



Review

Hot Beverages, Chemical Co-Exposures, and Esophageal Squamous Cell Carcinoma in the African Corridor: A Margin-of-Exposure Framework

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Abstract

The African esophageal squamous cell carcinoma (ESCC) corridor extends from Ethiopia to the Eastern Cape and contains some of the highest age-standardized ESCC incidence rates reported anywhere, with five-year survival below 5%. The corridor's heterogeneous incidence (sex ratios from 1:1 to 7:1; tenfold variation between adjacent populations) has resisted single-factor explanation through more than half a century of investigation. We synthesize the multicenter evidence accumulated since the IARC 2018 Group 2A classification of very hot beverages (>65 °C), with particular attention to the African Esophageal Cancer Consortium (ESCAPE) outputs and to whole-genome sequencing. We argue, on the convergent evidence of animal toxicology, human in vitro mucosa, and population genomics, that thermal exposure acts as a tumor promoter rather than an initiator. On this reading, the corridor's heterogeneous burden reflects heterogeneous chemical co-exposure profiles operating against a shared thermal-promoter substrate. Extending the comparative margin-of-exposure (MOE) methodology to esophageal squamous carcinogenesis, we present an MOE framework distinguishing genotoxic compounds (within-mode-of-action additive) from thermal exposure (separate companion figure) and apply it to two corridor scenarios. The framework supports a four-lever prevention strategy combining tobacco control, alcoholic-strength reduction in unrecorded spirits, clean-cookstove deployment, and graduated thermal-exposure reduction.

Keywords: esophageal squamous cell carcinoma; sub-Saharan Africa; hot beverages; margin of exposure; cumulative risk assessment; unrecorded alcohol; mycotoxins; biomass cooking



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1. Introduction

Esophageal cancer is the eleventh most common cancer worldwide and the seventh leading cause of cancer death, with about 511,000 new cases and 445,000 deaths estimated for 2022 [1]. Its two histological subtypes—esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC)—differ enough in distribution and etiology to warrant separate treatment [2,3]. ESCC predominates in three regions of high incidence: northern China, the Caspian-Central Asian belt centered on north-eastern Iran, and a corridor running through eastern and southern Africa [3,4]. Within these regions, age-standardized incidence rates differ by more than tenfold between adjacent populations.

The African corridor was first described by McGlashan in 1969 [5] and now extends from Ethiopia southwards through Kenya, Uganda, Tanzania, Malawi, Zambia, and Zimbabwe to the former Transkei region of the Eastern Cape (Figure 1) [4,6]. Several corridor populations have age-standardized ESCC incidence rates among the highest reported anywhere, with five-year survival below 5% in most settings [6].

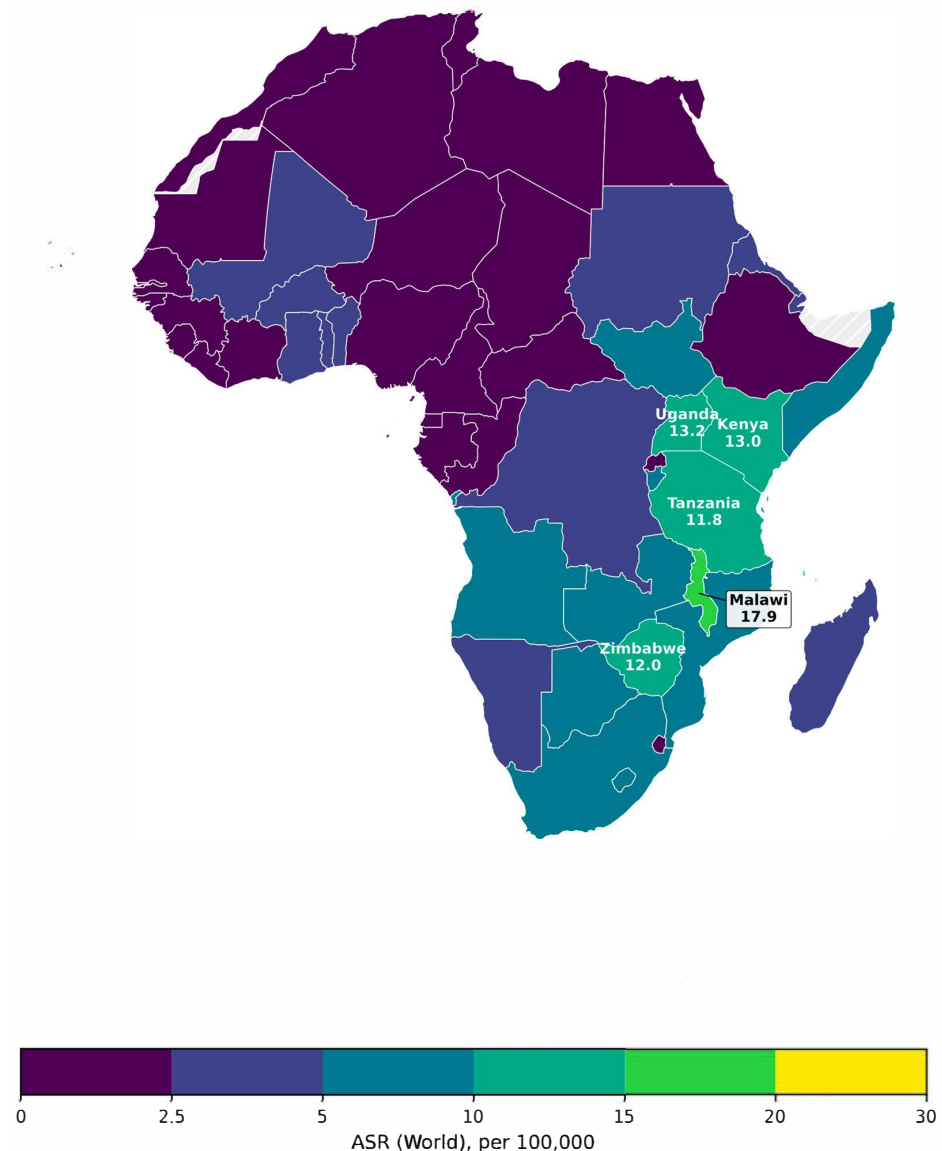


Figure 1. The African esophageal squamous cell carcinoma (ESCC) corridor. Country fill shows the age-standardized incidence rate (ASR, world standard) of esophageal cancer per 100,000, both sexes combined; labeled values give the rate for the highest-incidence corridor countries. Hatched areas indicate countries with no available data. Réunion (a French overseas department) is excluded from the African aggregation. Country-level rates do not capture the subnational concentrations documented in the corridor literature, including former Transkei (ASR 32.7 per 100,000 in 1998–2002, declining to 23.2 in 2008–2012) and Bulawayo (male ASR 58.6 per 100,000 in 1963–1977); these are discussed in Section 3.1. Data source: GLOBOCAN 2022, International Agency for Research on Cancer, Global Cancer Observatory (<https://gco.iarc.fr/today>), accessed on 5 May 2026.

A satisfactory etiological account has yet to emerge. Tobacco and alcohol—the principal risk factors in Western and East Asian populations—behave inconsistently across corridor countries; several primary studies report no detectable independent effect of alcohol despite strong tobacco effects in the same population. The male-to-female sex ratio of ESCC,

close to 4:1 in tobacco- and alcohol-driven populations, varies across the corridor from approximately 1:1 to 7:1 (Figure 2) [7,8]. Whole-genome sequencing of ESCC tumors from eight countries spanning the global incidence range identified no exogenous-mutagen mutational signature distinguishing high-incidence populations from low-incidence ones [9]. This suggests that the responsible exposures act through mechanisms other than direct deoxyribonucleic acid (DNA) damage. A range of corridor-specific co-exposures has been investigated in primary studies—hot-beverage consumption, unrecorded home-distilled spirits, maize-borne mycotoxins, biomass cooking smoke, poor oral health, and human immunodeficiency virus (HIV) infection [10]—but their joint contribution to ESCC risk remains uncharacterized in any single quantitative framework.

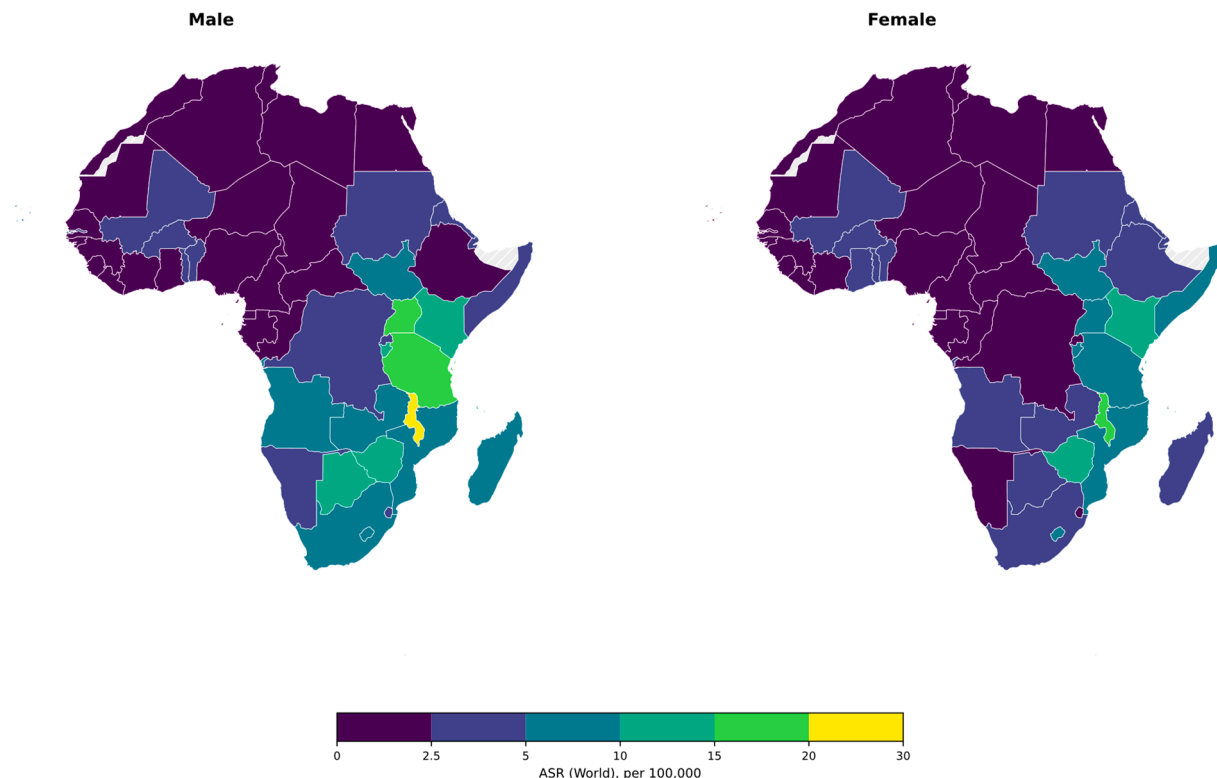


Figure 2. Sex-specific age-standardized incidence rates (ASR, world standard) of esophageal cancer per 100,000 across Africa, shown for males (left) and females (right). The corridor populations span a male-to-female sex-ratio range of approximately 1:1 to 7:1, exceeding that of any other high-incidence ESCC region with comparable data. Section 3.3 develops a two-cluster framework grouping corridor populations by sex ratio and dominant co-exposure profile. Hatched areas indicate countries with no available data. Réunion is excluded from the African aggregation. Data source: GLOBOCAN 2022, International Agency for Research on Cancer, Global Cancer Observatory (<https://gco.iarc.fr/today>), accessed on 5 May 2026.

The International Agency for Research on Cancer (IARC) classified the consumption of very hot beverages above 65 °C as Group 2A in its 2018 Monograph (Volume 116), citing limited evidence in humans and sufficient evidence in experimental animals for esophageal cancer [11,12]. Drinking coffee per se and drinking warm or cold maté were classified as Group 3. The IARC Working Group identified high-priority research needs around the temperature–response relationship, the interaction of thermal exposure with other environmental carcinogens, and the African corridor populations [11]. These priorities were reaffirmed in the 2024 IARC advisory for the 2025–2029 monograph program [13,14].

Earlier reviews have synthesized the corridor literature [6,15,16], but two developments since the most recent of these warrant a further look. Between 2018 and 2025, the

African Esophageal Cancer Consortium (ESCCAPE) published several large multicenter case-control studies along with a community-based thermal-exposure measurement study [17]. These enlarged the evidence base on hot-beverage exposure, alcohol, tobacco, oral health, and dental fluorosis. Mutational-signature analysis has been applied to ESCC across the global incidence range, and comparative margin-of-exposure (MOE) methodology has been developed for hot-beverage carcinogenicity. Together, these provide tools to combine epidemiological observation with toxicological reference points. We adopt a One Health perspective, treating corridor ESCC as the product of interacting environmental, dietary, infectious, and behavioral exposures, and address three questions: How should the corridor's geographic and demographic heterogeneity be characterized given the recent multicenter evidence? How do corridor-specific chemical co-exposures relate quantitatively, and how can their joint contribution be expressed within an MOE framework directly applicable to esophageal squamous carcinogenesis? What does the combined evidence imply for the operational temperature threshold currently used in regulatory carcinogen assessment? In answering these questions, the review departs from earlier syntheses of the corridor literature, which have cataloged the candidate risk factors individually. Here, they are instead placed within a single quantitative framework that separates genotoxic from thermal modes of action, treats thermal exposure as a promoter rather than an independent risk factor, and yields a cluster-specific rather than a corridor-wide prevention strategy.

2. Literature Selection

This narrative review synthesizes the peer-reviewed evidence on the African esophageal squamous cell carcinoma (ESCC) corridor with a particular focus on outputs from the African Esophageal Cancer Consortium (ESCCAPE) and on toxicological margin-of-exposure (MOE) methodology relevant to hot beverages, unrecorded alcohol, mycotoxins, and combustion-derived polycyclic aromatic hydrocarbons. Primary studies were identified through PubMed and Google Scholar searches conducted in May 2026, using combinations of the terms “esophageal cancer” or “esophageal cancer” and “Africa”, “corridor”, “Kenya”, “Tanzania”, “Malawi”, “Uganda”, “South Africa”, “Zimbabwe”, “Ethiopia”, together with topical terms including “hot beverages”, “unrecorded alcohol”, “aflatoxin”, “biomass smoke”, “tobacco”, “HIV”, “dental fluorosis”, “margin of exposure”, and “mutational signature”. The reference lists of key reviews were hand-searched, and citing articles were followed forward through Google Scholar to identify further primary studies. Priority was given to peer-reviewed case-control, cohort, and registry-based studies published between 2000 and 2026, with earlier landmark papers retained for historical anchoring. IARC Monograph volumes, EFSA scientific opinions, and UNSCEAR reports were consulted for regulatory reference points.

3. The Corridor: Geographic and Demographic Characterization

3.1. Geographic Extent and Registry Coverage

Population-based cancer-registry coverage across the corridor is uneven. Most country-level estimates depend on single-city registries (Kampala in Uganda, Bulawayo in Zimbabwe) or hospital-based case ascertainment [7,8,18]. The Eastern Cape registry, covering eight to ten magisterial districts of former Transkei with a catchment of approximately 1.3 million, is one of the few rural African registries with sustained operation across more than a decade [19,20]. Mozambique, parts of the Democratic Republic of the Congo bordering Zambia, and large areas of South Sudan have no operating ESCC registry; their inclusion in corridor maps depends on hospital case series rather than quantified incidence [15].

Several populations within this constrained surveillance landscape have sustained high incidence. In the former Transkei, the esophagus is the leading cancer site in men (age-

standardized incidence rate 32.7 per 100,000 in 1998–2002, declining to 23.2 by 2008–2012) and the second leading cancer in women (age-standardized rate (ASR) 20.2, falling to 14.5 over the same period) [19,20]. In Bulawayo, the male ASR for the registry's first decade of operation (1963–1977) was 58.6 per 100,000, with a female ASR of 8.1—among the most male-skewed cancer patterns reported anywhere [8]. In Malawi, although no population-based registry covers the country, hospital-based case ascertainment indicates the world's highest reported ESCC incidence and mortality, with 1756 incident cases and 1657 deaths in 2020 [18].

3.2. Time Trends

The Kampala (Kyadondo) registry provides one of the longest African ESCC time-trend series. Across four registry periods spanning 1960–1997, with a gap during 1972–1989 due to political instability, esophageal cancer incidence rose five- to sevenfold in both sexes [7]. Neither tobacco use nor commercial alcohol consumption increased in Uganda over this interval to a degree commensurate with the rise. In the Eastern Cape, by contrast, the ASR for ESCC declined approximately 30% between 1998–2002 and 2008–2012 in both sexes [20]. The authors attribute the decline partly to changes in maize storage and dietary patterns and partly to broader diversification of subsistence agriculture. The rise in Kampala and the decline in Transkei operate on different timescales and in different directions. The corridor therefore appears to respond to environmental and demographic changes that vary across its extent rather than to any single shared driver.

3.3. The Sex-Ratio Variation and a First-Approximation Cluster Framework

The male-to-female ratio of ESCC incidence varies more across the African corridor than in any other high-incidence region with comparable data. In Kyadondo, Uganda, the ratio among the sexes approached 1:1 across the 1960s–1990s registry record [6,7]. In Bomet County, western Kenya, the ratio is also approximately equal [21]. The Kilimanjaro case-control series enrolled men and women in roughly comparable numbers [22]. At the other end of the range, Bulawayo's first-decade registry data showed a ratio of approximately 7:1 [8]. In Lilongwe, Malawi, 62% of cases in the Lilongwe Esophageal Cancer Case-Control Study were male [18]. The male-to-female ASR ratio in former Transkei is approximately 2.3:1 [19], and the Muhimbili case-control series in Dar es Salaam recorded a ratio of approximately 2.8:1 [23].

A male predominance is the global norm for ESCC—close to 4:1 in Western and East Asian populations driven by tobacco and alcohol [1,2]. The corridor's range of approximately 1:1 to 7:1 cannot be reconciled with any single etiological model. The 1:1 ratios in Uganda, western Kenya, and northern Tanzania are inconsistent with a tobacco-and-alcohol-dominant etiology, since male tobacco prevalence exceeds female prevalence in all three countries. The 7:1 ratio in Bulawayo is consistent with substance-driven carcinogenesis: the same data show a tobacco relative risk of 5.7 in men smoking ≥ 15 g/day [8], and in the Eastern Cape, the joint exposure to tobacco and alcohol carries a population-attributable fraction of 64% in men [24].

As a first approximation, we group the corridor populations into two etiological clusters defined by sex ratio and corroborated post hoc by their dominant co-exposure profiles. A household-exposure cluster—Uganda Kyadondo, western Kenya, northern Tanzania-Kilimanjaro—has near-equal sex ratios consistent with exposures shared by men and women (hot beverages, biomass-cooking smoke, water-source contaminants). A substance-use cluster—Bulawayo and the male substance-using subpopulations of Lilongwe, Tanzania, and the Eastern Cape—has male-skewed ratios consistent with tobacco-and-alcohol-driven etiology. Several corridor populations sit ambiguously between the two clusters: Muhimbili, at a sex ratio of 2.8:1, represents a subpopulation in which migrant labor, occupational urban exposures, and household exposures combine [23].

The Eastern Cape at a ratio of 2.3:1 has dominant substance-use exposures in men but a substantial female ESCC burden as well. Western Kenya at a near-1:1 ratio has the household-exposure profile of the cluster framework but also the highest reported alcohol population attributable fraction (PAF) in any corridor population (48% in the heavy-drinker stratum, Section 9.2). The binary cluster framework is therefore a first approximation rather than an exhaustive taxonomy, and a more granular one may emerge from the cumulative PAF analysis identified as a research priority in Section 11.4.

3.4. Within-Country Heterogeneity and the Northern Lake Zone Signal

Within-country variation in ESCC incidence can be as large as cross-country variation, and larger in some places. In the former Transkei, ASR ratios between adjacent districts have ranged from three- to fourfold, with Kentani historically the highest-incidence district and Bizana the lowest [19,25]. In Kenya, the high-incidence area is concentrated in the Rift Valley and around Bomet [21,26], with Nairobi and the coast showing lower rates. In Ethiopia, qat-using populations of the central highlands appear to have higher incidence than non-qat-using populations of the lowlands [27].

The most striking within-country signal is in northern Tanzania. Buckle et al. [28] reanalysed the Mmbaga et al. case-control dataset [23] with age stratification and reported an adjusted odds ratio of 12.06 (95% CI 3.18–45.71) for residents in the Northern Lake Zone among early-onset (age 30–44) ESCC cases. The corresponding odds ratio in the older stratum was 1.57 (1.02–2.41) (likelihood-ratio test for age-effect difference $p = 0.011$). The Northern Lake Zone effect remained after adjustment for tobacco, alcohol, hot-beverage exposure, oral health, and biomass cooking. A signal of this size, surviving multivariable adjustment, concentrated in young adult cases, suggests an exposure operating relatively recently and from early in life rather than across decades. Candidate explanations include water-source contamination (the region surrounds Lake Victoria), localized dietary practices, ethnicity-specific behavior, or a localized environmental contaminant yet to be identified. The signal sits outside the manuscript's two-cluster framework and outside the MOE analysis of Section 8. We return to it in Section 11.5 as an unfollowed priority.

These within-country gradients constrain the kind of causal explanations that can logically be postulated. National risk factors cannot account for tenfold variation between adjacent districts. The gradients direct attention instead to environmental factors with strong local variation, which Section 7 examines.

3.5. Coverage Gaps and Methodological Caveats

Three coverage gaps shape what can and cannot be said about the corridor. First, several countries within the corridor's geographical extent have no population-based registry, and corridor maps that include them rely on extrapolation from hospital series [15]. Second, hospital-based case ascertainment is uneven within countries that do have registries: rural cases who do not present to a referral hospital are systematically under-counted [6]. Third, histological confirmation rates vary across the corridor case-control studies (44% in Mmbaga et al. [23]; 36% in Sewram et al. [24]). Where histology is missing, ESCC cannot be reliably distinguished from EAC, although the latter is uncommon in corridor populations and the corridor's incidence rates broadly reflect ESCC.

4. Thermal Exposure: The International Evidence Base

4.1. Pooled Epidemiological Evidence

Three meta-analyses published since 2015 have synthesized the case-control and cohort literature on hot-beverage consumption and esophageal cancer. Andrici and Eslick aggregated 16 case-control studies (3566 ESCC cases) and reported a pooled odds ratio (OR)

for ESCC of 2.29 (95% CI 1.79–2.93), with a stronger effect in studies from developing countries (OR 2.88) than from developed countries (OR 1.65) [29]. Luo and Ge pooled 23 reports across 34 individual studies and obtained an ESCC-specific pooled OR of 2.33 (95% CI 1.51–3.61, $I^2 = 77\%$), with no association detected for adenocarcinoma [30]. Zhong et al. pooled an OR of 2.04 (95% CI 1.78–2.31) for hot tea drinking [31]. The convergence on a pooled effect of approximately twofold for ESCC strengthens confidence in an exposure–response relationship. The Luo and Ge stratified analysis revealed a study-design effect: prospective cohort studies yielded a pooled OR of 1.25 (95% CI 0.95–1.65), substantially below the case–control pool (OR 1.63) and well below the hospital-based case–control pool (OR 3.36) [30]. The case–control inflation is consistent with classical recall and selection bias; this pattern recurs throughout the corridor literature and is propagated through to the PAF estimates discussed in Section 9.

4.2. Primary Cohort and Case–Control Evidence

The Golestan Cohort Study in northeastern Iran has produced the most detailed prospective evidence. Islami et al. reported hazard ratios (HR) of 1.41 for tea consumption at $\geq 60^\circ\text{C}$, 1.36 at $\geq 65^\circ\text{C}$, and 1.59 at $\geq 70^\circ\text{C}$ [32]. Sheikh et al. analyzed the same cohort with a richer multifactorial exposure model and reported an HR of 1.91 for tea $\geq 60^\circ\text{C}$ combined with >6 cups/day, alongside a cumulative-environmental-exposure score whose top quintile carried a hazard ratio (HR) of 7.12 and a PAF of 76% for the seven environmental risk factors examined [33]. The China Kadoorie Biobank cohort similarly reported elevated HRs for “burning hot” tea, with significant multiplicative interactions between hot tea and tobacco use and between hot tea and alcohol use [34]. The UK Biobank prospective analysis has recently extended the finding to a low-incidence population [35]. Primary case–control studies in China have produced similar effect estimates [36–38], with two recurring methodological issues: heterogeneity in the operational definition of “very hot” (cut-offs ranging from 60°C to 70°C ; qualitative ratings such as “burning hot”) and dependence on self-report rather than direct measurement.

4.3. Limitations of Self-Reported Temperature Exposure

Several lines of evidence indicate that self-reported drinking-temperature classification is an unreliable exposure metric. Munishi et al., comparing participants’ verbal ratings against measured cup temperatures in Kilimanjaro, reported a kappa coefficient of 0.04 between self-rated “hot” and objectively measured temperature [39]. Yu et al. reported a poor test–retest reliability of $\rho = 0.35$ for self-reported tea temperature in the China Kadoorie cohort [34], signaling too much random variation in the scores. Middleton et al., in the Kenyan ESCCAPE case–control study, found that the OR for “very hot” tea differed by approximately fivefold between two interviewers (8.49 vs. 1.79), with the pooled estimate of 3.66 representing the midpoint of two operationally distinct exposure constructs [40]. Section 5 develops the methodological consequences of these observations and the alternative measurement approaches deployed in corridor populations.

4.4. Temperature Thresholds from Toxicology and Human In Vitro Evidence

Animal and in vitro studies, examined in detail in Section 6, have established that thermal exposure to the esophageal mucosa acts as a tumor promoter rather than an initiator. Three observations bear on the relevant temperature threshold. The buccal-mucosa study of Ernst et al. detected cytotoxic and proliferative responses emerging at approximately 60°C in 73 northern Iranian participants [41]. The Golestan cohort detected significantly elevated HRs at the $\geq 60^\circ\text{C}$ cut-off [32]. Benchmark-dose modeling of the Li et al. [42] rat dataset by Okaru et al. yielded a benchmark dose (BMD) of 63.6°C and a benchmark dose lower confidence limit at 10% response (BMDL₁₀) of 56.3°C for the temperature effect [43]; the

contact-temperature analysis of Lachenmeier and Lachenmeier identifies a tissue contact-temperature injury threshold close to 46.5 °C in pilot sensory evaluation, with the contact-temperature corresponding to the IARC 65 °C beverage threshold being approximately 53 °C [44]. The IARC 65 °C operational threshold for “very hot beverages” sits within a range supported by these complementary evidence streams; the 2024 IARC advisory for the 2025–2029 monograph program has reaffirmed the priority of re-evaluation [13,14]. Section 10 returns to the regulatory implications.

The within-corridor variation in ESCC incidence and sex ratio described in Section 3 is not explicable by hot-beverage exposure alone, since drinking temperatures and consumption frequencies in corridor populations do not differ to a degree commensurate with the tenfold incidence variation between adjacent populations.

5. Exposure Measurement and the Limits of Self-Rated Thermal Categories

5.1. The Single-Temperature Exposure Metric

Most epidemiological studies of hot-beverage exposure characterize individual exposure with a single value: a self-reported preference category or, less commonly, a single measured temperature recorded at one point during a drinking episode. Neither captures what reaches the esophageal mucosa during habitual consumption. Three observations make this concrete.

First, the relationship between cup or surface temperature and the temperature actually delivered to the esophagus depends strongly on volume per sip and on drinking speed. The foundational human in vivo measurements of De Jong et al., using a thermistor probe at 39 cm from the incisor teeth, established that intra-esophageal liquid temperature (IELT) increases by approximately 0.38 °C per milliliter of coffee ingested at standardized serving temperatures of 55, 60, and 65 °C [45]. Two-way analysis of variance demonstrated that volume contributed approximately threefold more variance to IELT than temperature did, with no statistical interaction. The implication is that a 5 mL sip at 70 °C and a 15 mL sip at 60 °C deliver substantially different IELTs to the esophagus, even though the latter would be classified as “less hot” on any cup-temperature metric. In 209 measurements across 23 participants, 43% of recorded IELTs reached or exceeded 44 °C [45].

Second, surface temperature differs systematically from the contact temperature delivered to the oral and esophageal mucosa during a sip. Lachenmeier and Lachenmeier modeled the heat transfer with the contact-temperature relation $T_K = T_2 + (b_1 / (b_1 + b_2)) \cdot (T_1 - T_2)$, where b is thermal effusivity [44]. The model implies that, for water served at 70.9 °C, the contact temperature on the mucosa is approximately 46 °C. A pilot sensory test on human tongue tissue in vivo identified an indefinite-tolerance contact-temperature threshold of 46.5 °C, with shorter exposures tolerated up to approximately 48 °C; this threshold is anchored on a pilot test and carries substantial uncertainty.

Third, the relationship between self-rated temperature category and actual cup temperature is weak (Section 4.3).

5.2. Within-Dataset Dissociation Between Frequency and Self-Rated Temperature

The exposure-metric problem becomes most visible when alternative metrics are applied to the same dataset. The Tanzanian case-control dataset assembled at Muhimbili (471 cases/471 controls) was analyzed with self-rated temperature as the primary thermal exposure by Mmbaga et al. and with hot-beverage frequency by Buckle et al. The first analysis found self-rated “very hot or hot” tea consumption unrelated to ESCC risk (adjusted OR 0.99, 95% CI 0.65–1.53) [23]. The second analysis found a robust dose-response relationship between hot-beverage frequency and ESCC risk, particularly in early-onset cases (adjusted

OR 1.99 per additional daily serving in the 30–44-year stratum) [28]. The dissociation has at least three plausible interpretations—recall bias (self-rated temperature unreliably reported, frequency more concretely anchored), cumulative dose (frequency $\times$ volume $\times$ per-cup temperature integrating to a true cumulative thermal dose that single-cup metrics cannot capture), or confounding (frequency proxying a lifestyle bundle of which the actual carcinogenic exposure is one component). Whichever is correct, studies relying on self-rated temperature classifications can reach opposite conclusions from studies using objective frequency or volume metrics in the same population.

5.3. Direct Measurement Protocols in Corridor Populations

Three corridor studies have measured exposure directly with thermometer-during-interview protocols. Mwachiro et al. recorded a mean preferred initial tea (chai) temperature of 72.1 °C in 100 healthy adults in Bomet County, Kenya [46]. Munishi et al. measured a mean drinking-onset temperature of 70.6 °C in 84 healthy adults in Kilimanjaro [39]. Menya et al., extending direct measurement across age groups in western Kenya and southern Malawi, recorded mean first-sip temperatures of 66.5 °C in Kenyan adults and 67.8 °C in Malawian adults; 58% of Kenyan and 70% of Malawian first sips exceeded 65 °C [47].

The Menya et al. [47] protocol is the most extensive direct-measurement study and addresses the exposure-metric problem in three respects. It measures temperature at three points during the drinking episode (first, middle, late sip), records sip volume in addition to temperature, and compares pouring temperature against drinking temperature. Pour temperatures were 70.2 °C in Kenya and 74.6 °C in Malawi, but adults take protective small first sips ($\approx$ 11 mL) followed by larger middle and late sips ($\approx$ 20 mL), with the consequence that IELT peaks at the middle sip ($\approx$ 46–47 °C) rather than at the first sip ($\approx$ 44–45 °C) [47]. The De Jong volume effect is thus observed in the field: cup temperature falls across sips, but the accompanying increase in sip volume more than offsets this, raising IELT.

The same protocol identified a behavioral exposure modifier of practical importance. Poesha, a Swahili word meaning “to cool”, is a practice in which tea is poured between two cups before drinking to accelerate cooling; this practice was observed in approximately 20% of Kenyan child participants. Poesha-using children had substantially lower IELTs than non-poesha-using children. Approximately 22% of Kenyan child first sips and 19% of Malawian child first sips nevertheless exceeded 65 °C, indicating that the corridor’s thermal exposure is not exclusively an adult phenomenon [47].

5.4. Composite Thermal Exposure Indices and Implications

Masukume et al. proposed a composite thermal exposure index summing four self-reported metrics—perceived consumption temperature, waiting time before drinking, drinking speed, and burnt-tongue frequency—across three hot-food vehicles [48]. In the pooled Malawi–Tanzania case–control sample of 849 ESCC cases and 906 controls, the per-unit composite OR was 1.22 (95% CI 1.14–1.30), and the OR for composite ≥ 9 versus ≤ 3 was 4.6 (95% CI 2.1–10.0)—substantially stronger than any single component used alone. The Masukume composite remains a self-report instrument; its strength lies in its multidimensionality. A natural extension would combine the multidimensionality of the Masukume composite with the objectivity of the Menya direct measurement. No corridor study has yet to operationalize such an instrument at scale.

The toxicological reference points described in Section 4.4—the BMDL₁₀ of 56 °C derived from the Li et al. [42] rat dataset, the contact-temperature injury threshold of approximately 46.5 °C, and the in vitro cytotoxicity threshold of approximately 60 °C—are most appropriately compared against IELT or contact temperature rather than cup temperature. The Menya et al. [47] mean middle-sip IELT of 46–47 °C in corridor adults sits very close to

the Lachenmeier and Lachenmeier [44] indefinite-tolerance contact-temperature threshold. Section 8 develops this comparison quantitatively within a margin-of-exposure framework.

6. Mechanism: Thermal Exposure as a Tumor Promoter

Three independent rodent studies, each using a different design, support the same mechanistic interpretation: thermal exposure to the esophageal mucosa does not initiate carcinogenesis on its own, but amplifies the carcinogenic action of nitrosamines and other co-exposures. Li et al.'s F344-rat experiment showed that *N*-nitrosomethylbenzylamine (NMBA) combined with 65 °C drinking water increased esophageal tumor incidence to 8.0 ± 2.1 tumors per rat (versus 5.5 ± 1.5 with NMBA alone, $p < 0.05$), with carcinoma incidence rising from 17% to 30%; hot water at 55 °C or 65 °C without NMBA produced no tumors [42]. A 70 °C arm was abandoned because rats died by week 15, indicating the tested thermal exposure was at the upper limit of acute tolerability for the rodent esophagus. Rapozo et al.'s BALB/c-mouse experiment showed that 70 °C water alone produced acute coagulation necrosis followed by progressive epithelial adaptation; the combination of 70 °C water with *N*-nitrosodiethylamine (NDEA) prevented this adaptive recovery, and hyperproliferative premalignant lesions appeared in 52% of the combined group at 24 weeks against 13% under NDEA alone [49]. *N*-Nitrosodimethylamine (NDMA), which is not metabolically activated by the rodent esophagus, did not produce the same effect when combined with hot water, confirming that the synergy depends on metabolic activation in the target tissue rather than on a generic chemical–thermal interaction. Wang et al.'s F344-rat and C57BL/6-mouse experiments extended the model: animals receiving NMBA combined with 65 °C water developed moderate-to-severe esophageal dysplasia in significantly higher proportion than animals receiving NMBA with room-temperature water, the same combination raised esophageal expression of miR-132-3p, and brief ice-cold-water rinsing after the hot-water exposure significantly reduced the dysplastic lesion frequency [50]. The three studies, using two species, two nitrosamines, three thermal regimes, and one negative-control nitrosamine, NDMA, converge on the same conclusion: thermal injury at 65–70 °C does not initiate esophageal carcinogenesis but promotes the carcinogenic action of metabolically activated nitrosamines.

Direct measurements on human oral mucosa parallel the animal findings. Ernst et al. recruited 73 participants in a high-ESCC area of northern Iran for a buccal-mucosa micronucleus-cytome assay, with self-reported drinking temperatures verified by thermometer [41]. Cytotoxic markers (condensed chromatin, karyorrhexis, karyolysis) and basal-cell proliferation rate increased with drinking temperature, with effects emerging above approximately 60 °C; markers of direct DNA damage (micronuclei, nuclear buds) were not increased at any tested temperature. The dissociation between cytotoxic and genotoxic responses parallels the rodent finding that hot water alone is non-mutagenic. The same dissociation appears in population-genomic data: whole-genome sequencing of 552 ESCC tumors from eight countries by Moody et al. did not identify any mutational signature attributable to an unknown exogenous mutagen capable of explaining the geographic variation [9]. The dominant mutational processes—APOBEC-associated SBS2 and SBS13, the clock-like SBS1 and SBS5, the reactive-oxygen-species signature SBS18—are present universally and at broadly similar levels across countries. The technique has identified exogenous-mutagen signatures in other cancers—most distinctively the A:T → T:A transversion pattern of aristolochic acid in upper urothelial carcinoma [51]. The absence of any comparable signature in corridor ESCC is direct evidence that the responsible exposures do not act as classical mutagens.

The convergent evidence admits one coherent reading. Habitual exposure of the esophageal squamous mucosa to temperatures sufficient to cause cytotoxicity and barrier

disruption produces three effects relevant to carcinogenesis. The mucosal barrier is repeatedly damaged and repaired, with regenerative basal-cell proliferation that increases the cell-division rate at which subsequent mutagenic events accumulate. Inflammation persists through repeated injury and may not resolve, with prostaglandin and other inflammatory mediators contributing to a tumor-permissive microenvironment. The barrier function of the esophageal epithelium is reduced, allowing co-existing carcinogens—nitrosamines, mycotoxins, and acetaldehyde due to alcohol consumption—greater access to basal-layer keratinocytes. The third effect links Section 6 to Section 7: if thermal exposure is a tumor promoter rather than an initiator, the corridor's risk profile depends not only on the temperature distribution but on what other carcinogenic exposures are present alongside the high drinking temperatures. The corridor's incidence variation is then explicable not as a single-factor phenomenon but as the product of thermal exposure interacting with corridor-specific co-exposure profiles that vary across geography and demography.

7. Corridor-Specific Chemical Co-Exposures

The promoter framework developed in Section 6 implies that the corridor's incidence variation is shaped by the carcinogenic load that thermal injury makes accessible. This section examines four categories of co-exposure documented in corridor primary studies: unrecorded alcohol and its contaminants; biomass-cooking smoke and its polycyclic aromatic hydrocarbon load; oral health, dental fluorosis, and charcoal-based oral hygiene; and HIV infection.

7.1. Unrecorded Alcohol and Its Contaminants

Alcohol is associated with ESCC in some corridor populations and not in others. The ESCCAPE pooled case-control analysis of 1279 cases and 1346 controls across Kenya, Tanzania, and Malawi reported ever-drinking ORs of 2.88 (95% CI 1.98–4.21) for both sexes in Kenya, 1.96 (1.20–3.20) in Tanzania, and a protective OR of 0.65 (0.43–0.96) in Malawian men [52]. The Malawian inverse association was attributed by the authors to systematic under-reporting; null or inverse alcohol findings are also reported in Bulawayo (despite a tobacco risk ratio (RR) of 5.7 for smokers of ≥ 15 g/day) [8], in Lilongwe [18], in the Tanzanian-coastal Muhimbili series [23], and in the Zambian Kayamba series [53]. Alcohol is an established corridor risk factor in Kenya, Tanzania-Kilimanjaro, and the Eastern Cape, but its detectability in other corridor populations is degraded by under-reporting, lower exposure prevalence, or by both. The ESCCAPE-Kenya analysis is informative on the third possibility: 72% of controls who reported very-hot tea drinking were never-alcohol-drinkers; the reverse of the pattern was documented in Iranian and Chinese cohorts [54]. The Kenyan case-control found no interaction between alcohol consumption and hot-beverage temperature ($p = 0.32$), in contrast to the multiplicative interaction reported in the China Kadoorie cohort [34]. The hot tea-alcohol synergy that is robust in China does not generalize to Kenya, because hot tea drinkers and alcohol drinkers in Kenya are largely different people.

The interaction between alcohol and thermal exposure therefore behaves differently in the corridor than in the Asian high-incidence regions, and the difference is one of exposure distribution rather than of biology. Where the two exposures co-occur in the same individuals, as in the China Kadoorie cohort, their joint effect is multiplicative [34], which is mechanistically expected: thermal barrier disruption increases the permeability of the basal layer to co-exposed carcinogens (Section 5), while ethanol acts as a solvent facilitating their penetration and delivers acetaldehyde directly to the same mucosa. Where the two exposures are largely dissociated at the individual level, as the ESCCAPE-Kenya control data indicate [54], the same mechanism produces little population-level synergy, and the

corridor's burden is better described as two partially separate exposure profiles sharing a thermal substrate than as a single synergistic pathway. This distributional argument is what motivates the parallel rather than summed presentation of the genotoxic and thermal margins in Section 7.1. It also identifies the corridor stratum in which risk should be highest—men in the substance-use cluster who both drink unrecorded spirits and consume beverages at high temperature—for whom the expected joint effect is at least multiplicative but for whom no corridor study is presently powered to estimate an interaction term.

The contrast is one of exposure distribution rather than of biology. Where the two exposures coincide in the same individuals, thermal barrier disruption increases mucosal permeability to co-ingested carcinogens while ethanol delivers acetaldehyde to the same tissue, and the observed joint effect is multiplicative. Where they are dissociated, as in much of the corridor, the same mechanism yields little population-level synergy, which is why the genotoxic and thermal margins are presented in parallel rather than summed in Section 8.1. The stratum in which risk should be highest, men who both drink unrecorded spirits and consume beverages at high temperature, is precisely the one that no corridor study is yet powered to characterize.

Where alcohol is a corridor risk factor, the dominant exposure source is not commercial beer or spirits but unrecorded home-brewed beer and home-distilled spirits. In western Kenya, busaa—locally brewed sorghum, maize, or millet beer of approximately 4.5% ethanol, sold in 500 mL servings—is the largest single contributor to total ethanol intake [54]. Chang'aa, a distilled unrecorded spirit, confers a per-gram-ethanol risk that may exceed that of commercial beverages [55].

Three classes of contaminants in unrecorded spirits are relevant to ESCC. Acetaldehyde, classified by IARC since 2012 as a Group 1 carcinogen when associated with consumption of alcoholic beverages, accumulates in poorly distilled spirits and in long-fermentation home brews [56]. Ethyl carbamate (EC), a Group 2A carcinogen, is formed during fermentation and distillation from plants containing cyanogenic precursors (such as cassava or sorghum), which may be used in spirits such as chang'aa (Kenya) and kachasu (Malawi). Although minimal characterization of the occurrence of EC has been reported in the corridor, a Brazilian cachaça analysis found margins of exposure as low as 15 in heavy-binge scenarios for comparison [57]. Aflatoxin contamination of unrecorded beer derived from improperly stored maize has been documented in Kenyan busaa, establishing aflatoxin as an additional health risk in the same beverage that delivers the largest ethanol load [58]. The corridor's unrecorded-spirit drinker therefore carries a multi-substance simultaneous exposure: ethanol itself, acetaldehyde directly ingested with the beverage, possibly ethyl carbamate as a fermentation product, and aflatoxin from contaminated grain in maize-derived brews. Section 8 addresses this combination quantitatively.

7.2. Biomass-Cooking Smoke and Biomarker PAH

Polycyclic aromatic hydrocarbons (PAHs) reach corridor populations primarily through biomass-cooking smoke rather than through hot beverages. Direct measurement of urinary PAH metabolites by Mwachiro et al. in 305 asymptomatic adults in Bomet County, Kenya, established that levels among never-tobacco-users were 2.4 to 28 times higher than among never-tobacco-users in the United States National Health and Nutrition Examination Survey, the Iranian Golestan cohort, and the Brazilian MATCH study [59]. Female sex, indoor cooking, age below 50 years, and lower educational attainment were positively associated with biomarker concentrations; tobacco use was not. The dose-response with advanced esophageal squamous dysplasia was statistically significant for 2-hydroxynaphthalene (adjusted OR 4.19 per natural-log increase, 95% CI 1.01–17.47).

The Malawian and Zambian case–control series corroborate the biomass-PAH pathway. Mlombe et al. reported an adjusted odds ratio of 12.6 for firewood-only cooking overall, rising to 85.3 in women against 6.4 in men [60], and Kayamba et al. reported a multivariable OR of 3.0 for cooking with charcoal or firewood in Lusaka, Zambia [53]. The route distinction matters for prevention: the polycyclic-aromatic-hydrocarbon content of Kenyan tea was approximately an order of magnitude lower than that of contemporaneously measured yerba maté [46], and the comparative MOE analysis found PAH MOE values exceeding 100,000 in nearly all realistic beverage-consumption scenarios [43]. The corridor’s PAH burden is real, biomarker-confirmed, and dose-related to advanced esophageal squamous dysplasia, but its source is the kitchen and not the kettle. Reducing tea or coffee brewing temperature would not reduce PAH exposure in the corridor populations whose biomarker levels are highest; clean-cookstove programs, ventilation improvements, and reduction of charcoal use in oral hygiene (Section 7.3) would.

7.3. Oral Health, Charcoal Hygiene, and Dental Staining

Oral-health exposures contribute to ESCC risk independently of tobacco and alcohol in two corridor populations with detailed dental examination data. The ESCCAPE-Kilimanjaro analysis by Mmbaga et al. reported less-than-daily toothbrushing adjusted OR 2.77 (95% CI 1.20–6.43), chewed-stick brushing instead of modern toothbrush adjusted OR 2.28 (1.27–4.09), and oral charcoal use (ever but not daily) adjusted OR 2.33 (1.33–4.07), all in models adjusted for tobacco and alcohol [22]. Charcoal-based tooth cleaning was reported by 20% of women and 8% of men in the Kilimanjaro sample, providing a plausible direct route by which polycyclic aromatic hydrocarbons reach the upper aerodigestive tract independently of biomass smoke.

Dental fluorosis was originally reported as an independent risk factor in the ESCCAPE-Kenya analysis, with moderate-to-severe Thylstrup–Fejerskov Index (TFI ≥ 5) adjusted OR 9.4 overall and 27.1 in participants with decayed, missing and filled teeth (DMFT) ≥ 4 [61]. A subsequent photographic re-rating in the Kilimanjaro replication, conducted by a qualified dentist blind to case–control status, found that only 43% of TFI ≥ 5 ratings made by non-dental observers represented true fluorosis [22]. The misclassification was concentrated in participants with poor general dentition, which explains the original effect-modification pattern. The cleanest reading is that the fluorosis exposure variable is heavily contaminated by extrinsic staining and that the true fluorosis effect on ESCC is likely much smaller than the original odds ratios indicate, possibly null. The robust oral-health signals in the corridor are dental caries, less-than-daily brushing, chewed-stick brushing, and charcoal-based hygiene—not fluorosis specifically.

7.4. HIV Infection

HIV infection is associated with ESCC in two corridor primary case–control studies. Kaimila et al.’s Lilongwe analysis of 300 cases and 300 controls reported an HIV-positive-adjusted OR 4.0 (95% CI 1.8–9.0) [18]. Kayamba et al.’s Lusaka analysis reported HIV-adjusted OR 2.3 (95% CI 1.0–5.1), with stronger effects in cases below 60 years (OR 4.3) and in the 1:1 matched subset (OR 6.3) [53]. Earlier reports of larger HIV-ESCC effect estimates from the same region have not been replicated, and one has since been retracted; the present-day evidence for HIV-ESCC association in the corridor rests on the Kaimila and Kayamba studies. Human papillomavirus, in contrast, was not associated with ESCC in the Zambian sample, paralleling earlier negative findings in Kenyan and South African ESCC samples. Immunosuppression, chronic inflammation, and reduced clearance of premalignant lesions are the more likely mediators than HPV co-infection.

7.5. Implications

The four categories of co-exposure described above do not distribute uniformly across the corridor. Unrecorded alcohol exposure is concentrated in the substance-use-cluster populations of Section 3 and is null or under-detected in Malawian, Zambian, and Zimbabwian populations. Biomass-PAH exposure varies with cooking-fuel use and reaches its highest documented levels in the household-exposure-cluster of the Kenyan population. Oral-health exposures are distributed partly with sex and partly with cultural practice. HIV co-exposure varies with national prevalence. Section 8 develops the quantitative comparison within a margin-of-exposure framework, with thermal exposure as the common substrate-modifying factor that makes each more carcinogenic than it would be in an unexposed mucosa.

8. A Margin-of-Exposure Framework for Corridor ESCC

8.1. The Margin-of-Exposure Approach and Its Aggregation

The margin of exposure (MOE) is the ratio of a toxicological reference point—most commonly a BMDL₁₀ derived from animal carcinogenicity data—to an estimated human exposure. The European Food Safety Authority adopted the approach in 2005 for substances that are both genotoxic and carcinogenic, with an MOE of 10,000 or above considered to indicate low concern when the BMDL₁₀ is animal-derived [62]. The approach has been applied systematically to alcohol-borne carcinogens in a series of analyses, beginning with comparative drug assessments [63], extending to compound-specific reviews of acetaldehyde [56] and ethyl carbamate [57], aggregated into a master reference table for 18 carcinogenic compounds [62], and updated with an explicit individual and cumulative health-risk framing in 2021 [64]. The approach was extended to hot-beverage carcinogenicity by Okaru et al., who applied benchmark-dose modeling to the Li et al. [42] rat dataset and obtained a temperature BMD of 64 °C and BMDL₁₀ of 56 °C [43].

The thermal BMDL₁₀ was derived using the BMDS Power Model on Li et al. [42] Table II groups 4–6 ($n = 9$ per group; control 22 °C assumed per Organisation for Economic Co-operation and Development (OECD) guidance, since Li et al. [42] did not state the control temperature; benchmark response of 1 standard deviation from control mean; Akaike Information Criterion 67.07) [43]. Model selection, control-temperature assumption, and benchmark-response choice each carry sensitivity that is not formally explored in the source paper; the BMDL₁₀ should be understood as a single reasonable derivation rather than an irreducible reference value. The animal-derived BMDLs in Table 1 are anchored on rodent endpoints.

Table 1. Toxicological reference points. Values reproduced from Pflaum et al. (Table 3 in [62]), Okaru et al. [43], and EFSA [65,66].

Compound	BMDL ₁₀	Endpoint	Animal	Source
Thermal exposure	56 °C	NMBA-induced rat esophageal tumors	Rat (Li et al. [42])	Okaru et al. [43]
Ethanol	700 mg/kg bw/day	Hepatocellular adenoma/carcinoma	Rat	Pflaum et al. [62]
Acetaldehyde	56 mg/kg bw/day	Tumor-bearing animals (multi-site)	Male rat	Lachenmeier et al. [56]
Ethyl carbamate	0.3 mg/kg bw/day	Alveolar/bronchiolar neoplasms	Mouse	Lachenmeier et al. [57]
N-nitrosamine class (NDMA representative)	0.029 mg/kg bw/day	Total liver tumors	Rat	Pflaum et al. [62]

Table 1. Cont.

Compound	BMDL ₁₀	Endpoint	Animal	Source
Aflatoxin B ₁	0.4 µg/kg bw/day	Hepatocellular carcinoma	Rat	EFSA and Okaru et al. [58,65]
Polycyclic aromatic hydrocarbons (BaP)	0.07 mg/kg bw/day	Mouse alimentary-tract tumors	Mouse	EFSA [66]

Two methodological choices shape the analysis. The first is scope. The present analysis restricts itself to compounds with documented or biologically plausible direct contributions to esophageal squamous carcinogenesis. Beverage-borne PAH is excluded on the basis of MOE values consistently above 100,000 [43]; biomass-cooking-derived PAH is retained on the basis of corridor biomarker evidence (Section 7.2). Compounds with toxicological reference points anchored on tissues without a defensible ESCC pathway—including furan, 5-hydroxymethylfurfural, furfuryl alcohol, acrylamide, ochratoxin A, pyrrolizidine alkaloids, and fumonisin B-series—are not included.

The second methodological choice is aggregation, and it requires more careful treatment than has been customary in the cumulative-risk literature. The compounds in scope operate through two distinct mechanisms. Six are genotoxic carcinogens (ethanol-via-acetaldehyde, acetaldehyde directly, ethyl carbamate, *N*-nitrosamines, aflatoxin B₁, biomass-PAH) for which additive hazard quotients are a defensible default. Thermal exposure operates through a fundamentally different mechanism (tumor promotion via mucosal barrier disruption and sustained basal-cell proliferation). Summing hazard quotients across these two mode-of-action groups is methodologically inappropriate and we do not do so. Rather, we present a genotoxic cumulative MOE (across the six genotoxic compounds, expressed as $1/\Sigma(1/\text{MOE}_i)$) and a thermal companion MOE in parallel. This separation is more defensible than a single grand sum across modes of action and aligns with EFSA and Joint FAO/WHO Expert Committee on Food Additives (JECFA) convention for cumulative-risk frameworks. The promoter framework developed in Section 6 motivates the parallel framing; the genotoxic load and the thermal substrate-modifying factor together shape the corridor's risk profile, but they do so through distinct biological pathways and are most appropriately characterized separately.

8.2. Toxicological Reference Points

The seven compounds retained in the analysis are summarized in Table 1.

Inclusion is justified on three grounds: direct human or animal evidence linking the exposure to ESCC; genotoxic carcinogenicity combined with documented exposure to the upper aerodigestive mucosa; or a sufficiently established mode-of-action argument for trans-tissue applicability. The *N*-nitrosamine entry uses NDMA as a representative compound for the chemical class; the corridor-relevant nitrosamines are more likely *N*-nitroso-methylbenzylamine and related class members documented as esophageal-tropic in the Li et al. [42] and Rapozo et al. [49] rodent models, for which formal BMDLs are not derived. Tobacco-specific *N*-nitrosamines, *N'*-nitrosonornicotine (NNN) and (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), which are corridor-relevant in tobacco-using populations through the Stepanov et al. prospective biomarker dose-response in the Shanghai Cohort Study [67], are not included in Table 1 because no formal BMDL₁₀ for ESCC has been derived; we discuss them in narrative form below as a hazard-quotient contributor whose precise weight in the combined figure cannot be computed.

8.3. Single-Compound MOEs in Two Corridor Scenarios

We examine two scenarios with distinct exposure profiles. The substance-use cluster is represented by a Kenyan or Tanzanian male heavy chang'aa or busaa drinker who also consumes hot tea at corridor temperatures. The household-exposure cluster is represented by a Kenyan female who cooks with biomass, drinks chai at corridor temperatures, and consumes negligible alcohol. The single-compound MOEs are summarized in Table 2.

Table 2. Single-compound MOEs in two corridor scenarios. Values for chang'aa-class spirits in Scenario A are projected from analogous populations; direct chemical characterization of corridor unrecorded beverages is identified as a research priority (Section 11.1).

Exposure	Scenario A: Substance-Use Cluster	Scenario B: Household-Exposure Cluster	Source/Basis
Thermal exposure	<1 (~0.7 at 85 °C; ~2 at 65 °C)	<1 (same)	Okaru et al. [43]
Ethanol	0.1–0.5 (heavy chang'aa); 0.5–0.8 (4 drinks/day)	n/a (non-drinker)	Lachenmeier and Rehm [63]; Pflaum et al. [62]
Acetaldehyde	30–50 (cuxa analogue)	n/a	Lachenmeier et al. [56]
Ethyl carbamate	15–80 (cachaça/tiquira analogue)	n/a	Lachenmeier et al. [57]
Aflatoxin B ₁	7–27 (Kenyan busaa)	not quantified for corridor women specifically	Okaru et al. [58], recomputed with data from EFSA [65]
TSNAs	not formally quantified for corridor; biomarker dose-response	n/a	Stepanov et al. [67]
Biomass-PAH	partially relevant (smoking household)	not quantified; biomarker dose-response with advanced esophageal squamous dysplasia	Mwachiro et al. [59]

Scenario A—Substance-use cluster, heavy *chang'aa* or *busaa* drinker. Heavy busaa or chang'aa consumption, characterized in the ESCAPE-Kenya analysis as 1–3 L per day [54], delivers approximately 36–108 g ethanol per day in busaa and considerably more for drinkers who also consume the higher-strength chang'aa. The Lachenmeier and Rehm probabilistic analysis estimated an ethanol MOE of 1.3 (95% CI 0.6–2.7) using European per-capita alcohol consumption [63]; the Pflaum et al. heavy-drinking scenario, corresponding to approximately 60 g ethanol/day, yielded an ethanol MOE of 0.8 [62]. Heavy chang'aa drinkers consuming 100–300 g ethanol/day would yield an ethanol MOE in the range of 0.5 to 0.2.

The acetaldehyde, ethyl carbamate, and aflatoxin MOE values in Table 2 for the chang'aa drinker scenario are projected from analogous populations: the acetaldehyde MOE (30–50) is bracketed by the Lachenmeier et al. European P99 worst-case scenario (MOE 34) and the cuxa-Guatemala daily-drinker analogue [56]; the ethyl carbamate MOE (15–80) is projected by analogy with cachaça and tiquira in the Lachenmeier et al. analysis [57]; the aflatoxin MOE (7–27) is from Okaru et al.'s direct measurement of Kenyan unrecorded beer (mean 36, range 15–58% alcohol by volume [58] against the EFSA reference from 2007 [68]), recomputed against the more stringent EFSA BMDL₁₀ of 400 ng/kg bw/day from 2020 [65]. Chang'aa, busaa, kachasu, and gongo have not been analytically characterized for ethyl carbamate or for acetaldehyde concentration distributions; the values direct attention to the chemical-characterization priority in Section 11.1, not to estimates of the true corridor exposures, which could be substantially higher or lower.

Scenario B—Household-exposure cluster, Kenyan female biomass cook, hot tea consumer, non-drinker. The dominant contributors are thermal exposure and biomass-PAH; the acetaldehyde, ethyl carbamate, and tobacco specific nitrosamine (TSNA) contributions

are absent or minimal. The biomass-PAH MOE has not been formally computed for corridor exposures; the Mwachiro et al. [59] biomarker observation that urinary PAH metabolite levels in Kenyan women cooking with biomass exceed those reported among comparable populations by 2.4-fold to 28-fold indicates that any MOE computed against the EFSA's benzo[a]pyrene (BaP) BMDL₁₀ [66] in this population would yield values substantially below 10,000.

8.4. Combined Concern by Mode of Action

The genotoxic cumulative MOE in Scenario A, computed as $1/\Sigma(1/\text{MOE}_i)$ using conservative central estimates from Table 2 (ethanol 0.3, acetaldehyde 40, ethyl carbamate 50, aflatoxin 15), evaluates to approximately 0.29. The figure is dominated by ethanol. The ethanol hazard quotient ($1/0.3 \approx 3.33$) accounts for approximately 89% of the total hazard quotient sum (3.45). The contaminants (acetaldehyde, ethyl carbamate, aflatoxin) contribute the remaining 11% on top of the ethanol baseline. The thermal companion MOE in the same scenario is below 1 for corridor-typical drinking temperatures. Both the genotoxic cumulative MOE and the thermal companion MOE are below the conventional thresholds of concern (genotoxic: 10,000; thermal: typical regulatory anchor near 1 for exposure approaching the BMDL).

The genotoxic cumulative MOE in Scenario B is dominated by aflatoxin (if maize-storage exposure is present) and biomass-PAH, neither of which has been formally quantified in MOE terms for corridor women. The available biomarker evidence [59] and the Mlombe et al. [60] firewood-cooking adjusted OR of 85.3 in women are consistent with a genotoxic cumulative MOE substantially below conventional thresholds, but the precise value cannot be computed without further dose-estimation work. The thermal companion MOE in Scenario B is the same as in Scenario A.

Two implications follow. First, the substance-use-cluster genotoxic cumulative MOE is dominated by ethanol, with the additional contaminants adding only modestly on top of the ethanol baseline. This is consistent with the Pflaum et al. [62] conclusion that ethanol itself is “quantitatively the most important carcinogen in alcoholic beverages” and has a regulatory implication that Section 10 develops: alcohol-strength reduction is the most actionable single lever for reducing alcohol-attributable carcinogen exposure. Second, both scenarios reach genotoxic cumulative MOE values below conventional thresholds and thermal MOE values below 1, but they do so by different routes. Scenario A is dominated by ethanol and Scenario B by biomass-PAH (and aflatoxin where present), with the thermal substrate common to both. The convergence supports the manuscript's argument that the corridor's heterogeneous incidence reflects heterogeneous chemical co-exposure profiles operating against a shared thermal-promoter substrate.

The MOE figures are heuristics, not precise estimates. The Scenario A values for acetaldehyde and ethyl carbamate carry substantial uncertainty in both direction and magnitude; chang'aa, busaa, kachasu, and gongo have not been analytically characterized. A more fundamental limitation applies to Scenario B: no quantitative exposure estimates exist for the genotoxic carcinogens delivered by biomass-cooking smoke, since the corridor evidence is biomarker-based rather than dose-based and no inhalation-to-esophagus dosimetry has been established. The framework is therefore quantitatively resolvable only where alcohol dominates the exposome; in the biomass-dominated cluster, it remains a structured but unquantified description of concern. What the framework establishes is that two distinct corridor sub-populations accumulate simultaneous exposure to multiple individually concerning carcinogenic agents at levels that, taken together, exceed the conventional thresholds below which any single compound would be considered acceptable. Section 9 discusses population-attributable fractions and their implications.

9. Population-Attributable Fractions and Cluster-Specific Prevention

9.1. PAF Interpretation

The margin-of-exposure analysis in Section 8 expresses the carcinogenic load on an individual corridor consumer who falls into one of two scenario categories. Population-attributable fractions express the complementary question of what proportion of the corridor's ESCC burden could be averted if a given exposure were removed from the population (Table 3). The MOE asks how close to a toxicological threshold the typical exposed individual sits; the PAF asks what fraction of cases observed in a population would not have occurred had a given exposure been absent. The PAF estimates discussed below are derived predominantly from corridor case-control studies, and the case-control inflation problem documented in Section 4 (cohort-vs-case-control effect-size gap of approximately twofold in the Luo and Ge stratified analysis) propagates through to these estimates. Where multiple PAFs from different exposures are reported in the same population, they should not be summed, because exposures interact and because each PAF is computed conditional on the population's exposure prevalence; the figures discussed below are cluster-conditional contributions to the population fraction rather than additive components of a corridor-wide attributable fraction.

9.2. Tobacco and Alcohol PAFs in the Substance-Use Cluster

In the Eastern Cape of South Africa, Sewram et al. estimated PAFs of 58% for tobacco use, 48% for alcohol consumption, and 64% for the two combined in their hospital-based case-control study of 670 cases and 1188 controls [24]. The study found a multiplicative joint effect (interaction $p = 0.37$), with combined heavy users carrying an OR of approximately 8.5. The combined 64% PAF implies that approximately one-third of the Transkei region's ESCC burden remains unexplained by tobacco and alcohol combined and requires alternative explanation through the maize-mycotoxin and biomass-cooking pathways examined in Section 7.

In the East African ESCCAPE pooled analysis of 1279 cases and 1346 controls across Kenya, Tanzania, and Malawi, Middleton et al. estimated PAFs for ever-drinking of 65% in Kenyan men and 56% in Tanzanian men [52]. The same study estimated counterfactual PAFs for alcoholic-strength reduction: if heavy chang'aa, gongo, and kachasu consumers had instead consumed only low-strength (<30% alcohol-by-volume) beverages, the alcohol PAF would be reduced to 39% in Kenyan men and 30% in Tanzanian men. The strength-reduction counterfactual would therefore avert approximately 26 percentage points of alcohol-attributable ESCC in each country, without requiring any reduction in total alcohol consumption volume or in cultural practice. The 26-percentage-point figure is the manuscript's most actionable corridor-specific quantitative recommendation. Among Kenyan ESCCAPE participants, Menya et al. estimated a 48% PAF for the heavy-drinker stratum (>2 drinks per day), with the highest contribution among male tobacco users [54]. The consumption of no- and low-alcohol beverages, which remains low in this corridor, should be encouraged, as should abstinence from high-strength alcoholic beverages [69,70].

9.3. Biomass Cooking and Hot-Beverage PAFs

In Malawi, Mlombe et al. estimated an adjusted odds ratio of 12.6 (95% CI 4.2–37.7) for firewood-only cooking compared with electricity or charcoal as primary cooking fuel [60]. The sex-stratified analysis is striking: the firewood-cooking adjusted OR was 85.3 in women and 6.4 in men, paralleling the household-exposure-cluster pattern in which women carry the largest cooking-fuel-related burden. The Lusaka Kayamba series reported a multivariable OR of 3.0 for cooking with charcoal or firewood [53]. The published corpus does not contain a single corridor-wide PAF estimate for biomass-cooking smoke comparable in precision to the alcohol PAFs.

Table 3. Major documented ESCC risk factors across representative African corridor populations, organized by the two-cluster framework developed in Section 3.3.

Population (Country)	Cluster	Sex Ratio (M:F)	Tobacco	Alcohol (Unrecorded High-Strength)	Hot Beverages	Biomass Cooking Smoke	Maize Mycotoxins	Oral Health/Dental	HIV	Key Source
Kyadondo (Uganda)	Household	~1:1	Modest	Modest	Documented (chai)	Widespread	Not systematically assessed	Not systematically assessed	Elevated	Wabinga et al. [7]
Bomet County (Kenya)	Household	~1:1	Modest	High (busaa, chang'aa; PAF 48% heavy drinkers)	Documented, direct measurement (72.1 °C preferred initial tea temperature)	High (PAH biomarker 2.4–28× reference)	Documented in unrecorded beer	Charcoal hygiene not specific	Not primary driver	Menya et al. [54]; Mwachiro et al. [46,59]
Kilimanjaro (Tanzania)	Mixed	~1:1	Documented	Documented	Documented, direct measurement (70.6 °C)	Documented	Not systematically assessed	Charcoal hygiene aOR 2.33; less-than-daily brushing aOR 2.77	Not primary driver	Mmbaga et al. [22]; Munishi et al. [39]
Muhimbili (Dar es Salaam, Tanzania)	Mixed	~2.8:1	Documented	Documented	Frequency-related risk (Buckle et al. [28])	Widespread	Not systematically assessed	Not systematically assessed	Not primary driver	Mmbaga et al. [23]; Buckle et al. [28]
Northern Lake Zone (Tanzania)	Distinct	Not fully characterized	Modest, adjusted	Modest, adjusted	Adjusted	Adjusted	Not systematically assessed	Adjusted	Adjusted	Buckle et al. [28]
Lilongwe (Malawi)	Substance-use	~1.6:1	Primary driver	Under-reported (protective OR in men suggests under-reporting)	Documented, direct measurement (Malawi: 67.8 °C first sip, 74.6 °C pour)	Firewood-cooking aOR 12.6 overall, 85.3 in women	Not systematically assessed	Not systematically assessed	Elevated (HIV aOR 4.0)	Kaimila et al. [18]; Mlombe et al. [60]; Menya et al. [47]
Lusaka (Zambia)	Substance-use	Not corridor-typical	Documented	Not documented	Not systematically assessed	Firewood/charcoal aOR 3.0	Not systematically assessed	Not systematically assessed	Elevated (HIV aOR 2.3)	Kayamba et al. [53]
Bulawayo (Zimbabwe, 1963–77)	Substance-use	~7:1	Dominant driver (RR 5.7 for ≥15 g/day)	Not detected	Not systematically assessed for period	Not systematically assessed	Not systematically assessed	Not systematically assessed	Not primary driver for period	Vizcaino et al. [8]
Former Transkei (Eastern Cape, South Africa)	Substance-use	~2.3:1	Primary driver (PAF 58%)	Primary driver (PAF 48%; combined PAF 64%)	Not systematically assessed	Widespread	Documented (Fusarium/fumonisin [25])	Not systematically assessed	Not primary driver	Sewram et al. [24]; Rheeder et al. [25]; Somdyala et al. [19,20]

Hot-beverage consumption PAFs across the corridor have been estimated less consistently, partly because of the exposure-measurement difficulties analyzed in Section 5. The Masukume et al. composite thermal-exposure index analysis reported a per-unit composite OR of 1.22 and a top-tertile-versus-bottom-tertile OR of 4.6 [48], substantially stronger than any single component used alone. The Sheikh et al. Golestan analysis reported a 76% PAF for the seven-factor environmental cumulative-exposure-score top quintile [33]—a methodological precedent for cumulative-exposure PAF that the corridor literature has not yet replicated. Hot-beverage consumption contributes to corridor ESCC across both clusters; the precise PAF magnitude is sensitive to the exposure metric used and to the case-control inflation noted above.

9.4. The Two-Cluster Prevention Framework

The corridor's heterogeneity in sex ratio, dominant chemical co-exposures, and MOE composition supports a prevention strategy organized around the cluster framework rather than a single corridor-wide intervention package. For the substance-use cluster—Eastern Cape men, Bulawayo, Lilongwe, and the male substance-using subpopulations of Tanzania-Kilimanjaro and Kenya—the largest preventable PAFs are tobacco and alcohol. Tobacco control via the WHO MPOWER framework remains the single highest-yield intervention as evidenced in the Taiwan SimSmoke study [71].

Alcoholic-strength reduction, the lever quantified by Middleton et al. at 26 percentage points of avertable ESCC in Kenyan and Tanzanian men, is the most actionable corridor-specific addition. Chang'aa, gongo, and kachasu deliver the same ethanol load as commercial spirits at a per-gram-ethanol carcinogenic excess (ORs 1.20–1.26 per 10% ethanol contribution) [52], because of the contaminant burden carried alongside ethanol (Section 7.1).

For the household-exposure cluster—Uganda Kyadondo, western Kenya including Bomet and the Rift Valley, northern Tanzania-Kilimanjaro, and Eastern Cape women—the largest preventable burdens are biomass cooking smoke and hot-beverage thermal exposure. Clean-cookstove programs already piloted in several corridor countries through health and climate channels would address a corridor-specific carcinogen burden alongside the respiratory and climate co-benefits these programs were designed for. The hot-beverage thermal-exposure intervention has fewer documented precedents. Mirzaei et al. conducted the only published intervention specifically on hot tea consumption in a high-risk population, an educational campaign in 130 primary-school female students in Iran, with significant pre-post change in tea-temperature behavior over 4 weeks [72]. A corridor-specific behavioral intervention building on the poesha cup-pouring practice observed in approximately 20% of Kenyan children in the Hot-ESCAPE study would have the advantage of cultural anchoring [47]; whether poesha can be promoted at scale among adults, where the practice is rare, is an empirical question the corridor literature has not yet addressed.

9.5. Cross-Cluster Considerations

HIV testing and antiretroviral access programs already in place across the corridor address the immunosuppression component identified in Section 7.4. Oral-health interventions—daily toothbrushing, replacement of chewed-stick toothbrushes with modern brushes, and elimination of charcoal-based oral hygiene—apply across cluster types, with adjusted ORs of 2.28 to 2.77 in the Kilimanjaro ESCAPE analysis [22]. Endoscopic screening for esophageal squamous dysplasia at the level conducted in the Mwachiro Bomet STEP study [21] (14% asymptomatic dysplasia prevalence) is a tertiary-prevention measure whose population-level deployment is not currently supported by corridor health-

system capacity; targeted screening of identified high-risk groups may be feasible in selected settings.

10. Regulatory Implications

10.1. The 2018 IARC Threshold as a Deliberate First Step

The IARC classification [11] of very hot beverages above 65 °C as Group 2A established the first internationally recognized regulatory anchor for thermal carcinogenicity in food and drink. The threshold's value lies less in any biological precision—the underlying evidence base supports cytotoxic responses emerging at lower contact temperatures and a benchmark-dose-derived BMDL₁₀ of 56 °C—than in its operational tractability. The 65 °C value sits within the range of habitual beverage temperatures across many populations, is measurable with widely available equipment, and aligns with longstanding occupational and consumer-safety guidance for scald avoidance.

Cultural change in habitual food and beverage practice is slow. Habitual drinking temperature is among the most persistent food-culture practices, shaped by infancy onward—Section 5 documented direct measurements showing that approximately 22% of Kenyan and 19% of Malawian children take first sips above 65 °C. A graduated regulatory approach is more likely to produce real-world reductions than a threshold revision driven by maximalist toxicological extrapolation. Under such an approach, an initial threshold is established, behavioral and supply-side interventions are mobilized against it, and any subsequent revision is informed by the population's response. The IARC 2024 Advisory Group's recommendation to re-evaluate the 2018 classification—including the possibility of an upgrade from Group 2A to Group 1 [13,14,73]—provides the proper international channel for any future tightening of the regulatory anchor. The recommendations that follow take the 2018 threshold as a working baseline.

10.2. Hot-Beverage Temperature Reduction: Supply and Demand

The supply-side lever operates through brewing and serving temperatures rather than individual consumer behavior. Lachenmeier et al.'s triangle-test sensory experiment with five trained cuppers and 515 consumer assessors found that consumers could not discriminate brews at 86 °C versus 93 °C with greater than chance accuracy (38.8% correct identifications versus 33% expected by chance) [73]. As roast intensity increased, consumer preference shifted toward lower brewing temperatures: 26.7% of light roast consumers preferred 80 °C over 93 °C, rising to 62.4% of moderately dark roast consumers. The sensory evidence supports the recommendation that machine brewing settings can be reduced to ≤90 °C and serving temperatures to below 65 °C without consumer resistance. Brewing at the microbially safe minimum of approximately 55 °C is likewise compatible with the IARC threshold.

The corridor-specific application of supply-side regulation is constrained by the fact that the dominant route of hot-beverage consumption in many corridor populations is household-prepared chai and porridge, not commercial coffee from automated machines. The supply-side lever is most relevant for the corridor's growing urban food-service sector and for institutional settings (workplaces, schools, hospitals) where temperature can be controlled by procurement specifications.

The demand-side lever operates through consumer behavior. The poesha cup-pouring practice observed in approximately 20% of Kenyan children in the Hot-ESCAPE study [47] is the corridor's only documented behavioral intervention candidate that is culturally anchored rather than externally imposed. The Mirzaei et al. [72] educational-campaign protocol establishes a proof of concept that tea-temperature behavior is modifiable. A corridor-specific behavioral intervention combining brewing-then-waiting practice with

poesha-like cooling-pour techniques would have the advantage of cultural anchoring; such an intervention has not been piloted at scale and is identified as a research priority in Section 11.

10.3. Alcohol-Strength Reduction in Unrecorded Spirits

The most actionable corridor-specific regulatory recommendation supported by the manuscript's evidence base concerns alcohol strength rather than alcohol volume. Section 8 established that ethanol itself dominates the genotoxic cumulative MOE in the substance-use cluster. Section 9 quantified that the alcoholic-strength reduction scenario would avert approximately 26 percentage points of alcohol-attributable ESCC in Kenyan and Tanzanian men, without requiring any reduction in total alcohol consumption volume. The Pflaum et al. [62] European analysis quantified a 3.8-fold improvement in cumulative MOE from a single beverage-strength reduction (4 bottles of 5.5% beer yielding MOE 0.5 versus 1.9 for the same volume of 1.5% beer) [62].

Translating this evidence into corridor-specific regulation is more complex than for European commercial markets. Chang'aa, gongo, and kachasu are produced and traded informally; in Kenya, chang'aa was illegal until 2010 and remains regulated patchily. A more practicable approach than prohibition or comprehensive product reformulation may be a regulatory framework that legalizes and licenses the production of low-strength alternatives. These would be sorghum and millet beers in the busaa range of 4–5% alcohol-by-volume rather than 30–40% distilled spirits, retaining cultural continuity with traditional beverages. The available evidence base supports the case for a corridor-wide alcohol-strength regulatory framework as the highest-yield single-lever intervention for the substance-use cluster. Effectiveness, however, depends on enforcement and on consumer substitution behavior that the published literature has yet to characterize.

10.4. Clean-Cookstove Programs and Cross-Cluster Measures

Clean-cookstove programs have been deployed across multiple corridor countries through health and climate financing channels. The biomarker evidence reviewed in Section 7.2 supports adding ESCC prevention to the existing rationale for these programs; the Mlombe Malawian women-specific OR of 85.3 identifies women as the principal beneficiary group. The manuscript's contribution is to add the ESCC rationale to the existing case for these programs, not to propose a separate vertical intervention.

10.5. Implementation Framework

The four primary levers—supply-side and demand-side hot-beverage temperature reduction, alcohol-strength reduction in unrecorded spirits, clean-cookstove deployment, and tobacco control—operate through different administrative and financing channels and address different sub-populations. A coherent corridor-wide prevention strategy would integrate them through a population-attributable-fraction-weighted prioritization. Tobacco control, which carries the largest single PAF, deserves first-line attention; alcohol-strength reduction, the most actionable corridor-specific lever, follows closely; clean-cookstove deployment leverages existing implementation infrastructure; and thermal-exposure reduction is the longest-term but most universal lever, applicable across all corridor populations and directly addressing the mucosal-injury substrate identified as the corridor's common factor in Section 6. The corridor's complexity does not lend itself to a single regulatory recommendation. It does support a graduated framework in which the IARC 2018 threshold serves as a working baseline, the four primary levers are deployed through their respective channels, and the regulatory anchor is revised in due course as evidence accumulates and as habitual practices respond to intervention.

11. Research Priorities

11.1. Direct Chemical Characterization of Corridor Unrecorded Beverages

The MOE estimates for the substance-use cluster (Section 8.3) rely on values projected from analogous populations. Direct analytical characterization of a representative sample of corridor unrecorded beverages would either confirm or revise the magnitude of the combined concern. The Okaru et al. [58] analytical work on aflatoxin in 58 Kenyan unrecorded beers across 16 counties [58] establishes the feasibility of corridor-wide chemical sampling; extension to ethyl carbamate and acetaldehyde, with stratification by production method, substrate, and producer, is technically straightforward. Until that work is done, the biomass-dominated cluster cannot be placed on the same quantitative footing as the substance-use cluster, and the comparison between the two scenarios in Section 7.4 remains partly qualitative. The corresponding gap on the biomass side is larger: quantifying that cluster's genotoxic load in MOE terms would require personal monitoring of kitchen-air PAH, nitrosamines, and aldehydes, together with a defensible route-to-target-tissue dose assumption for the esophageal mucosa.

11.2. An Objective Composite Thermal-Exposure Metric

A composite score incorporating measured first-sip cup temperature, sip volume, drinking speed, and total daily volume—combining the multidimensionality of the Masukume et al. [48] composite with the objectivity of the Menya et al. [47] direct measurement and applying the De Jong et al. IELT equation [45]—would yield comparable exposure estimates across populations and resolve the heterogeneity that current self-reported metrics introduce into pooled analyses. Pilot deployment in a single corridor population would establish field-feasibility before corridor-wide adoption.

11.3. The Poesha Cooling-Pour Intervention Trial

A randomized cluster trial in adult corridor populations would test three propositions: that poesha uptake is achievable through community-level promotion in months to years; that uptake produces measurable IELT reductions in adopters; and that the reductions translate into measurable changes in early ESCC-relevant endpoints such as esophageal squamous dysplasia prevalence. The Mirzaei et al. [72] educational-campaign protocol establishes a proof of concept that tea-temperature behavior is modifiable; the poesha trial would extend this to a behavior-anchored intervention with cultural roots already present in the corridor.

11.4. A Corridor-Specific Cumulative Population-Attributable-Fraction Analysis

The Sheikh et al. [33] Golestan analysis combined seven environmental risk factors into a cumulative-environmental-exposure score with a population-attributable fraction of 76%. The corridor primary studies have generated single-exposure PAFs but no corridor cumulative-PAF analysis has yet been performed. The data infrastructure already exists in the ESCCAPE consortium pooled dataset (1279 cases, 1346 controls). A cumulative-PAF analysis combining tobacco, alcohol, alcohol type, hot-beverage exposure (Masukume et al. [48] composite), oral health, biomass cooking, and HIV status, applied separately to each cluster, would produce the first corridor-specific quantitative answer to the question of how much of corridor ESCC is preventable by addressing the assembled risk factors simultaneously, and would identify the residual fraction requiring explanation by exposures not yet adequately characterized. Such an analysis would also resolve the methodological question of whether corridor cluster assignment requires a more granular taxonomy than the binary framework of Section 3.3.

11.5. Resolving the Northern Lake Zone Signal

The Buckle et al. [28] Northern Lake Zone signal (Section 3.4: adjusted OR 12.06 in early-onset cases, surviving multivariable adjustment) is the corpus's single most clearly defined unfollowed lead. An exposure-resolution study combining environmental sampling, household survey, and biomarker analysis in matched ESCC cases and community controls would determine whether the signal reflects water-source contamination, localized dietary practices, ethnicity-specific behavior, or a localized environmental contaminant not yet identified.

11.6. Ionizing Radiation from Atmospheric Nuclear-Testing Fallout

Ionizing radiation is an established cause of esophageal cancer in high-dose exposure settings, including atomic-bomb survivors and populations exposed to local fallout from the Semipalatinsk nuclear-testing site, and could in principle be considered as a candidate exposure for corridor ESCC via global-fallout radionuclide deposition from mid-twentieth-century atmospheric weapons testing. The available evidence does not support this. Global-fallout committed effective doses to sub-Saharan African populations are estimated at well below 1 mSv over the entire testing era [74], approximately three orders of magnitude below the exposures for which the Semipalatinsk cohort demonstrated an ESCC excess [75]. The whole-genome-sequencing analysis of 552 ESCC tumors from eight countries including three corridor countries (Kenya, Tanzania, Malawi) reported no exogenous-mutagen mutational signature capable of explaining the corridor's incidence [9], and specifically no signature resembling the small-deletion pattern characteristic of ionizing-radiation-induced tumors [76,77]. The corridor populations show no accompanying excess in other radiogenic cancers (leukemia, thyroid, breast) that a radiation-primary etiology would predict.

11.7. Limitations

Several limitations of the available evidence and of the framework developed here should be acknowledged. First, the corridor evidence base is dominated by case-control studies and cross-sectional registry data; prospective cohort evidence directly from corridor populations remains scarce, and the risk-factor associations reported throughout Section 7 depend on the assumption that recall bias, selection bias, and control-group representativeness are broadly comparable across the primary studies. Second, direct chemical characterization of unrecorded corridor beverages (chang'aa, busaa, kachasu, gongo) is limited to a small number of published analytical surveys; the acetaldehyde, ethyl carbamate, and aflatoxin MOE values presented in Section 8.3 for the substance-use cluster are therefore best regarded as placeholders projected from analogous unrecorded-alcohol populations rather than as directly measured corridor values. Third, the two-cluster etiological framework developed in Section 3.3 is proposed as a first approximation and does not fully accommodate populations with ambiguous or intermediate exposure profiles, most notably western Kenya, Muhimbili, and the Eastern Cape; a more granular taxonomy is a research priority. Fourth, the mutational-signature evidence cited in Section 6 covers three corridor countries out of the eight countries sequenced; the null result for an exogenous-mutagen signature is highly informative but is not literally exhaustive of the corridor's genomic diversity. Fifth, the margin-of-exposure framework in Section 8 combines hazard quotients within mode of action following EFSA/JECFA convention, but the framework treats thermal exposure and genotoxic exposures in parallel rather than as fully integrated; a mechanistic multi-scale dose-response model integrating tumor-promoter and initiator processes remains beyond the scope of the current evidence base. Sixth, the geographic scope of the manuscript is deliberately restricted to the East and Southern African corridor and

does not attempt a comparative synthesis with the Central Asian esophageal-cancer belt or northern China, where the etiological profile differs and where additional insights into thermal and chemical co-exposure interactions may become available as those literatures mature. Finally, several of the recommended interventions (alcohol-strength reduction, cookstove deployment, thermal-exposure reduction) are supported by counterfactual modeling rather than by direct intervention-trial evidence in corridor populations; the current framework identifies these as the most actionable single levers, but the empirical case for their impact on corridor ESCC incidence awaits implementation-and-evaluation studies.

11.8. *A Prospective Corridor Cohort and Its Research Priorities*

The corridor's evidence base remains predominantly cross-sectional and case-control. The hot-beverage epidemiology of the international literature is anchored on prospective cohort studies—Golestan in Iran (50,045 participants since 2004) and the China Kadoorie Biobank (456,000 since 2004)—that no corridor population has yet matched in scale. A prospective corridor cohort would baseline-recruit in one or more high-incidence ESCCAPE catchments and follow participants through the development of dysplasia and ESCC. Such a cohort would resolve the case-control inflation problem documented in Sections 4 and 9, allow temporal-precedence analysis of the hot-beverage-temperature association, and provide the longitudinal exposure data required to disentangle the cumulative early-life-exposure framework.

Four methodological priorities should be embedded in such a cohort from the outset. First, standardized temperature-measurement protocols would replace the self-reported temperature-preference categories used in most existing corridor case-control studies, which correlate weakly with actual consumption temperature (Section 5.2). Harmonized probe-based measurement across corridor sites would generate comparable exposure data across countries. Second, biomarker-based exposure assessment for the corridor's principal chemical co-exposures—urinary polycyclic-aromatic-hydrocarbon metabolites for biomass smoke exposure, aflatoxin M₁ or aflatoxin-albumin adducts for aflatoxin exposure, and ethyl glucuronide or acetaldehyde-protein adducts for alcohol—would replace questionnaire-based exposure estimates with quantitative biomarker measurements, enabling dose-response analyses within the cohort. Third, prospective ascertainment of dysplasia and early ESCC through periodic endoscopic screening in a subset of participants would resolve the reverse-causation and recall-bias problems that limit case-control designs, and would generate the temporal-precedence data required to distinguish tumor-initiating from tumor-promoting exposures. Fourth, validation of the margin-of-exposure framework developed in Section 8 requires longitudinal exposure data of the kind only a prospective cohort can generate: cumulative exposure estimates for ethanol, aldehydes, aflatoxin, biomass-derived PAH, and thermal exposure across each participant's follow-up window, cross-referenced against incident dysplasia and ESCC cases, would allow the framework's central prediction—that the corridor's heterogeneous incidence reflects heterogeneous chemical co-exposure profiles operating against a shared thermal-promoter substrate—to be tested directly.

The ESCCAPE consortium's existing multicenter infrastructure across Kenya, Tanzania, and Malawi provides a platform on which such a cohort could realistically be built, and the four methodological priorities above are the minimum requirements for the resulting data to advance the corridor's etiological understanding beyond what the existing cross-sectional evidence supports.

12. Conclusions

The African ESCC corridor has been recognized for more than half a century, and its persistence at among the highest ESCC incidence levels documented anywhere has

resisted single-factor explanation throughout that period. The accumulated evidence reviewed here supports a different reading. The corridor's burden is the product of multiple chemical co-exposures operating against a shared substrate of habitual mucosal thermal injury, with dominant exposures and resulting risk profiles varying across two distinguishable population clusters. The margin-of-exposure framework expresses this multifactorial picture quantitatively, with both clusters reaching simultaneous concern below the conventional thresholds of safety.

Four practical prevention levers follow from this framework and are actionable in low-resource corridor settings through existing regulatory and implementation channels rather than new tertiary-care infrastructure. Alcohol-strength reduction targeting unrecorded home-distilled spirits offers a modeled 26-percentage-point reduction in alcohol-attributable ESCC among Kenyan and Tanzanian men, deliverable through licensing frameworks for low-strength substitutes without reducing total consumption volume. Tobacco control through the WHO MPOWER framework addresses the largest cluster-conditional attributable fraction in the substance-use cluster and awaits implementation rather than new evidence. Clean-cookstove programs deployed through existing health and climate financing channels address the biomass-cooking-smoke pathway carrying the largest sex-specific attributable burden in corridor women. Graduated thermal-exposure reduction—via brewing-and-serving temperature specifications in urban food service, workplace, school, and hospital procurement, and behavioral interventions building on culturally anchored cooling practices such as *poesha*—is the most universal lever applicable across all corridor populations. Cluster-conditional targeting of these levers, informed by each corridor population's dominant exposure profile, allows national health ministries and district-level practitioners to direct finite prevention resources at the exposures most prevalent in each sub-population.

The corridor's prevention is not constrained primarily by limits on what is known about its causes, but by the gap between the available evidence and the implementation channels through which evidence is translated into population-level practice. Bridging that gap does not await the completion of further primary research; it awaits the sustained engagement of national regulatory agencies, district-level public-health services, and the multilateral agencies whose implementation platforms already reach the affected populations.

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Abbreviations

The following abbreviations are used in this manuscript:

ASR	age-standardized (incidence) rate
BaP	benzo[a]pyrene
BMD	benchmark dose
BMDL ₁₀	lower 95% confidence limit of the benchmark dose for 10% extra risk
CI	confidence interval
DMFT	decayed, missing, and filled teeth (dental index)
DNA	deoxyribonucleic acid
EAC	esophageal adenocarcinoma
EFSA	European Food Safety Authority
ESCC	esophageal squamous cell carcinoma
ESCAPE	African Esophageal Cancer Consortium (ESCC African Prevention Research)
ESD	esophageal squamous dysplasia
HIV	human immunodeficiency virus
HR	hazard ratio
IARC	International Agency for Research on Cancer
IELT	intra-esophageal liquid temperature
JECFA	Joint FAO/WHO Expert Committee on Food Additives
MOE	margin of exposure
MPOWER	WHO tobacco-control package (Monitor, Protect, Offer, Warn, Enforce, Raise)
NDEA	N-nitrosodiethylamine
NDMA	N-nitrosodimethylamine
NMBA	N-nitrosomethylbenzylamine
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	N'-nitrosomornicotine
NTP	National Toxicology Program (United States)
OR	odds ratio
PAF	population-attributable fraction
PAH	polycyclic aromatic hydrocarbon
RR	risk ratio
TFI	Thylstrup–Fejerskov index (dental fluorosis severity)
TSNA	tobacco-specific N-nitrosamine
WHO	World Health Organization

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