creating a permissive environment for aberrant cell proliferation and carcinogenesis.

to arsenic in drinking water [24]. While many epidemiologic studies use total urinary arsenic, arsenic speciation can be more informative; specific metabolites (e.g., MMA) have been consistently associated with arsenical skin lesions and cancers. Interpretation should also consider potential confounders (e.g., diet, sex, and age). Finally, external contamination can artefactually elevate arsenic concentrations measured in hair and nails. A recent translational advance is our artificial intelligence (AI)-based, noninvasive approach for estimating arsenic exposure using standardized photographs of hands and feet. This tool leverages cutaneous stigmata (e.g., hyperkeratosis patterns) to classify exposure categories and may enable scalable screening when laboratory testing is limited [25].

Immune perturbation as a unifying mechanism in arsenic-related disease

Arsenic-related outcomes span malignant and non-malignant phenotypes, suggesting systems-level disruption. Immune perturbation may connect these outcomes through four non-mutually exclusive modes: (1) barrier and epithelial stress signaling, (2) altered antigen presentation and local immune surveillance, (3) shifts in T-cell polarization and regulatory balance, and (4) epigenetic and transcriptional rewiring. These processes were synthesized in our prior review and remain useful for integrating new data [12].

Cutaneous carcinogenesis: keratinocyte pathways and the immune microenvironment

Skin as a sentinel organ for exposure and immune disruption

The skin provides visible markers of chronic exposure and a biologically informative site where arsenic can drive epithelial transformation alongside immune dysregulation (Figure 2). Clinical hallmarks such as lesion multiplicity and recurrence support a role for impaired immune surveillance and dysregulated inflammatory signaling in arsenic-associated cutaneous carcinogenesis. Arsenic is classified by the International Agency for Research on Cancer (IARC) as a Group 1 carcinogen, yet it is often considered a weak mutagen; during chemical carcinogenesis, arsenic is generally viewed as acting predominantly at the promotion stage rather than the initiation stage. After decades of exposure, skin cancer and keratosis may precede the development of internal cancers, including bladder, lung, and liver, making the skin a sentinel organ and an early surrogate indicator of arsenic exposure.

Only a subset of people exposed to arsenic develop adverse health effects [26]. The observation that arsenic exposure induces cancers in only a minority of exposed populations suggests that host factors, including immune responses, may modulate the process of carcinogenesis [27]. In patients with arsenic-associated cancers, the *in vivo* delayed-type hypersensitivity response—relevant to antigen-presenting cells and T cells—is impaired [28]. In patients with blackfoot disease, anti-endothelial cell IgG antibodies induce endothelial proliferation and VEGF-dependent angiogenesis, highlighting the potential role of humoral immunity in collateral neovascularization [29].

The skin immune system includes resident epidermal keratinocytes, dermal myeloid cells (including macrophages), epidermal Langerhans cells, and adaptive immune populations such as T and B cells. A dysregulated immune system contributes to many aspects of arsenic-induced disease, including infections, allergy, carcinogenesis, and angiogenesis [1]. For example, the Health Effects of Arsenic Longitudinal Study (HEALS) cohort in rural Bangladesh showed that exposure to low-dose arsenic in early life alters innate immune function in children (n = 51) [30]. We have also reported that cumulative arsenic exposure is associated with fungal infections in cohort studies (n~3000) conducted in the southwestern and northeastern basins in Taiwan [31].

Experimentally, arsenic can differentially affect activation, differentiation, and apoptosis across immune cell types [27, 32]. We previously reported that arsenic selectively induces Fas-dependent apoptosis of Th2 lymphocytes [33]. Macrophages from people exposed to arsenic show reduced cell-adhesion capacity and impaired phagocytic ability [34]. Monocytes from children exposed to arsenic produce less superoxide anion and nitric oxide [35]. In line with this, we have demonstrated that arsenic mobilizes epidermal Langerhans cells (professional epidermal antigen-presenting cells) and polarizes the Th1 response in arsenical cancers [36].

Cytokines from T-cell subsets and keratinocytes

Translating mechanistic findings across models requires caution. Many *in vitro* and small-animal studies use higher arsenic doses over shorter durations than those encountered in human chronic exposure. Such designs may better capture acute immunotoxicity than the longer-term immune remodeling that characterizes chronic arsenic-associated skin disease. Moreover, many studies focus on systemic immune changes, whereas fewer directly assess the cutaneous immune microenvironment in arsenic-related lesions. The following summary highlights reported immune signatures associated with chronic arsenic exposure in the context of arsenic-related skin lesions and cancers. Because not all studies quantify T-cell subsets in skin biopsies, some statements may reflect systemic immune alterations observed in patients with arsenic-associated skin disease.

For Th1 responses, we have reported that, in a mouse epicutaneous sensitization model, arsenic exposure increased ovalbumin (Ova) antigen-driven lymph node cell proliferation and elevated IFN-γ and IL-12 secretion, supporting context-dependent Th1 polarization [36]. However, in humans with arsenic-induced skin lesions, stimulated T-cell proliferation has been reported to be dose-dependently impaired, with reduced secretion of IFN-γ, TNF-α, and IL-2, consistent with impaired Th1-type effector output [37].

For Th2 responses, population studies of arsenic-induced skin lesions in Bangladesh reported elevated circulating type 2 cytokines (IL-4, IL-5, IL-13), eotaxin, and IgE, with trends toward higher levels in more advanced lesions—suggesting type 2-skewed inflammatory remodeling [38]. In contrast, *ex vivo* stimulation assays in chronically exposed individuals with skin lesions showed reduced secretion of IL-4 and IL-5 alongside broader cytokine suppression, indicating that type 2 signatures may differ by assay (steady-state serum versus stimulated T-cell capacity) and by disease stage [37].

For Th17/Treg-associated pathways, one review reported that arsenic can impair human Th17 differentiation and reduce IL-17 and RORγt via signaling effects (e.g., the JNK/c-Jun pathway) [32]. However, analyses of human skin samples in arsenic-related pathology have reported increased IL-6 and IL-17 levels, with progressive increases across worsening skin-damage severity. For regulatory pathways, functional T-cell assays from exposed individuals with skin lesions have also reported decreased IL-10 secretion [39].

For IL-1 family and inflammasome signaling, keratinocyte-driven innate pathways are a consistent theme in mechanistic studies. Subchronic arsenic exposure has been shown to activate the AIM2 inflammasome in human keratinocytes and mouse skin, leading to caspase-1 activation and increased IL-1β and IL-18 production [40]. The IL-36 axis comprises IL-1 family cytokines produced largely by keratinocytes that can act as inflammatory amplifiers in the epidermis; IL-36R/MyD88 signaling can promote IL-17-driven skin inflammation. However, direct evidence specifically quantifying IL-36 pathway activation in arsenicosis lesions remains limited compared with IL-1β/IL-18 and IL-6/IL-17. Further investigation of this axis is warranted.

Tissue remodeling and susceptibility: TIMP3 polymorphisms

Tumor progression involves extracellular matrix remodeling, immune cell trafficking, and stromal signaling. In an arsenic-exposed cohort, TIMP3 promoter polymorphisms (−1296 T>C and −915 A>G) were associated with increased susceptibility to arsenic-induced skin cancer, and *in silico* analyses suggested allele-specific transcription factor binding effects [41].

Functionally, TIMP3 influences matrix metalloproteinase activity and tissue architecture, providing a plausible interface between arsenic exposure, tissue remodeling, and immune context.

Limited evidence linking chronic arsenic exposure to allergic disease in adults

Growing evidence indicates that arsenic exerts immunosuppressive effects in epidemiologic studies, *in vitro* systems, and small-animal models. However, many *in vitro* experiments use relatively high arsenic concentrations over short exposure periods and therefore may reflect acute toxicity rather than chronic immune remodeling. Similarly, in small-animal studies, doses required to elicit measurable effects are often high—levels that would be sublethal or even lethal in humans. In human epidemiologic research, exposure–outcome associations can be evaluated, but detailed mechanistic inference is often challenging. Only a few studies have examined associations between chronic arsenic exposure and allergic disease in adults. In Bangladesh, individuals with high chronic arsenic exposure had significantly elevated serum IgE levels compared with unexposed persons, along with increased respiratory complications, including asthma [42]. Hossain et al. showed that elevated serum periostin levels were positively associated with serum levels of Th2 mediators, including interleukin (IL)-4, IL-5, and IL-13, and with increased odds of asthma [43]. In a study of 553 blood samples from arsenic-exposed individuals, arsenic exposure was positively associated with serum Th2 mediators (IL-4, IL-5, IL-13, and eotaxin) without significant changes in Th1 mediators (interferon-γ and tumor necrosis factor-α) [44]. Nonetheless, the mechanistic links between arsenic exposure and allergic disease remain incompletely defined and warrant further investigation.

Perinatal exposure and allergic diseases

The fetal and early postnatal immune system is highly plastic, and prenatal exposures can influence immune maturation and allergic trajectories. In a Taiwanese birth cohort with 15-year follow-up, prenatal heavy metal exposure (including arsenic) was associated with cord blood IgE levels and distinct IgE trajectory patterns in relation to atopic diseases [45]. The maternal cohort study also found that prenatal exposure to inorganic arsenic was associated with a higher risk of atopic dermatitis in young children [46]. A U.S. cord-blood study showed that maternal arsenic exposure levels were inversely associated with cord-blood T helper memory cells and activated T helper memory cells, but not with other T-cell subsets [47]. Prenatal co-exposure to other metals may further modify risk; for example, a study from China reported that prenatal co-exposure to higher levels of arsenic and thallium may contribute substantially to the combined risk of allergic rhinitis [48]. Together, these findings highlight developmental immunotoxicology as a key Frontier for integrating arsenic exposure, cutaneous immunology, and allergic disease risk across the life course.

Dose-response relationships between arsenic exposure and immune alterations

Across human and experimental studies, dose-response patterns are often endpoint-specific (e.g., innate inflammatory activation versus adaptive immune function) and affected by the exposure metric used (water concentration versus urinary/blood arsenic; speciation). Because arsenic can bind to many biological components, dose-response relationships may be non-linear (including biphasic or non-monotonic patterns) rather than strictly monotonic. Within low-to-moderate exposure ranges, several studies support dose-related shifts toward innate immune activation and systemic inflammation. For example, in rural women from West Bengal exposed to 11–50 μg/L arsenic in groundwater (versus <10 μg/L controls), arsenic exposure correlated strongly with increased monocyte CD14 expression, TNF-α and NF-κB signaling, and elevated circulating TNF-α, IL-6, IL-8, and IL-12, while IL-10 was reduced [49]. Complementing these individual studies, a systematic review/meta-analysis reported higher levels of several pro-inflammatory cytokines—particularly IL-6, IL-8, and IL-12—in arsenic-exposed groups, with lower IL-2 overall, consistent with a measurable inflammatory signature across populations despite robust heterogeneity [50].

At higher cumulative exposures or in patients with established arsenic-associated cancers, evidence points toward adaptive immune suppression, particularly impaired T-cell responsiveness. For example, our study showed a defective delayed-type hypersensitivity response to 2,4-dinitrochlorobenzene and a reduction in T-cell and T helper cell percentages in arsenic-induced skin cancers [28]. In a study of individuals with arsenic-induced skin lesions in West Bengal, there was a marked dose-dependent suppression of ConA-induced T-cell proliferation, accompanied by broadly reduced secretion of TNF-α, IFN-γ, IL-2, IL-4, IL-5, and IL-10, supporting a dose-associated immunosuppressive phenotype in heavily exposed individuals [37].

Genetic and epigenetic susceptibility

Joint effects of genomic markers and methylation capacity

Inter-individual differences in arsenic methylation are repeatedly implicated in differential disease risk. In our cohort

FIGURE 3
Precision prevention pipeline: scalable screening to risk-stratified surveillance. Pipeline schematic integrating community exposure context (water testing and dietary assessment), Tier 1 screening (clinical cutaneous markers and noninvasive AI-based hand/foot imaging), Tier 2 confirmation (urinary arsenic speciation with PMI/SMI; optional hair/nail arsenic), and Tier 3 susceptibility profiling (targeted genotypes and optional epigenetic markers). Action pathways include mitigation reinforcement, dermatologic surveillance, urothelial surveillance, and counseling on perinatal exposure reduction.

subset with an average 15-year follow-up, joint effects of genomic markers and urinary methylation capacity associated with inorganic arsenic metabolism were linked to cancer occurrence, supporting an integrated host–biomarker approach to susceptibility [51].

Epigenetic architecture of arsenic metabolism loci

Beyond metabolic phenotypes, inherited variation may couple to DNA methylation and gene expression states relevant to arsenic handling. For example, AS3MT haplotype status has been associated with DNA methylation and expression of multiple genes near AS3MT, illustrating how germline variation can shape epigenetic context for exposure response [52]. These insights motivate studies that integrate genotype, methylation, immune phenotyping, and clinical outcomes in exposed populations.

Discussion

This updated synthesis supports immune perturbation as a central axis of arsenic-related health hazards, linking cutaneous carcinogenesis, internal cancers, and allergic phenotypes. Several translational points emerge. First, exposure assessment must be scalable yet context-aware: urinary speciation remains valuable but requires careful interpretation in seafood-consuming populations. At the same time, noninvasive image-based estimation may enable field-deployable screening and cohort enrichment. Second, mitigation reduces population burden but does not immediately eliminate risk; long-latency outcomes and susceptibility heterogeneity argue for targeted follow-up in previously exposed communities (Figure 3). Third, perinatal exposure represents a critical window for immune programming that may influence early allergic outcomes and potentially shape later-life inflammatory susceptibility. Finally, genetic and epigenetic susceptibility should be operationalized in risk stratification by combining metabolic indices with candidate genotypes and emerging epigenetic biomarkers. Key research gaps include human bridging studies connecting keratinocyte stress pathways to immune phenotypes in arsenical lesions, and longitudinal immunophenotyping that predicts lesion progression, recurrence, and internal cancer development.

Conclusion

Arsenic-driven immune perturbation offers a coherent framework for understanding arsenic-associated cancers and broader health hazards. Integrating exposure source characterization, developmental timing, and host susceptibility—using both molecular biomarkers and scalable

phenotyping tools—can accelerate precision prevention and improve outcomes in exposed communities.

Author contributions

C-HH: data collection and interpretation, manuscript drafting. SY: summarization of exposure assessment. S-LW: perinatal health hazards and manuscript editing. H-SY: critical review and edit for the arsenic related allergy. C-HL: manuscript review, data clarification, logical contents. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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