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Women and Smoking: The Effect of Gender on the Epidemiology, Health Effects, and Cessation of Smoking

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Abstract

Smoking is still the leading cause of premature morbidity and mortality. This paper examines new research on gender differences and the epidemiology of smoking, smoking-related morbidity and mortality, and factors that affect smoking cessation. The rate of decline in the prevalence of smoking has been slowing, especially among adolescent girls. New research suggests that, compared with men, women may be more susceptible to smoking-related morbidity and mortality. Gender-related barriers to smoking cessation include weight gain, sex hormones, and mood. Furthermore, the sensory aspects of smoking may have more of an effect on smoking treatment for women than for men. We discuss new studies that examine smoking-cessation interventions that may be particularly beneficial for women, including exercise (as an adjunct intervention), very low nicotine content cigarettes, and a variety of pharmacotherapy. Further research is needed to identify and target the gender-specific needs of smokers.

Keywords

Smoking; Nicotine; Health Effects; Cessation; Sex Hormones; Women; Gender

Introduction

Smoking is a leading cause of preventable morbidity and mortality in the United States [1-3]. Fortunately, smoking cessation at any age can reduce excess risk of mortality, with quitting smoking before age 40 reducing excess risk of mortality by an estimated 90 % [4,

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Compliance with Ethics Guidelines

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5]. Although the prevalence of smoking is somewhat greater among men than women, women may have a higher risk of smoking-related morbidity and mortality, and face different barriers to smoking cessation that warrant intervention. The purpose of this review is to provide an update (since 2010) on research on women and smoking and, where appropriate, gender differences related to smoking behavior. We will review the epidemiology and health effects of smoking, and factors that may affect cessation. Although the literature on smoking and pregnancy is rapidly expanding, that topic will not be included because several recent reviews have been published [6, 7].

Epidemiology of Smoking

In 2011, approximately 19 % of Americans reported current cigarette smoking [8]. More men than women smoke from when they are adolescents in middle school (4.0 % women vs. 4.5 % men) to middle age (45–64 year olds; 18.5 % women vs. 24.5 % men) [8, 9]. Conversely, among those aged 65 and older the prevalence of smoking is slightly higher for women (9.3 % women vs. 8.9 % men) [8].

Although the prevalence of smoking among adolescents and adults has declined over the past ten years, the rate of decline is slowing [8, 9]. These trends vary by gender and age, such that among adolescents the prevalence of smoking has declined less in females, whereas among adults a greater decline has been observed in women. For instance, from 2009 to 2010, the prevalence of smoking declined by 17.5 % among middle-school females versus a 24.4 % decline among middle-school males [9]. In adults from 2010 to 2011, smoking prevalence among men essentially remained stagnant, whereas a 5 % reduction was observed among women [8]. These data indicate that the gender gap in smoking prevalence may be narrowing, and that additional efforts to reduce smoking prevalence among teenage girls and older women are warranted.

Health Effects of Smoking

The health effects of smoking are extensive and well documented [1-3]. Although the prevalence of smoking is declining, the relative risk of death for current and former smokers continues to rise [10•]. Each year in the United States 200,000 men and 180,000 women die as a result of smoking [11]. In a study of over 1.2 million women in the United Kingdom, Pirie et al. [4•] found that approximately 66 % of deaths among smokers 50–70 years old were directly attributable to smoking, resulting, on average, in a loss of 10 years of life [4•]. Although obesity places smokers at an even greater risk of premature mortality, heavy smokers (>20 cigarettes a day) have the greatest risk of middle-aged death, regardless of body mass index [12].

Smoking and Cancer

The effect of smoking on the risk of specific cancers may be stronger for women than men. Compared with their non-smoker peers, women smokers are at significantly greater risk of advanced colorectal neoplasia after as little as 10 pack-years of smoking, whereas for men it takes 30 or more pack-years for the risk to reach statistical significance [13]. Previous

studies revealed a gender difference in the effect of smoking on bladder cancer risk; however, one recent study following approximately 500,000 participants reported that smokers, regardless of gender, were at a 50 % higher risk for developing bladder cancer compared with never smokers [14]. Women have additional risk for gender-specific cancers. In a sample of nearly 80,000 postmenopausal women, Luo et al. [15•] observed a 9 % and 16 % increased risk of breast cancer among former smokers and current smokers, respectively, compared with never smokers. Although current smoking was not significantly associated with acquiring human papillomavirus (HPV), it was associated with an increased risk of high-grade cervical intraepithelial neoplasia (CIN), suggesting that smoking may increase the risk of progression from HPV to CIN [16].

Smoking and Cardiovascular Health

Although smoking increases the risk of coronary heart disease for both genders, several studies have noted gender differences in the association between smoking and cardiovascular health: women who smoke have a 25 % greater increased risk of coronary heart disease than their male-smoker counterparts [17]. The factors contributing to the gender difference in the risk of negative cardiovascular health outcomes in smokers remain unknown, but sex hormones may have a function. Cupisti et al. [18] observed that smoking was associated with increased levels of fasting insulin, free testosterone, and free androgen index for a sample of 346 women with polycystic ovary syndrome. These increased levels resulted in aggravated insulin resistance and, potentially, increased risk of cardiovascular disease [18]. A second contributing factor may be the differential gender effect of smoking on arginine vasopressin (AVP), which has a direct effect on the cardiovascular system. In one small study, it was observed that among non-smokers, men had higher AVP than women, whereas among smokers, women had higher AVP than men [19]. A third contributing factor may be the effect of smoking on arterial hypertension and endothelial dysfunction: compared with their non-smoking peers, hypertensive female smokers had lower fasting glucose levels, higher diastolic and systolic blood pressure, higher heart rate, and higher intima-media complex in the right carotid artery [20]. Although smoking cessation can significantly reduce this risk, post-cessation weight gains limit the benefits of cessation. Smokers who gained as little as five kilograms (e.g. 11 pounds) during smoking cessation did not have a significant reduction in risk of coronary heart disease compared with current smokers [21••]. Therefore, exercise during smoking cessation may be especially useful for cardiovascular health because it would not only reduce post-cessation weight gain, but has also been shown to improve inflammation (e.g. white blood cells, prothrombotic factor), cholesterol profiles, and cardiovascular fitness (e.g. maximum oxygen consumption) during cessation [22•].

Smoking and sex Hormones

The effect of smoking on sex hormones has been a topic of increasing interest, given smoking's mediating effect on sex hormones and the subsequent risk of chronic disease, including both cancer and cardiovascular health problems [23, 24]. The effect of smoking on sex hormones seems to vary by menopausal status. Six new studies examining the relationship between smoking and sex hormone levels have been conducted on premenopausal women. Although one study observed no significant differences in sex

hormones by smoking status [25], the remaining five studies noted significant differences. Smokers had higher progesterone [26•], higher testosterone [18, 26•], and lower absolute levels and less menstrual phase variation of estrogen [26•, 27]. Furthermore, among women and infertile couples undergoing in-vitro fertilization, female smokers had significantly lower antimullerian hormone levels and antral follicle counts, and worse overall in-vitro fertilization outcomes [28, 29].

Two studies have examined the association of smoking and sex hormones for perimenopausal women. Although both studies observed lower antimullerian hormone levels in smokers, the differences reached statistical significance in only one of the studies [30, 31]. Waylen et al. [31] also observed significantly lower inhibin-B values in never smokers compared with current smokers. Consequently, like Freour et al., they concluded that the risk of premature ovarian failure (e.g. early onset menopause) may be related to smoking [28, 29].

Two studies of sex hormones and smoking have also been conducted on postmenopausal women. One study observed significantly higher testosterone, androstenedione, estrone, and 17-hydroxy-progesterone in postmenopausal smokers compared with never smokers [32]. The authors also identified an interaction between smoking status and weight: sex-hormone-binding globulin was significantly higher in lean female smokers only, whereas estradiol was significantly higher in overweight female smokers only. A second study of postmenopausal women on estrogen therapy examined the difference in estrogen kinetics by smoking status. This study observed significantly lower estrone and estradiol concentrations in smokers compared with nonsmokers after administration of exogenous estrogen [33].

Overall, these data indicate that, compared with their non-smoking peers, female smokers may have higher progesterone and lower antimullerian hormone levels. Levels of estradiol seemed to vary on the basis of smoking status, menopausal status, and weight, such that significantly lower levels were observed in premenopausal smokers, whereas overweight postmenopausal smokers had significantly higher levels compared with non-smokers. Fortunately, sex hormones may return to levels observed for never smokers soon after cessation: studies did not observe differences between former and never smokers as little as one year post smoking cessation [27, 32].

Smoking and Other Adverse Health Outcomes

Recent research has also indicated that current smoking is associated with a variety of other adverse health conditions. The effect of smoking on asthma has recently been shown to be moderated by weight and gender. Specifically, women who smoke have higher rates of asthma regardless of weight, whereas for men higher rates of asthma are observed only in normal-weight or under-weight smokers [34].

Women smokers may also have higher rates of incontinence compared with non-smokers; urgency and frequency, but not nocturia or stress incontinence, were observed to be approximately three times more common in current smokers than never smokers [35]. The mechanisms behind this observation remain unknown, but we investigated two possible

causes—increased respiratory symptoms and tobacco exposure—within a small cross-sectional sample of smokers. We observed that female smokers, overall, had significantly greater symptoms of incontinence compared with male smokers. Furthermore, regardless of gender, those with self-reported symptoms of incontinence had significantly greater levels of urinary cotinine, a greater number of pack-years of smoking, and a worse self-reported cough [36]. Additional research is needed investigate the relationship between smoking and incontinence prospectively, and to examine whether smoking cessation improves incontinence symptoms.

Factors That Affect Smoking Cessation

In 2011, more than half of smokers had made a quit attempt in the past year but less than 6 % successfully achieved abstinence [8]. Smoking cessation rates vary by gender and by type of intervention. In general, men may be more likely to respond to nicotine replacement therapy (e.g. transdermal nicotine patch or nicotine gum) whereas women may benefit more from non-nicotine medications or behavioral interventions [37]. Despite these differences, there are currently no gender-specific smoking cessation clinical guidelines available [37, 38]. As detailed below, factors that affect smoking cessation and vary by gender include fear of weight gain, sex hormones, and mood and personality, among others.

Weight Gain

Women are particularly sensitive to weight gain at all stages of smoking [37]. Compared with their non-obese peers, obese young women have a two times higher probability of developing a severe nicotine addiction [39•]. Among women who are attempting to quit smoking, those who are dieting may experience greater withdrawal symptoms than those who are not dieting [40]. Women gain more weight than men during attempted smoking cessation, and those of greater age (e.g. 56–64 years old) gain more weight than younger individuals [41]. Significant weight gain occurs for women during attempted cessation regardless of outcomes, with those who are successful typically gaining more weight [22•, 42]. Weight gain during cessation is related to significant increases in both fat and muscle mass [42]. The average weight gain six months post-cessation was ten pounds for a sample of female prisoners, who arguably have a stable energy intake and output [43]. These data are particularly concerning given that women smokers who gained more than ten pounds during cessation obtained markedly reduced cardiovascular benefits from quitting smoking [21••]. Therefore, smoking cessation interventions that also limit weight gain are urgently needed, particularly for older women.

Interventions to address cessation-related weight gain may focus on energy intake, energy expenditure, or use of pharmacotherapy. First, regarding energy intake, Kimokoti et al. concluded that those with poor diet quality experienced greater weight gain during smoking cessation than those with a more healthy diet [44]. A higher quality diet may also be associated with improved smoking cessation outcomes: those who self-reported higher fruit and vegetable consumption before attempted cessation were more than three times more likely to report smoking abstinence [45].

Second, exercise could address post-cessation weight gain via increasing energy expenditure. In a small pilot study, participants randomized to a yoga treatment, as compared with a wellness time-control treatment, had a more than three times higher probability of being abstinent three months post quit date; however, there were no significant differences at six months [46•]. Two small studies examined the effect of exercise on smoking cessation. Although neither of these trials observed significant differences in smoking cessation, perhaps because of small sample sizes, the study by Williams et al. observed higher cessation in the exercise group versus the time-control wellness condition group (48.3 % versus 23.3 %, respectively) [47] whereas the study by Napolitano et al. observed lower cessation in the exercise group versus the group undergoing an intervention that focused on improving body image (10.0 % versus 18.2 %, respectively) [48]. The difference in these observations may be related to the study sample or the “dose” of exercise: Napolitano et al. focused on college students exclusively and provided one 45-minute exercise class per week, whereas Williams et al. enrolled female smokers in general and instructed them to complete 50 min brisk walking three times per week. Unfortunately, exercise interventions for smoking cessation have been subject to problems of adherence. In these studies, those assigned to the exercise group attended 55.6–86.4 % of intervention sessions [46•, 47, 48]. Williams et al. observed a significant dose–response relationship between the number of intervention sessions attended and probability of cessation for the exercise group but not the control group, suggesting the lack of a significant difference in cessation by treatment group may be attributable to compliance with treatment rather than the treatment itself [47]. To encourage exercise intervention adherence, the authors of these studies recommend including a run-in period, offering flexible schedules, increasing monetary incentives, and/or offering group challenges.

A third potential method of limiting weight gain during smoking cessation is pharmacotherapy. Among participants randomized to naltrexone (versus placebo) for smoking cessation, men were more likely to achieve smoking cessation than women, whereas women gained significantly less weight during smoking cessation than men [49•]. Although the nicotine patch, compared with placebo patch, may increase calorie intake during cessation, those who were randomized to extended use of nicotine patch (24 weeks) gained significantly less weight than those who used the nicotine patch for eight weeks [50, 51]. Finally, our recently published pilot study of topiramate for smoking cessation found that topiramate may be useful for cessation and reducing weight gain [52].

Overall, for both men and women, obesity exacerbates smoking-related morbidity and mortality. Given rising rates of obesity, and the strong probability of weight gain during smoking cessation, there is an urgent need to identify successful smoking cessation interventions that limit weight gain. Weight-concerned and overweight or obese smokers are likely to be receptive to weight management programs as an adjunct to smoking cessation interventions: offering a weight management program has been shown to increase attendance and abstinence [53]. Additional research is needed to examine the use of nutritional counseling, exercise, and/or pharmacotherapy to limit weight gain during smoking cessation.

Sex Hormones

Sex hormones (primarily estradiol and progesterone) have been implicated as a possible mechanism for gender differences in smoking behavior and cessation. Specifically, progesterone may protect against nicotine addiction, whereas estradiol may enhance vulnerability [54]. The luteal phase (high progesterone to estradiol (PE) ratio), compared with the follicular phase (low PE ratio), may be associated with increased levels of withdrawal symptoms, but there are substantial difficulties in interpreting the literature because of lack of consistency in method, constant fluctuations of endogenous hormonal levels, and problems with selection bias [55]. That said, we recently found that higher levels of anger and craving were associated with greater risk of smoking relapse among women randomized to quit smoking in the follicular phase, but not in the luteal phase [56]. Furthermore, in one study exogenous progesterone treatment (increasing the PE ratio) was associated with a reduced urge to smoke for both male and female smokers during short-term abstinence [57].

A series of studies has been published examining the effect of sex hormones on response to nicotine and smoking. First: after overnight abstinence, nicotine was administered intravenously to men and women, resulting in a greater physiological response (e.g. heart rate) to nicotine in males, whereas the subjective ratings (e.g. craving) were greater for females [58]. Furthermore, for females the follicular phase was associated with greater subjective reduction in craving after nicotine administration than the luteal phase [58]. These data are similar to our recent observations, of women without depressive symptoms, revealing that the follicular phase, as compared with the luteal phase, was associated with a more pronounced physiological response to nicotine nasal spray during short-term smoking abstinence (e.g. greater diastolic blood pressure and heart rate, and higher maximum concentrations of nicotine) [59]. Similarly, Schiller et al. [60•] observed that lower PE ratios were associated with increased smoking. They further concluded that, compared with other hormonal measures, the PE ratio and change in estradiol and progesterone over time were the best predictors of smoking behavior [60•]. This finding suggests that both hormones, and their changes over time, may affect smoking behavior. Overall, these data suggest that women may be more responsive to nicotine during the follicular phase (low PE ratio). Prior studies have shown that if women are assigned nicotine replacement therapy, relapse is less likely to occur during the follicular than the luteal phase [61, 62]. On the other hand, women without nicotine replacement experienced greater relapse during the follicular than the luteal phase [63, 64].

We have recently begun investigating the effect of allopregnanolone, a stress-reducing neuroactive steroid metabolized from progesterone, on smoking behavior. Allopregnanolone had numerous associations with smoking-related symptoms and nicotine response during short-term smoking abstinence. Although several of these associations were favorable (i.e. higher allopregnanolone was associated with lower perceived stress on the day before quitting, and higher levels of pleasantness on the fourth day of smoking abstinence), some were not (i.e. higher allopregnanolone was associated with greater premenstrual symptoms on the day before quitting, and increased subjective report of physical symptoms on the fourth day of smoking abstinence) [65].

Overall, these data concur with previous literature indicating that menstrual phase, and related sex hormones, affect smoking behavior [55]. Additional research is needed to investigate how exogenous hormones (e.g. progesterone), other sex hormones (e.g. testosterone), and/or other variables that vary by menstrual phase (e.g. allopregnanolone) may affect smoking behavior and risk of smoking relapse for men and women.

Negative Mood and Personality

The extent to which negative affect predicts smoking relapse varies by gender, and is conflicting. For women, depressive mood, anxiety, anger, and perceived stress were all predictive of time to relapse, whereas for men, craving was a unique predictor of relapse [66]. Although Cofta-Woerpel et al. [67] did not include men, their data reveal that women who had an early smoking lapse reported significantly higher negative mood on quit date when faced with a temptation to smoke, compared with those who remained abstinent. Similarly, Perkins et al. [68] found that, compared with men, women are more likely to increase their puff duration in response to a negative mood. Stress and/or negative affect cues, but not smoking cues, resulted in significantly greater increases in craving, stress and arousal for women compared with men [69]. Conversely, continued smoking and inconsistent former smoking were significant predictors of “negative attitudes towards self” for men, but not women [70]. Also, compared with women, men increased their smoking more during negative mood induction in a lab setting, and in response to negative affect in a natural environment [68, 71].

Men may be more susceptible to anger-related problems than women. Recent research indicates that men with childhood conduct problems have a slightly higher probability of future cigarette smoking than women [72]. For both genders, those who experienced problematic anger had a higher probability of smoking daily, being nicotine dependent, being a heavy smoker, and having a lifetime history of unsuccessful quit attempts [73]. The effect of anger and anger reduction on smoking cessation is unknown.

Smoking cessation success predictions provided by personality patterns differ for men and women smokers. Men with compulsive personality were more likely to quit smoking, whereas men with depressive, antisocial, sadistic, negativistic, masochistic, schizotypal, borderline, and/or impulsivity personalities were less likely to quit smoking. Among women, those with schizoid and/or sociability personality were less likely to quit smoking [74, 75]. For women in late mid-life, nicotine dependence was predicted by maladaptive personality attributes (for example depression or anxiety), marital or partner conflict, and financial difficulties [76].

Possible new interventions to address the effect of mood on cessation include exercise and pharmacotherapy. During cessation, a yoga intervention (versus a time-control treatment) resulted in significant improvements in mood, perceived health, and overall well-being [46]. Although yoga and other forms of exercise have not been evaluated as a smoking cessation intervention for those with depression or other mental illness, available research suggests this may be well received: qualitative interviews with women indicated that most were receptive to using exercise with smoking cessation [77]. Regarding pharmacotherapy, Cinciripini et al. [78] compared three randomized treatments for smoking cessation

(varenicline, bupropion SR, or placebo) and observed that, although both active treatments were associated with increased cessation rates, only those assigned to varenicline had suppression of depression and reduced smoking reward. Overall, mental health and personality attributes affect smoking and smoking cessation, and these relationships vary by gender. Although research on yoga and/or exercise and on varenicline seems promising, additional research is needed to identify the gender-specific needs of smokers.

Other Aspects

Finally, studies have been conducted to address other factors that may minimize the effort of smoking cessation for women. First, we recently compared the combination of very low nicotine content (VLNC) cigarettes paired with the nicotine patch versus either treatment alone (VLNC only or patch only). Women randomized to VLNC alone were more likely to quit smoking than women randomized to patch alone, whereas men randomized to patch alone were more likely to quit smoking than men randomized to VLNC alone [79]. These data support the idea that women tend to smoke more for the non-nicotine factors (e.g. smoking cues, sensation of smoke), whereas men smoke to maintain nicotine levels [37]. Next, Cropsey et al. [80] found that, within a sample of female prisoners, reducing the number of cigarettes smoked per day before a quit attempt may help with preparation for quitting or serve as a marker of motivation to quit smoking, but does not assist with cessation: reduction was unrelated to long-term quit rates. Third, Wetter et al. [81] examined the use of a relapse prevention program for women, delivered via palm pilot, and observed no difference in relapse between the intervention and control groups. Finally, in a study by Weiss et al. [82], young women exposed to aged images of themselves reported increased motivation to quit smoking. More research is needed to identify novel interventions that address gender-specific smoking cessation needs.

Conclusions

The literature on the effect of smoking-related morbidity and mortality continues to accumulate. For unknown reasons, some of these associations vary by gender such that women are at greater risk, but some do not. Recently the rate of decline in the prevalence of smoking has slowed, indicating the urgent need to identify new and innovative smoking interventions. Smoking has a bidirectional relationship with several factors (e.g. mood and sex hormones); these relationships vary by gender and, ultimately, may limit the ability of an individual to achieve smoking cessation. To address the gender-related needs of smokers, future interventions could use self-care (e.g. exercise or nutrition) and financial assistance (e.g. free child care to attend support groups) as new adjuncts to smoking cessation interventions, and investigate alternative tobacco products and/or novel pharmacotherapy (e.g. very low nicotine content cigarettes or topiramate). Although this review did not examine the effects of ecigarettes, menthol cigarettes, and other tobacco products (e.g. hookah and bidis), additional research is needed to examine the effect these products have on adverse health and smoking cessation outcomes.

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