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Influence of dose and cessation of *kiraiku*, cigarettes and alcohol use on the risk of developing oral leukoplakia

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Data from a previously-reported study of oral leukoplakia-associated risk factors in a Kenyan population were further analyzed to determine the influence of dose and cessation. Specifically, risk analysis was made with respect to *kiraiku* (a traditional Kenyan type of home-made, hand-rolled tobacco product), cigarettes, and commercial beer. The relative risk (RR) of oral leukoplakia among those who smoked >10 cigarettes was 14.7, as compared to 6.7 among those who smoked ≤10 cigarettes. With regard to duration, the RR increased from 7.4 in those who had smoked for ≤15 years to 10.8 in those who had smoked for ≥30 years. Among those who had quit smoking, RR value was significant only in ex-kiraiku smokers (RR=4.9, 95% confidence interval (CI)=2.3–20.4) and was dependent on both the duration of smoking and duration since quitting. For commercial beer, the RR was significant in consumers of >10 bottles per drinking day (RR=4.2, 95% CI=1.0–3.9) and in those whose who drank for ≥ 5 days per month (RR=3.8, 95% CI=1.0–15.1). Duration of beer consumption did not significantly influence the RR of oral leukoplakia. The RR in ex-beer consumers was not statistically significant. These findings suggest a dose-dependent association between oral leukoplakia and the use of tobacco and alcohol, in which the number of cigarettes smoked, the quantity of beer consumed, and the frequency of consumption were more important than the duration of use of these products. Furthermore, while oral leukoplakia due to cigarette smoking may regress completely, those due to kiraiku may persist for more than 10 years after cessation of these habits

Key words: oral leukoplakia; relative risks; *kiraiku*; cigarettes; alcohol; dose; cessation

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Among the important criteria for testing a causal hypothesis is the determination of the influence of the degree of exposure to the suspected risk factor(s), and removal of such factor(s), on the risk of developing the disease (1, 2). In a preceding paper (3), we reported that smoking traditionally processed hand-rolled tobacco (*kiraiku*), (relative risk (RR=10.0)) and smoking cigarettes (RR=8.4) were the most strongly associated with the development of oral leukoplakia in a sub-population resident in Kenya. In addition, the association of this lesion with commercial (bottled) beer (RR=2.0) and wines and spirits (RR=2.1) was weak but statistically significant. However, the association with Khat (RR=1.8), traditional beer (RR=1.3), chilies (RR=1.7) and sugar cane chewing (RR=0.5) was not statistically significant.

In order to further estimate the relative rôles of kiraiku, cigarettes and commercial beer in the development of oral leukoplakia, analysis of the effect of dose and cessation of their use on the risk of developing oral leukoplakia was considered. It is useful at the outset to note that unlike commercially processed tobacco, kiraiku preparation entails the wrapping of home grown tobacco leaves in, among other plant materials, dried peelings from banana plant

stems. In one of the popular methods, the wrapped tobacco is then patched near the roof of the hut and directly above the fire place to dry. The tobacco is then unwrapped and sun dried prior to crushing for use in preparation of *kiraiku*. Additives, such as tobacco flowers and seeds may be added during the drying process to enhance potency. In situations where other end products such as tobacco snuff are desired, trona (unrefined sodium bicarbonate) and animal oils are added to the dried tobacco leaves during the milling process. The sievings are then used for making kiraiku rolls. It is noteworthy that the materials used in the making of *kiraiku* rolls range from dried banana leaves and stem peelings, dry corn husks, to newspapers and other types of wrapping papers.

Materials and methods

This was a case control study in which study subjects were identified in a house to house survey of individuals aged 15 years and above. The procedures for sample size estimation, examination, the definition and identification of cases and controls, and the diagnostic criteria used for oral leukoplakia have earlier been described (3). For the 85 oral leukoplakia cases identified on the basis of clinical diagnosis (3, 4) and 141 controls, matched for sex, age (± 3 years) and cluster origin, the following retrospective information on dose of kiraiku and cigarettes smoked and commercial beer consumed was obtained from current and ex-habiters through direct interviews by a trained field worker, using a structured questionnaire: average number of cigarettes smoked per day, average number of kiraiku rolls smoked per day, average number of bottles of beer consumed in each drinking day, and average number of days in a month that beer was consumed. In addition, the duration (years) in which these habits had been practiced was also considered as a parameter of dose (in estimation). Wines and spirits including a local distillate (*changaa*) were not quantified due to lack of standard units of measure.

To assess the influence of dose on the RR of oral leukoplakia, the various exposure groups in current and ex-habiters were compared with the unexposed group (never-habiters). Similarly, to assess the influence of cessation of the risk habits, current and ex-habiters were separately compared with never-habiters.

The methods used to estimate RR and the test of significance applied have been previously described (3). In consideration of limits set by sample size and intensity, duration and frequency of exposure, assessment of dose was limited at most to three levels of exposure (1, 2). Categorization of levels of exposure was a post facto decision which was governed by among other factors, the magnitude of exposure, frequency, and the pattern of distribution of cases and controls in the various exposure levels (1, 2).

Since the average number of rolls of *kiraiku* smoked was in general small, for instance, 74.9% of ex-smokers claimed to have smoked only 5 rolls or less per day, the influence of intensity of smoking kiraiku on the RR of oral leukoplakia was not determined.

Table 1

The RR of oral leukoplakia in relation to duration of smoking and number of cigarettes smoked

Dose variable	Cases	Controls	RR	95% CI
never smoked	18	78	1.0	–
cigarettes/day[a]				
≤10	45	29	6.7	3.2–14.3
>10	17	5	14.7	4.3–53.4
duration of smoking[a]				
≤15 years	34	20	7.4	3.3–16.9
16–29 years	18	8	9.8	3.3–29.4
≥30 years	10	4	10.8	2.7–47.1

[a] For all levels of exposure $p < 0.001$.

Table 2

The RR of oral eukoplakia in relation to quantity of alcohol consumed, duration and frequency of consumption.

Dose variable	Cases	Controls	RR	95% CI
never consumed beer	26	62	1.0	–
quantity of beer consumed/drinking day				
≤10 bottles	32	43	1.8	0.9–3.6
>10 bottles	7	4	4.2[b]	1.0–3.9
duration of beer consumption				
≤10 years	23	30	1.8	0.9–4.0
>10 years	16	17	2.2	0.9–5.5
frequency of beer consuption				
<5 days/month	31	42	1.8	0.9–3.6
≥5 days/month	8	5	3.8[b]	1.0–15.1

[b] $p \leq 0.05$

Results

The RR of oral leukoplakia in current cigarette smokers increased with both the number of cigarettes smoked and duration of smoking (Table 1). The RR was significant in all smoking categories. For commercial beer, the RR of this lesion increased with the quantity of beer consumed, duration, and frequency of consumption (Table 2). However, this RR was statistically significant only in those who consumed more than 10 bottles of beer per drinking

Table 3

The RR of oral leukoplakia in current and ex-habiters

Risk factor/habit status	Cases	Controls	RR	95% CI
Cigarettes				
never smoked	18	78	1.0	–
ex-smokers	5	31	0.7	0.2–2.3
current smokers	62	32	8.4**	4.1–17.4
kiraiku				
never smoked	42	120	1.0	–
ex-smokers	29	17	4.9**	2.3–10.4
current smokers	14	4	10.0**	2.9–43.4
Commercial beer				
never consumed	26	62	1.0	–
ex-consumers	36	49	1.5	0.7–3.3
current consumers	39	47	2.0*	1.0–3.9

*$P<0.05$; **$P<0.001$.

Table 4

The RR of oral leukoplakia in relation to duration of time since quitting kiraiku smoking and duration of smoking before quitting.

Dose variable	Cases	Controls	RR	95% CI
never smoked *kiraiku*	42	120	1.0	–
duration of smoking before cessation*				
≤10 years	24	15	4.6	2.1–10.2
>10 years	5	2	7.1	1.1–76.6
duration after cessation*				
≤4 years	6	2	8.6	1.4–88.7
5–9 years	12	7	4.9	1.7–14.9
≥10 years	11	8	3.9	1.4–11.6

* For all exposure levels $P<0.05$.

day, and in those whose frequency of consumption was 5 days and above per month. Cessation of cigarette smoking habit markedly reduced RR of oral leukoplakia (Table 3). The RR in ex-cigarette smokers (RR=0.7) was not significantly different from that in never smokers. In contrast, the RR in ex-*kiraiku* smokers (RR=4.9), though lower than that in current smokers (RR=10.0), was significant and nearly 5 × that in those who never smoked *kiraiku* (95% CI=2.3–10.4). The influence of duration of smoking *kiraiku* before quitting and duration of time since quitting this habit on the RR of oral leukoplakia is shown in Table 4. There was a gradual decrease in RR of this lesion with increase in duration since quitting the habit. However, even the RR in the last category of those who quit since ≥10 years earlier (RR=3.9) was statistically significant (95% CI=1.4–11.6), and almost 4× that in those who had never smoked *kiraiku*. The RR of oral leukoplakia increased, with increase in duration of smoking before quitting the habit.

Discussion

The findings of this analysis demonstrated a probable dose-response relationship between cigarette smoking and the risk of oral leukoplakia. For example, those who smoked more than 10 cigarettes per day (RR = 14.7) appeared to be 2.2 × more likely to develop oral leukoplakia than those who smoked 10 or less cigarettes (RR = 6.7) (Table 1).

Based on the levels of exposure studied, the number of cigarettes smoked appear to be more important than the duration of smoking. Although the influence of intensity of smoking *kiraiku* on the risk of oral leukoplakia could not be determined, it is notable that the RR in ex-*kiraiku* smokers was dependent on both the duration of smoking before quitting and the duration of time since quitting this habit (Table 4). These observations on dose dependent relationship between tobacco use and oral leukoplakia are in agreement with findings from previous studies (8–11). In contrast, the dose response for commercial beer was generally weak. It would appear that only those who consumed more than 10 bottles of beer in each drinking day (RR = 4.2), and those whose frequency of consumption was 5 or more drinking days per month (RR = 3.8), were at significantly greater risk of developing oral leukoplakia. Duration of beer consumption even for more than 10 years did not have a statistically significant influence on the RR of oral leukoplakia. As was the case with cigarettes, it appeared that within the limits of dose-response details studied, the quantity of beer consumed and the frequency of consumption was more important than the duration of consumption. These findings further support our earlier incrimination of beer as a weak but significant risk factor for oral leukoplakia (3). The influence of the frequency of alcohol consumption on the risk of oral leukoplakia and moreover potential synergy with tobacco in the aetiology of this lesion has been reported (12, 13). In contrast, it is notable that in our study community commercial beer did not significantly influence the RR of oral leukoplakia among tobacco smokers (3, 14). However, the possibility that the dose response observations made for beer could be accounted for by another variable that had not been considered could not be entirely ruled out.

It has been shown by previous authors that the majority of oral leukoplakia lesions due to tobacco use regress upon cessation of the habits (5, 15–18) and that the rate of regression is dependent on the type of tobacco habit (5). In our study, a most striking finding was that while the RR of oral leukoplakia in ex-cigarette smokers (RR=0.7) was comparable to that in never-smokers, the RR in ex-*kiraiku*

smokers was nearly 5× that in never-smokers (Table 3). Furthermore, the RR in those who had quit this habit ≥10 years earlier (RR=3.9) was still significantly higher (Table 4). In this respect, we have previously suggested a similarity between *kiraiku* and the Indian bidi on the basis of the persistence of associated leukoplakia lesions (3, 5, 14). This similarity may possibly be attributed to among other factors, the traditional curing methods used in preparation of both *kiraiku* and bidi tobacco (3, 6, 7). It is also notable that smoke from the Indian bidi contains a higher concentration of 'tar', carcinogenic hydrocarbons (benz[a] anthracene and benzo[a] pyrene) and tumor promoting volatile phenols than cigarettes (6). We believe that the traditional curing and production processes of *kiraiku* leaves higher residual concentration of toxic constituents.

We acknowledge that, in addition to the number of cigarettes or *kiraiku* rolls smoked and duration of smoking that were considered in our study, the degree of inhalation, the frequency of puffs, the left-over length of butt (8), and the quantity of tobacco used as cigarette or *kiraiku* roll filler are important parameters. In the case of beer, the size of beer bottle and the quantities of left over can also influence dose. Furthermore, sample size and magnitude of exposure as estimated by respondents limited the dose response details studied (1, 2) at most to simple trichotomization. Despite these limitations, since dose response and the influence of cessation of risk habits are important indicators of causality (1, 2, 18), these findings generally strengthen our incrimination of *kiraiku* and cigarettes (3). It is also evident that unlike cigarette associated oral leukoplakia lesions, *kiraiku* associated lesions are more persistent upon cessation of the habits.

Although the number of *kiraiku* smokers in our study was relatively small, the proportion of users of this product is unknown at the national level. However, given anecdotal information which suggest that the use of *kiraiku* is determined by inability to purchase cigarettes, it is likely that this practice may continue for a long time. Therefore, it is necessary to conduct detailed studies on the traditional methods used in curing and processing tobacco used in making *kiraiku* rolls, the prevalence of smoking *kiraiku*, and analysis of smoke from this product with a view to establishing methods of reducing the risks associated with the use of *kiraiku*. In addition, the significance of apparent persistence of *kiraiku*-associated oral leukoplakia lesions with respect to their risk of malignant transformation also merits further studies in order to facilitate community based dissemination of accurate information regarding these risks (19).

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