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The Effects of Smoking on Hair Health: A Systematic Review

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Smoking · Nicotine · Hair loss · Alopecia · Premature hair graying

Abstract
Smoking is not only a preventable cause of significant systemic disease but also affects the follicular growth cycle and fiber pigmentation. Ambient tobacco smoke exposure results in nicotine accumulation in hair follicles and the hair shaft. This review summarizes the evidence on the association between smoking and hair health, as denoted by alopecia and premature hair graying (PHG). In July 2020, a review of the literature using PubMed/MEDLINE and CINAHL databases identified 32 studies investigating the relationship between smoking, PHG, and alopecia (androgenetic alopecia and frontal fibrosing alopecia). The prevalence of hair loss and PHG is more prevalent in smokers than nonsmokers. Smoking is associated with negative effects on hair health as evidenced in PHG and alopecia. Smoking status should be assessed in patients who are presenting to their dermatologist for evaluation of alopecia and PHG.

Introduction

Alopecia (hair loss) is a common chief complaint of patients' presenting to their dermatologist's and primary care providers [1]. The etiology of the most common type of alopecia, androgenetic alopecia (AGA), is multifactorial. Systemic androgens have been shown to play a role in the pathogenesis of AGA by causing hair miniaturization and transforming terminal to vellus hairs [2, 3]. The role of environmental factors, such as smoking, has been implicated to negatively affect hair growth.

Smoking is a risk factor for many preventable morbidities, including cerebrovascular, pulmonary disease, malignancy, and oral mucocutaneous disease. More recently, the role of smoking in skin aging and hair loss has been a great topic of interest and research [4, 5]. Animal studies in mice have indicated that environmental factors, including tobacco smoke exposure, can lead to alopecia and premature hair graying (PHG). Chemical components found in tobacco smoke, such as nicotine, are capable of accumulating in hair, and have become reliable biomarkers for detecting smoke exposure [6]. Smoking has also been shown to cause a relative hypo-estrogen state in women via hydroxylation of estradiol and inhibi-

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tion of aromatase, thus potentially affecting androgen-dependent hair patterns [2].

Additional studies have also suggested a relationship between smoking and PHG [3, 4]. Interestingly, in immunological staining studies of melanocytes in gray hair, melanosomes are found within vacuoles or autophagolysosomes, rendering them defective. In addition, hair bulbs exposed to oxidative stress tend to be increasingly vacuolated. This causes increased reactive oxygen species and oxidative stress around the follicle, leading to damage to melanocytes and decreased melanin production [5]. Currently, no universal criteria have been established to clinically diagnose PHG, yet many have classified subjects by number of gray hairs (0, <10, 10–100, >100) and defined PHG as graying before the age of 30-year old [6, 7]. While hair graying is a normal physiological process associated with aging, PHG can decrease self-esteem and interfere with social and sexual communication, as noted by Akin et al. [6] where subjects with PHG were noted to have higher perceived stress scale scores.

The objective of this review was to investigate and report the evidence supporting the association between smoking and alopecia and premature graying. Evidence of this association can be used to clinically promote smoking cessation and emphasize the consequences of smoking on hair.

Materials and Methods

A primary literature review was conducted in July 2020 utilizing PubMed/MEDLINE and CINAHL databases with the following search terms: (Smoking OR tobacco OR nicotine) AND (Premature Graying OR Graying hair OR Hair color OR Hair Follicle OR Hair Loss OR Alopecia OR Hair OR Follicle OR Gray Hair). Exclusion criteria included studies that were written in languages other than English and studies not conducted on humans. Studies included for review were stratified using the Oxford Center for Evidence-Based Medicine 2011 Levels of Evidence.

Results

The systematic review identified 32 articles that met inclusion criteria including, 7 cross-sectional studies, 21 case-control, and 4 cohort studies (n = 23,685 patients) (Table 1). No randomized control trials were found. Ten studies investigated the association of smoking and alopecia, 8 articles studied the relationship between smoking and PHG, and 2 studies reported the effects of smoking on both. The majority of studies included patients with diagnosed AGA (n = 11,826) and frontal fibrosing alopecia (FFA) (n = 710) in association with smoking and nicotine use.

Smoking and Alopecia

The majority of epidemiologic studies recognize a positive association between smoking and alopecia, particularly in patients with AGA [3, 8–13, 53]. One survey-based study of 740 Asian men with a diagnosis of AGA reported that current smokers of twenty cigarettes or more per day, with a history of smoking, or those with a greater smoking intensity (defined as smoking duration × amount per day) were at a higher risk of moderate or severe AGA (Norwood type IV) [8]. This study is in concordance with a study from the UK, which also found a link between quantity of smoking and AGA in patients (n = 268 M, 338 F) from a general surgery clinic [3, 7]. A case-control study with 991 Korean AGA patients (n = 613 M, 378 F) showed that current smokers experienced more severe cases of AGA when compared to noncurrent smokers. The subjects with a current smoking history had higher rate of U-type pattern alopecia according to the basic and specific classification system (p = 0.004) [9]. Twin studies on male (n = 92) and female (n = 98) patients with AGA conclude that increased pack-years of smoking was associated with more dramatic frontal hairline thinning [10, 11]. The twin female smokers had increased temporal hair loss (p = 0.096; n = 10), while male smokers had more vertex hair loss than nonsmokers (p = 0.047, n = 20) [10, 11]. A cross-sectional study conducted by Fortes et al. [12] focused specifically on severe cases of AGA and noted a 3 times greater risk of developing moderate/severe alopecia in those with a higher frequency of smoking (≥10 cigarettes daily) (n = 351). A hospital-based cross-sectional study including 50 men with diagnosed early onset AGA (Norwood grade III or above developing before 36 years) and 50 case-controls reported a higher prevalence of smoking in subjects with AGA (52%) compared to controls (22%) (p = 0.002) [13]. One propensity-matched retrospective study of 5,508 subjects from the Partners Healthcare Research Patient Data Repository revealed a higher frequency of current or past smokers (56.5%) with alopecia areata compared to subjects with alopecia areata who have never smoked (42.6%) [14]. Additionally, univariate analysis of 75 subjects with clinically diagnosed FFA, in a retrospective cross-sectional study, revealed a strong association between smoking and mild hairline recession (p = 0.128) [15]. A cross-sectional study including 1,000 male patients attending a dermatology clinic reported a greater prevalence of AGA among

Table 1. A summary of the current studies on the association between smoking and hair loss and PHG

Author	Quality rating	Study design	Patients, *n*	Primary diagnosis	Study subjects characteristics	Smoking frequency	Study findings	PHG grading
Yeo et al. [53]	III	Controlled, retrospective trial	*n* = 1,371 (945 M, 426 F), 1,743 dropouts	AGA	Mean age of onset: M 33.6 yr, F 29.8 yr. BASP classification system-M: type M (82.2%) >type C (7.5%) >type L (7.3%) >type U (3.0%). F: type M (52.7%) >type L (36.9%) >type C (10.1%) >type U (0.3%)	Not included	F: no correlation between smoking and hair loss. M: subjects who both drank and smoked had more severe hair loss ($p = 0.019$) than other groups who did not drink or smoke	Not included
Su and Chen [8]	IV	Uncontrolled, retrospective trial	*n* = 740 M, 184 dropouts	AGA	Mean age: 65 yr (40–91 yr). Norwood and Ludwig classification system. In age-groups 40–49, 50–59, 60–69, and ≥70, the age-specific prevalence's of Norwood type A variants were 5.1, 1.1, 8.1, and 7.4%, respectively, and those of female pattern AGA were 0.0, 2.1, 1.6, and 2.4%, respectively	Smoking status group included "Never," "quit," "current smoker of <20 cigarettes per day," or "current smoker of >20 cigarettes per day"	Smokers had an increased risk of having moderate or severe AGA (Norwood type IV) (OR, 1.61; 95% CI, 1.05–2.46). A positive association was established between moderate or severe AGA and smoking status (OR, 1.77; 95% CI, 1.14–2.76), current cigarette smoking of 20 cigarettes or more per day (OR, 2.34; 95% CI, 1.19–4.59), and smoking intensity (smoking duration × amount per day) (OR, 1.78; 95% CI, 1.03–3.07)	Not included
Gatherwright et al. [11]	III	Controlled, retrospective trial	*n* = 98 F	AGA	98 F identical twins (49 sets). Mean age 53 yr (18–77 yr)	Not included	Less frontal hair loss in twins who had never smoked ($p = 0.021$; $n = 8$). Increased frontal hair thinning associated w/being a current smoker and increased pack-years of smoking ($p = 0.013$ and $p = 0.034$; $n = 10$ and $n = 24$, respectively). Increased temporal hair loss was observed in current smokers ($p = 0.096$; $n = 10$)	Not included
Gatherwright et al. [11]	III	Controlled, retrospective trial	*n* = 92 M	AGA	92 M identical twins (46 sets). Mean age: 52 yr (23–84 yr)	Not included	Positive correlation between smoking history and frontal hair loss ($p < 0.001$), but quantity of smoking was not statistically significant. Each twin who started smoking earlier ($r = -0.798$; $p < 0.001$; $n = 20$) and stopped smoking later ($r = -0.544$; $p = 0.097$; $n = 12$) had more frontal hair loss. Twins who smoked had more vertex hair loss than their nonsmoking siblings ($p = 0.047$, $n = 20$)	Not included

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Table 1 (continued)

Author	Quality rating	Study design	Patients, *n*	Primary diagnosis	Study subjects characteristics	Smoking frequency	Study findings	PHG grading
Mosley and Gibbs [3]	II	Controlled, retrospective trial	*n* = 606 (268 M, 338 F)	PHG + hair loss	All subjects were over >30 yr. 152 M and 152 F w/a h/o or current smoking. Hamilton baldness scale (a 5-point scale: score of 1 indicating no hair loss, and 5 indicating extreme baldness). Baldness regarded as present on category III or greater-Bald smokers: 103 M, 2 F; Bald nonsmokers: 63 M, 2 F. PHG smokers: 37 M, 126 F; PHG nonsmokers: 33 M, 110 F	Not included	The odds ratio for the association of smoking and baldness in men was 1.93 (95% confidence interval 1.13–3.28). No corresponding calculation was carried out for females (*n* = 4). A significant association between gray hair and smoking for all age-groups, in both sexes, w/an overall odds ratio of 4.40 was found (95% CI 3.24–5.96)	Not included
Fortes et al. [12]	IV	Uncontrolled, retrospective trial	*n* = 351 (237 M, 114 F)	AGA	Mean age: 35 yr. M: 133 subjects w/ mild (Hamilton-Norwood classifications I–III) and 104 subject's w/moderate/severe (Hamilton-Norwood classifications IV-VII). F: 104 subjects w/mild (Ludwig type I) and 10 subjects moderate/severe (Ludwig types II and III)	Four categories: "Never," "quit," "current smokers (<10 cigarettes daily)" "and current smokers (≥10 cigarettes daily)"	Subjects w/more severe AGA tended to smoke more cigarettes per day (≥10 cigarettes daily) than subjects w/less severe AGA (17.5 vs. 7.6%, $p = 0.05$). AGA subjects that were heavy smokers (≥10 cigarettes per day) had almost 3 times an increased risk of having a moderate/severe alopecia in comparison w/never smokers ($p = 0.05$)	Not included
Fonda-Pascual et al. [24]	IV	Uncontrolled, retrospective trial	*n* = 72 F	FFA	Mean age at diagnosis 61 yr (32–85 yr)	Documented as "no tobacco exposure" in nonsmokers, and "positive tobacco exposure" in ex-smokers and active smokers. Smoking histories documented in pack-years	Higher prevalence of severe FFA among nonsmokers ($p = 0.001$). Tobacco exposure was a protective factor against FFA ($p = 0.04$)	Not included
Acer et al. [33]	IV	Controlled, retrospective trial	*n* = 1,192 (655 F, 537 M)	PHG	655 F, 537 M (18–20 yr). 377 of the 1,192 subjects had PHG. Mean age of subjects w/PHG was 18.88 yr. Mean onset age of PHG was 16.90 yr (ranges: 7–20 yr). Of the 337 subjects w/PHG, 259 subjects had <10 Gy hairs (68.7%), 88 had (23.3%) 10–100 Gy hairs, and 30 had (8%) >100 Gy hairs	Defined by either the presence or absence of smoking	No relation between smoking and PHG. Of the 377 subjects w/PHG, 288 did not smoke, and 89 were smokers ($p = 0.729$)	The number of graying hairs was classified as <10, 10–100, and >100
Gould et al. [34]	III	Controlled, retrospective trial	*n* = 50, 11 dropouts	PHG	12 of 50 patients had premature graying. PHG started at an early age, ranging from 20 to 35 yr w/an average of 29 yr	Defined by either the presence or absence of smoking in pack-years	Premature graying was not related to the prevalence of smoking	Not included

Table 1 (continued)

Author	Quality rating	Study design	Patients, *n*	Primary diagnosis	Study subjects characteristics	Smoking frequency	Study findings	PHG grading
Sabharwal et al. [28]	II	Controlled, retrospective trial	*n* = 120	PHG	Mean age: 48.16 yr (smokers), 33.56 yr (tobacco chewers), 33.33 yr (smokers + chewers), and 34.9 yr (control group)	Group I: smoking tobacco (*n* = 30). Group II: chewing tobacco (*n* = 30). Group III: smoking + chewing tobacco (*n* = 30). Group IV: control group (*n* = 30)	Increase in the frequency of individuals w/gray hair was observed in 3 groups (groups I, II, and III) when compared w/the control (group IV) ($p < 0.05$)	Not included
Sharma and Dogra [7]	III	Controlled, retrospective trial	*n* = 240	PHG	Mean age at onset of graying 13.80 yr (2–22 yr)	Not included	Smoking was associated w/PHG ($p = 0.000$)	PHG was defined as >5 Gy hair in the scalp in subjects <25 yr. Subjects graded into 4 groups: (1) no gray hair, (2) mild: <10 Gy hair, (3) moderate: 10–100 Gy hair, and (4) severe: >100 Gy hair
Shin et al. [32]	III	Controlled, retrospective trial	Pilot *n* = 1,069 M, 35 dropouts main survey *n* = 6,390 M, 268 dropouts	PHG	Main survey: of the 6,390 participants, 1,618 (25.3%) presented w/PHG. Subjects had to be <30 yr	Participants w/a smoking history of >5 pack-years were regarded as smokers	Pilot study results: smoking was not associated w/PHG. Main survey: smoking was associated w/PHG ($p = 0.014$)	Number of gray hairs was self-reported as follows: 0, <10, 10–100, and >100
Jo et al. [29]	III	Controlled, retrospective trial	*n* = 1,002	PHG	522 M and 480 F (12–91 yr). Average overall age at onset of hair graying was 41.6±13.1 yr (M: 40.8±14.1 yr) (W: 42.4±11.9 yr). The prevalence of gray hair by age was 51.5% in their thirties, 81.1% in their forties, and 95.3% in their fifties	Subjects w/a smoking history of >3 pack-years were considered smokers	Age and smoking behavior were correlated w/hair graying. The risk of hair graying increased by 14.9% each year ($p < 0.001$), and the risk in smokers was 1.99 times higher than that in nonsmokers ($p = 0.008$)	Subjects estimated the extent of grayness themselves. Grade 1 (<20% of total hair), grade 2 (20–40%), grade 3 (40–60%), grade 4 (60–80%), and grade 5 (>80%). Trained investigators assessed extent of grayness w/a photographic scale (grade 1–5)

Table 1 (continued)

Author	Quality rating	Study design	Patients, *n*	Primary diagnosis	Study subjects characteristics	Smoking frequency	Study findings	PHG grading
Aggarwal et al.[31]	III	Controlled, retrospective trial	*n* = 236 M	PHG	Young subjects (<45 yr)	Group 1: chronic smokers ≤45 yr (*n* = 62); group 2: subjects w/CAD ≤45 yr and chronic smokers (*n* = 60); group 3: subjects w/no smoking or cardiac history ≤45 yr (*n* = 114)	Group II (i.e., smokers w/CAD) had maximum prevalence of graying compared to control ($p = 0.000$) as well as smoker (group II vs. I $p = 0.000$) groups. Smokers also had a higher proportion of graying than the control group (group I vs. III $p = 0.031$)	A 25% or more graying of hair on scalp and/or beard on visual inspection was taken as a positive criterion for graying in the patient
Belli et al. [6]	IV	Controlled, retrospective trial	*n* = 1,119 (372 M, 747 F)	PHG + hair loss	Of 1,119 subjects, 315 (207 F, 108 M; age ranges 14–20 yr, mean age 17.8 yr) had PHG and 804 (540 F, 264 M; age range 14–20 yr, mean age 17.2 yr) did not. The mean onset age of hair graying was 15.6 yr (ranges 5–20 yr)	A smoking history of >1 pack-year was recommended as the cutoff for smoking	Of the 315 participants w/PHG, 254 had fewer than 10 Gy hairs, 54 had 10-100 Gy hairs, and 7 had >100 Gy hairs. Hair loss was higher in participants w/PHG ($p = 0.01$). Smoking was not associated w/PHG ($p = 0.13$)	Number of gray hairs was classified as 0, <10, 10–100, >100. Subjects ≥1 Gy hairs are considered to have PHG.
Zayed et al. [30]	IV	Controlled, retrospective trial	*n* = 207 (94 M, 113 F)	PHG	Average age of 44 yr. Average age PHG onset 31.7 yr. Of the 207 subjects, 104 had first appearance of gray hair before the age of 30 (PHG group), while the other 103 were considered normal hair graying group	A nonsmoker was defined as someone who never smoked	The prevalence of smokers in the "PHG" group was higher (40.2 vs. 24.7%, $p = 0.031$). Smokers had earlier onset of hair graying (smokers: 31 [7.4] versus nonsmokers: 34 [8.6], $p = 0.034$). Smokers were 2 and half times more prone to develop PHG (95% CI: 1.5–4.6)	PHG was defined as the first appearance of gray hair before the age of 30
Matilainen et al. [17]	III	Controlled, retrospective trial	*n* = 324 F	AGA	Hair status of women was assessed by a modification of Ludwig's scale. The prevalence of extensive hair loss (at least grade II or III on Ludwig's scale) was high (31.2%)	Not included	The prevalence of current smoking was low and equal (13.6%) in both groups, normal hair and extensive hair loss ($p = 0.918$)	Not included
Park et al. [9]	II	Controlled, retrospective trial	*n* = 1,884 (915 M, 969 F)	AGA	Average age of 56.6 yr. 991 was AGA patients (613 M, 378 F. Of the 991 AGA patients, 443 subjects were classified as having mild AGA, 381 had moderate AGA, and 167 had severe AGA. BASP classification was used to evaluate hair loss	Defined by either the presence or absence of smoking	The prevalence of smokers in the AGA group 334/991 (33.7%) was higher than the non-AGA group 214/893 (24.0%) ($p = 0.0000$). More severe forms of AGA had a higher frequency of smokers (mild: 125/443 [28.2%], moderate: 143/381 [37.5%], severe: 66/167 [39.5%]) ($p = 0.004$)	Not included

Table 1 (continued)

Author	Quality rating	Study design	Patients, *n*	Primary diagnosis	Study subjects characteristics	Smoking frequency	Study findings	PHG grading
Severi et al. [18]	II	Controlled, retrospective trial	*n* = 1,390 M	AGA	Interviewers scored AGA according to a set of 4 pictures adapted from the Hamilton-Norwood scale. No balding *n* = 350 (Hamilton-Norwood stage I), frontal balding *n* = 447 (Hamilton-Norwood stages II, III, IIIa, and IVa), vertex balding *n* = 238 (Hamilton-Norwood stage III-vertex and V) and frontal AGA concurrent w/vertex AGA *n* = 335 (Hamilton-Norwood stages IV, V, Va, VI, and VII)	Defined as either nonsmokers, current smokers, or ex-smokers	The prevalence of frontal only AGA was higher in nonsmokers (199/447) than in current (73/447) and ex-smoker groups (175/447). Vertex only AGA was higher in nonsmokers (106/238) than in current (41/238) and ex-smokers (91/238). Frontal AGA concurrent w/vertex AGA was higher in nonsmokers (173/335) than current (47/335) and ex-smokers (135/335) ($p > 0.05$)	Not included
Salman et al. [19]	IV	Controlled, retrospective trial	*n* = 954 (419 M, 535 F)	AGA	Average age of 37.7 yr. Average age of AGA onset was 31.1 yr in men and 40.3 in women. AGA prevalence found was 67.1% (*n* = 281) in men and 23.9% (*n* = 128) in women. Severity of AGA was evaluated with Norwood-Hamilton scale in men and Ludwig classification in women	Not included	No significant difference was found in terms of smoking habits between patients with and without AGA in both genders ($p > 0.05$)	Not included
Fortes et al. [20]	III	Controlled, prospective trial	*n* = 214 M	AGA	104 subjects with AGA and 108 subjects without AGA were included. Average age of subjects with AGA was 28.5 yr and 38.9 in subjects without AGA. Hair pattern was classified according to the Hamilton baldness scale, as modified by Norwood	Cigarette smoking was categorized in 4 groups never, quit, and current smokers (<10 cigarettes; ≥10 cigarettes daily)	No statistical difference was found regarding smoking frequency between AGA subjects when compared to non-AGA subjects ($p = 0.13$)	Not included
Danesh-Shakiba et al. [21]	III	Controlled, prospective trial	*n* = 512 M	AGA	256 patients with AGA and 256 age-matched control subjects were included with a mean age of 38.3 and 38.4 yr, respectively. The Norwood-Hamilton scale was employed to determine the presence and severity of AGA in all study participants by one single physician	Current smokers and those who had smoked cigarettes or hookah in the past 30 days were considered cigarette smokers or hookah smokers, respectively	Smoking prevalence was not statistically significant among AGA subjects 72 (28.1%) compared to control subjects 66 (25.8%) ($p = 0.550$). The prevalence of hookah smoking (smoking water pipe) was not statistically significant among AGA subjects 36 (14%) compared to control subjects 38 (14.8%) ($p = 0.801$). Although smoking was not significantly more common in patients with mild to moderate hair loss compared to those with severe hair loss ($p = 0.276$), hookah use was significantly more prevalent in the former group ($p < 0.001$)	Not included

Table 1 (continued)

Author	Quality rating	Study design	Patients, *n*	Primary diagnosis	Study subjects characteristics	Smoking frequency	Study findings	PHG grading
MacDonald et al. [25]	IV	Uncontrolled, retrospective trial	*n* = 60 W	FFA	Mean age at onset was 60.4 yr and average disease duration was 3.4 years (ranges: 6 months–30 years)	Not included	Data regarding smoking status in FFA patients were available for 52 patients; 37 patients (71%) had never smoked, 5 patients (10%) were current smokers, and 10 patients (19%) were ex-smokers. These data show a significant preponderance of nonsmokers within this cohort, compared with national data regarding smoking status of Scottish women ($p = 0.01$)	Not included
Vora et al. [13]	IV	Controlled, prospective trial	*n* = 100 M	AGA	50 subjects with AGA and 50 age-matched control subjects were included with a mean age of 29.32 and 31.5 yr, respectively. The mean age of onset of AGA was 27.08 yr. The degree of androgenic alopecia was based on the Norwood scale (III-VII). AGA developing before 36 yr of age and reaching at least Stage III of Hamilton-Norwood classification is termed as early onset AGA	Not included	The prevalence smoking was higher in male patients with early onset AGA 26 (52%) as compared to controls 11 (22%) ($p = 0.002$)	Not included
Lai et al. [22]	III	Controlled, prospective trial	*n* = 354 M	AGA	Subjects were men from 35 to 65 yr. The Norwood-Hamilton scale was employed to determine the presence and severity of AGA	Not included	Smoking frequency in subjects with a Hamilton-Norwood scale score of I-III was 175 (59.5%) in smokers and 119 (40.5%) in nonsmokers, while those with a Hamilton-Norwood scale of IV–VII, has a smoking frequency of 35 (58.3%) in smokers and 25 (41.7%) in nonsmokers ($p = 0.86$)	Not included
Huang et al. [14]	III	Controlled, retrospective trial	*n* = 5,508 (2,142 M, 3,366 F)	AA	1,377 (517 M, 860 F) subjects with AA and 4,131 (1,625 M, 2,504 F) controls were included with a mean age of 45.0 and 44.4 yr, respectively	Smoking status was considered positive if the patient was a current or past smoker	A higher frequency of current or past smokers (56.5%) with AA was seen compared to subjects with AA who have never smoked (42.6%)	Not included
Arias-Santiago et al. [23]	III	Controlled, retrospective trial	*n* = 154	AGA	77 (40 M, 37 F) subjects with early onset AGA and 77 (40 M, 37 F) controls were included. The degree of AGA was determined by the Ebling scale (III–V) for male patients and the Ludwig scale (II–III) for female patients	Smoking status was considered positive if subject smoked >5 cigarettes per day)	Tobacco use was higher in male subjects with AGA (27.5%) versus control subjects (22.5%) *p* value 0.48. The opposite was true among female smokers with AGA (13.5%) versus control subjects (29.7%) ($p = 0.09$)	Not included

Table 1 (continued)

Author	Quality rating	Study design	Patients, *n*	Primary diagnosis	Study subjects characteristics	Smoking frequency	Study findings	PHG grading
Vañó-Galván et al. [26]	IV	Uncontrolled, retrospective trial	*n* = 355 (12 M, 343 F)	FFA	The mean age of onset of FFA was 56 yr (21–81 yr). The clinical severity of FFA was classified based on a clinical scale, measuring the area of cicatricial skin produced by the recession of the frontal and temporal hairline. This classification included 5 grades of severity: I (<1 cm), II (1–2.99 cm), III (3–4.99 cm), IV (5–6.99 cm), and V (>7 cm), which were grouped as mild FFA (grades I and II) and severe FFA (grades III, IV, and V)	Smoking was categorized as active smokers, former smokers and those who have never smoked	Smoking habit was recorded in 274 patients or which 237 had never smoked (87%), 26 were former smokers (9%), and 11 (4%) were active smokers	Not included
Imhof et al. [27]	IV	Uncontrolled, retrospective trial	*n* = 148 F	FFA	The mean age of FFA diagnosis was 62.1 yr (28–86 yr). The mean age of FFA symptom onset was 57.4 yr (range, 26-81 yr). Distribution of hair loss was frontal in 147 (99.3%), temporal in 77 (52%), and occipital in 45 (30.4%)	Smoking was categorized as active smokers, former smokers, and those who have never smoked	Smoking history was available for 146 (98.7%) of FFA subjects, with 92 (63%) having never smoked, 54 (37%) were former smokers, and none were active smokers	Not included
Thompson et al. [35]	IV	Controlled, prospective trial	*n* = 467 (113 M, 354 F)	PHG	216 subjects with a history of PHG and 251 without were included	Smoking history was categorized as never smoker, former smoker, and current smoker	Smoking history ($p = 0.015$) was significantly negatively correlated with history of PHG. When examining the response from Caucasian participants only, history of PHG remained significantly negatively associated with smoking history ($p = 0.008$)	PHG was defined as the first appearance of gray hair before the age of 30. Severity of graying was classified as 0, <10, 10–100, >100 gray hairs
Maldonado Cid et al. [15]	IV	Uncontrolled, retrospective trial	*n* = 75 (2 M, 73 F)	FFA	Diagnosis was based on the presence of scarring alopecia with recession of the frontotemporal hairline bilateral diffuse alopecia of the eyebrows, and compatible trichoscopic signs. Of the 75 subjects, mild hairline recession was observed in 56.0% (*n* = 42) subjects at the first consultation. The mean extent of hairline recession was 2.2±1.5 cm. A diffuse hairline recession pattern was observed in 56.9% (*n* = 37) of subjects	Smoking history was categorized as nonsmokers, ex-smokers and smokers	While most of the subjects were nonsmokers. Univariate analysis revealed a significant association between smoking and mild hairline recession ($p = 0.128$)	Not included

AA, alopecia areata; AGA, androgenic alopecia; BASP, basic and specific; F, female; h/0, history of; L, linear; M, male; *n*, number of patients; PHG, premature hair graying; RMF, risk multiplication factor; w/, with; w/o, without; FFA, frontal fibrosing alopecia.

smokers, those who smoke >10 cigarettes per day and for more than a year, compared to nonsmokers ($p < 0.001$) [16]. Of the 500 smokers, 85% showed evidence of AGA, of which 47% had grade III AGA and 24% had grade IV AGA ($p < 0.01$) [16]. To a lesser extent, just 40% of 500 nonsmokers presented with AGA, with 20% of this group having grade II AGA and 10% having either grade III or IV AGA ($p < 0.01$) [16].

Despite the high prevalence of extensive alopecia (31.2%) among 324 Finnish women (average age 63 years), a cross-sectional cohort survey reported the prevalence of smoking was the same between those with extensive (Ludwig's scale II or greater) and minimal/normal alopecia in this group ($p = 0.92$) [17]. On the contrary, a large population-based case-control study on Australian men aged 40-69 years reported that subjects with lengthier smoking histories, irrespectively of being current or previous smokers, were less likely to develop AGA compared to nonsmokers ($n = 1{,}390$ M) [18]. This study suggests the previously proposed association between smoking and alopecia could instead be explained by an increased risk of smoking because of having AGA. Additionally, a cross-sectional case-control study including 954 subjects (419 M, 535 F) reported no significant difference in smoking habits between patients with AGA or controls, in both genders ($p > 0.05$) [19]. However, interpretation of the results from both studies was impacted by a lack of detail provided in the smoking history and age of AGA diagnosis [18, 19]. Questionnaire results from a hospital-based, controlled study reported no statistical difference in the frequency of subjects with or without AGA who were current smokers of <10 cigarettes per day ($n = 214$ M) ($p = 0.13$) [20]. The study results are limited by the younger age of subjects with AGA (28.5 years) compared to controls (38.9 years), which may limit the generalizability of the results [20]. In a case-controlled study including 256 subjects with AGA and 256 age-matched controls, no significant difference in cigarette smoking status was reported between subjects with or without AGA ($p = 0.550$). Additionally, the frequency of hookah (water pipe) smoking was similar between AGA (14%) and healthy control (14.8%) subjects ($p = 0.801$) [21]. Limitations of this study include a lack of detail provided in the smoking history and subjects with minimal cigarette or hookah smoking exposure, including any subject who had smoked in the past 30 days [21]. A case-controlled prospective study including 354 men from ages 35-65 years failed to identify a statistically significant correlation between cigarette smoking and AGA in subjects with either a Hamilton-Norwood scale scores I-III or IV-VII [22]. However, this inconsistency with study's who report a significant correlation between smoking and AGA can be explained by differences in sampling methods, including balancing the ratios of smokers and nonsmokers in both AGA and control groups [22]. Similarly, a case-control study including 77 early onset AGA subjects and 77 healthy controls failed to report a significant increase in smoking history (>5 cigarettes per day) in men ($p = 0.48$) or women ($p = 0.09$) [23]. These results are limited by a small sample size [23]. A cross-sectional retrospective study found that tobacco exposure had a protective role in the development of clinically diagnosed FFA in 1 Asian and 71 Caucasian female subjects. Compared to nonsmokers with severe FFA (frontal regression ≥3 cm), this study reported a lower incidence of severe FFA in subjects with a smoking history of >20 pack-years, even after smoking cessation ($p = 0.04$). Notably, the study was limited by a small sample size and did not include an equivalent control group [24]. Additionally, 3 retrospective reviews, mainly including women (12 M, 551 F), failed to reveal a significant frequency of smoking in subjects with FFA [25–27]. MacDonald et al. [25] reported a high prevalence of nonsmokers (71%) in a review of 60 cases of FFA, further suggesting the possible protective role smoking may play in developing FFA ($p = 0.01$). Additionally, Vañó-Galván et al. [26] reported a greater prevalence of nonsmokers (87%) with FFA, in a review of 355 subjects from 12 Spanish centers. Similar results were published in a review of 148 women with FFA, which reported 92 (63%) subjects having never smoked and no active smokers [27]. However, limitations seen in all 3 studies include their retrospective design and incomplete or short length of follow-up [25–27].

Smoking and Premature Hair Graying

A positive correlation between smoking and PHG, defined as presence of gray hair <30 years, was described in 7 studies [3, 7, 28–32]. In an observational study, Mosley and Gibbs [3] reported a higher incidence of hair graying in smokers over 30-year old than in nonsmokers regardless of age-group or gender ($n = 606$). Subjects, in an observational study, who were exposed to smoking tobacco, chewing tobacco, or a combination of the 2, had a higher incidence of premature graying compared to controls ($n = 120$) [28]. Furthermore, a questionnaire in Korean patients ages 12-91 years reported a 14.9% increased risk of developing premature gray hair for every year a subject smokes ($n = 522$ M, 480 F, $p < 0.001$), and an overall 1.99 times higher risk of graying prematurely compared to nonsmokers [29]. Premature graying in subjects with a

reported history of smoking was also observed in a cross-sectional study conducted by Zayed et al. [30] (n = 207, p = 0.031), and a case-control study of chronic smokers compared to subjects with no smoking history (n = 236, p = 0.031) [31]. In 2 similar studies by Sharma and Dogra [7] and Shin et al. [32], a significant number of patients with PHG also confirmed a history of smoking, with a correlation reported with a minimum smoking history of 5 pack-years (n = 240).

On the contrary, 2 large cross-sectional studies evaluating the socio-clinical risk factors associated with PHG found no association seen between smoking history and PHG [6, 33]. Both studies included subjects younger than 21-year old with a limited smoking history including rate and duration of smoking [6, 33]. Acer et al. [33] classified subjects as either current smokers or nonsmokers, while Belli et al. [6] required a smoking history of more than 1 pack-year to be considered a smoker. Questionnaire results from a third study reported no correlation between smoking history and PHG due to a similar incidence of smoking, between ages 20- and 35-year old (n = 50) [34]. Similarly, a more recent case-controlled survey study found a negative association between smoking history (defined as never, former, and current smokers) and PHG (0, 1–10, 11–100, and >100 self-reported gray hairs beginning age ≤30) (n = 467) [35]. This discrepancy with previous studies that report a significant association between smoking and PHG can be explained by the use of chronological smoking history (never, former, and current) rather than quantity of smoking [35]. Also, participants' responses and results of survey studies may be subject to recall bias [34, 35]. Unlike the hair loss controversy, there are no studies that support a protective role for smoking or nicotine and hair graying.

Discussion

While genetic factors play an important role in alopecia and PHG, environmental factors, including smoking and nicotine exposure, should be taken into consideration. The current scientific evidence drawn foremost from cross-sectional studies shows a positive correlation between the length of smoking history and alopecia severity in patients with AGA [10, 11, 16]. Severe presentations of AGA were observed in subjects who smoked a larger quantity of cigarettes per day [8, 10–13]. Several studies reported no association between smoking and alopecia [17–27]. Among these, a cross-sectional retrospective study reported a higher prevalence of scarring alopecia, severe FFA, in subjects with no previous tobacco exposure [24]. Several hormonal deregulations, including decreased prolactin, have been linked to chronic tobacco exposure and may explain the higher prevalence of FFA among nonsmokers.

A possible association between female androgenetic alopecia (FAA) and acute telogen effluvium has been observed in previous studies [36, 37]. Furthermore, a retrospective analysis has identified triggering causes, such as iron deficiency and thyroid dysfunction, which hold a greater risk of developing concurrent FAA and acute telogen effluvium [38]. Also, a report has provided support that some cases of telogen effluvium may rapidly progress to FAA [39].

An earlier onset and higher prevalence of hair graying were also observed in smoker groups compared to controls [7, 28, 30, 31]. A positive smoking history was also shown to increase the risk of hair graying each year a subject continued to smoke [29]. This correlation was not found to be true for smokers under the age of 21-year old, presumably because of shorter duration of smoking and time frame of study [6, 33, 34].

While the mechanism responsible for hair loss in subjects exposed to nicotine or tobacco smoke is unknown, it is thought to be similar to the mechanism by which smoking increases skin aging. Nicotine is known to cause constriction of dermal hair papilla and local ischemia, accumulation of DNA damage, dysregulation of protease/antiprotease systems involved in the hair growth cycle, and upregulation of local pro-inflammatory cytokines implicated in follicular inflammation and fibrosis [40, 41]. A hypothesis exists that exogenous nicotine from smoking can cause overstimulation of the cellular nicotinic acetylcholine receptors leading to desensitization of the receptor. This in turn contributes to hair follicle destruction by activation of programmed cell death pathways present in keratinocytes [42–44].

Studies in C57BL/6 mice, a strain prone to hair loss, may hold the explanation for increased hair loss in subjects who smoke. When the mice were exposed to whole-body, environmental tobacco smoke (ETS) for 3 months, they showed evidence of hair loss and PHG, with circular alopecic patches and graying reported on their backs [45]. The patches grew larger with longer ETS exposure, and at 4 months, all ETS-exposed mice had developed irregular and scattered regions of gray hair. Neither hair loss nor PHG was observed in the control group. On histology, alopecic areas showed fewer and shorter hair follicles and diminished hair bulbs with decreased and irregular pigmentation, with markers of cellular apoptosis. These

findings were thought to be secondary to metabolic changes induced by inhaled smoke-associated genotoxins leading to a dystrophic anagen pattern [45, 46]

Long-term, high-dose nicotine treatment on A/J mouse models commonly used to investigate the carcinogenic effects of nitrosamines, a downstream metabolite produced by the nitrosation of nicotine, are related to hair loss [47–49]. Mice treated with subcutaneous injection of nicotine daily, after 8-9 months of treatment, started to lose hair in discrete patches. Another study in rats infused with nicotine showed evidence of hair follicle fibrosis, chronic inflammatory infiltrate, and extravasation of erythrocytes [50].

The image of health is negatively impacted by hair loss and graying [51, 52]. More recently, "smokeless tobacco" products have been heavily marketed, but these too contain high dosages of nicotine, and this new and growing trend may also pose a substantial risk to hair health.

This review was limited by a lack of randomized control trials or case-series in the literature, reports of association rather than causation, lack of scalp biopsies to confirm a link between smoke-induced oxidative stress and AGA, and recall bias due to the use of questionnaires. Also, the use of small sample sizes and hospital- or outpatient-based rather than community-based studies make it difficult to generalize the data to the general population. Results supporting no association between smoking and hair loss could not be accurately interpreted due to small sample size, incomplete smoking histories, and inequivalent control groups [17, 18, 24]. Reports that failed to demonstrate and association between smoking and PHG were limited by young subjects under 21-year old [6, 33, 34].

Conclusion

In addition to a wide variety of systemic and cutaneous health concerns, an association exists between smoking and alopecia as well as smoking and PHG. While there is more evidence in AGA, the reports in FFA are controversial. Dermatologist and physicians alike have an additional role in promoting smoking cessation by offering an opinion on the detrimental effects of smoking on hair [41]. Further studies, notably randomized controlled trials, should be conducted to assess for causality and to further investigate the mechanism of action responsible for this phenomenon.

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Arash Babadjouni was responsible for reviewing the literature, analyzing the data collected, and writing the final review. Dr. Natasha Mesinkovska, Dr. Delila Pouldar Foulad, Bobak Hedayati, and Dr. Evyatar Evron were involved in formulating the initial study design and editing the final review.

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