more irregular results due to faster separation despite meticulous agitation.

Emulsifying agents influence safety through their effect on formula stability, which is required for uniform and reproducible results. We do not recommend adopting JBS, or unstable formulas, based on these findings.

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Analysis of factors associated with relapse in patients on their second course of isotretinoin for acne vulgaris

To the Editor: Oral isotretinoin has been used for decades to treat moderate to severe recalcitrant nodulocystic acne.[1] One way to evaluate the effectiveness of treatments is to measure relapse rates after treatment completion. Prior studies have found factors such as cumulative dose, male sex, young age, severity, and treatment duration to be associated with acne recurrence after isotretinoin.[2-5] We sought to further investigate factors associated with relapse after isotretinoin.

The study was approved by the University of California, Los Angeles institutional review board. A retrospective review was performed of medical records of patients treated by University of California, Los Angeles Dermatology between January 2013 and June 2018 with a diagnosis of acne (International Classification of Diseases, 10th Revision: L70.0; International Classification of Diseases, Ninth Revision: 706.1) who received a prescription for isotretinoin. Case patients included those with 2 courses of isotretinoin with at least 3 months off between the 2 courses. Control patients were those who completed only 1 course of isotretinoin, confirmed through the iPLEDGE program, and were documented to be clear of acne after their course.

Demographic data and information on the patients' acne and isotretinoin courses were collected. Statistical analysis was performed for continuous variables using Wilcoxon's rank sum test and categorical variables with the chi-square or Fisher's exact test.

Table I. Basic demographics of all patients

Characteristics	All patients	Control group	Case group
Patients, n	242	160	82
Age, y, mean ± SD	25.29 ± 6.64	21.63 ± 6.31	21.42 ± 6.49
<18 years old, n	85	58	27
≥18 years old, n	157	102	55
Female patients, n (%)	114 (47.11)	78 (48.75)	36 (43.90)
Female patients by medication, n			
Oral contraceptives	31	21	10
Spironolactone	14	11	3
Both oral contraceptives and spironolactone	38	19	19
Ethnicity			
White	140	90	50
Black or African American	6	3	3
Asian	27	20	7
American Indian or Alaska	1	1	0
Multiple races	3	2	1
Other	41	23	18
Patient refused	14	12	2
Unknown	10	9	1

SD, Standard deviation.

Eighty-two case patients and 160 control patients met the inclusion criteria. Demographic information is summarized in Table I. Compared with control patients who received only 1 course of isotretinoin, patients requiring a second course were more likely to have received a lower cumulative dose (128.1 vs. 159.0 mg/kg, $P < .005$) and to have a shorter duration of isotretinoin treatment after acne clearance (32.0 vs. 65.4 days, $P < .005$) (Table II). There were no statistically significant differences between the case and control groups in age at isotretinoin initiation, acne distribution, acne subtype, or sex, even when patients were stratified by age or concurrent hormonal treatment with an oral contraceptive or spironolactone.

In our study, 57 of 82 (69.5%) patients requiring a second course of isotretinoin relapsed within 2 years after treatment. The average time to relapse was 460 days. These findings suggest that unsuccessful acne treatment with isotretinoin will be apparent shortly after treatment completion. Our findings also suggest that cumulative isotretinoin dose and duration of treatment after acne clearance are strong predictors of acne relapse. The benefit of extending the isotretinoin treatment course well beyond the acne clearance date is a relatively new concept,[5] and in our study, patients who relapsed had discontinued treatment on average 1 month earlier than those who did not relapse (32.0 vs. 65.4 days).

Limitations include analyzing retrospective data. We were unable to determine if any control patients relapsed but decided not to pursue a second course of isotretinoin. Our numbers may also be too small to show the impact of hormonal acne on relapse.

The results from this study reinforce the benefit of targeting a higher cumulative dose of isotretinoin and also suggest that continuing treatment for a longer duration after acne clearance (at least 2 months) is important in preventing acne relapse.

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Table II. Comparison of variables between case patients, who required a second isotretinoin course, and control patients, who required only a single course

Characteristics	Control patients (n = 160)	Case patients (n = 82)	*P* value
Acne vulgaris severity, n (%)			
Mild	12 (7.5)	2 (2.4)	.8180
Mild/moderate	15 (9.4)	5 (6.1)	
Moderate	77 (48.1)	34 (41.5)	
Moderate/severe	29 (18.1)	15 (18.3)	
Severe	27 (16.9)	26 (31.7)	
Acne vulgaris location: face, n (%)			
Yes	160 (100.0)	82 (100.0)	
Acne vulgaris location: chest, n (%)			
No	99 (61.9)	52 (63.4)	.8149
Yes	61 (38.1)	30 (36.6)	
Acne vulgaris location: back			
No	83 (51.9)	42 (51.2)	.9230
Yes	77 (48.1)	40 (48.8)	
Acne vulgaris type: comedones			
No	81 (50.9)	43 (53.1)	.7534
Yes	78 (49.1)	38 (46.9)	
Acne vulgaris type: papules			
No	9 (5.7)	8 (9.9)	.2286
Yes	150 (94.3)	73 (90.1)	
Acne vulgaris type: nodular			
No	127 (79.9)	62 (76.5)	.5508
Yes	32 (20.1)	19 (23.5)	
Acne vulgaris type: scarring			
No	52 (32.7)	30 (37.0)	.5033
Yes	107 (67.3)	51 (63.0)	
Acne vulgaris type: pustules			
No	83 (52.2)	50 (61.7)	.1602
Yes	76 (47.8)	31 (38.3)	
Acne vulgaris type: cysts			
No	117 (73.6)	59 (74.7)	.8557
Yes	42 (26.4)	20 (25.3)	
Time between clear date and end date, days, mean ± SD	65.4 ± 64.99	32.0 ± 43.31	<.0001
Maximum daily dose, mg/day, mean ± SD	63.4 ± 13.90	59.9 ± 18.45	.1448
Maximum daily dose, mg/kg/day, mean ± SD	0.96 ± 0.22	0.90 ± 0.25	.0678
Cumulative dose, mg/kg, mean ± SD	158.97 ± 50.86	128.13 ± 50.91	.0001
Number of case patients who relapsed within 2 years	—	57 (69.5)	
Average time between first ISO end date and second ISO start date, months, mean ± SD	—	15.34 ± 9.97	
Time between completion of ISO course and last dermatology clinic visit, months, mean ± SD	12.56 ± 23.34	—	
Time between completion of ISO course and last nondermatology clinic visit, months, mean ± SD	22.19 ± 23.61	—	
Medications (female patients only), n (%)			
Both oral contraceptives and spironolactone	19 (37.3)	19 (59.4)	.1134
Oral contraceptives only	21 (41.2)	10 (31.3)	
Spironolactone only	11 (21.6)	3 (9.4)	

ISO, Isotretinoin; *SD*, standard deviation.

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Association of breast and colorectal cancer in patients with central centrifugal cicatricial alopecia: A retrospective, cross-sectional pilot study

To the Editor: Nearly 25% of patients with central centrifugal cicatricial alopecia have reduced peptidyl arginine deiminase 3 expression,[1] which may play a role in colorectal cancer pathogenesis, upstream of the CKS1/p27 tumorigenesis pathway, as well as breast cancer proliferation.[2,3] Given the potential roles of peptidyl arginine deiminase 3 in these diseases, we sought to examine the relationship between breast cancer and colorectal cancer in patients with central centrifugal cicatricial alopecia.

This cross-sectional study consisted of black women aged 18 years or older who presented to the University of Pennsylvania Health System from April 13, 2016, to April 13, 2020. Electronic medical records were queried through the EPIC Clarity database, using *International Classification of Diseases, Ninth Revision (ICD-9)* or *ICD-10* codes. Women with central centrifugal cicatricial alopecia were identified with *ICD-10* code L66.9. The electronic medical records were reviewed to identify biopsy-proven central centrifugal cicatricial alopecia. Patients with a history of breast cancer or colorectal cancer were identified with at least 1 *ICD-9* or *-10* code. To assess the associations between breast cancer or colorectal cancer and central centrifugal cicatricial alopecia, logistic regression was performed. The mean age of breast cancer diagnosis between cohorts was compared with a *t* test. All analyses were performed with R, version 4.0.2 (The R Foundation for Statistical Computing, Vienna, Austria) at a significance level of 5%. The institutional review board of the University of Pennsylvania approved this study.

During the 4-year period, 225,416 black women were treated within the University of Pennsylvania Health System. Of the 742 women with code L66.9, 35 (4.7%) had a history of breast cancer compared with the 4079 controls (1.8%; odds ratio 2.61; 95% confidence interval 1.78-3.68; $P < .001$). Of the patients with biopsy-proven central centrifugal cicatricial alopecia (159 of 742), 4.4% had a history of breast cancer compared with the 4079 controls (1.8%) (odds ratio 2.49; 95% confidence interval 1.06-4.92; $P = .02$). The prevalence of colorectal cancer among women with code L66.9 did not significantly differ between cohorts (odds ratio 0.48; 95% confidence interval 0.027-2.10; $P = .46$) (Table I). The average age at diagnosis with breast cancer and overall age distribution were similar between cohorts (Table II).

Our results show that women with central centrifugal cicatricial alopecia and biopsy-proven central centrifugal cicatricial alopecia were nearly 3 times more likely to have a history of breast cancer compared with race-, age-, and sex-matched controls. This association may be due to a shared

Table I. Characteristics of study population and association of breast and colorectal cancer in patients with central centrifugal cicatricial alopecia

Characteristics	Patients with cancer, no. (%)	OR (95% CI)	*P* value
History of BC			
History of CCCA			
Yes (n = 742)	35 (4.7)	2.61 (1.78-3.68)	<.001
No (n = 224 674)	4079 (1.8)	1 [Reference]	NA
History of BP CCCA			
Yes (n = 159)	7 (4.4)	2.49 (1.06-4.92)	.02
No (n = 224 674)	4079 (1.8)	1 [Reference]	NA
History of CRC			
History of CCCA			
Yes (n = 742)	1 (0.13)	0.48 (0.027-2.10)	.46
No (n = 224 674)	701 (0.31)	1 [Reference]	NA

The *P* values, odds ratios, and 95% confidence intervals were calculated from logistic regression models.
BC, breast cancer; *BP*, biopsy-proven; *BP CCCA*, biopsy-proven central centrifugal cicatricial alopecia; *CI*, confidence interval; *CCCA*, central centrifugal cicatricial alopecia; *CRC*, colorectal cancer; *OR*, odds ratio.