Skin Lighteners and Hair Relaxers as Risk Factors for Breast Cancer

Skin Lighteners and Hair Relaxers as Risk Factors for Breast Cancer: Results from the Ghana Breast Health Study

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Abstract

Skin lighteners and hair relaxers, both common among women of African descent, have been suggested as possibly affecting breast cancer risk. In Accra and Kumasi, Ghana, we collected detailed information on usage patterns of both exposures among 1,131 invasive breast cancer cases and 2,106 population-controls. Multivariate analyses estimated odds ratios (OR) and 95% confidence intervals (CIs) after adjustment for breast cancer risk factors. Control usage was 25.8% for ever use of *s*kin lighteners and 90.0% for use of hair relaxers for >1 year. The OR for skin lighteners was 1.10 (95% CI 0.93-1.32), with higher risks for former (1.21, 0.98-1.50) than current (0.96, 0.74-1.24) users. No significant dose-response relations were seen by duration, age at first or frequency of use. In contrast, an OR of 1.58 (95% CI 1.15-2.18) was associated with hair relaxers, with higher risks for former (2.22, 1.56-3.16) than current (1.39, 1.00-1.93) users. Although numbers of burns were inconsistently related to risk, associations increased with duration of use, restricted to women who predominately used non-lye products (*p for trend<0.01)*. This was most pronounced among women with few children and those with smaller tumors, suggesting a possible role for other unmeasured lifestyle factors. This study does not implicate a substantial role for skin lighteners as breast cancer risk factors, but the findings regarding hair relaxers were less reassuring. The effects of skin lighteners and hair relaxers on breast cancer should continue to be monitored, especially given some biologic plausibility for their affecting risk.

Keywords: Breast cancer, skin lighteners, hair relaxers, etiology, African women

Summary: Although skin lighteners were unrelated to breast cancer, hair relaxer findings were less reassuring, with elevated risks seen for former and long-duration users of non-lye products. The extent to which this was due to biology, chance or confounding is unclear.

Introduction

Much recent attention has focused on rising rates of breast cancer across Africa (1), with estimates that there will be an approximate doubling in the numbers between 2012 and 2030 (2). The increases will be particularly profound for younger women, where it is estimated that the number of breast cancer cases among women less than 65 years of age will increase from 111,169 to 186,012. Despite this dramatic anticipated increase, few epidemiologic studies have attempted to identify reasons for rising rates. Previous studies suggest that a substantial proportion of disease occurrence may be due to an increased prevalence of factors responsible for breast cancers in other parts of the world, including decreasing parity, later ages at first childbirth, and increasing body sizes (3). However, it remains unclear whether other unique factors could contribute to breast cancers among African women.

Several lifestyle characteristics of Africans and African Americans possibly involved in the etiology of breast cancers have recently come under scrutiny (4). These include the use of skin lighteners (5-7) and hair relaxers (8, 9), both extremely common practices among women of African descent. Skin lighteners are composed of a variety of substances, including topical steroids, mercury, and hydroquinones (10). They may also contain hormonally active compounds, such as phthalates (11), which are often reported under the terms 'fragrances' or 'perfumes' (12), and are rarely regulated, even in the U.S. (13).

Hair relaxers are generally classified as being either lye or non-lye, with lye relaxers comprised of sodium hydroxide and non-lye relaxers comprised of potassium hydroxide, lithium hydroxide, guanidine carbonate, or ammonium thioglycolate (thio-relaxers) (9). These products can also contain hormonally active compounds, such as phthalates (14) as well as other contaminants, including formaldehyde (15) and various metals (16, 17). Given that hair relaxers

can cause burns and lesions in the scalp (18), concern has been expressed over the ability of their constituents to systemically spread and affect other organs, including the breast.

It is recognized that breast cancers occurring among women of African descent tend to have unique clinical characteristics, being diagnosed at earlier ages than Caucasians and more often having poor prognostic factors, including hormone receptor negativity (1). Whether lifestyle characteristics, such as use of skin lighteners and hair relaxers, are associated with these unique characteristics has not yet been assessed in any epidemiologic study.

To shed further light on the relationship of skin lighteners and hair relaxers on breast cancers among African women, we used data from the Ghana Breast Health Study, a recently completed population-based case-control study conducted in two large metropolitan areas. Women were asked detailed questions regarding their use of both practices, including ages at first use, frequency of use, types of products used, and, for hair relaxers, how often scalp burns were experienced. These parameters were evaluated in relation to the overall development of breast cancers as well as to specific breast cancers which predominate among African women (e.g., early onset and advanced tumors).

Methods

To elaborate the effects of skin lighteners and hair relaxers as well as other factors on breast cancer risk, we conducted a multi-disciplinary population-based case-control study in two areas of Ghana, Accra and Kumasi. The methodology of this investigation is described in more detail elsewhere (3). In brief, patients for the study were recruited at the time they presented with lesions suspicious of breast cancer at three hospitals: Korle Bu Teaching Hospital (Accra), Komfo Anoyke Teaching Hospital (Kumasi), and Peace and Love Hospital (Kumasi). These

hospitals are the primary providers of treatment for breast cancer in Ghana, allowing for cases in our study to represent the vast majority of breast cancers diagnosed in these areas during the study period. Cases for this study comprised women aged 18-74 years who were from defined catchment areas (chosen to be within restricted travel times from the study hospitals given that the study also involved the recruitment of population controls from their homes) who lived in these areas for at least one year and who were subsequently diagnosed with pathologically confirmed invasive breast cancers.

A national census conducted in Ghana in 2010 enabled selection of population controls, who were frequency matched to the cases in the two study areas (Accra and Kumasi) on age, with similar restrictions regarding catchment areas and at least one year of residence in these areas. The census was used to select enumeration areas (EA) (areas comprised of approximately 750 residents) from the districts from which cases were expected to derive. Trained census workers enumerated all households with respect to the sexes and ages of the residents. When households were enumerated, a brochure was left explaining the study and encouraging participation should an individual be selected for inclusion. After selected EAs had been enumerated, individuals were randomly selected to approximate the age distribution of female breast cancer cases expected during the study. Study personnel visited subjects' homes to determine eligibility, inform them of study selection, and invite them for a hospital visit.

Both cases and controls were approached for in-person interviews by trained personnel who recorded information on standardized questionnaires. Interviews were generally conducted in the hospitals, although a few were administered at the subjects' homes. Interview response rates were 99.2% in cases and 91.9% in controls. A pathology review as well as genotyping efforts resulted in a few changes in eligibility status from the original methodology as described

previously (3), resulting in the inclusion in the present analysis of 1,131 invasive breast cancer cases and 2,106 controls.

The questionnaire focused on established breast cancer risk factors (demographic factors, menstrual and reproductive characteristics, family history of breast cancer, medical history, occupational history, anthropometric and physical activity variables) as well as on several more speculative factors, including use of skin lighteners (any soap, cream or other product to lighten or brighten the skin) and hair relaxers (perms or other relaxers). Subjects were asked whether they had ever used either product and, if so, the age at which they first began using them, currency of use, last usage (if a non-current user), and duration of use. For skin lightener user, subjects were asked on which parts of the body creams were applied (all over, face, arms, chest, other parts) and how frequently products were applied. For hair relaxers, women were asked to provide information on whether they generally used lye or non-lye products and how many times over their lives they had experienced burns (i.e., not just tingling but actual skin breakage).

Following the interview, interviewers were requested to record the length of the interview and rate the patient's extent of cooperation (very good, good, fair, poor) as well as the overall quality of the interview (high quality, generally reliable, questionable, unsatisfactory). The median time to complete an interview was 41 minutes in cases and 38 minutes in controls. A total of 99.1% of the case interviews were deemed generally reliable or of high quality, as compared to 99.8 % of the control interviews.

Odds ratios (OR) and 95% confidence intervals (CI) were calculated for various parameters of usage of skin lighteners and hair relaxers. We adjusted for study site and age (as a categorical variable) as well as for the major identified risk factors in this study population, namely education, family history of breast cancer, body size, and parity. Several risk factors

identified in other populations, such as usage of alcohol or menopausal hormone therapy, were infrequent in this population and unrelated to risk. We calculated p values for differences between study groups as well as p values for linear trends. Tests for trend were constructed for categorizations of hair relaxer and skin lightener use using the continuous data, when applicable, or the mid-value in each level as a continuous covariate. P-values from Wald F-tests were reported. We also assessed the extent to which associations with skin lighteners and hair relaxers varied across levels of identified risk factors, including age, education, and parity. Tests for interaction were assessed using log-likelihood test statistics (likelihood ratio test), where models with and without interaction terms were compared. Associations by tumor size at the time of biopsy ($\leq$ vs. > 5 cm.) were also assessed, with all risks calculated in reference to the total series of controls. For all analyses, p-values <0.05 were considered statistically significant. All statistical tests (p-values quoted) were two sided. All analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC).

Finally, a number of sensitivity analyses were pursued, including using different referent groups for assessing the relation of hair relaxer use to risk given that the vast majority of women reported usage. In addition, analyses were conducted that were restricted to interviews judged by interviewers to be of the highest quality (48.9% in cases, 48.8% in controls).

Results

Cases were significantly older than controls with respect to age (mean ages in cases vs. controls of 50.1 vs. 45.6 years), reflecting that controls were frequency matched to the entire population of women with lesions suspicious for cancer, with many ultimately not being diagnosed with cancer (3). Cases also tended to significantly more often to report higher levels

of education, family histories of breast cancer, larger body sizes, later ages at menarche, fewer children and later ages at first birth (Table 1).

Skin lightener use was quite common in this population, with 25.8% of the controls reporting ever use. Hair relaxer use was reported by 93.4% of the controls. Because of the high rates of hair relaxer use, we combined the never users with those who had used relaxers for less than or equal to one years' time to derive a more stable referent. This reduced the usage rate among controls to 90.0%.

When these two practices were examined among the controls by various levels of identified risk factors (Table 2), we found that skin lightener use was significantly more common among older women (≥45 years of age). In addition, higher rates of usage were found among women with fewer years of educations and those who had their first child at a young age. Skin lightener use did not vary significantly by family histories of breast cancer, reported body sizes or ages at menarche.

Hair relaxer use was most frequently reported by women between the ages of 35 and 54 years of age, with lower percentages among the youngest and oldest women in the study. Usage was significantly more common among women who reported family histories of breast cancer, later ages at menarche, and multiple births. Usage rates did not vary significantly by education or body sizes.

Ever use of skin lighteners was unrelated to breast cancer risk (OR=1.10, 95% CI 0.93-1.32), with similar relations seen in Accra (1.26, 0.93-1.71) and Kumasi (1.02, 0.82-1.27) (Table 3), despite the slightly higher rates of usage in controls in Kumasi compared to Accra (27.9% vs. 22.0%). Former users were at somewhat higher risk than current users (ORs and 95% CIs of 1.21, 0.98-1.50 vs. 0.96, 0.74-1.24), a trend seen in both cities. However, there were no

distinctive trends by length of use, age at first use, or frequency of use. No further discrimination of risks was seen when these parameters were examined by currency of use (data not shown). Risks were most elevated among those who reported first usage at ages 26-30 years (but not at earlier or later ages at first use) as well as those who reported usage once a day (OR=1.38, 95% CI 1.06-1.79), with no elevations seen for those reporting use on a more frequent basis. These relations largely reflected elevated risks seen in Accra. Most controls (90.5%) reported applying skin lighteners all over their bodies (data not shown). There were a fair number of women who were unable to provide information regarding detailed usage patterns, and this category was often at significantly increased risk (e.g., OR for unknown age at first use was 1.56, 95% CI 1.02-2.41). Elevated risks associated with unknown responses were observed more frequently in Kumasi than in Accra.

Ever use of hair straighteners was associated with a 58% increase in breast cancer risk (95% CI 1.15-2.18) (Table 4). This association was mostly limited to an increased risk among patients in Accra (OR=2.31, 1.40-3.82), with no meaningful increase seen in Kumasi (1.22, 0.80-1.88). However, in both sites as well as overall, former users were at higher risks than current users and these risks were statistically significant (ORs and 95% CIs for both sites of 2.22, 1.56-3.16 vs. 1.39, 1.00-1.93). In Accra, there was a significant trend in risk with increasing length of use (*p for trend<0.01)* which was not observed in Kumasi (*p for trend=0.26).* A number of subjects were unable to provide information on this parameter. A higher risk was observed for use of non-lye compared to lye hair relaxers (ORs and 95% CIs for both sites of 1.88, 1.34-2.64 vs. 1.38, 0.99-1.93), a trend seen in both Accra and Kumasi. There was an approximate 70-80% increased risk seen both among subjects who had never experienced burning with hair relaxer use as well as among those with 5 or more lifetime burns, but this pattern of risk was observed

only in Accra. In Kumasi, the number of episodes of burns was not significantly related to risk (*p for trend=0.99)* (Table 4).

When we classified currency of use, length of use and frequency of burns by whether the usual hair relaxer use was lye or non-lye (Table 5), we saw no association of any of these parameters of use among the lye users. However, among the non-lye users, former users were at a significantly increased risk (OR=3.18, 95% CI 2.08-4.87) and there was a dose response relation with length of use (*p for trend<0.01*), increasing to a risk of 2.61 (1.65-4.10) among users of more than 30 years. Similar statistically significant trends in risk with duration of use for non-lye users were seen in both Accra and Kumasi (Supplementary Table 1). An especially pronounced risk was seen overall for former, long-duration users (OR=2.73, 95% CI 1.55-4.49) (data not shown).

An analysis of ever use of skin lighteners or hair relaxers by levels of identified risk factors in the study showed no significant heterogeneity by age (Table 6). There was also no variation in skin lightener use by years of education, number of full-term pregnancies or by whether the tumor was ≤5 cm. or >5 cm. at the time of biopsy. However, for hair relaxer use (among both lye and non-lye hair relaxer users), we did observe significant heterogeneity in relation to all three of these parameters, with stronger relations for women with primary/junior secondary school and those fewer births. Cases with smaller tumors (≤5 cm.) also showed stronger relations with both lye and non-lye hair relaxers use.

Given that few women had not used hair relaxers, we employed different referent groups to lead to more stable comparisons (expanding referent to include those with ≤5 or ≤10 years of use). For instance, expanding our comparison group to include never users as well as those who had ≤5 years of use increased the referent group to 85 cases and 304 controls. However, these

additional analyses had little impact on derived conclusions. We also conducted analyses restricted to interviews that were deemed by the interviewers to be of the highest quality. Although we had fewer women with unknown responses for the detailed usage characteristics, our conclusions regarding the associations of hair relaxers to breast cancer risk remained unchanged.

Discussion

Despite increasing incidence, little attention has focused on identifying risk factors for breast cancers in African women. Several lifestyle factors have come under recent scrutiny, including the prevalent use of skin lighteners and hair relaxers, which both have constituents that raise concern. We had the opportunity to evaluate both exposures in the present investigation as these practices were quite prevalent in Ghana. Our results were generally reassuring regarding potential effects for skin lightener usage. However, for hair relaxers, the results were more complicated to interpret, with some increases, particularly among users of non-lye products.

There has been increasing recent attention regarding cultural determinants of use of skin lighteners, which are believed to enhance beauty and lead to greater social privileges, including better jobs and marital prospects (6, 19). As documented by a number of recent surveys (6, 20-22), including one in Ghana (21), skin lightener use is quite prevalent, particularly in Africa. In fact, in our study, we found usage occurring in approximately a quarter of our study subjects. These products were frequently used, oftentimes applied several times a day all over the body, with most subjects reporting many years of exposure.

Skin lighteners are of particular concern with respect to breast cancer given that many contain steroids and hydroquinones, which since 2001 are no longer authorized for use in

cosmetic skin lightening in European Union countries (23). Nonetheless, studies document that hydroquinones (5, 10, 24), as well as mercury (25, 26), are still quite prevalent in skin lightening products used in a variety of countries, including Africa. Although hydroquinones, a primary metabolite of benzene, are not currently classified as carcinogenic to humans, there is recent evidence that it can have a variety of adverse topical and systemic repercussions, including hypopigmentation, ochronosis, changes in skin consistency, striae, and infections (19, 21). Hydroquinones (10, 23, 24) as well as mercury (25, 26) can also generate DNA damage and immunosuppressive responses. In addition, a number of personal care products, including both skin lighteners and hair relaxers, commonly contain phthalates, which can be absorbed by the skin or inhaled (11, 27-29). Phthalates have been shown to have estrogenic effects in cell (30) and animal (31) models, with some additional speculation that as endocrine disruptors they may act as human breast carcinogens (32, 33).

We observed some increases in risk related to certain patterns of usage of skin lighteners, but the elevations were not consistent with meaningful biologic effects (e.g., highest risk only among subjects who used them once a day as opposed to more often). Thus, it appeared that these risks were either chance findings or due to different selection biases. We also observed some elevations among women who were unable to provide information on their precise usage patterns, a not surprising finding given the relatively low educational status of many of the subjects, which could have led to some of the anomalous significant elevations in risk that we observed. Thus, our data in aggregate do not raise large concerns regarding the effects of skin lighteners on breast cancer risk among African women, despite their very common usage.

Although there has been much attention on the relation of hair dyes to breast cancer risk, with the relationship remaining unresolved (34), only two previous epidemiologic studies have

assessed the relation of hair relaxers to breast cancer risk (35, 36). In one investigation that focused on African-American women (36), there were no increases in risk associated with any categories of duration of hair relaxer use, frequency of use, age at first use, number of burns experienced during use, or type of relaxer used. However, in that same investigation, an enhanced risk of uterine leiomyomas was observed in relation to hair relaxer use, with positive trends observed for frequency of use, duration of use, and number of burns (37), suggesting that these products could have harmful hormonal effects. In contrast, in the most recent investigation on the relation of hair relaxers to breast cancer risk, that included both African-American and white women (35), use among white women was associated with significantly elevated breast cancer risks, particularly for estrogen receptor negative diseases. No association with use, however, was seen among the African-American women in the study.

Hair relaxers raise concern regarding breast cancer risk due to the burns they can cause, allowing systemic entry of hair relaxer constituents and effects on the immune system, which is increasingly being recognized as important in breast carcinogenesis (38, 39). Although lye products have generally been regarded as more toxic than non-lye products, both have been associated with scalp inflammation and scarring alopecia (40).

In our study, we observed significantly elevated risks associated with certain parameters of hair relaxer usage. The elevated risks did not appear to relate to the number of episodes of burns, which has been hypothesized as a mechanism for systemic effects. However, we observed evidence of elevated risks for former hair relaxer users and for users of non-lye products. In addition, among the users of non-lye products, there were increasing trends with longer durations of use. Although there were some differences in usage patterns as well as in associated risks between the two study sites, the elevated risks for former users and users of non-

lye products were seen in both Accra and Kumasi, raising concern regarding a potential biologic relation of these products to breast cancer risk.

Given that we had not hypothesized that we would observe higher risks associated with use of non-lye than lye products, the elevated risks that we observed for users of non-lye products must be cautiously interpreted. The fact that we observed the highest risks among former and long-term users suggests that any association, if real, might have been driven by constituents that were part of hair relaxers marketed in the past. Although recent attention has focused on effects of various endocrine disruptors, including phthalates (11) and lithium hydroxide (41), a potential carcinogenic role of various contaminants in hair products has also been recognized. Although we did not have information on the constituents of the various hair products used, studies have noted detection of relatively high levels in hair relaxers of such contaminants as formaldehyde, arsenic, cadmium, as well as other metals (15, 42). More recent evaluations of the levels of these elements in hair products seem to indicate more effective control of levels (43), possibly explaining why risks were higher in our study for former versus current users.

Although a biologic relation at this point cannot be entirely dismissed, other explanations for our observed associations should also be considered. For instance, the fact that the highest risks associated with hair relaxer use were seen only among women who were at elevated risks of breast cancer from well-established risk factors (e.g., decreased parity) suggests that the association may have been driven by other unmeasured factors. Further, the association was strongest for women with smaller tumors, which we have previously demonstrated to relate to a variety of unique characteristics (44). Nonetheless, we cannot dismiss a possible biologic

association of hair relaxer use with breast cancer risk and suggest that future studies continue to assess relations, particularly as related to specific constituents of the hair relaxers used.

Our study has several strengths, including a large sample size and collection of detailed information on both the exposures of interest as well as other breast cancer predictors. However, we were limited by the frequency at which information on detailed parameters of exposure, including durations of use and ages at first use, could not be provided. More cases than controls could not provide this information; thus, if these women were less likely to have extensive exposures, our derived risks--particularly as related to long-duration non-lye hair relaxer use--could be over-estimated. Our results also might have been affected by the fact that we considered all breast cancers as a single entity, whereas substantial heterogeneity is well-established, with risks varying by tumor subtypes (particularly those defined by hormone receptor status) (45). Thus, molecular subtyping, which is currently ongoing in our investigation, will be important to further clarify our understanding of any etiologic variation.

In summary, our results were reasonably reassuring regarding the effects of skin lighteners on breast cancer risk. However, for hair relaxers, the findings were more complicated and indicated some increased risks associated with long-term usage for women who primarily used non-lye products. Given that this was not the group that we had hypothesized would be at highest risk, it is difficult to discern the extent to which the findings are a reflection of confounding by other risk factors or of selection and reporting biases. Given that the constituents of both skin lighteners and hair relaxers have biologic plausibility for exerting effects on cancer risk, it would seem worthwhile for these exposures to continue to be evaluated in future studies of women of African descent.

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Table 1. Characteristics of the Study Population

	Controls (N=2,106)		Cases (N=1,131)		
	Number	Percent	Number	Percent	P-value
Age					<0.01
<35	435	20.7	114	10.1	
35-44	561	26.6	278	24.6	
45-54	554	26.3	332	29.4	
55 or older	546	25.9	403	35.6	
Unknown	10	0.5	4	0.4	
Education					<0.01
No formal education/some primary school	498	23.6	254	22.5	
Primary school	369	17.5	153	13.5	
Junior secondary school	654	31.1	262	23.2	
≥Senior secondary school	512	24.3	388	34.3	
Unknown	73	3.5	74	6.54	
Family History of Breast Cancer					<0.01
No	2036	96.7	1039	91.9	
Yes	46	2.2	78	6.9	
Unknown	24	1.1	14	1.2	
Body Size					0.02
Slight	585	27.8	254	22.5	
Average	827	39.3	434	38.4	
Slightly heavy	470	22.3	263	23.3	
Very heavy	163	7.7	104	9.2	
Unknown	61	2.9	76	6.7	
Age at Menarche					0.07
<15	568	27.0	268	23.7	
15	548	26.0	257	22.7	
16	383	18.2	223	19.7	
≥17	395	18.8	229	20.2	
Unknown	212	10.1	154	13.6	
Number of Full-term Pregnancies					<0.01
Nulliparous	228	10.8	107	9.5	
1	241	11.4	135	11.9	
2-3	638	30.3	382	33.8	
4-6	717	34.0	405	35.8	
≥7	274	13.0	98	8.7	
Unknown	8	0.4	4	0.4	

Age at First Full-term Pregnancy (Among Parous)					<0.01
<19	555	29.6	236	23.0	
19-21	510	27.2	266	26.0	
22-24	303	16.1	200	19.5	
25-27	213	11.3	123	12.0	
≥28	218	11.6	137	13.4	
Unknown	79	4.21	62	6.05	

Table 2. Use of Skin Lighteners and Hair Relaxers Among Controls by Identified Study Risk Factors

	Use of Skin Lighteners[1]			Use of Hair Relaxers[2]		
	No (N=1,560)	Yes (N=542)	P-value	No (N=186)	Yes (N=1,681)	P-value
Age			<0.01			<0.01
<35	82.7	17.3		15.9	84.1	
35-44	75.8	24.2		6.9	93.1	
45-54	69.4	30.6		6.1	93.9	
55 or older	70.6	29.4		12.3	87.7	
Education			<0.01			0.34
No formal education/ some primary school	74.1	25.9		12.1	87.9	
Primary school	72.4	27.6		9.8	90.2	
Junior secondary school	70.9	29.1		9.0	91.0	
≥Senior secondary school	80.0	20.0		9.0	91.0	
Family History of Breast Cancer			0.14			0.03
No	74.8	25.2		10.1	89.9	
Yes	65.2	34.8		0.0	100.0	
Body Size			0.07			0.86
Slight	77.9	22.1		9.1	90.9	
Average	73.8	26.2		10.6	89.4	
Slightly heavy	72.3	27.7		10.0	90.0	
Very heavy	69.3	30.7		10.1	89.9	
Age at Menarche			0.18			0.04
<15	71.5	28.5		12.7	87.3	
15	75.0	25.0		8.3	91.7	
16	77.3	22.7		9.5	90.5	
≥17	72.2	27.8		7.5	92.5	
Number of Full-term Pregnancies			0.31			0.01
Nulliparous	84.6	15.4		23.8	76.2	
1	71.4	28.6		13.8	86.2	
2-3	75.3	24.7		7.1	92.9	
4-6	71.1	28.9		6.8	93.2	
≥7	74.5	25.5		9.9	90.1	
Age at First Full-term Pregnancy (Among			<0.01			0.48

Parous)

<19	68.5	31.5	8.1	91.9
19-21	69.7	30.3	8.4	91.6
22-24	78.2	21.8	5.4	94.6
25-27	75.1	24.9	9.5	90.5
≥28	79.3	20.7	8.9	91.1
Unknown	82.3	17.7	24.1	75.9

[1]Excludes 4 controls with missing information on skin lightener use.
[2]Excludes 239 controls with missing information on hair relaxer use.

Table 3. Breast Cancer Risk by Various Parameters of Use of Skin Lighteners

Skin Lightener Use	All sites				Accra				Kumasi			
	Controls	Cases	OR[1]	95% CI	Controls	Cases	OR[1]	95% CI	Controls	Cases	OR[1]	95% CI
Ever Use												
No	1560	818	1.00	Referent	571	280	1.00	Referent	989	538	1.00	Referent
Yes	542	307	1.10	(0.93-1.32)	161	99	1.26	(0.93-1.71)	381	208	1.02	(0.82-1.27)
Currency of Use												
Former	302	194	1.21	(0.98-1.50)	92	67	1.44	(1.00-2.09)	210	127	1.09	(0.84-1.42)
Current	240	113	0.96	(0.74-1.24)	69	32	1.00	(0.63-1.59)	171	81	0.92	(0.68-1.25)
Length of Use (years)												
<1	95	38	0.97	(0.65-1.45)	36	15	0.92	(0.48-1.77)	59	23	1.00	(0.59-1.68)
1-5	97	56	1.13	(0.79-1.62)	19	17	2.07	(1.01-4.24)	78	39	0.89	(0.58-1.35)
6-10	79	38	1.05	(0.69-1.59)	17	12	1.81	(0.82-4.00)	62	26	0.87	(0.53-1.43)
11-20	106	64	1.26	(0.89-1.77)	22	17	1.43	(0.73-2.81)	84	47	1.15	(0.77-1.71)
≥21	100	52	0.85	(0.59-1.23)	23	10	0.70	(0.32-1.54)	77	42	0.88	(0.58-1.34)
Unknown	65	59	1.45	(0.96-2.18)	44	28	1.27	(0.72-2.21)	21	31	1.82	(0.97-3.40)
P for trend			*0.96*				*0.74*				*0.69*	
Age at First Use (years)												
<21	180	82	0.96	(0.72-1.28)	38	23	1.39	(0.79-2.45)	142	59	0.83	(0.59-1.17)
21-25	113	55	0.96	(0.68-1.37)	37	12	0.64	(0.32-1.29)	76	43	1.10	(0.73-1.66)

26-30	74	49	1.39	(0.94-2.06)	19	16	2.14	(1.04-4.40)	55	33	1.11	(0.69-1.80)
≥31	118	67	1.04	(0.75-1.45)	28	20	1.21	(0.65-2.27)	90	47	0.96	(0.65-1.43)
Unknown	57	54	1.56	(1.02-2.41)	39	28	1.39	(0.78-2.46)	18	26	1.87	(0.95-3.69)
P for trend			*0.72*				*0.36*				*0.73*	
Frequency of Use												
Once per day	181	119	1.38	(1.06-1.79)	50	42	1.93	(1.22-3.06)	131	77	1.16	(0.84-1.60)
≥2 times/day	332	160	0.97	(0.78-1.21)	88	45	1.08	(0.72-1.62)	244	115	0.90	(0.69-1.17)
Unknown	29	28	1.01	(0.53-1.90)	23	12	0.63	(0.27-1.50)	6	16	2.13	(0.72-6.27)
P for trend			*0.83*				*0.27*				*0.50*	

[1]All risks in referent to never users of skin lighteners (4 controls and 6 cases with unknown usage excluded). Risks adjusted for age, study site, education, family history of breast cancer, body size, and parity.

Table 4. Breast Cancer Risk by Various Parameters of Use of Hair Relaxers

	All sites				Accra				Kumasi			
Hair Relaxer Use	Controls	Cases	OR[1]	95% CI	Controls	Cases	OR[1]	95% CI	Controls	Cases	OR[1]	95% CI
Ever Use												
No[2]	186	58	1.00	Referent	93	23	1.00	Referent	93	353	1.00	Referent
Yes	1681	877	1.58	(1.15-2.18)	485	269	2.31	(1.40-3.82)	1196	608	1.22	(0.80-1.88)
Currency of Use												
Former	339	268	2.22	(1.56-3.16)	117	97	3.12	(1.79-5.43)	222	171	1.80	(1.13-2.88)
Current	1342	609	1.39	(1.00-1.93)	368	172	2.01	(1.20-3.36)	974	437	1.08	(0.70-1.67)
Length of Use (years)												
1-10	307	84	1.10	(0.73-1.64)	86	21	1.46	(0.72-2.94)	221	63	0.92	(0.55-1.54)
11-20	528	249	1.68	(1.18-2.40)	145	69	2.38	(1.34-4.25)	383	180	1.36	(0.86-2.17)
21-30	503	280	1.54	(1.08-2.20)	139	76	2.02	(1.14-3.59)	364	204	1.25	(0.78-1.99)
≥31	295	218	1.67	(1.15-2.43)	72	60	2.49	(1.35-4.62)	223	158	1.35	(0.83-2.19)
Unknown	48	46	2.81	(1.66-4.77)	43	43	3.73	(1.94-7.17)	5	3	1.23	(0.25-6.04)
P for trend			*0.01*				*<0.01*				*0.26*	
Age at First Use (years)												
<21	1063	476	1.39	(1.00-1.94)	280	116	1.84	(1.08-3.12)	783	360	1.16	(0.75-1.80)
21-25	307	208	1.87	(1.30-2.69)	101	71	2.78	(1.56-4.96)	206	137	1.45	(0.90-2.34)
26-30	115	76	1.70	(1.10-2.64)	32	19	2.12	(0.98-4.55)	83	57	1.52	(0.87-2.63)
≥31	150	69	1.38	(0.89-2.14)	33	21	2.34	(1.10-4.98)	117	48	1.04	(0.60-1.81)

Unknown	46	48	3.07	(1.81-5.21)	39	42	3.91	(2.02-7.57)	7	6	1.83	(0.51-6.66)
P for trend			*0.05*				*<0.01*				*0.77*	
Type of Hair Relaxer Most Frequently Used												
Lye	998	472	1.38	(0.99-1.93)	225	110	1.99	(1.17-3.39)	773	362	1.10	(0.71-1.70)
Non-lye	655	385	1.88	(1.34-2.64)	252	150	2.54	(1.50-4.28)	403	235	1.55	(0.98-2.45)
Unknown	28	20	1.69	(0.86-3.30)	8	9	4.65	(1.57-13.80)	20	11	0.84	(0.35-2.00)
Frequency of Burns (lifetime)												
Never had burns	640	353	1.66	(1.18-2.34)	139	90	2.52	(1.45-4.38)	501	263	1.30	(0.83-2.04)
1-2 times	461	232	1.33	(0.94-1.90)	152	75	2.06	(1.18-3.59)	309	157	1.05	(0.66-1.67)
3-4 times	239	101	1.29	(0.87-1.92)	79	23	1.28	(0.65-2.54)	160	78	1.16	(0.70-1.94)
≥5 times	288	139	1.76	(1.20-2.58)	63	41	2.88	(1.51-5.48)	225	98	1.29	(0.79-2.12)
Unknown	53	52	2.92	(1.76-4.86)	52	40	3.27	(1.72-6.22)	1	12	27.38	(3.25-230.75)
P for trend			*0.45*				*0.32*				*0.99*	

[1]Risks adjusted for age, study site, education, family history of breast cancer, body size, and parity.
[2]All risks in referent to never users and users of <1 year of hair relaxers (58 cases, 186 controls).

Table 5. Breast Cancer Risk by Currency of Use, Length of Use or Frequency of Burns and Whether Usual Relaxer was Lye or Non-Lye

Hair Relaxer Most Commonly Used	Lye Use			Non-lye Use		
	Exposed Cases	OR[1]	95% CI	Exposed Cases	OR[1]	95% CI
Currency of Use[2]						
Former	143	1.89	(1.28-2.79)	117	3.18	(2.08-4.87)
Current	329	1.20	(0.84-1.70)	268	1.76	(1.23-2.53)
Length of Use[2] (years)						
1-10	46	1.16	(0.72-1.88)	37	1.24	(0.74-2.07)
11-20	144	1.71	(1.15-2.55)	100	1.79	(1.17-2.75)
21-30	144	1.18	(0.79-1.75)	128	2.14	(1.41-3.26)
≥31	118	1.18	(0.77-1.80)	97	2.61	(1.65-4.10)
Unknown	20	2.25	(1.11-4.55)	23	4.07	(2.00-8.28)
P for trend		*0.95*			*<0.01*	
Frequency of Burns[2] (lifetime)						
Never had burns	202	1.51	(1.04-2.18)	144	1.97	(1.33-2.93)
1-2 times	143	1.14	(0.77-1.67)	85	1.93	(1.25-2.98)
3-4 times	50	1.13	(0.71-1.82)	48	1.60	(0.97-2.64)
≥5 times	59	1.40	(0.88-2.21)	76	2.23	(1.42-3.50)
Unknown	18	3.18	(1.45-6.99)	32	3.21	(1.76-5.86)
P for trend		*0.63*			*0.60*	

[1]Risks adjusted for age, study site, education, family history of breast cancer, body size, and parity.
[2]All risks in referent to never users and users of <1 year of hair relaxers (58 cases, 186 controls).

Table 6. Breast Cancer Risk by Skin Lightener and Hair Relaxer Usage by Other Demographic and Clinical Characteristics

Demographic and Clinical Characteristics	Skin Lightener Use				Lye Hair Relaxer Use				Non-Lye Hair Relaxer Use			
	Exp Cases	OR[1]	95% CI	P_{het}	Exp Cases	OR[1]	95% CI	P_{het}	Exp Cases	OR[1]	95% CI	P_{het}
Age				*0.70*				*0.53*				*0.73*
<45	84	1.07	(0.79-1.45)		181	1.54	(0.88-2.68)		143	2.04	(1.16-3.61)	
45-54	99	1.02	(0.74-1.41)		129	1.16	(0.53-2.55)		122	1.75	(0.80-3.85)	
≥55	123	1.26	(0.93-1.72)		162	1.25	(0.72-2.17)		118	2.05	(1.13-3.71)	
Education				*0.52*				*0.01*				*0.04*
No formal education/some primary school	116	1.15	(0.87-1.52)		169	1.01	(0.64-1.61)		133	1.82	(1.11-2.99)	
Primary/Junior secondary school	86	1.17	(0.84-1.64)		124	4.53	(1.53-13.47)		99	5.30	(1.77-15.90)	
≥Senior secondary school	79	0.89	(0.62-1.27)		177	1.29	(0.67-2.48)		151	1.64	(0.86-3.14)	
Number of full-term Pregnancies				*0.98*				*<0.01*				*<0.01*
0-1	63	1.10	(0.73-1.66)		102	3.47	(1.57-7.70)		88	6.46	(2.78-14.99)	
2-3	99	1.03	(0.75-1.41)		170	1.56	(0.79-3.07)		133	1.87	(0.93-3.75)	
≥4	145	1.20	(0.93-1.55)		200	0.85	(0.52-1.38)		164	1.28	(0.77-2.13)	
Tumor Size												
≤5 cm.	102	1.02	(0.78-1.34)		169	2.06	(1.04-4.11)		138	3.01	(1.48-6.11)	
>5 cm.	169	1.13	(0.91-1.40)		253	0.95	(0.64-1.41)		202	1.54	(1.02-2.31)	

[1]All risks in referent to never users or users of hair relaxers for <1 year. Risks adjusted for age, study site, education, family history of breast cancer, body size, and parity.