

Table 2
Benzene-induced dysplasia (BID) and benzene poisoning (BP) risks by TNF genotype for preferred^a logistic regression models

Case type	Controls	Genotype	OR	95% CI
BID	Worker	–238	7.41	1.23–44.8
BID	Worker	–308	1.03	0.29–3.66
BID	Worker	–857	0.79	0.22–2.93
BID	Worker	–863	1.55	0.57–4.21
BID	All	–238	7.40	1.23–44.7
BID	All	–308	0.95	0.27–3.32
BID	All	–857	0.70	0.20–2.51
BID	All	–863	1.48	0.56–3.88
BP	Worker	–238	1.47	0.38–5.66
BP	Worker	–308	1.52	0.68–3.40
BP	Worker	–857	0.56	0.22–1.42
BP	Worker	–863	0.37	0.15–0.93

^a Preferred model has greatest explanatory power, see Section 2.

the three other TNF polymorphisms, models with or without confounders produced very similar OR's which were not elevated or statistically significant.

When cases of BID were compared to worker controls only, the OR for the –238A polymorphism alone (OR = 7.2, $p = 0.001$) was similar to that generated when using all controls. Again, no other polymorphism was statistically associated with BID, and the model with greatest explanatory power for the BID versus worker control contrast possessed the same covariates as the model with combined controls, and very similar results for each TNF polymorphism (Table 2).

For BP cases, there were no significant differences compared to worker controls for age, gender, and alcohol use. More BP cases smoked compared to controls (OR = 4.8, 95% CI 1.7–13.3). As expected, both cumulative and average career benzene exposure differed significantly among BP cases versus controls ($p = 0.03$ and 0.01 , respectively). The OR's for successive categories of cumulative and average career benzene exposure were 1.16 and 1.29, respectively.

Odds ratios for the –238A, –308A, and –857T polymorphisms were not significantly different among BP cases when compared to worker controls (Table 2). Adjusting for benzene exposure did not alter this observation. There was a reduced OR of 0.41 for the –863A polymorphism which was marginally significant ($p = 0.06$) without adjustment, and statistically significant with adjustment for either career average (OR = 0.30, $p = 0.02$) or cumulative exposure (OR = 0.36, $p = 0.04$) to benzene, as well as adjustment for smoking (OR = 0.37, $p = 0.03$). However, each of these models was compromised in terms of the variance explained (pseudo- r^2 values were 0.06 or less).

4. Discussion

A growing body of evidence has established that chronic inflammation plays an important role in the pathogenesis of a number of human malignancies, primarily those of epidermal origin as well as certain lymphoid neoplasms

[25–28]. Nevertheless, the precise mechanisms that explain the association between chronic inflammation and neoplastic progression remain unclear. Immune-mediated inhibition of hematopoiesis is thought to play a causal role in the pathogenesis of aplastic anemia [29]. However, chronic inflammation as a predisposing factor in the development of the hematopoietic neoplasms, MDS or AML, has not previously been demonstrated. Activated CD8+ cells and TNF- α have been described in MDS [19], and severe inflammation and clonal expansion of activated T lymphocytes are prominent features of the bone marrow pathology encountered in BID [1].

Several studies have implicated altered regulation of NF- κ B and pro-inflammatory cytokines, such as TNF- α , in the development of cancers driven by inflammation [25–28]. However, the role of TNF- α in inflammation and cancer is complex, being pro-tumorigenic or anti-tumorigenic, depending on the cell type, microenvironment, and intracellular signaling triggered in response to the cytokine [26,30–33]. Even though TNF- α is generally understood to be an important mediator in inflammation and cancer, interpretation of the precise role individual TNF- α polymorphisms play in biology and disease is complicated by the enormous linkage disequilibrium associated within the MHC Class III site. For example, the –308A and –238A polymorphisms have been linked in extended haplotypes. However, these two polymorphisms almost never occur in tandem. Further, the –308A haplotype is associated with higher TNF- α production and is implicated in acute solid organ transplant rejection while the –238A haplotype is not. Finally, although –308A has been linked with certain HLA haplotypes, the association of –238A with severity of chronic infection and autoimmune disease has not been linked to specific HLA genes [12,13].

In this study, only –238A (AA/AG) of the four single nucleotide TNF- α polymorphisms analyzed was significantly associated with the development of BID. The number of cases of BID available for analysis in this study was relatively small. However, the relationship between the –238A polymorphism and BID was robust and did not diminish when cumulative exposure, average exposure intensity or confounders were accounted for. Moreover, the association with –238A was specific for persistent BID but was not observed for *de novo* MDS, or BP. Therefore our findings suggest that the –238A polymorphism may be over-represented in a subpopulation of individuals with increased risk of selectively developing persistent bone marrow disease and dysplasia following chronic exposure to high concentrations of benzene.

An explanation for the role of –238A in the pathogenesis of BID may be forthcoming from studies that implicate TNF- α in hematopoietic stem cell regulation. The –238A allele appears to be unique in that it is associated with cell-specific de-repression of TNF- α production [6,12,14]. Membrane bound TNF- α expressed on CD34+ cells also has been implicated in the induction of tolerance in haploidentical bone marrow transplantation [34], suggesting a role for regulation of TNF- α expression in hematopoietic stem cell survival. These findings suggest the possibility that cell-specific alter-