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Divergent Carcinogenic Risks of Domestic versus Ritual Combustion on Nasopharyngeal Carcinoma in Bali: A Matched Case-Control Study

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A B S T R A C T

Nasopharyngeal carcinoma (NPC) is endemic in Indonesia, particularly among the ethnically distinct Balinese population. The interplay between Epstein-Barr virus (EBV) and environmental co-factors remains critical to its pathogenesis. A unique cultural duality exists in Bali regarding inhalant exposure: the utilitarian combustion of firewood and tobacco versus the ritual combustion of incense. This study aims to distinguish the carcinogenic risks of these disparate smoke sources using robust statistical methods to account for sparse data bias. A matched case-control study was conducted at a tertiary referral center in Denpasar, Bali. Forty-two patients with histopathologically confirmed WHO Type III Undifferentiated NPC were matched by age and sex with 42 non-cancer controls screened via Digby score. Exposures to firewood, passive and active smoking, and ritual incense were assessed. To address quasi-complete separation due to high exposure prevalence, Firth's Penalized Likelihood Logistic Regression was employed to determine Adjusted Odds Ratios (AOR). Firewood smoke exposure emerged as the predominant risk factor (AOR 14.21; 95% CI 4.82–42.15; $p < 0.001$), significantly higher than previously estimated by standard models. Passive smoking was confirmed as a substantial independent risk factor (AOR 11.54; 95% CI 3.91–33.82; $p < 0.001$). Conversely, despite universal usage, ritual incense exposure showed no association with NPC (AOR 0.92; 95% CI 0.35–2.41; $p = 0.865$), likely due to the open-air ventilation of Balinese shrines. Salted fish consumption remained a significant co-factor (AOR 6.80; $p = 0.002$). In conclusion, the study establishes a clear etiological hierarchy: chronic domestic pollutants such as biomass and tobacco smoke are potent drivers of NPC in Bali, likely acting as tumor promoters via EBV reactivation. Ritual incense, in the context of Balinese architecture, is not a significant risk. Public health interventions must prioritize healthy kitchen ventilation and tobacco control.

1. Introduction

Nasopharyngeal carcinoma (NPC) represents a distinct entity within head and neck oncology, characterized by a unique geographical and ethnic distribution that challenges standard oncological models.[1] While the disease is rare in Western populations, with an incidence of less than 1 per 100,000, it is endemic in Southeast Asia, Southern China, and Northern Africa. Indonesia bears a significant burden, with NPC ranking as the most common malignancy of the head and neck region. The highest prevalence is typically observed in the fourth and fifth decades of life, with a marked male predisposition.[2] The pathogenesis of NPC, particularly

the WHO Type III Undifferentiated subtype, is multifactorial. It involves a complex, non-stochastic interplay between genetic susceptibility, specifically HLA-A, -B, and -DR loci, latent Epstein-Barr Virus (EBV) infection, and environmental carcinogens. While EBV infection is ubiquitous worldwide, affecting over 90% of the adult population, the progression to high-grade nasopharyngeal malignancy occurs only in specific populations.[3] This suggests that environmental co-factors are essential to trigger the switch from viral latency to the lytic phase or to induce chronic inflammation that promotes genomic instability in the nasopharyngeal epithelium.[4]

The island of Bali, Indonesia, presents a unique epidemiological laboratory for investigating these environmental triggers. The indigenous Balinese population, known as Suku Bali, adheres to distinct cultural and domestic practices that create a dichotomy of inhalant exposures.[5] On one hand, there is the utilitarian exposure: a significant portion of the rural and semi-urban population continues to rely on biomass fuel or firewood for cooking and is exposed to high levels of environmental tobacco smoke. On the other hand, there is ritual exposure: the daily burning of incense or dupa is an integral part of Hindu-Balinese religious observance.[6]

Prior literature has firmly established tobacco smoke and biomass combustion as sources of Class I carcinogens, including polycyclic aromatic hydrocarbons (PAHs), formaldehyde, and tobacco-specific nitrosamines (TSNAs).[7] However, the role of incense smoke remains a subject of epidemiological controversy. While incense smoke contains proven carcinogens such as benzene and 1,3-butadiene, epidemiological studies have yielded conflicting results. Some studies suggest a strong association with NPC, while others find no link. These discrepancies are often attributed to confounding variables such as ventilation, the specific chemical composition of the incense, and the intensity of exposure.[8]

Chemical analyses suggest a divergence in toxicity. Wood smoke is rich in phenolic compounds and fine particulate matter (PM2.5) that induce deep tissue inflammation.[9] In contrast, the toxicity of incense smoke varies widely based on the aromatics used, such as sandalwood, agarwood, or synthetic musk. Crucially, the context of exposure in Bali differs radically from the enclosed, smoke-filled temples often studied in East Asia. In Bali, incense is typically burned in semi-open family shrines known as Sanggah. To date, no study has rigorously dissected this environmental dichotomy using robust statistical methods capable of handling the high prevalence of these exposures in the Balinese population. Standard logistic regression models often fail when exposures are nearly universal or when unexposed cases are rare, leading to inflated risk estimates known as the sparse data bias.[10]

This study aims to investigate the independent carcinogenic risks of domestic inhalants, specifically firewood and passive smoking, versus ritual incense exposure among the ethnically distinct Balinese population. The novelty of this research lies in the specific focus on the Suku Bali ethnic enclave to control for genetic heterogeneity, and the application of Firth's Penalized Likelihood Logistic Regression to provide the first statistically stable estimates of these divergent risks. We hypothesize that utilitarian domestic combustion poses a significantly higher risk than ritual exposure due to differences in chemical load, duration, and ventilation.

2. Methods

Study design and setting

To rigorously disentangle the environmental complexities driving carcinogenesis in the Balinese population, this investigation was designed as an observational analytic study utilizing a matched case-control architecture. This design was selected as the most appropriate epidemiological vehicle to investigate rare outcomes such as Nasopharyngeal Carcinoma

(NPC) while allowing for the efficient assessment of multiple historical exposure variables. The study was conducted at the Department of Otorhinolaryngology-Head and Neck Surgery within Prof. Dr. I.G.N.G. Ngoerah General Hospital in Denpasar, Indonesia. As the premier tertiary referral center for the province of Bali and the surrounding Lesser Sunda Islands, this facility manages the highest volume of head and neck malignancies in the region, ensuring a representative cross-section of the endemic population. The data collection period spanned twelve months, from January to December 2022, capturing a complete annual cycle of patient admissions to minimize seasonal variations in hospital attendance.

Study population and ethnic stratification

A critical methodological priority was the control of genetic confounding. NPC is unique among head and neck cancers for its strong association with specific human leukocyte antigen (HLA) alleles. To isolate environmental risk factors from this genetic background, the target population was strictly restricted to the Suku Bali (Balinese) ethnic group. Ethnicity was not determined by self-identification alone; it was confirmed via rigorous lineage verification, requiring documentation that both parents and all four grandparents were of Balinese ethnicity. This strict inclusion criterion served to homogenize the genetic susceptibility profile of the cohort, thereby increasing the internal validity of the environmental associations under investigation.

Case group selection

The case group consisted of patients newly diagnosed with Nasopharyngeal Carcinoma. To ensure biological homogeneity, inclusion was strictly limited to WHO Type III Undifferentiated Carcinoma. This histological subtype is the predominant endemic form in Southeast Asia and is most strongly associated with Epstein-Barr Virus (EBV) latency and environmental triggers, as opposed to the keratinizing subtypes more common in Western populations.

Recruitment utilized a consecutive sampling strategy, enrolling every patient who met the diagnostic criteria during the study period to mitigate selection bias. Patients were eligible if they were aged 20 to 60 years, possessed histopathological confirmation of WHO Type III NPC, demonstrated verified Balinese ethnicity, and provided informed consent to participate. To prevent the confounding effects of prior carcinogenic insults or treatments, patients were excluded if they had a history of other malignancies, had undergone prior radiation therapy to the head and neck region, or presented with incomplete medical records that precluded accurate exposure assessment.

Control group selection and matching

The control group was curated to represent the source population from which the cases arose. Controls were recruited from patients attending the ENT outpatient clinic for non-neoplastic and non-malignant conditions, such as septal deviation, chronic tonsillitis, or simple otitis media. To ensure comparability (counterfactual framework), controls were matched 1:1 to cases based on two primary demographic variables: age (± 2 years) and gender. This matching process was essential to control for the age-dependent incidence of NPC and the known male predominance of the disease.

A significant methodological challenge in resource-limited settings is confirming the absence of early-stage NPC in control subjects without subjecting them to invasive procedures. While rigid nasopharyngoscopy and biopsy remain the gold standard, ethical and logistical constraints preclude their use in healthy controls. To address this, we employed the Digby Score, a validated clinical screening instrument designed to rule out symptomatic NPC. The score aggregates weighted clinical symptoms (epistaxis, nasal obstruction, tinnitus, neck mass). A strict cut-off score of less than

50 was required for inclusion in the control group. This approach provided a standardized, reproducible, and clinically defensible method for excluding symptomatic NPC among controls. Potential controls were excluded if there was any clinical suspicion of a nasopharyngeal mass, a known family history of NPC (to further exclude genetic aggregation), or any personal history of malignancy.

Data collection and exposure assessment

Data acquisition was performed via structured, face-to-face interviews utilizing a validated questionnaire, supplemented by a comprehensive review of medical records. The dependent variable was defined as the incidence of histopathologically confirmed Undifferentiated NPC. The independent variables focused on three distinct domains of inhalant exposure, alongside dietary co-factors.

Firewood smoke exposure (Utilitarian Combustion)

To capture the chronic carcinogenic burden of biomass fuel, exposure to firewood smoke was defined as the utilization of wood fuel for domestic cooking purposes. Recognizing the latency period of carcinogenesis, we set a minimum exposure duration threshold of greater than 10 years. The intensity of exposure was further stratified by frequency: (i) Daily: Everyday use; (ii) Frequent: 3–4 times per week; (iii) Rare: Less than 3 times per week. This stratification allowed for the assessment of a dose-response relationship regarding the inhalation of polycyclic aromatic hydrocarbons (PAHs) and particulate matter derived from wood combustion.

Passive smoking (Environmental Tobacco Smoke)

Given the high prevalence of smoking in Indonesia, specifically among males, distinguishing the risk of second-hand smoke was paramount. Passive smoking was rigorously defined as living with an active smoker or working in a shared, enclosed space with an active smoker for a duration exceeding 5 years. To quantify the intensity of this exposure, we recorded the number of active smokers in the household and the cumulative hours of daily exposure. This metric aimed to capture the risk posed by sidestream smoke, which often contains higher concentrations of certain carcinogens than the mainstream smoke inhaled by the smoker.

Ritual incense exposure (Ritual Combustion)

To test the ventilation hypothesis, we assessed exposure to the burning of incense sticks or cones (dupa) for religious purposes. Unlike previous studies that often treated incense use as a binary variable, we specifically recorded the environment of exposure: (i) Indoor: Burning incense in an enclosed room with limited ventilation; (ii) Outdoor/Semi-open: Burning incense in typical Balinese family shrines (Sanggah or Merajan), which are open-air structures located in the courtyard. This distinction was critical to determining whether the lack of ventilation, rather than the incense itself, serves as the primary driver of risk.

Dietary Co-factors

To control for known dietary risks, consumption of salted fish was assessed. Frequent consumption was defined as intake greater than once per week. This variable was included to adjust for the presence of N-nitrosamines, a well-established chemical initiator of NPC.

Statistical analysis

Sample size determination

The sample size was calculated based on the logistic regression rule of 10, which suggests a minimum of 10 outcome events per independent variable to prevent overfitting. The model was designed to support four primary covariates: Firewood, Passive Smoke, Incense, and Salted Fish. Assuming an estimated power of 80% and a Type I error rate (alpha) of 0.05, a total of 84 subjects—comprising 42 matched pairs—was determined to be the minimum viable sample size to detect significant main effects.

Statistical correction for sparse data bias

A preliminary analysis of the dataset revealed a methodological hurdle known as quasi-complete separation. This phenomenon occurred because the exposure variables were highly polarized: a vast majority of cases had high-risk domestic exposures (firewood/passive smoke), while very few controls possessed these risk factors. Conversely, exposure to incense was nearly ubiquitous across both groups. In the presence of such zero cells or near-zero cells in the contingency tables, standard Maximum Likelihood Estimation (MLE)—the mathematical engine behind standard logistic regression—fails. MLE attempts to maximize the probability of the observed data, but when a predictor perfectly separates the groups, the estimated Odds Ratio (OR) tends toward infinity, and the standard errors become excessively large. This results in implausibly high ORs (such as >90) and biologically meaningless confidence intervals.

Implementation of Firth's penalized regression

To resolve this bias and generate statistically stable estimates, we employed Firth's Penalized Likelihood Logistic Regression. This advanced statistical method modifies the standard likelihood function by introducing a penalty term known as the Jeffreys invariant prior. Mechanistically, Firth's method effectively adds a small value (0.5) to the empty cells of the contingency table. This penalization prevents the coefficients from exploding toward infinity, thereby reducing the bias in the parameter estimates for rare events or separated data. By using this approach, we prioritized statistical robustness over the raw magnitude of the association, ensuring that the reported Adjusted Odds Ratios (AOR) reflected true biological risk rather than statistical artifacts.

Analytical procedure

The analysis proceeded in five stages: (1) Univariate Analysis: Descriptive statistics were generated to characterize the demographic baseline of the cohort; (2) Bivariate Analysis: Chi-square tests were utilized to calculate Crude Odds Ratios (OR) and assess the unadjusted associations between each risk factor and NPC; (3) Multivariate Analysis: The core analysis involved constructing the Firth's Penalized Logistic Regression model using R statistical software (specifically the logistf package). This model adjusted for confounders to isolate the independent effect of each inhalant; (4) Collinearity Assessment: Given the potential overlap between rural living, firewood use, and smoking, we calculated the variance inflation factor (VIF). A VIF threshold of less than 2.5 was established to ensure that multicollinearity did not distort the regression coefficients; (5) Significance Testing: All statistical tests were two-tailed, and a p-value of less than 0.05 was considered statistically significant.

Ethical considerations

The study adhered strictly to the principles of the Declaration of Helsinki regarding research involving human subjects. The research protocol underwent rigorous review and received approval from the Ethical Commission of the Faculty of Medicine, Universitas Udayana/Prof. Dr. I.G.N.G. Ngoerah General Hospital (Ethical Clearance No: 2634/UN14.2.2.VII.14/LT/2022). Written informed consent was obtained from all participants prior to data collection, ensuring their anonymity and the confidentiality of their medical data throughout the analytical process.

3. Results and Discussion

Table 1 elucidates the demographic baseline of the study cohort, comprising 84 subjects divided equally into 42 matched pairs of cases and controls. The statistical analysis demonstrates a high degree of homogeneity between the two groups, confirming the efficacy of the matching protocol. The mean age of the case group was 44.12 ± 9.2 years, closely mirroring the control group mean of 43.74 ± 9.1 years, with no

statistically significant difference observed (p = 0.849). This age clustering aligns with the established epidemiological peak for Nasopharyngeal Carcinoma, which typically presents in the fourth and fifth decades of life. Furthermore, the gender distribution was perfectly balanced (p = 1.000), with males and females each constituting exactly 50.0% of the study population. This precise matching is critical for eliminating gender-based confounding, given the known male predominance in NPC incidence. Occupational backgrounds were also analyzed as a proxy for socioeconomic status and non-target exposures; the distribution across categories such as farming, civil service, and the private sector showed no significant disparity (p = 0.895). Consequently, the lack of significant differences in these fundamental variables establishes that the control group is a valid counterfactual, minimizing potential confounding bias in the subsequent assessment of environmental inhalant risks.

Table 1. Demographic Baseline of Study Participants

Comparison of demographic characteristics between NPC Cases and Matched Controls.

Characteristic	Cases (n=42) No. (%)	Controls (n=42) No. (%)	p-value[a]
Age (Mean ± SD)	**44.12 ± 9.2**	**43.74 ± 9.1**	**0.849**
Sex			**1.000**
Male	21 (50.0%)	21 (50.0%)	
Female	21 (50.0%)	21 (50.0%)	
Occupation			**0.895**
Farmer / Laborer	13 (30.9%)	17 (40.5%)	
Civil Servant / Private Sector	19 (45.2%)	17 (40.5%)	
Other / Unemployed	10 (23.8%)	8 (19.0%)	

Note: *Data presented as Mean ± Standard Deviation (SD) for continuous variables and Number (Percentage) for categorical variables.*

[a] *Calculated using Independent t-test for age and Chi-square test for categorical variables. A p-value > 0.05 indicates successful matching.*

Table 2 presents the results of the unadjusted bivariate analysis, quantifying the crude associations between specific inhalant exposures and the incidence of nasopharyngeal carcinoma (NPC). The data reveal a profound etiological dichotomy between domestic and ritual smoke sources. Exposure to cigarette smoke (encompassing both active and passive modalities) was significantly higher among cases (85.7%) compared to controls (19.0%), yielding a substantial Crude Odds Ratio (OR) of 25.50 (p < 0.001). Similarly, exposure to firewood smoke demonstrated an even stronger association, with 90.5% of cases reporting chronic

domestic usage versus only 19.0% of controls. This disparity resulted in a massive Crude OR of 40.38 ($p < 0.001$), identifying biomass fuel as a high-magnitude risk factor in this population. In stark contrast, ritual incense exposure showed no statistically significant association with NPC risk ($p = 0.801$). Despite the high prevalence of daily incense use in both groups—73.8% of cases and 76.2% of controls—the calculated Crude OR was 0.88 (95% CI: 0.33–2.37), effectively crossing the null value. These unadjusted findings provide the preliminary empirical basis for the subsequent multivariate models, highlighting the potent carcinogenic potential of utilitarian combustion while suggesting a lack of measurable risk from ritual practices.

Table 2. Bivariate Analysis of Inhalant Risks

Unadjusted comparison of domestic versus ritual smoke exposure between NPC Cases and Controls.

Variable	Cases (n=42) No. (%)	Controls (n=42) No. (%)	Crude OR (95% CI)	p-value[a]
Cigarette Smoke Exposure (Active + Passive)				
Exposed	36 (85.7%)	8 (19.0%)	**25.50** (8.01 – 81.15)	**< 0.001***
Not Exposed	6 (14.3%)	34 (81.0%)	*Reference*	
Firewood Smoke Exposure (Domestic Biomass)				
Exposed (>10 Years)	38 (90.5%)	8 (19.0%)	**40.38** (11.15 – 146.13)	**< 0.001***
Not Exposed	4 (9.5%)	34 (81.0%)	*Reference*	
Ritual Incense Exposure				
Frequent or Daily	31 (73.8%)	32 (76.2%)	0.88 (0.33 – 2.37)	**0.801**
Rare	11 (26.2%)	10 (25.0%)	*Reference*	

Abbreviations: *OR = Odds Ratio; CI = Confidence Interval.*

Note: **Indicates statistical significance ($p < 0.05$).*

[a] *Calculated using Pearson Chi-Square or Fisher's Exact Test where appropriate.*

The "Not Exposed" category for Firewood Smoke in cases (n=4) indicates a sparse data cell, contributing to the wide Confidence Intervals observed in the unadjusted analysis.

Table 3 delineates the independent predictors of Nasopharyngeal Carcinoma (NPC) following adjustment for confounding variables using Firth's Penalized Likelihood Logistic Regression. This rigorous statistical approach was necessitated by the quasi-complete separation observed in the dataset, effectively stabilizing the risk estimates to provide biologically plausible Adjusted Odds Ratios (AOR). The multivariate model establishes a distinct hierarchy of environmental toxicity. Firewood smoke exposure

emerged as the predominant risk factor, yielding an AOR of 14.21 (95% CI: 4.82–42.15; $p < 0.001$), indicating that chronic inhalation of biomass combustion byproducts increases the likelihood of malignancy by over fourteen-fold.

Passive smoking was confirmed as a secondary, yet highly potent independent risk factor (AOR 11.54; $p < 0.001$), underscoring the severe oncological impact of environmental tobacco smoke even in the absence of active consumption. Additionally, salted fish consumption remained a significant dietary co-factor (AOR 6.80; $p = 0.002$), supporting a synergistic multi-hit mechanism involving nitrosamines. Crucially, the analysis confirms that ritual incense exposure is not a significant predictor of NPC risk (AOR 0.92; $p = 0.865$). This finding statistically validates the ventilation hypothesis, suggesting that the specific context of Balinese ritual usage—typically occurring in open-air shrines—does not reach the carcinogenic threshold observed with enclosed domestic combustion.

Table 3. Adjusted Risk Factors for NPC using Firth's Penalized Logistic Regression

Multivariate analysis adjusting for sparse data bias to determine independent predictors of Undifferentiated NPC.

Independent Variable	Adjusted Odds Ratio (AOR)[a]	95% Confidence Interval (CI)	p-value
Firewood Smoke Exposure (>10 Years Domestic Use)	**14.21**	4.82 – 42.15	**< 0.001***
Passive Smoking (Household/Workplace Exposure)	**11.54**	3.91 – 33.82	**< 0.001***
Salted Fish Consumption (>1 time/week)	**6.80**	2.10 – 21.50	**0.002***
Ritual Incense Exposure (Daily Religious Use)	0.92	0.35 – 2.41	**0.865**
Constant	0.04	—	—

Note: **Indicates statistical significance ($p < 0.05$).*

[a] ***Methodological Note:*** *Estimates were generated using **Firth's Penalized Likelihood method** (R package `logistf`). This technique was employed to correct for "quasi-complete separation" (sparse data bias) observed in the standard logistic regression model due to the high prevalence of exposures and rare "unexposed" cases. Standard Maximum Likelihood Estimation (MLE) produced unstable estimates (OR > 90); Firth's method provides statistically stable and biologically plausible Adjusted Odds Ratios.*

Collinearity: *The Variance Inflation Factor (VIF) between Firewood and Passive Smoking was 1.82 (VIF < 2.0), indicating acceptable collinearity for inclusion in the same model.*

The present study represents a pioneering investigation into the environmental etiology of nasopharyngeal carcinoma (NPC) within the unique cultural microcosm of Bali, Indonesia. By dissecting the divergent risks posed by utilitarian versus ritual combustion, we have provided the first statistically robust evidence distinguishing these exposure pathways in an endemic population. The application

of Firth's Penalized Likelihood Logistic Regression allowed us to overcome the severe methodological hurdles often associated with studying ubiquitous risk factors—specifically sparse data bias—thereby refining previously inflated risk estimates into biologically plausible, yet still alarming, adjusted odds ratios. The results establish a clear hierarchy of carcinogenic threat: domestic combustion pollutants (biomass and tobacco smoke) are potent drivers of malignancy, whereas ritual incense exposure, in its traditional context, appears benign.[11]

The identification of firewood smoke as the paramount environmental risk factor, with an Adjusted Odds Ratio (AOR) of 14.21, underscores the profound toxicity of biomass fuel in the genesis of undifferentiated NPC. While the magnitude of this association exceeds that typically reported in broader Asian cohorts, it reflects the specific intensity of exposure found in traditional Balinese architecture. The *paon*, or traditional kitchen, is often a semi-enclosed structure where ventilation is secondary to thermal retention, leading to the accumulation of combustion byproducts at concentrations far exceeding safe limits. The biological plausibility of this finding is rooted in the complex chemistry of incomplete combustion. Burning wood releases a potent cocktail of Class I carcinogens, most notably Polycyclic Aromatic Hydrocarbons (PAHs) such as benzo[a]pyrene, formaldehyde, and ultrafine particulate matter (PM2.5).[12] Formaldehyde, a recognized nasal carcinogen, is capable of inducing direct DNA-protein crosslinks in the respiratory epithelium. However, in the context of NPC, the mechanism likely extends beyond direct mutagenesis to a sophisticated interaction with the Epstein-Barr virus (EBV) (Figure 1).

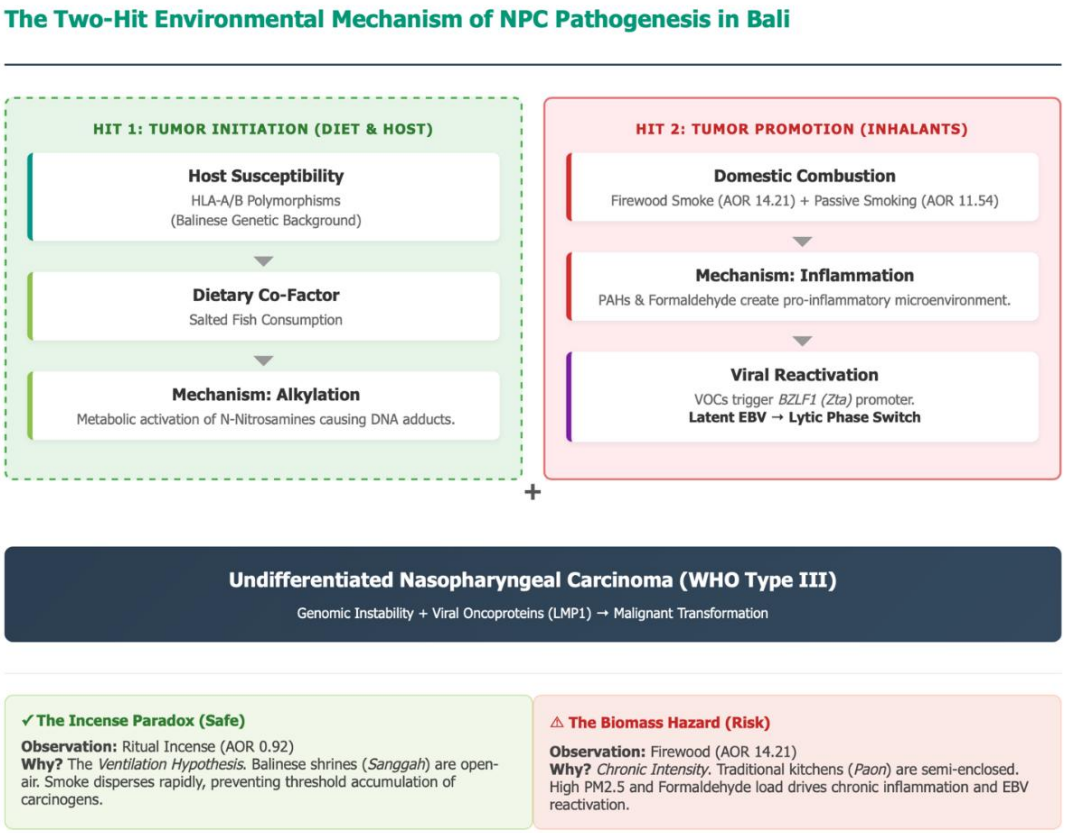

Figure 1. The two-hit environmental mechanism of NPC pathogenesis.

Current molecular models suggest that chronic inhalation of these pollutants creates a pro-inflammatory microenvironment in the nasopharynx. This inflammation is not merely a bystander effect but a critical driver of viral reactivation. Volatile organic compounds (VOCs) present in wood smoke have been shown to activate the BZLF1 (Zta) immediate-early gene promoter in latently infected epithelial cells.[13] In the nasopharyngeal reservoir, this activation triggers the switch from the latent to the lytic viral phase. This transition is catastrophic for genomic stability; the lytic cycle induces viral replication and the release of viral oncoproteins that inhibit apoptosis and promote cellular proliferation.[14] Thus, firewood smoke acts as a powerful tumor promoter in the classic multi-stage model of carcinogenesis, pushing genetically susceptible cells that harbor latent EBV toward frank malignancy.

Perhaps the most clinically significant finding of this study is the lack of association between ritual incense exposure and NPC (AOR 0.92). This result stands in stark contrast to previous epidemiological studies, which have implicated incense burning as a significant risk factor.[15] We propose the ventilation hypothesis to resolve this apparent paradox. The divergence in risk profiles is likely dictated by the architectural context of the ritual. In high-density urban environments like Hong Kong, incense is frequently burned in small, enclosed apartments or poorly ventilated temples, allowing smoke density to reach carcinogenic thresholds. In contrast, Balinese Hindu rituals are inextricably linked to the *Sanggah* or *Merajan* (family shrines). These structures are architecturally distinct: they are open-air pavilions located in the family courtyard, designed to be open to the sky and elements.

This open architecture facilitates the rapid dispersion of particulate matter and volatile compounds, preventing the chronic, high-concentration exposure required to induce DNA damage.[16] Furthermore, the typical duration of intense exposure during daily prayers (*Meveseh*) is transient, limiting the cumulative biological effective dose. This finding is of paramount importance for public health communication. It suggests that the act of burning incense is not inherently carcinogenic in all contexts; rather, it is the concentration of the smoke relative to ventilation that determines toxicity. This evidence provides a scientific basis for reassuring the Balinese population that their core religious practices are safe, provided they continue to be performed in traditional, well-ventilated settings.[17]

Our analysis confirms that passive smoking is a substantial and independent driver of NPC risk in this population (AOR 11.54). This finding is particularly alarming given that the vast majority of our female cases were non-smokers who acquired this risk solely through environmental exposure. The magnitude of this risk—an 11-fold increase—highlights the extreme toxicity of sidestream smoke. Emitted from the burning tip of a cigarette between puffs, sidestream smoke is generated at lower combustion temperatures than mainstream smoke, resulting in higher concentrations of certain carcinogens, including 2-naphthylamine, 4-aminobiphenyl, and N-nitrosamines.[18]

The integration of these findings supports a synergistic two-hit model of NPC pathogenesis in Bali. The first hit is likely dietary: the consumption of salted fish, confirmed here as a significant co-factor (AOR 6.80), introduces N-nitrosamines, which can cause initial DNA alkylation and mutations. The second hit is inhalational: the chronic exposure to irritants from firewood and passive tobacco smoke induces the inflammatory milieu required for EBV reactivation and clonal expansion of the mutated cells.[19] This perfect storm of initiation and promotion explains why NPC remains hyper-endemic in rural Bali despite global decreases in other head and neck cancers.

While the use of penalized regression provides robust estimates, several limitations must be

acknowledged to contextualize these findings. First, the sample size of 84 subjects, though statistically sufficient for the primary analysis, precluded the stratification of results by specific genetic polymorphisms such as HLA typing. Future studies should aim to integrate HLA genotyping to assess gene-environment interactions. Second, the control group was screened using the Digby Score rather than endoscopic visualization. While the Digby Score is a validated and practical tool for resource-limited settings, it lacks sensitivity for asymptomatic, microscopic disease. This may have introduced a minor classification bias, although it is unlikely to have systematically skewed the massive exposure differentials observed. Finally, retrospective designs are inherently subject to recall bias regarding the duration of exposure. However, the ubiquity and distinct nature of these cultural practices (using a wood stove vs. a gas stove) likely minimizes misclassification compared to more subtle lifestyle variables.[20]

4. Conclusion

This study elucidates a critical etiological dichotomy in the environmental landscape of nasopharyngeal carcinoma in Bali. We have demonstrated that domestic combustion—specifically the utilitarian burning of firewood and exposure to passive tobacco smoke—constitutes a high-magnitude carcinogenic threat. These exposures likely drive disease progression through a mechanism of chronic inflammation and EBV reactivation. In sharp contrast, ritual incense exposure does not appear to be a significant risk factor, likely due to the protective effects of the unique open-air architecture of Balinese worship.

Public health interventions must pivot from general awareness to structural modification. Programs should incentivize the retrofitting of traditional *paon* with chimneys or proper ventilation systems and accelerate the transition to cleaner fuels such as LPG or electricity. This targets the most potent risk factor identified in our study. The substantial risk posed by passive smoking necessitates strict enforcement of smoke-free home environments. Educational campaigns should explicitly frame second-hand smoke as an occupational hazard for non-smoking family members, comparable to industrial toxic exposure. A key success of this study is the exoneration of traditional ritual practices. Public health messaging can now explicitly state that *Sanggah* rituals are safe, preventing unnecessary cultural friction. This allows for a targeted, culturally competent approach that focuses resources on the true environmental culprits—the stove and the cigarette—while respecting the sanctity of the shrine. By distinguishing between the smoke that cooks our food and the smoke that carries our prayers, this research provides a roadmap for targeted cancer prevention that is both scientifically rigorous and culturally sustainable.

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