Published in final edited form as:
Clin Rheumatol. 2008 September ; 27(9): 1183–1187. doi:10.1007/s10067-008-0937-6.

Is lipstick associated with the development of systemic lupus erythematosus (SLE)?

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Abstract

Lipstick use has been hypothesized to be a risk factor of developing systemic lupus erythematosus (SLE). The objective of this study was to investigate the association between lipstick use and risk of SLE. We performed an Internet-based case–control study of SLE with Google™ users searching on medical key terms as the source population. Cases were diagnosed within 5 years and met ≥4 ACR criteria for SLE by medical record review. Controls were matched to cases on age, gender, race, ethnicity, region of residence, reference year, education, and income using propensity score. Demographic characteristics and lifestyle factors were collected using an online questionnaire. Conditional logistic regression models were used for the analyses with smoking, alcohol consumption, permanent hair dye use, and chemical hair straightener use adjusted. The analysis included 124 cases and 248 matched controls of whom 96% were females and 81% were whites. The median of disease duration was 2 years (range 0–4 years). Using lipstick at least 3 days/week was significantly associated with increased risk of SLE (adjusted OR = 1.71, 95%CI = 1.04–2.82). There was a trend of greater risk with earlier age of initiation of lipstick use (<16 years vs. never use; OR = 1.95, 95%CI = 1.01–3.76, *p* trend = 0.02) and with increased frequency of use (7 days/week vs. never use; OR = 1.75, 95%CI = 0.89–3.44, *p* trend = 0.07). Biologic effects of chemicals present in lipsticks absorbed across the buccal mucosa and confounding from unmeasured lifestyle factors could be the explanation of this association. Epidemiologic studies of SLE should include this exposure in exploring its environmental triggers.

Keywords

Case–control; Internet; Lipstick; Systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a debilitating autoimmune disorder of unknown cause. While there is substantial evidence to support a genetic predisposition, discordance between identical twins [1] and among dispersed people of same ethnic group [2] suggests that environmental factors contribute importantly to the disease expression. SLE predominantly affects women, but hormonal and reproductive factors do not appear to fully explain the difference of risk between genders and within each gender [3].

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Relatively few epidemiologic studies have examined environmental factors that have preferential exposure among women, such as cosmetics. Lipsticks, in particular, contain a variety of chemical agents whose properties might increase the risk for SLE. These include eosin, 2-octynoic acid (a xenobiotic), and phthalate isomers that have been linked to lupus and other autoimmune disorders in vitro and in animals [4–8]. The privileged absorption of the lipstick through the buccal mucosa and oral ingestion may further aggravate the negative effects of these chemicals. Indeed, Burry postulated that lipstick use might be a cause of SLE in humans [9]. However, there are so far no systemic studies examining the association between lipstick usage and risk of SLE. In this case–control study, we sought to examine if lipstick use is associated with increased risk of SLE.

Materials and methods

Study design

We performed an Internet-based case–control study of SLE. The details of the design and validation of this approach has been previously described [10]. Briefly, we constructed a study website to solicit participants and conduct the study. We placed sponsored links on the Google™ search engine web page, which appeared when a user entered one of a set of prespecified key terms in the search field. The sponsored link pointed toward our study website. The homepage of the study website provided information about the study and links to the consent form, eligibility screening, and questionnaires. The study received approval from the Institutional Review Board at Tufts Medical Center.

Study population

The source population of the study comprised individuals living within the US, aged over 18 years, and searching on Google™ using medical key terms.

Cases—We advertised for individuals with SLE using sponsored links on Google™ triggered by lupus-related terms (e.g., lupus, SLE, and systemic lupus erythematosus). We asked individuals who came to the study website via these links to answer a set of SLE screening questions. This screen identified people likely to meet the criteria for SLE. The questions solicited a recent (<5 years) physician diagnosis of SLE, use of appropriate SLE medications (corticosteroids, antimalarials, azothiaprine, cyclophosphamide, and methotrexate), and nonuse of other rheumatic disease medications (gold, sulfasalazine, and penicillamine). In prior research, we found this algorithm to have a positive predictive value for SLE of 0.84 [11]. We asked case candidates that passed the screen to sign a release form to obtain medical records from their physicians/rheumatologists. An individual whose combined chart review and physician's checklist documented the presence of ≥4 criteria for American College of Rheumatology (ACR) criterion classification of SLE [12, 13] was classified as SLE case.

Controls—We recruited control participants through the study website over the same period as case recruitment using terms derived from a list of medical disorders most frequently searched through Google™. Initially, we selected the nine most commonly entered terms for diseases not known to share risk factors with SLE and not exclusive to men (e.g., migraine, hypertension, sinusitis, and fibroids). Later, we changed the approach to one in which we randomly selected ten key terms every 4 weeks from a list of 80 common medical key terms. From the reservoir of eligible controls, a one to two case–control match on gender, age, race, ethnicity, region of residence, reference year, education, and household income was performed to create a matched case–control dataset.

Data collection

Participants completed an online questionnaire, which included standardized questions derived from previous studies [11, 14] and covered detailed information on demographics, socioeconomic status, medications, comorbidities, disease epiphenomena such as herpes zoster, urticaria, allergy to sulfonamides, and miscarriage, and common environmental exposures such as smoking, alcohol consumption, lipstick use, permanent hair dye use, and chemical hair straightener use, etc. Questions were constructed to ascertain lifetime exposure, current exposure, age at first exposure, and exposure before diagnosis (cases) or before the reference year (controls). Lipstick use was defined as ever-wearing lipstick at least 3 days/week. For each new control participant, a computational subroutine was applied to assign a reference year in lieu of the date of diagnosis from the real-time frequency distribution of diagnosis year (0–4 years) among currently enrolled cases, so that the frequency distribution of the reference year among cases and controls were similar.

Data analysis

We used the propensity score matching method [15] to generate a matched case–control dataset. Briefly, we first used the multivariate logistic regression model including gender, age, race, ethnicity, region of residence, reference year, education, and household income as independent variables to compute each applicant's propensity score. We then preformed a one to two case–control match on propensity score using five-digit greedy match algorithm. This matching procedure was performed using a modified user-written SAS® Macro [16]. The associations between the use of lipstick and the incidence of SLE were examined using conditional logistic regression models. Potential lifestyle confounders including smoking, alcohol consumption, permanent hair dye use, and chemical hair straightener use were adjusted in the analyses. We analyzed the association by ever use, frequency of use (days/week), duration of use (total years), and age started using with "never use" as the reference. Frequency, duration, and age at initiation was each divided into three levels using the cut-points that resulted in a similar number of controls in each level. All analyses were performed using SAS (v9.1, SAS Institute, Cary, NC, USA). A two-sided test with $p < 0.05$ was considered statistically significant.

Results

During the 25-month recruitment phase, 1,727 people applied to join as cases and 1,379 as controls from whom 402 cases and 693 controls screened eligible and finished the online questionnaires. One-hundred twenty-four cases had documentation of ≥4 ACR criteria for definite SLE, among whom 29% had been diagnosed within 1 year and 67% within 3 years. The median of disease duration was 2 years. Two hundred twenty-eight controls matched to the cases. The majority of the study subjects were females (96%), whites (81%), and non-Hispanics (92%). The mean age was 41 years. Subjects with SLE and their matched controls exhibited highly concordant distributions for demographic and socioeconomic characteristics (Table 1). Chart review showed a broad representation of SLE clinical manifestations among cases, including severe disease (Table 2).

Lipstick use was common among our study samples with 60% controls and 71% cases reporting a positive history of using lipstick at least 3 days/week. After adjustment for smoking, alcohol consumption, permanent hair dye use, and chemical hair straightener use, ever-using lipstick at least 3 days/week was significantly associated with an increased risk of SLE (OR = 1.71, 95%CI = 1.04–2.82) (Table 3). Initiation of using lipstick at younger ages conferred even higher risks (<16 years vs. never use: OR = 1.95, 95%CI = 1.01–3.76, p trend for age at initiation = 0.02). The risk also appeared to increase if using lipstick more frequently (days of using lipstick per week, p trend = 0.07). Among SLE patients, using

lipstick was not associated with the presence of particular SLE manifestations (data not shown). Excluding males from the analyses did not change the results (data not shown).

Discussion

Burry postulated in 1969 that lipstick use might be a predisposing factor for SLE [9]. Our Internet-based case–control study of SLE suggests that this might indeed be the case. We found that report of lipstick use, 3 days or more per week, was associated with an over 70% greater risk of SLE. The risk increased further with younger age of starting and with frequency of use.

Lipstick is one of the most commonly used cosmetic products, especially among women. Several chemicals commonly contained in the lipstick have been associated with autoimmune phenomena. Eosin is a red dye that has been implicated in photosensitivity [9] and lupus flares [5]. Phthalate, another common ingredient in lipsticks, can induce anti-DNA antibody responses and SLE-like syndromes in lupus-prone mice [6–8]. 2-Octynoic acid is a xenobiotic that can modify the immunodominant E2 component of pyruvate dehydrogenase complexes (PDC-E2) and induce the antimitochondrial antibody response in primary biliary cirrhosis [4]. Furthermore, the application of products to the lips confers a unique potential to increase the amount of chemical exposure through oral ingestion and proximity to the buccal mucosa, a site of privileged absorption that evades “first-pass” hepatic metabolism. Our finding of stronger associations with lipstick use at a younger age suggests that early exposure to these chemicals might potentiate their participation in the triggering of autoimmune processes.

We used an Internet-based methodology to perform this study. We have previously described the feasibility and construct validity of this design [10]. Because this was one of the first case–control studies to use this approach, it would be prudent to view our results as hypothesis-generating. Nevertheless, the design conferred a number of strengths. We were able to recruit individuals with relatively recently diagnosed SLE, which should reduce misclassification of exposure caused by inaccuracy of recall and other protopathic biases (e.g., change in behavior after disease onset). Also, we had sufficient numbers to achieve a close case–control match on demographic and socioeconomic characteristics, minimizing the potential for confounding due to these characteristics. In addition, we controlled for lifestyle factors such as smoking, alcohol consumption, permanent hair dye use, and chemical hair straightener use in the analyses. On the other hand, the Internet-based recruitment could impact the generalizability of the results. It has been indicated that methodologically sound case–control studies can be performed in special subsets of the population [17], justifying the validity of the associations found for our samples.

Of course, there remains a possibility that the observed association between lipstick and SLE was due to other unknown factors that correlate with lipstick usage. For example, sharing lipsticks may increase the chance of infection of Epstein–Barr virus, an agent linked to SLE [18] and usually transmitted through saliva. The use of other cosmetic products such as face cream, body lotion, and shampoo might also confound our results. In addition, because SLE is a disease with a strong genetic component, studies considering both lipstick exposures and related genetic predisposition will be helpful to elucidate the biological mechanisms underlying these associations.

Our study has limitations with respect to the ascertainment of the exposure. We did not collect data on wearing lipsticks for less than 3 days/week, therefore, we could not conduct sensitivity analyses using 1 or 2 days as cut-offs. We did not collect information on the type of lipstick and could not analyze specific chemicals that may vary by products. We could

not distinguish lipsticks with sunscreen from those without sunscreens. However, if the sunscreen in the lipsticks had protective effects against SLE, lack of differentiation would have only biased the results toward null, which could not explain the positive association we observed in this study. Also, we did not have longitudinal information on disease activity, therefore, could not analyze the effects of using lipstick on lupus activity. However, this should not influence our conclusions on the association between lipstick and SLE incidence.

In summary, use of lipstick appears to be associated with the increased risk of SLE. While the biologic effects of chemicals present in lipsticks absorbed across the buccal mucosa could explain this association, the potential for confounding from many unmeasured lifestyle factors associated with wearing lipstick also remains a strong possibility in the interpretation of the results. Nevertheless, we suggest that epidemiologic studies of SLE should include this exposure in exploring its environmental triggers.

Acknowledgments

This work was supported by grant P60 AR47785 from the National Institutes of Health (NIH) and National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS).

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Table 1

Basic characteristics of study participants

	Cases (*n* = 124)	Controls (*n* = 248)	*p* trend
Gender, *n* (%)			
Female	118 (95)	238 (96)	0.5
Male	6 (5)	10 (4)	
Race, *n* (%)			
White	102 (82)	199 (80)	0.9
African American	11 (9)	25 (10)	
More than one race	7 (6)	16 (6)	
Others[a]	4 (3)	3 (1)	
Did not say	0 (0)	5 (2)	
Ethnicity, *n* (%)			
Non-Hispanic	115 (93)	229 (92)	0.9
Hispanic	5 (4)	12 (5)	
Did not say	4 (3)	7 (3)	
Age			
Mean (SD)	41.1 (11.5)	41.2 (11.6)	0.9
Region of residence, *n* (%)			
Northeast	19 (15)	43 (17)	0.9
Midwest	22 (18)	45 (18)	
South	52 (42)	97 (39)	
West	31 (25)	63 (25)	
Education level, *n* (%)			
High school graduate or less	14 (11)	35 (14)	0.8
Some college	51 (41)	101 (41)	
College graduate	30 (24)	56 (23)	
Professional or graduate school	26 (21)	51 (21)	
Did not say	3 (2)	5 (2)	
Household income, *n* (%)			
Less than $25K	26 (21)	52 (21)	0.7
$25K–$50K	32 (26)	74 (30)	
$50K–$100K	34 (27)	67 (27)	
$100K+	19 (15)	30 (12)	
Did not say	13 (10)	25 (10)	

[a]Others included Asians and American Indians.

Table 2

Prevalence of SLE clinical manifestations among cases (n = 124)

SLE clinical manifestations	Percentage
Malar rash	56
Discoid rash	12
Photosensitivity	53
Oral ulcers	38
Arthritis	83
Serositis	34
Renal disease	10
Neurologic disorder	6
Psychosis	3
Hematologic disorder	45
Immunologic disorder	70
Antinuclear antibodies	96

Table 3

Associations between lipstick use and SLE

	Cases (%)	Controls (%)	OR (95%CI)[a]
Lipstick use (≥3 days/week)			
Never use	36 (29)	99 (40)	1.0 (ref)
Ever use	88 (71)	149 (60)	1.71 (1.04–2.82)
Frequency, days/week[b]			
Never use	36 (32)	99 (41)	1.0 (ref)
3–4	23 (20)	47 (20)	1.31 (0.67–2.56)
5–6	27 (24)	46 (19)	1.68 (0.87–3.25)
7	28 (25)	47 (20)	1.75 (0.89–3.44)
			p trend=0.07
Duration, year			
Never use	36 (30)	99 (40)	1.0 (ref)
0–9	21 (17)	39 (16)	1.59 (0.81–3.13)
10–19	28 (21)	38 (15)	2.29 (1.17–4.49)
≥20	39 (32)	72 (29)	1.55 (0.87–2.75)
			p trend=0.1
Age at initiation, year			
Never use	36 (29)	99 (40)	1.0 (ref)
>18	24 (19)	49 (20)	1.37 (0.70–2.68)
16–18	39 (31)	62 (25)	1.81 (1.01–3.23)
<16	25 (20)	38 (15)	1.95 (1.01–3.76)
			p trend=0.02

[a] Adjusted for smoking, alcohol consumption, permanent hair dye use, and chemical hair straightener use.

[b] Ten cases and nine controls had frequency (days/week) missing.