

## Short Communication

# Individual Differences in Nicotine Intake per Cigarette<sup>1</sup>

Freda Patterson, Neal Benowitz, Peter Shields,  
Vyga Kaufmann, Christopher Jepson, Paul Wileyto,  
Susan Kucharski, and Caryn Lerman<sup>2</sup>

Abramson Cancer Center and Department of Psychiatry, University of Pennsylvania Health Sciences and the Annenberg Public Policy Center, Philadelphia, Pennsylvania 19104 [F. P., V. K., C. J., P. W., S. K., C. L.]; Division of Clinical Pharmacology and Experimental Therapeutics, Department of Medicine, University of California San Francisco, San Francisco, California [N. B.]; and Lombardi Cancer Center, Georgetown University Medical Center, Washington, D.C. [P. S.]

### Abstract

The increase in levels of blood nicotine that occurs from smoking a single cigarette, sometimes referred to as a “nicotine boost,” is an individualized measure of how much nicotine has been extracted from smoking a cigarette. This study investigated the demographic, smoking status, and psychological predictors of nicotine boost in a sample of 190 treatment-seeking smokers. Boost was assessed by comparing plasma nicotine levels before and after participants smoked one of their own brand cigarettes *ad libitum*. Positive affect (mood) was a significant positive predictor of nicotine boost, controlling for baseline cotinine levels and cigarette brand (Federal Trade Commission) nicotine delivery. However the proportion of variability accounted for in the model was relatively small (5%). Future research on individual differences in nicotine boost is warranted to clarify the role of psychological, physiological, and cigarette-related determinants.

### Introduction

The increase in blood plasma nicotine level after smoking a cigarette (referred to as “nicotine boost”) is a measure of the absorbed dose of nicotine, which in turn reflects exposure to other smoke constituents (1). The dose of nicotine taken by a smoker is determined by a variety of factors. These include the way in which the cigarette is smoked (topography), characteristics of the cigarette, and, possibly, individual factors such as level of dependence, type of reward sought from smoking, gender, race, and pulmonary-related symptoms (2–6). Although there are individual differences in nicotine metabolism rate, such differences have little impact on nicotine boost given the brief time interval between

smoking and measurement of nicotine levels. In this period, minimal metabolism of nicotine occurs (the metabolic half-life of nicotine is about 2 h; Ref. 7).

Smoking topography encompasses factors such as the depth and speed of inhalation and the number of puffs taken (2, 4). Smokers who inhale deeply, puff frequently, and take long puffs typically maximize their intake of smoke constituents (3). Females are less likely to smoke an entire cigarette and have a smaller depth of inhalation than males (8). African Americans smoke more of their cigarettes, have shorter exhalation periods, exhibit higher carbon monoxide boost, and have higher nicotine intake/cigarette than Caucasians (9–11).

Cigarette characteristics, such as the tar and nicotine yield and additives (*e.g.*, menthol *versus* nonmenthol), have also been shown to impact smoking topography and therefore impact nicotine boost. For example, mentholated cigarettes are thought to anesthetize the airways and enable the smoker to inhale deeper and longer, thus facilitating higher levels of boost and exposure (11, 12). Similarly, smoking topography changes have been found among smokers who switch from a higher to a lower tar and nicotine yield cigarette, whereby the smoker may compensate by working harder to extract more tar and nicotine from the lower yield cigarette (2). Females are more likely than males to smoke lower nicotine cigarettes and are more likely to switch from higher to lower nicotine cigarettes (13, 14), African Americans are more likely to smoke menthol cigarettes as compared with Caucasians (5, 11, 15).

The basis of individual differences in nicotine boost has not been well studied. Insofar as nicotine boost is an approximate measure of nicotine intake/cigarette, the amount of nicotine extracted from each cigarette could be postulated to relate to the reinforcement sought by the smoker (16). For example, smokers seeking the pharmacological effects of nicotine to modulate affective states may attempt to achieve a higher nicotine boost than a smoker who is seeking to maintain steady-state nicotine levels to avoid withdrawal symptoms. This hypothesis is supported, in part, by evidence for effects of expectations of positive and negative reinforcement from smoking on subsequent smoking behavior (17).

In this study, we examined the demographic, smoking history, and psychological predictors of boost in smokers seeking treatment. Nicotine boost was assessed in a more naturalistic setting where participants smoked their own cigarettes. We hypothesized that (a) negative affect would be associated with higher levels of nicotine boost (presumably to attenuate negative mood symptoms) and (b) African Americans and males would have higher nicotine boost levels than Caucasians and women.

### Materials and Methods

#### Subjects

Participants were 95 male and 95 female treatment-seeking smokers ages 18–75 years who reported smoking at least 10

Received 8/23/02; revised 2/4/03; accepted 2/15/03.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

<sup>1</sup> Supported by Transdisciplinary Tobacco Use Research Center Grant P50 CA84718 from the National Cancer Institute and National Institute on Drug Abuse (to C. L.) and by USPHS Grants DD02277 and DA01696 from the National Institute on Drug Abuse (to N. B.).

<sup>2</sup> To whom requests for reprints should be addressed, at 3535 Market Street, Suite 4100, University of Pennsylvania, Philadelphia, PA 19104. Phone: (215) 746-7141; Fax: (215) 746-7140; E-mail: clerman@mail.med.upenn.edu.

cpd.<sup>3</sup> They were recruited from April 2000 to April 2001 through newspaper advertisements in the Washington, D.C. area. Exclusion criteria were as follows: planning a pregnancy; pregnant; lactating; current drug addiction treatment; skin allergies or chronic dermatitis; or a major psychiatric disorder. All participants provided written informed consent.

Of the 190 participants, 63% were Caucasian, 25% were African American, and 12% were Hispanic, Asian, or other mixed ethnic ancestry. Participants ranged in age from 20–78 years (median age, 45.8 years; SD, 11.01 years), and the majority (91.1%) had at least some college education. With the possible exception of race, these sample characteristics are consistent with those reported in other smoking cessation trials (e.g., Refs. 18 and 19).

### Design and Procedures

Data for these analyses were collected as part of the baseline assessment in an ongoing clinical trial of nicotine replacement therapy. To standardize levels of smoking deprivation, all participants were instructed to smoke a cigarette immediately before entering the research center. All participants had levels of 7 ppm or greater for exhaled carbon monoxide. To assess nicotine boost, participants provided a blood sample immediately before and after (within 3 min) smoking one of their own-brand cigarettes. To enhance the naturalistic smoking environment, participants smoked the cigarette in a comfortable ventilated living room area in a building separate from the hospital setting. Time lapsed between the previsit cigarette and the boost cigarette was approximately 40 min (with an approximate range of 35–50 min). Pre- and postcigarette plasma nicotine and cotinine levels were determined by gas chromatography-mass spectrometry.

### Measures

**Demographic Factors.** Age, gender, education, race, and body mass index (based on measured weight and height) were assessed.

**Cigarette-related Factors.** Cigarette type (regular *versus* light; menthol *versus* nonmenthol) was recorded based on labeling on the participant's cigarette pack. Nicotine yield of their cigarette brand was determined based on FTC brand levels. Participants completed the six-item Fagerstrom Test for Nicotine Dependence including questions about daily smoking rate (20). Baseline cotinine and nicotine levels and the nicotine: cotinine ratio were determined from the blood samples that were drawn before smoking the boost cigarette.

**Mood Factors.** The Positive and Negative Affect Schedule was used to assess overall levels of positive affect and negative affect experienced in the past 7 days (21). The CES-D scale was used to assess depressive symptomatology (22).

Nicotine Boost was determined by subtracting the precigarette plasma nicotine levels from postcigarette nicotine levels.

### Results

**Descriptive Data.** Sixty percent of participants smoked 11–20 cpd, 22% smoked 21–30 cpd, and 11% smoked over 30 cpd (7% reported smoking 1–10 cpd, suggesting that some participants reduced their smoking rate after the eligibility screen-

ing). Twenty-nine percent of participants smoked menthol cigarettes, and 66% smoked light cigarettes. The mean Fagerstrom Test for Nicotine Dependence score was  $5.5 \pm 2.2$ , the mean baseline plasma cotinine level was  $289 \pm 131$  ng/ml, and the mean baseline nicotine level was  $19.3 \pm 10.2$  ng/ml. Forty-two percent smoked within 5 min of waking, 35% smoked between 6 and 30 min after waking; 14% smoked within 31–60 min after waking, and 9% waited at least an hour after waking. With regard to the mood variables, mean positive affect score was  $30.2 \pm 7.4$ , mean negative affect score was  $19.1 \pm 7.3$ , and mean CES-D was  $12.8 \pm 9.2$ . The mean nicotine boost was  $10.9 \pm 5.1$  ng/ml. Affect and CES-D scores were comparable with published norms (21, 23).

**Predictors of Nicotine Boost.** ANOVA, *t* tests, and Pearson correlations were used to examine the associations of predictor variables with nicotine boost (Table 1). Factors associated with baseline nicotine and cotinine are also presented in the table for comparison. Race was a significant predictor of boost for the comparison of African-American with Caucasian participants [ $t = -2.28$ ;  $P = 0.02$  (because of the small number of members in other racial groups, they were not considered in this analysis)]. Age ( $r = -0.14$ ;  $P = 0.06$ ) was marginally associated with nicotine boost, but gender ( $t = 0.68$ ;  $P = 0.50$ ), education ( $t = 1.4$ ;  $P = 0.18$ ), and body mass index ( $r = 0.13$ ;  $P = 0.10$ ) were not. Among the smoking-related variables, cotinine level ( $r = 0.12$ ;  $P = 0.09$ ) and smoking rate ( $F = 2.26$ ;  $P = 0.08$ ) were marginally associated with boost, whereas nicotine/cotinine ratio ( $r = 0.11$ ;  $P = 0.13$ ), menthol/nonmenthol brand ( $t = 0.49$ ;  $P = 0.63$ ), cigarette type [*i.e.*, light ( $t = 1.6$ ;  $P = 0.11$ )], and nicotine dependence ( $r = -0.07$ ,  $P = 0.31$ ) were not. Negative affect ( $r = -0.03$ ;  $P = 0.69$ ) and depression symptoms ( $r = -0.06$ ;  $P = 0.38$ ) were not related to nicotine boost. However, a significant positive relationship between levels of positive affect and nicotine boost was found ( $r = 0.15$ ;  $P = 0.04$ ).

Predictor variables were tested in a linear regression model, controlling for potential confounder variables [baseline cotinine, smoking rate, and cigarette brand (FTC) nicotine level]. Higher nicotine boost was significantly associated with higher levels of baseline positive affect ( $\beta = 0.11$ ;  $P = 0.03$ ). No other variables were significant in the model ( $R^2$  model = 0.05;  $P = 0.03$ ).

To examine the degree of difference in boost as a function of positive affect, we conducted an ANOVA comparing boost levels in smokers by tertile of baseline positive affect. The groups were significantly different ( $F = 3.52$ ;  $P = 0.03$ ), with boost levels of  $9.3 \pm 5.2$  in the lowest tertile of positive affect and levels of  $11.3 \pm 4.6$  in the highest tertile of positive affect.

### Discussion

The current study is the first to examine demographic, smoking behavior and dependence, and psychological variables as predictors of nicotine boost assessed in a nonlaboratory setting. The novel and unexpected finding of our study was that nicotine boost was significantly higher among smokers who reported more positive affect during the 7 days before the boost assessment. Although previous studies have documented increases in positive subjective effects after nicotine administration (e.g., Ref. 24), our results are the first to suggest that levels of positive affect may lead smokers to take in more nicotine from their cigarettes.

Russell and Feyerabend (16) proposed that smokers may differ in whether they seek intermittent high blood levels of nicotine (peak seekers) or whether they seek to maintain steady

<sup>3</sup> The abbreviations used are: cpd, cigarettes/day; FTC, Federal Trade Commission; CES-D, Center for Epidemiological Studies Depression.

Table 1 Univariate predictors of nicotine boost

| A. Mean and SD     |                  |                         |                            |                           |
|--------------------|------------------|-------------------------|----------------------------|---------------------------|
| Predictor          | Level            | Boost                   | Baseline cotinine          | Baseline nicotine         |
|                    |                  | Median (SD)             | Median (SD)                | Median (SD)               |
| Race               | Caucasian        | 10.2 (5.2) <sup>a</sup> | 271.3 (116.6) <sup>b</sup> | 18.9 (10.5)               |
|                    | African American | 12.3 (5.3)              | 343.1 (157.7)              | 21.3 (9.9)                |
| Gender             | Male             | 11.1 (5.5)              | 315.1 (151.0) <sup>b</sup> | 20.58 (11.1) <sup>c</sup> |
|                    | Female           | 10.6 (4.8)              | 263.0 (101.0)              | 18.0 (8.9)                |
| Education          | < College        | 11.4 (5.1)              | 304.8 (131.1)              | 20.0 (9.4)                |
|                    | ≥ College        | 10.4 (5.1)              | 275.7 (129.6)              | 18.7 (10.7)               |
| Smoking rate       | 1–10 cpd         | 11.6 (4.4) <sup>c</sup> | 257.1 (99.3)               | 16.6 (5.0)                |
|                    | 11–20 cpd        | 11.5 (5.4)              | 278.2 (121.2)              | 19.0 (10.9)               |
|                    | 21–30 cpd        | 9.8 (4.7)               | 307.4 (163.8)              | 19.1 (9.9)                |
|                    | >30 cpd          | 9.1 (4.3)               | 328.8 (118.3)              | 22.7 (8.3)                |
| Menthol cigarettes | Yes              | 11.2 (5.5)              | 316.5 (147.5) <sup>c</sup> | 20.9 (10.3)               |
|                    | No               | 10.8 (5.0)              | 276.5 (119.2)              | 19.3 (10)                 |
| Cigarette type     | Light            | 10.5 (4.9)              | 266.7 (120.4) <sup>a</sup> | 17.8 (8.8) <sup>b</sup>   |
|                    | Regular          | 11.7 (5.4)              | 315.8 (135.0)              | 22.2 (11.0)               |

  

| B. R and predictors     |                    |                    |                   |
|-------------------------|--------------------|--------------------|-------------------|
|                         | Boost              | Baseline cotinine  | Baseline nicotine |
|                         | r                  | r                  | r                 |
| Age                     | −0.14 <sup>c</sup> | 0.15 <sup>a</sup>  | 0.02              |
| Nicotine dependence     | −0.07              | 0.29 <sup>b</sup>  | 0.22 <sup>b</sup> |
| Body mass index         | 0.13               | −0.13              | 0.15 <sup>c</sup> |
| Nicotine/cotinine       | 0.11               | −0.24 <sup>b</sup> | 0.47 <sup>b</sup> |
| Baseline cotinine level | 0.12 <sup>c</sup>  |                    | 0.61 <sup>b</sup> |
| Baseline nicotine level | 0.14 <sup>a</sup>  | 0.61 <sup>b</sup>  |                   |
| FTC nicotine delivery   | 0.12               | 0.10               | 0.24 <sup>b</sup> |
| Depression symptoms     | −0.06              | 0.04               | −0.07             |
| Negative affect         | −0.03              | −0.01              | −0.10             |
| Positive affect         | 0.15 <sup>a</sup>  | −0.07              | −0.02             |

<sup>a</sup>  $P < 0.05$ .<sup>b</sup>  $P < 0.01$ .<sup>c</sup>  $P < 0.10$ .

levels of nicotine throughout the day (trough maintainers). Nicotine boost is one way to examine the tendency to be a peak seeker. Peek seekers may be seeking more positive reinforcement from smoking, such as modulation of arousal. Trough maintainers are suspected to smoke more for negative reinforcement, that is, to avoid withdrawal symptoms. Positive affect states are often associated with higher levels of stimulation, and conceivably, smokers with positive affect take in more nicotine to enhance (or reduce) arousal level (25). Whereas the direction of causality cannot be determined definitively from the present study, the fact that positive affect (over the last week) predicted boost when cotinine levels were controlled suggests that positive affect may be an antecedent of nicotine boost.

Although there were differences in boost between African Americans and Caucasians in the univariate analysis, the final model did not provide evidence for significant racial or gender differences. This is in contrast to previous research (8–11). However, it should be noted that the absence of racial differences in boost and a lack of association with cigarette characteristics (*e.g.*, menthol) may be attributable to the relatively small number of African Americans in the sample.

There are some additional limitations of our study. First, our sample comprised treatment seekers, and as such, these results may not be generalizable to a non-treatment-seeking population. Second, the “boost” cigarette smoked by participants was not standardized in terms of tar and nicotine level. In

addition, although we did attempt to standardize nicotine deprivation to about 40 min (to reflect the average inter-cigarette interval), different results may have been achieved with a longer deprivation period. Finally, we only studied nicotine boost after smoking one cigarette in the middle of the day, and we did not collect data on the number of cigarettes smoked that day. Smokers may smoke differently at different times of day, depending on daily nicotine intake. However, to some extent, this should have been addressed by controlling for baseline cotinine levels.

Despite these limitations, the present study provides potentially important new information about the relationship between positive affect and nicotine boost. Given the significant variability in boost and the fact that positive affect accounts for only 5% of this variance, additional work in this area is warranted. One possible extension of this study would be to examine the role of individual differences in nicotine boost as measured by arterial blood levels. In addition, because nicotine boost is a measure of self-administration, and self-administration predicts relapse (26), future studies should explore whether smokers with higher levels of nicotine boost are more prone to relapse. It is possible that smokers who work to achieve higher levels of boost may be more responsive to nicotine replacement therapies that deliver nicotine more rapidly compared with therapies like transdermal nicotine, which deliver nicotine slowly. If this hypothesis is confirmed, nicotine boost could be

a useful tool for tailoring nicotine replacement therapy to individual smokers' needs.

### Acknowledgments

We thank Lita Ramos, who performed the nicotine analyses, and Maryanne Foster, who assisted with manuscript preparation.

### References

- Rowland, M., and Tozer, T. *Clinical Pharmacokinetics: Concepts and Applications*. Baltimore, MD: Williams and Wilkins, 1995.
- Zancy, J., Stitzer, M., Brown, F., Yingling, J. E., and Griffiths, R. R. Human cigarette smoking: effects of puff and inhalation parameters on smoke exposure. *J. Pharmacol. Exp. Ther.*, *240*: 554–564, 1987.
- Bridges, R. B., Humble, J. W., Turbek, J. A., and Rehm, S. R. Smoking history, cigarette yield and smoking behavior as determinants of smoke exposure. *Eur. J. Respir. Dis.*, *146* (Suppl.): 129–137, 1986.
- Ahijevych, K., and Gillespie, J. Nicotine dependence and smoking topography among black and white women. *Res. Nurs. Health*, *20*: 505–514, 1997.
- McCarthy, W. J., Caskey, N. H., and Jarvik, M. E. Ethnic differences in nicotine exposure. *Am. J. Public Health*, *82*: 1171–1173, 1992.
- Clark, K. D., Wardrobe-Wong, N., Elliott, J. J., Gill, P. T., Tait, N. P., and Snashall, P. D. Cigarette smoke inhalation and lung damage in smoking volunteers. *Eur. Respir. J.*, *12*: 395–399, 1998.
- Benowitz, N. L., Perez-Stable, E. J., Fong, I., Modin, G., Herrera, B., and Jacob, P., III. Ethnic differences in *N*-glucuronidation of nicotine and cotinine. *J. Pharmacol. Exp. Ther.*, *291*: 1196–1203, 1999.
- Eissenberg, T., Adams, C., Riggins, E. C., III, and Likness, M. Smokers' sex and the effects of tobacco cigarettes: subject-rated and physiological measures. *Nicotine Tob. Res.*, *1*: 317–324, 1999.
- Perez-Stable, E. J., Herrera, B., Jacob, P., III, and Benowitz, N. L. Nicotine metabolism and intake in black and white smokers. *J. Am. Med. Assoc.*, *280*: 152–156, 1998.
- Clark, P. I., Gautam, S., and Gerson, L. W. Effect of menthol cigarettes on biochemical markers of smoke exposure among black and white smokers. *Chest*, *110*: 1194–1198, 1996.
- Ahijevych, K., and Parsley, L. A. Smoke constituent exposure and stage of change in black and white women cigarette smokers. *Addict. Behav.*, *24*: 115–120, 1999.
- Sidney, S., Tekawa, I., and Friedman, G. D. Mentholated cigarette use among multiphasic examinees, 1979–86. *Am. J. Public Health*, *79*: 1415–1416, 1989.
- Blair, A., Blair, S. N., Howe, H. G., Pate, R. R., Rosenberg, M., Parker, G. M., and Pickle, L. W. Physical, psychological, and sociodemographic differences among smokers, exsmokers, and nonsmokers in a working population. *Prev. Med.*, *9*: 747–749, 1980.
- Silverstein, B., Feld, S., and Kozlowski, L. T. The availability of low-nicotine cigarettes as a cause of cigarette smoking among teenage females. *J. Health Soc. Behav.*, *21*: 383–388, 1980.
- Wagenknecht, L. E., Cutter, G. R., Haley, N. J., Sidney, S., Manolio, T. A., Hughes, G. H., and Jacobs, D. R. Racial differences in serum cotinine levels among smokers in the Coronary Artery Risk Development in (Young) Adults study. *Am. J. Public Health*, *80*: 1053–1056, 1990.
- Russell, M. A., and Feyerabend, C. Cigarette smoking: a dependence on high-nicotine boli. *Drug Metab. Rev.*, *8*: 29–57, 1978.
- Cohen, L. M., McCarthy, D. M., Brown, S. A., and Myers, M. G. Negative affect combines with smoking outcome expectancies to predict smoking behavior over time. *Psychol. Addict. Behav.*, *16*: 91–97, 2002.
- Hurt, R., Dale, L., Croghan, G., Croghan, I., Gomez-Dahl, L., and Offord, K. Nicotine nasal spray for smoking cessation: pattern of use, side effects, relief of withdrawal symptoms, and cotinine levels. *Mayo Clin. Proc.*, *73*: 118–125, 1998.
- Dale, L. C., Hurt, R. D., Offord, K. P., Lawson, G. M., Croghan, I. T., and Schroeder, D. R. High-dose nicotine patch therapy. Percentage of replacement and smoking cessation. *J. Am. Med. Assoc.*, *274*: 1353–1358, 1995.
- Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., and Fagerstrom, K. O. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br. J. Addict.*, *86*: 1119–1127, 1991.
- Watson, D., Clark, L., and Tellegen, A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J. Pers. Soc. Psychol.*, *54*: 1063–1070, 1988.
- Radloff, L. The CES-D scale: a new self-report depression scale for research in the general population. *Appl. Psychol. Meas.*, *1*: 385–401, 1977.
- Son, B. K., Markovitz, J. H., Winders, S., and Smith, D. Smoking, nicotine dependence, and depressive symptoms in the CARDIA Study. Effects of educational status. *Am. J. Epidemiol.*, *145*: 110–116, 1997.
- Soria, R., Stapleton, J. M., Gilson, S. F., Sampson-Cone, A., Henningfield, J. E., and London, E. D. Subjective and cardiovascular effects of intravenous nicotine in smokers and non-smokers. *Psychopharmacology (Berl.)*, *128*: 221–226, 1996.
- Klitzke, M., Irwin, R., Lombardo, T. W., and Christoff, K. A. Self-monitored smoking motives. *J. Subst. Abuse*, *2*: 121–127, 1990.
- Perkins, K., Broge, M., Gerlach, D., Sanders, M., Grobe, J., Cherry, C., and Wilson, A. Acute nicotine reinforcement, but not chronic tolerance, predicts withdrawal and relapse after quitting smoking. *Health Psychol.*, *21*: 332–339, 2002.

## Individual Differences in Nicotine Intake per Cigarette

Freda Patterson, Neal Benowitz, Peter Shields, et al.

*Cancer Epidemiol Biomarkers Prev* 2003;12:468-471.

**Updated version** Access the most recent version of this article at:  
<http://cebp.aacrjournals.org/content/12/5/468>

**Cited articles** This article cites 25 articles, 3 of which you can access for free at:  
<http://cebp.aacrjournals.org/content/12/5/468.full#ref-list-1>

**Citing articles** This article has been cited by 10 HighWire-hosted articles. Access the articles at:  
<http://cebp.aacrjournals.org/content/12/5/468.full#related-urls>

**E-mail alerts** [Sign up to receive free email-alerts](#) related to this article or journal.

**Reprints and Subscriptions** To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at [pubs@aacr.org](mailto:pubs@aacr.org).

**Permissions** To request permission to re-use all or part of this article, use this link  
<http://cebp.aacrjournals.org/content/12/5/468>.  
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.