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Smokeless tobacco (snuff) and site-specific cancer risks in adult Black South African women: Findings from the Johannesburg Cancer Study

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Abstract

Smokeless tobacco (SLT) use is an established carcinogen to the nasal cavity, lip, and oropharynx, however, few studies have examined cancer risks in older African women among whom SLT use is common. We investigated snuff use and the risk of site-specific cancers among 15,336 newly diagnosed female cancer patients in the Johannesburg Cancer Study, South Africa. We designed case–control comparisons across multiple cancer outcomes: (a) known SLT-associated cancers; (b) other tobacco-related cancers and (c) genital cancers owing to intravaginal snuff use. Controls ($n = 2961$) comprised all other cancer patients. We also investigated (d) each control cancer type versus the remaining controls to explore possible associations with other cancers. Logistic models were fitted to estimate odds ratios adjusted for age, education, tobacco smoking, alcohol, HIV, and language. Overall, ever use of snuff was 22% among control cancers. Ever snuff use was associated with cervical (OR 1.14 [95%CI 1.00–1.30]) and eye and adnexa cancer (OR 1.95 [95%CI 1.03–3.70]). Associations with vulva cancer were less clear, 95% CI's for the main effects included 1 but a subgroup analysis restricted to never-smokers of

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current-versus-never users was positive (OR 2.10 [95%CI 1.25–3.50]). Surprisingly SLT users have lower risks of stomach cancer (OR 0.60 [95%CI 0.37–0.99]) and Hodgkin Lymphoma (OR 0.48 [95%CI 0.23–0.97]). Snuff use may increase the risk for cervical and vulva cancer in women, which is plausible via intravaginal use. Further research on the impact of SLT on female genital cancers with more detailed exposure data, including timing, intensity, and routes of use are required.

KEYWORDS

cancer, Johannesburg cancer study, smokeless tobacco use, snuff use, South Africa

What's new?

In South Africa, snuff, a form of smokeless tobacco, is used in certain traditional and social practices. Although possibly perceived by users as a safe alternative to tobacco smoking, snuff use is linked to elevated cancer risk. Here, associations between snuff use and site-specific cancer risk was evaluated among females in Johannesburg using a series of case-control comparisons within the Johannesburg Cancer Study. Among ever users, positive associations were identified between snuff use and cervical, eye, and adnexal cancers. The findings offer new insight into cancer risk particularly among Black South African women, among whom snuff use is relatively common.

1 | INTRODUCTION

Comprehensive tobacco control policies on taxation, smoke-free laws, health warning labels, bans on advertisement, promotion and sponsorship, and cessation programs implemented in high-income countries (HICs) have led to a significant decline in tobacco smoking prevalence.[1–4] Whilst these have tackled tobacco smoking, there has been an increased use of smokeless tobacco (SLT) products.[5] Such SLT products are unsmoked tobacco-containing products made from finely ground, powdered, or pulverized tobacco leaves, which may be flavored.[5–7] They are often used either intranasally (i.e., snuff) or intraorally.[5,6] Intraorally, there are small pouches of SLT or loose SLT that can be chewed and placed between the gums (teeth) and the lips. Intranasally use of dry and moist snuff is sniffed or inhaled through the nose.[6]

In South Africa, SLT use is mainly in the form of snuff use of finely ground tobacco, mixed with other plant products. In this country, snuff is commonly available both as a traditionally homemade and commercial product.[5,8] Black South African women are often viewed as low prevalence for tobacco use because of their low smoking prevalence, however, they have high snuff use.[9] In South Africa, certain traditional and social practices influence the use of SLT products such as snuff (sniffed or placed in the nasal cavity) and chewed tobacco leaves.[5,10] For instance, traditionally among pedi-speaking women use of snuff was taboo until they were past childbearing age. Traditionally the use of snuff has been normalized as a remedy for relieving stress, headaches, toothaches, and nosebleeds post-childbearing.[8,10] Snuff has also been used intravaginally as it is thought to increase sexual pleasure.[11,12] Another important use of snuff in the South African context is as an absolute necessity in African traditional religion, divination, Sangomas, traditional healers, and mediums practice as a way to communicate with ancestors.[13]

In South Africa, the purchase of SLTs is regulated by the Tobacco Product Control Act of 1993 which bans sales for those aged under 18.[14] Regardless of the Act, the prevalence of SLT is rising. According to the first South African Demographic and Health Survey, the national prevalence of SLT products in 1998 was 6.7% in both sexes combined, but use was higher at 13.2% among Black women.[15,16] In 2005, the prevalence among Black women, aged 30 and older increased to 28.1%.[5,17] This increase is possibly due to the perception that it is a safer alternative to tobacco smoking.[5,9,18,19]

Both tobacco smoking and SLT use have been classified by the International Agency for Research on Cancer (IARC) Monographs program as carcinogenic to humans (Group 1).[20] However, whereas the adverse health outcomes associated with tobacco smoking are well established and extensively studied in different populations, including South Africa,[21] studies of SLT use, are fewer.[5,18] Most SLT products are known to contain more than 30 potential carcinogens, including tobacco-specific N-nitrosamines (TSNAs), nitrite, nitrate, and heavy metals such as nickel, cadmium, and chromium.[6,22] The levels of these carcinogens vary widely among the SLT products consumed in different countries.[23]

The IARC Monographs program has found that there is sufficient evidence in humans that SLT causes cancers of three sites: oral cavity, esophagus, and pancreas; however, SLT is not listed as having either sufficient or limited evidence in humans for several cancer topographical sites which have sufficient evidence for tobacco smoking.[24] Thus, further research is needed to explore the risk of developing cancer across different cancer sites associated with SLT.[23] This should include South African settings where snuff use is common among older women.[17,25,26]

In the present study, we designed a series of case–control comparisons within the Johannesburg Cancer Study (JCS)[27] to evaluate

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the association of snuff use and risk for site-specific cancers among females in Johannesburg, South Africa. We also describe snuff use and its variations by socio-demographics and other cancer risk factors.

2 | METHODS

2.1 | The Johannesburg Cancer Study

This study is embedded within the JCS which is under the auspices of the South African National Cancer Registry. The JCS response rates were >90%, as is described in detail elsewhere.[27] In brief, the study recruited consecutive consented, treatment-naïve adults with incident cancer who self-defined as Black, in the southern Gauteng province of South Africa. This cancer case series included people with cancers of any type. Recruitment took place at the medical and radiation oncology departments of the largest tertiary referral public hospitals in Johannesburg (mainly Charlotte Maxeke Johannesburg Academic Hospital) between 1995 and 2016. Over 95% of cancers were confirmed by histopathology. Cancers were coded for topography and morphology using the International Classification of Diseases for Oncology Version 3 (ICD-O3) and presented in ICD-10 format.

2.2 | Questionnaire

At the time of recruitment, trained nurse interviewers used a standard questionnaire to interview all consenting participants in their preferred language (mostly isiZulu, Sesotho, or English). Participants were interviewed within 6 months of diagnosis. The three-page questionnaire covered questions on the leading and emerging risk factors for cancer. Questions included the key exposure of interest, and snuff use, upon which the question was: "have you ever used snuff?" with answers yes (now), in the past/former use (not time specific), or never. For former and current snuff users, the frequency of daily snuff use was asked: "in the past five to ten years how often do you use snuff each day (specify the number/times of use per day)?" Other variables collected included age at diagnosis, marital status, education level, home language, place of residence, alcohol consumption, tobacco smoking (current, former, and never), HIV status (serologically confirmed), parity, number of sex partners, and use of contraceptives.

2.3 | Present study design

Etiological studies can be conducted within the JCS by designing "case–control" studies within this cancer case series. By recruiting patients with any cancer, the JCS is amenable to multiple case–control comparisons. Cases comprise the cancer types of interest and controls are made up of cancers for which the exposure of interest is not a risk factor under investigation.[28,29] This approach needs to be augmented by analyses excluding each cancer type contributing to the control group, both to ensure that new cancer sites associated with a given exposure can be identified, as well as to investigate potentially biased odds ratios (ORs) (toward the null if exposure contrasts are reduced).

2.4 | Analytical sample

Female participants aged 18–74 years, Black, residents of South Africa, with a new (incident) diagnosis of cancer provided they had not begun chemotherapy or radiation treatment and had given written or witnessed oral, informed consent were included in the analyses. The JCS included 24,390 cancer patients, 8038 men and 16,352 women. In the present analysis, all men were excluded as snuff use was rare (198 males, ever snuff use was 2.5%). Among the 16,352 women, we excluded the following: 382 women aged 75+, 63 women born outside South Africa, 32 with missing primary cancer sites, 524 with incorrect or missing data, and 15 participants with missing data on snuff use, leaving 15,336 women in the analytical sample. We analyzed snuff use in relation to risk of 26 site-specific cancers (or cancer groups) for which there were at least 50 cases. Controls were participants diagnosed with cancers that have no known relationships to SLT or smoked tobacco. These cancers are anus, bone, central nervous system (CNS), endocrine gland, endometrium, eye and adnexa, fallopian tube, Hodgkin lymphoma, Kaposi's sarcoma, melanoma, myeloma, non-Hodgkin lymphoma, peritoneum and retroperitoneum, placenta, small intestine, soft tissue sarcoma, squamous cell carcinoma, thymus, thyroid, vagina, vulva, gall bladder, other sarcomas and digestive organs totally; 2961 controls for most analyses.

We also used each of the cancer sites in the control group as "cases" (and in those analyses used the remaining cancer sites as the control group) to assess other possible cancer sites associated with snuff use. Specifically, we constructed four case groups. The first comprised cancer types for which there are known associations with SLT viz: esophagus nasal, lip, oral cavity and pharynx and pancreas and, the second being other tobacco-associated cancer types (viz: cervix, colon, liver, lung and trachea, nasal and nasopharynx, ovaries, stomach and breast cancer) and cancers not currently related to tobacco smoking or smokeless tobacco, but with known vaginal tobacco exposure routes in South Africa (viz: vagina and vulva cancer). Lastly currently not related to tobacco smoking or smokeless tobacco. (viz: anus, bone, endometrium, eye and adnexa, Hodgkin Lymphoma, Kaposi sarcoma, other sarcomas, melanoma, myeloma, non-Hodgkin lymphoma, Squamous cell carcinoma, and Thyroid cancer). Cancers currently not related to tobacco smoking or SLT were used as the control group.

2.5 | Statistical analysis

The descriptive summary (frequencies and percentages) of ever-snuff use was first examined by socio-demographic characteristics

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TABLE 1 Prevalence of snuff use among control group study participants by socio-demographics and other risk factors.

	Snuff use		
	Never *N* (%)	Ever *N* (%)	Total
Variables	**2312 (78.1)**	**649 (21.9)**	**2961**
Age group			
18–24	166 (93.8)	11 (6.2)	177
25–34	588 (86.9)	89 (13.2)	677
35–44	520 (79.6)	133 (20.4)	653
45–54	412 (71.9)	161 (28.1)	573
55–64	373 (72.0)	145 (28.0)	518
65+	253 (69.7)	110 (30.3)	363
Marital status			
Single	797 (83.5)	157 (16.5)	954
Married	834 (79.0)	222 (21.0)	1056
Widowed	369 (71.7)	146 (28.4)	515
Separated	306 (71.5)	122 (28.5)	428
Education level			
None	177 (62.1)	108 (37.9)	285
Primary	830 (72.3)	318 (27.7)	1148
Secondary	1134 (84.4)	209 (15.6)	1343
Tertiary	169 (92.9)	13 (7.1)	182
Language			
Zulu	613 (83.4)	122 (16.6)	735
Xhosa	283 (78.4)	78 (21.6)	361
Sotho	296 (69.0)	133 (31.0)	429
Pedi	139 (79.4)	36 (20.6)	175
Tswana	274 (68.0)	129 (32.0)	403
Venda	37 (92.5)	3 (7.5)	40
Swazi	96 (76.8)	29 (23.2)	125
Shangaan	90 (92.8)	7 (7.2)	97
Ndebele	97 (82.2)	21 (17.8)	118
Afrikaans	14 (73.7)	5 (26.3)	19
Other	80 (97.6)	2 (2.4)	82
Place of residence			
Urban	2066 (78.7)	560 (21.3)	2626
Rural	239 (73.5)	86 (26.5)	325
Alcohol consumption			
No	1807 (79.6)	463 (20.4)	2270
Yes	505 (73.1)	186 (26.9)	691
Ever smoking			
No	1903 (77.4)	555 (22.5)	2458
Yes	408 (81.6)	92 (18.4)	500
HIV status			
Negative	1058 (76.1)	332 (23.9)	1390
Positive	1161 (80.5)	282 (19.5)	1443
Parity			
0	79 (85.0)	14 (15.1)	93
1–2	1021 (80.2)	252 (19.8)	1273
3 or more	960 (74.1)	336 (25.9)	1296
Unknown	252 (84.3)	47 (15.7)	299
Number of sexual partners			
0–1	229 (80.9)	54 (19.1)	283
2–5	1248 (76.3)	388 (23.7)	1636
6 or more	260 (75.4)	85 (24.6)	345
Unknown	575 (82.5)	122 (17.5)	697
Contraceptive use			
Never	948 (74.9)	318 (25.1)	1266
Ever	1358 (80.5)	329 (19.5)	1687
Freq. of daily snuff use[a] (times/day)			
1–2	-	172 (27.0)	
3–4	-	240 (37.7)	
5–9	-	118 (18.5)	
10+	-	107 (16.8)	

Note: Participants with missing data on marital status were 8, 3 for education level, 377 for language, 10 for place of residence, 3 for smoking, 128 on HIV status, 8 contraceptive use. A total of 12 participants did not have data on frequency of snuff use (this question was answered by current and ex snuff users).

[a]All percentages are row % except for daily snuff use.

of participants (Table 1). The socio-demographic variables included, age group at enrolment, marital status (single, married, widowed or separated), education level (none, primary, secondary or tertiary), language spoken, place of residence (urban/rural), alcohol consumption (no/yes), ever tobacco smoking (no/yes), HIV status, parity (none, 1–2, 3 or more), number of sexual partners (0–1, 2–5, 6 or more), contraceptive use (ever/never) and frequency of daily snuff use per day (1–2, 2–4, 5+ times/day).

Table 2 shows the distribution of the cases and controls, as well as the ever-snuff use prevalence for each cancer site. For case–control analyses, unconditional logistic regression models were used to calculate multivariate odds ratios of developing a specific cancer type associated with ever compared to never snuff users, current to never snuff users, and former versus never users. An additional analysis where we restricted the analysis to participants who self-reported as non-smokers was also done (Tables 3 and 4). ORs were adjusted for age, education level, language, smoking, and alcohol consumption. The statistical analysis was done using STATA software version 17.0 (Stata Corp, College Station, Texas).

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TABLE 2 Description of the cases and the control group by cancer type and the prevalence of ever snuff use.

		Cases			Controls	
Cancer type	**IARC-level of evidence[a]**	**No.**	**Mean age (SD)**	**Ever snuff use *N* (%)**	**No.**	**Mean age (SD)**
Cancer sites with sufficient or limited evidence for smokeless tobacco						
Esophagus[b]	Sufficient (smoking and smokeless)	503	57.9 (9.8)	148 (29.4)	2961	45.3 (14.5)
Lip oral cavity and pharynx[b]		249	52.1 (12.4)	45 (18.1)	2961	45.3 (14.5
Pancreas[b]		77	56.3 (11.7)	20 (26.0)	2961	45.3 (14.5)
Cancer sites not related to smokeless tobacco but with sufficient or limited evidence for smoking tobacco						
Cervix	Sufficient (smoking)	4984	49.7 (10.9)	1410 (28.3)	2961	45.3 (14.5)
Colon	Sufficient (smoking)	447	51.1 (12.6)	104 (23.3)	2961	45.3 (14.5)
Liver	Sufficient (smoking)	65	47.7 (12.6)	14 (21.5)	2961	45.3 (14.5)
Lung and trachea	Sufficient (smoking)	235	56.6 (10.2)	56 (24.0)	2961	45.3 (14.5)
Myeloid leukemia	Sufficient (smoking)	225	45.9 (15.7)	56 (24.9)	2961	45.3 (14.5)
Nasal cavity and nasopharynx	Sufficient (smoking)	79	43.9 (15.4)	21 (26.6)	2961	45.3 (14.5)
Ovaries	Sufficient (smoking)	379	52.3 (12.5)	111 (29.3)	2961	45.3 (14.5)
Stomach	Sufficient (smoking)	150	54.3 (12.8)	26 (17.3)	2961	45.3 (14.5)
Breast[c]	Limited (smoking)	4812	50.0 (11.3)	1174 (24.4)	2961	45.3 (14.5)
Cancer sites not currently related to tobacco smoking or smokeless tobacco, but with known vaginal tobacco exposure routes in South Africa						
Vagina	-	57	50.9 (13.9)	18 (31.6)	2904	45.2 (14.5)
Vulva	-	243	47.6 (11.7)	65 (26.8)	2718	45.1 (14.7)
Cancer sites not currently related to tobacco smoking or smokeless tobacco as per IARC monographs						
All "control" cancers combined	-	-	-	649 (22.0)	2961	45.3 (14.5)
Anus	-	59	48.3 (12.4)	10 (17.0)	2902	45.3 (14.5)
Bone	-	57	39.7 (17.0)	16 (28.1)	2904	45.4 (14.4)
Endometrium	-	427	59.9 (11.0)	108 (25.3)	2534	42.8 (13.5)
Eye and adnexa	-	56	36.9 (8.9)	18 (32.1)	2905	45.4 (14.5)
Hodgkin lymphoma	-	150	37.1 (12.3)	15 (10.0)	2811	45.7 (14.5)
Kaposi sarcoma	-	691	34.9 (9.1)	128 (18.5)	2270	48.4 (14.4)
Other sarcomas	-	224	47.9 (14.2)	53 (23.7)	2737	45.1 (14.5)
Melanoma	-	56	54.4 (12.5)	16 (28.6)	2905	45.1 (14.5)
Myeloma	-	174	55.2 (10.0)	42 (24.1)	2787	44.7 (14.5)
Non-Hodgkin lymphoma	-	382	40.8 (11.9)	71 (18.6)	2579	45.9 (14.7)
Squamous cell skin carcinoma	-	96	47.8 (13.4)	22 (22.9)	2865	45.2 (14.5)
Thyroid	-	53	52.7 (12.5)	14 (26.4)	2908	45.1 (14.5)

[a]*Source*: https://monographs.iarc.who.int/wp-content/uploads/2019/07/Classifications_by_cancer_site.pdf
[b]Cancer sites known to be associated with SLT use with sufficient evidence in humans.
[c]For breast cancer there is limited evidence in humans on the association with tobacco use or SLT. Control group: cancer sites that have no evidence in humans of relationships to SLT or smoked tobacco. In analyses of the specific constituent cancer as the case-group, these people do not form part of the control group. The control group cancers of the: anus, bone, CNS, endocrine gland, endometrium, eye and adnexa, fallopian tube, Hodgkin lymphoma, Kaposi's sarcoma, melanoma, myeloma, non-Hodgkin lymphoma, peritoneum and retroperitoneum, placenta, small intestine, soft tissue sarcoma, squamous cell carcinoma of the skin, thymus, thyroid, vagina, vulva, gall bladder, other sarcomas and digestive organs (cancers in the control group with less than 50 participants were not presented in the table). The analysis was done for cancers with >50 participants (cancer of the thymus and the fallopian tube). Colon includes rectum which is a tobacco related cancer. The nasal cavity (tobacco related) was combined with the nasopharynx (unrelated to tobacco).

3 | RESULTS

The prevalence of ever-snuff use among the controls group was 22%. Approximately 51% of these ever users were current users (328/649), Table 1. Among the ever users, 73% of women reported taking snuff three or more times in a day. Most snuff users were aged 45 or older with those aged 65+ having the highest prevalence (30%). The highest prevalence of ever snuff use was among widowed and separated women (28%–29%) compared to 21% amongst married women. Snuff use was highest among women with no level of education (38%), compared to 7% among those with tertiary education. Snuff use also differed by language spoken by the participants. Ever use was an

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TABLE 3 Univariate and multivariate-adjusted odds ratios (95% CI) for specific cancer sites associated with current versus never snuff use and former versus never snuff use.

Cancer (outcome)	Ever versus never		Current versus never	Former versus never
	Univariate odds ratio (95% CI)	Multivariate odds ratio (95%CI)	Multivariate odds ratio (95%CI)	Multivariate odds ratio (95%CI)
Breast	1.15 (1.03–1.28)	0.97 (0.85–1.10)	0.92 (0.78–1.09)	1.01 (0.86–1.19)
Cervix	1.41 (1.26–1.56)	**1.14 (1.00–1.30)**	**1.30 (1.10–1.53)**	0.99 (0.84–1.17)
Colon	1.08 (0.85–1.37)	1.02 (0.79–1.34)	1.03 (0.72–1.47)	1.03 (0.73–1.45)
Esophagus[a]	1.49 (1.20–1.83)	0.97 (0.75–1.27)	0.74 (0.51–1.09)	1.21 (0.87–1.67)
Lip oral cavity and pharynx[a]	0.79 (0.56–1.10)	0.69 (0.48–1.02)	0.59 (0.34–1.03)	0.79 (0.49–1.26)
Liver	0.98 (0.54–1.78)	1.19 (0.58–2.45)	1.27 (0.50–3.17)	1.07 (0.40–2.87)
Lung and trachea	1.11 (0.82–1.52)	0.99 (0.69–1.44)	0.66 (0.37–1.16)	1.30 (0.84–2.02)
Myeloid leukemia	1.18 (0.86–1.62)	1.15 (0.74–1.80)	0.58 (0.27–1.24)	**1.71 (1.04–2.80)**
Nasal cavity and nasopharynx	1.29 (0.78–2.14)	1.34 (0.75–2.38)	1.07 (0.48–2.39)	1.57 (0.80–3.10)
Ovaries	1.48 (1.16–1.87)	1.27 (0.97–1.68)	1.10 (0.75–1.62)	**1.45 (1.03–2.02)**
Pancreas[a]	1.25 (0.75–2.10)	1.09 (0.62–1.92)	0.44 (0.15–1.25)	1.74 (0.94–3.21)
Stomach	0.75 (0.49–1.15)	**0.60 (0.37–0.99)**	**0.46 (0.22–0.97)**	0.73 (0.40–1.33)
Anus[b]	0.72 (0.36–1.43)	0.55 (0.25–1.20)	0.42 (0.13–1.40)	0.67 (0.26–1.76)
Bone[b]	1.40 (0.78–2.51)	1.60 (0.80–3.21)	1.01 (0.34–3.06)	2.16 (0.99–4.75)
Endometrium[b]	1.25 (0.98–1.58)	0.77 (0.56–1.04)	0.95 (0.64–1.40)	**0.61 (0.40–0.93)**
Eye and adnexa[b]	1.71 (0.97–3.01)	**1.95 (1.03–3.70)**	1.68 (0.69–4.12)	**2.49 (1.16–5.34)**
Hodgkin lymphoma[b]	0.38 (0.22–0.66)	**0.48 (0.23–0.97)**	0.36 (0.11–1.16)	0.57 (0.24–1.35)
Kaposi sarcoma[b]	0.76 (0.62–0.95)	1.23 (0.92–1.65)	1.45 (0.97–2.16)	1.08 (0.74–1.58)
Melanoma[b]	1.44 (0.80–2.58)	1.16 (0.60–2.24)	1.59 (0.72–3.50)	0.80 (0.30–2.12)
Myeloma[b]	1.14 (0.80–1.64)	0.85 (0.55–1.32)	**0.42 (0.21–0.87)**	1.36 (0.82–2.25)
Non-Hodgkin lymphoma[b]	0.79 (0.60–1.04)	0.85 (0.62–1.16)	**0.79 (0.29–0.82)**	1.19 (0.83–1.72)
Other sarcomas[b]	1.11 (0.81–1.54)	0.91 (0.64–1.31)	1.01 (0.64–1.62)	0.83 (0.51–1.35)
Squamous cell carcinoma (Skin)[b]	1.06 (0.65–1.72)	0.97 (0.55–1.70)	0.90 (0.41–1.95)	0.99 (0.49–2.00)
Thyroid[b]	1.28 (0.69–2.38)	0.73 (0.31–1.72)	1.25 (0.50–3.14)	0.20 (0.03–1.53)
Vagina[b]	1.66 (0.94–2.93)	0.64 (0.90–3.02)	1.78 (0.83–3.81)	1.40 (0.63–3.13)
Vulva[b]	1.33 (0.99–1.80)	1.09 (0.76–1.58)	1.49 (0.95–2.33)	0.73 (0.43–1.25)

Note: Multivariate analysis minimally adjusted for age group, language, education, smoking and alcohol consumption. Additionally, cancers associated with HIV were adjusted for HIV status (anus, cervix, vulva, eye and adnexa, Hodgkin lymphoma, Kaposi sarcoma, liver, lung and trachea and melanoma). Breast cancer was adjusted for parity. The bolded values are tthe statistically significant Odd Ratios.

[a]Cancer sites known to be caused by SLT use with sufficient evidence in humans.

[b]Control group; cancer sites that have no known relationships to SLT or smoked tobacco. In analyses of the specific constituent cancer as the case-group, these people do not form part of the control group.

absolute 7% higher among rural than urban women. Snuff use was higher among alcohol consumers, making this a potential positive confounder for alcohol-related cancers, whereas ever use was lower among tobacco smokers, that is, rendering smoking a potential negative confounder. Snuff use was lower among HIV+ women and higher among those with three or more children and two or more sexual partners (Table 1).

Table 2 shows that the prevalence of snuff use by cancer site varied from 10% among 150 participants with Hodgkin lymphoma to 32% among 56 participants with eye and adnexa cancer. Table 2 also shows the control group size and composition for each cancer-site analyses, illustrating that with the exception of cervical and breast cancer, there were more controls compared to cases in every analysis. Thereafter ORs for ever, current, and former snuff use are provided in Table 3. Among the three cancers documented in external studies to be associated with snuff use (ever versus never snuff users), there was no association with ever snuff use in these data, for esophageal (OR 0.97 [95%CI 0.75–1.27]), pancreatic cancer (OR 1.09 [95%CI 0.62–1.92]) and for lip, oral cavity and pharyngeal cancer (OR 0.69 [95%CI 0.48–1.02]). Of the remaining 23 cancer sites examined, ever snuff use was associated with a decreased risk of Hodgkin lymphoma (OR 0.48 [95%CI 0.23–0.97]) and of stomach cancer (OR 0.60 [95%CI 0.37–0.99]).

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TABLE 4 Univariate and multivariate logistic regression analysis of risk of specific cancer sites among snuff users restricted to non-smokers.

	Ever versus never		Current versus never	Former versus never
Cancer type	Univariate	Multivariate	Multivariate	Multivariate
Breast	1.18 (1.05–1.33)	1.02 (0.89–1.17)	0.96 (0.80–1.15)	1.09 (0.92–1.31)
Cervix	1.44 (1.29–1.62)	1.14 (0.99–1.31)	**1.25 (1.05–1.51)**	1.03 (0.86–1.24)
Colon	1.05 (0.81–1.35)	1.00 (0.75–1.34)	1.00 (0.68–1.46)	1.05 (0.73–1.52)
Esophagus[a]	1.90 (1.48–2.43)	1.19 (0.87–1.62)	0.79 (0.51–1.23)	**1.62 (1.12–2.36)**
Lip oral cavity and pharynx[a]	1.06 (0.69–1.62)	1.05 (0.65–1.71)	0.79 (0.39–1.61)	1.35 (0.76–2.40)
Liver	0.86 (0.44–1.67)	1.02 (0.44–2.34)	0.66 (0.19–2.33)	1.40 (0.51–3.84)
Lung and trachea	1.16 (0.76–1.75)	1.15 (0.72–1.84)	0.44 (0.18–1.06)	**1.94 (1.15–3.27)**
Myeloid leukemia	1.20 (0.86–1.67)	1.20 (0.74–1.93)	0.63 (0.29–1.38	**1.79 (1.05–3.07)**
Nasal cavity and nasopharynx	1.40 (0.82–2.37)	1.59 (0.88–2.87)	1.25 (0.55–2.87)	1.88 (0.94–3.77)
Ovaries	1.43 (1.10–1.85)	1.23 (0.91–1.66)	0.95 (0.61–1.46)	**1.52 (1.06–2.18)**
Pancreas[a]	1.32 (0.75–2.34)	1.13 (0.61–2.11)	0.27 (0.06–1.17)	**2.04 (1.06–3.93)**
Stomach	0.79 (0.49–1.26)	0.64 (0.37–1.10)	0.47 (0.21–1.05)	0.79 (0.41–1.53)
Anus[b]	0.68 (0.30–1.54)	0.69 (0.29–1.63)	0.40 (0.09–1.72)	0.94 (0.35–2.53)
Bone[b]	1.08 (0.54–2.14)	1.29 (0.57–2.92)	0.77 (0.21–2.80)	1.76 (0.69–4.51)
Endometrium[b]	1.28 (0.99–1.65)	0.75 (0.53–1.05)	0.89 (0.58–1.36)	**0.63 (0.39–0.99)**
Eye and adnexa[b]	1.96 (1.09–3.52)	**2.21 (1.13–4.33)**	1.90 (0.75–4.81)	**2.94 (1.32–6.58)**
Hodgkin lymphoma[b]	0.40 (0.23–0.69)	0.52 (0.25–1.08)	0.40 (0.12–1.30)	0.62 (0.26–1.49)
Kaposi sarcoma[b]	0.80 (0.63–1.01)	1.25 (0.91–1.71)	1.41 (0.92–2.16)	1.14 (0.76–1.71)
Melanoma[b]	1.28 (0.67–2.44)	1.14 (0.56–2.33)	1.78 (0.79–4.00)	0.58 (0.17–1.97)
Myeloma[b]	1.16 (0.80–1.70)	0.81 (0.51–1.30)	**0.37 (0.17–0.80)**	1.36 (0.79–2.32)
Non-Hodgkin lymphoma	0.69 (0.52–0.93)	0.75 (0.54–1.05)	**0.43 (0.25–0.74)**	1.08 (0.73–1.59)
Other sarcomas	1.03 (0.73–1.46)	0.84 (0.57–1.25)	0.98 (0.59–1.61)	0.72 (0.42–1.26)
Squamous cell carcinoma (Skin)[b]	1.10 (0.62–1.95)	0.90 (0.46–1.75)	0.81 (0.33–2.01)	0.93 (0.40–2.15)
Thyroid[b]	1.32 (0.69–2.52)	0.69 (0.28–1.73)	1.12 (0.41–3.04)	0.21 (0.03–1.61)
Vagina[b]	1.56 (0.83–2.96)	1.49 (0.75–2.98)	1.67 (0.71–3.93)	1.22 (0.49–3.08)
Vulva[b]	1.82 (1.27–2.61)	1.50 (0.97–2.32)	**2.10 (1.25–3.50)**	0.88 (0.46–1.69)

Note: Univariate and multivariate-adjusted odds ratios (95% CI). Minimally adjusted for age group, language, education and alcohol consumption. Additionally, cancers associated with HIV were adjusted for HIV status (anus, cervix, vulva, Hodgkin lymphoma, Kaposi sarcoma, liver, lung and trachea, melanoma and eye and adnexa). Breast cancer was adjusted for parity. The bolded values are tthe statistically significant Odd Ratios.

[a]Cancer sites known to be caused by SLT use with sufficient evidence in humans.

[b]Control group; cancer sites that have no known relationships to SLT or smoked tobacco. In analyses of the specific constituent cancer as the case-group, these people do not form part of the control group.

In further analyses, we separated ever-snuff analyses into current versus never users and former versus never users (Table 3), expecting stronger associations for current use if quitting SLT use had some protective effect (compared to continuing). The positive associations with cervical and inverse with stomach cancers were indeed stronger in current users than in past users. For example, current snuff use was associated with increased risk of cervical cancer (OR 1.30 [95%CI 1.10–1.53]), whilst the OR for past users was near 1. Current versus never snuff use was associated with reduced risk of stomach cancer (OR 0.46 [95%CI 0.22–0.97]). However, for myeloma and non-Hodgkin lymphoma, the ORs of SLT for current (protective) and past users (risk increasing) were in opposing directions and thus were not consistent with an overall protective effect. In contrast, for eye and adnexa, it was former SLT users that had a greater risk (OR 2.49 [95% CI 1.16–5.34] vs. never SLT use) than current users. Former snuff users had lower risk of endometrial cancer (OR 0.61 [95%CI 0.40–0.93]).

Restricting the analysis to women who reported never having smoked tobacco so as to assess the exclusive use of SLT in the absence of other forms of tobacco, did not change the overall findings (Table 4). Notably, increased risks of SLT were seen for cervical, which were stronger in current than past users, an increased risk of eye cancers was restricted to past SLT use (and not current use) whilst lower risks of myeloma, NHL and—with 95% CIs that included 1, were associated with current SLT use.

The findings for vulva cancer were not clear-cut. Crude analyses of ever v never snuff use were suggestive of a positive association (OR1.33 [95%CI 0.99, 1.80]) but this became null upon multivariate

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adjustment. Nevertheless, in analyses of current versus never snuff users, the multivariate ORs were raised (OR 1.49) with a 95% CI compatible with raised risks for much but not all of its range: 0.95–2.33 (Table 3). In analyses restricted to never-tobacco smokers, ever and current snuff users also had raised risks of vulva cancer (Table 4).

Given the significant findings for cervical cancer, we conducted post hoc analyses. The analyses included breast cancer in the control group due to the high number of breast cancer cases and consistent trend of null odds across this cancer. As a result, cervical cancer was associated with ever snuff use (OR 1.14 [95%CI 1.04–1.26]) and current use (OR 1.30 [95%CI 1.15–1.25]) (Table Supplementary 1). Further sensitivity analyses of the control group composition for cervical cancer involved calculating the ORs after removing one cancer type at a time (Figure Supplementary 1). The overall OR of 1.14 remained in the range of 1.10–1.28 for the various compositions.

The dose response analysis investigated the association between frequency of snuff use per day (up to 10 uses of snuff per day) and risk of specific cancers. The analysis did not yield additional insights into the overall results (Table Supplementary 2, 3). Less than 10 daily uses of snuff among ever-snuff users was associated with an increased risk of cancer of the nasal cavity and nasopharynx (OR 1.45 [95%CI 1.04–2.01]) and lip and oral cavity (OR 1.38 [95%CI 1.05–1.83]) (Table Supplementary 3). Restricting the analysis to participants who were HIV negative snuff use was associated with cervical, eye, and adnexa cancer (Table Supplementary 4).

4 | DISCUSSION

The present study assesses snuff use prevalence in Black South African women diagnosed with cancer in Johannesburg during 1995 through 2016 and the associated risks of site-specific cancers. We document the high prevalence of snuff use in postmenopausal women with cancer—exceeding 30% in certain ethnic groups and in the less educated. The prevalence estimates are consistent with the South African Demographic Health Survey findings on the SLT use prevalence from 3.2% among Black women aged 15%–24 and 28.9% among those aged 65 and older in 1998,[16] suggesting that the "other cancers" control group may be reasonably representative of this population. In our study, there were no associations between snuff use (ever vs. never) and the cancers previously associated with snuff use, namely esophagus, lip oral cavity and pharynx, and pancreas. We provide evidence for an association of ever-snuff use with an increased risk of cervical, eye, and adnexa cancer, whilst the findings for vulva cancer were less clear-cut, but some positive associations were observed. We found reduced risks of stomach cancer and Hodgkin lymphoma (ever vs. never).

Regarding cervical cancer, SLT is listed by IARC as having limited evidence of carcinogenicity.[20] Despite this cancer not being in the respiratory or digestive systems with a more direct exposure route, there is sufficient evidence of increased cervical cancer risks associated with tobacco smoking.[20] A study in Noida, India, reported an increased risk for development of premalignant and malignant cervical lesions among SLT users[30] with SLT exposure routes include sniffing, chewing, or placing in the mouth between the lower lip and the gum or in the cheek. Therefore, there is some limited evidence that SLT may be carcinogenic even when there is no direct exposure to SLT. Whilst in South Africa snuff use is predominantly associated with nasal routes, it has been reported that some women in Zambia insert snuff intravaginally in the belief that it helps stimulate sexual drive and tightens the vagina. This practice has also been reported in Zimbabwe, South Africa, and the Democratic Republic of Congo.[31,32] For the JCS the route of exposure was not collected, but the traditional nasal use of snuff may also be accompanied by genital applications. This would result in direct exposure to SLT. In this study we have identified association of SLT use with cervical and ovarian cancer (former versus never snuff users), but protective association for endometrial cancer. A potential genital exposure route is also of interest in relation to the findings for vulva cancer, however, they were notably less clear-cut. The overall multivariate association of ever versus never snuff users was null for vulva cancer, whilst positive associations were only observed in subset analyses among non-smokers. Because of the multiple positive—but not unambiguous—findings for multiple female reproductive organs, there might be a genuine biological association for which future studies with more refined exposure data, including on exposure routes, are needed.

The suggestive positive associations for eye and adnexa cancer (OR 1.95 [95%CI 1.03–3.70]) were based on small sample sizes of less than 60 cases. These cancers have no known association to tobacco smoking or SLT. In 2001, a study in Chennai, India, assessing the development of glaucoma reported an association between SLT use and nuclear cataract (OR 1.67 [1.16, 2.39]).[33] After using fingers to place snuff in the nose, there may easily be direct snuff contact with the eyes if fingers are not cleaned properly. These women are more likely to have lower socio-economic status and less education, and those who use snuff for sexual pleasure might have higher risk of HIV.[34,35] At the same time, as we have examined associations with many cancer outcomes with limited sample sizes, thus the possibility of false positive findings cannot be ruled out.

In our study, we found a significant decrease in risk of stomach cancer associated with snuff use (OR 0.60 [0.37, 0.99]), this association was not present when restricted to non-smokers. This is in contrast to a meta-analyses that included studies from North America and Europe, which reported no association (RR 1.03 (0.88, 1.20)).[19] Our findings for Hodgkin lymphoma showing an inverse association differs from what is otherwise reported in the literature, as systematic reviews on cancer and SLT reported a non-significant reduction in risk.[19,36] This association was not present when restricted to non-smokers. We have no obvious explanation for these findings.

We did not find clear evidence of increased risk of the three cancers known to be associated with ever snuff use—esophagus, lip, oral cavity, and pharynx, nor pancreatic cancer; however former users did have an increased risk. Cancer of the lip, oral cavity, and pharynx was associated with snuff use dose response (number of uses per day), this could be attributed to confounding factors not controlled for in the ever never association. Our data were limited, however, in not having

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the age at quitting (nor age at uptake of) snuff use, rendering it difficult to understand why some of these aforementioned associations were stronger in former than current snuff users. Our findings of no association between ever-snuff use and cancers of the esophagus, lip, oral cavity pharynx, and pancreatic cancer contrasts with the evidence of an association identified by the IARC monograph findings on SLT and causes of cancer and other findings from studies from the European region.[6,18,22,23,37–39] Reasons for the observed differences may be due to snuff use being common among older women in this setting, that is, a later age at first exposure, generally lower amount used, and shorter exposure duration. The differences in snuff composition between regions could contribute to variations in carcinogenic effects observed in different studies.[40]

The high prevalence of snuff ever use among older Black women indicates that the use of SLT products such as snuff use is common, and reflects that snuff is widely accepted in this population. In the JCS, overall snuff use prevalence was at least 28% for over 45-year-olds and exceeded 20% in Tswana, Sotho, Xhosa, and Zulu women from age 35 upwards. As the use of SLT is high and is increasing in many populations, also worryingly from younger ages, the possible associations to cancer risk need to be further studied and better characterized.[6]

Our study highlights the high prevalence of ever-snuff use in Black South African women. There is a need to raise awareness about the adverse health effects of SLT products, advocate for stringent tobacco control policies that encompass the use of SLT products, to initiate public mass media campaigns and programs encouraging SLT-specific cessation.[17,39,41] It is also important to refute and counteract the claims of tobacco industry regarding the relative safety of the use of SLT products as a possible alternative for those quitting smoking.[23] Campaigns to educate the public about the cancer risks of snuff use could reverse the normalization and cultural acceptability of snuff use. SLT products are generally cheaper and more accessible than cigarettes in the South African setting, imposing tax on SLT products could manage the risk posed by these products.[41]

Our findings should be considered in light of possible limitations inherent in case control studies and in circumstances where other cancer types are used as controls. In the primary study, the route of snuff use, age at first use (uptake), and the duration of use were not collected. It is worth noting that some cancer sites had few participants (approximately 60 individuals). Despite these limitations, these data remain an important source to understand cancer risk among adult Black South African women who reported ever using snuff. It is also plausible that increases in cancer risk are modest in the JCS as most exposures commenced later in life, as indicated by the variation in prevalence by age. However, if age at first use becomes much younger, as is the recent trend, then latency periods sufficiently long for realized cancer risks may behave differently.

5 | CONCLUSION

There is a high prevalence of snuff use among Black South African women. In our study, we found very variable associations of snuff use with cancer risks. Increased risks of cervical cancer among ever versus never snuff users and vulvar cancers were seen among current versus never users, analysis restricted to non-smokers, this may result from intra-vaginal snuff use; whereas an increased risk of eye and adnexa cancers was inexplicably stronger in past SLT users. Contrary to the established effects of snuff use, no associations were seen with cancers of the esophagus, lip, oral cavity pharynx, and pancreatic cancer. An apparent protective effect of snuff on stomach cancers needs further investigations to further investigate confounding, bias, or potential mechanisms.

AUTHOR CONTRIBUTIONS

Melitah Motlhale: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; writing – original draft; writing – review and editing. **Freddy Sitas:** Conceptualization; investigation; methodology; project administration; supervision; writing – review and editing. **Chantal Babb de Villiers:** Investigation; methodology; writing – review and editing. **Hannah Simba:** Writing – review and editing. **Ariadna Feliu:** Writing – review and editing. **Wenlong Carl Chen:** Conceptualization; methodology; project administration; writing – review and editing. **Joachim Schüz:** Conceptualization; writing – review and editing. **Mazvita Muchengeti:** Conceptualization; investigation; methodology; project administration; writing – review and editing. **Valerie McCormack:** Conceptualization; investigation; methodology; project administration; resources; supervision; writing – review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The University of the Witwatersrand Human Research Ethics Committee (Medical) approved the primary study and the current study (Clearance certificate number: M230279). Written informed consent was obtained from all participants.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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