Invited Commentary: Menthol Cigarettes and Risk of Lung Cancer

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Abbreviations: NPCR, National Program of Cancer Registries; SEER, Surveillance, Epidemiology, and End Results.

The paper by Brooks et al. (1) in this issue of the American Journal of Epidemiology addresses a topic of considerable public health importance and academic interest. It contributes to our understanding about the role of mentholated cigarettes in lung carcinogenesis, and it forces us to consider methodological issues that need to be addressed if we are to continue research on this topic.

Historical context and lung cancer rate disparities

The association between lung cancer and cigarette smoking was first established with the publication of several important papers in the middle of the last century (2–4). A decade and a half later, the 1964 US Surgeon General’s report on Smoking and Health (5) provided a clear and definitive judgment on the challenge of smoking, which continues to play an important role in public health, individuals’ pain and suffering, and domestic and foreign politics (6–9).

Despite the overwhelming evidence linking tobacco smoke, particularly from cigarettes, and lung cancer, anomalies are evident when comparing aggregate, population-level exposures with tobacco and lung cancer rates of populations. These anomalies can be seen in international comparison studies (10) and in comparisons of subgroups at varying risk within countries, as Brooks et al. (1) note. Prominent among these are the high lung cancer rates for US Blacks.

According to statistics from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (11), lung cancer incidence rates for Black men are 50 percent higher than for White men, while the combined data of the National Program of Cancer Registries (NPCR) and SEER (12) indicate a 26 percent higher incidence in Black men. Differences in the incidence rates of lung cancer are interesting in that over the period of etiologic relevance for these incident cancers (i.e., about 20–25 years previously), the prevalence of smoking (about 20 percent higher in Blacks) and the average number of cigarettes consumed per smoker (about 30–40 percent higher among Whites) combine such that overall exposure to the primary risk factor of interest actually appears to have been lower in Black men than in White men (13–15).

In the most recent data, lung cancer incidence rates for Black women are similar to those for White women, that is, about 3 percent higher in the 1996–2000 SEER data (11) and 7.5 percent lower in the 1999 NPCR-SEER data (12). Smoking prevalence rates from the previous 20–25 years indicate a slightly higher rate of smoking overall (33 percent vs. 29 percent) (13–15). Despite this apparent consistency between smoking and lung cancer rates, a disparity exists; Black women smoke many fewer cigarettes: 60 percent (vs. 30 percent of Whites) smoke fewer than 15 cigarettes a day, and only 6 percent (vs. 22 percent of Whites) smoke 25 or more cigarettes a day (14).

Underscoring their public health significance, lung cancer mortality rates track well against incidence in women and men of both races, with women’s death rates lagging slightly (11) mainly because their smoking rates rose after those for men (13–15). Because lung cancer tends to be a fatal disease, unexplained elevations in incidence place a large burden on a population subgroup already beset by a host of other health problems. Cancers of the upper aerodigestive tract also have been shown to be related to exposure to tobacco (16, 17), and unexplained racial disparities in these rates disfavor Blacks to an even greater extent (11, 12). This fact has added further impetus to the search for the cause(s). This search has led in a number of directions, such as exploring intrinsic differences in levels of enzymes that metabolize products of tobacco combustion (18–21) and, more recently, investigating various genetic polymorphisms that could influence the carcinogenicity of tobacco (22–26); evaluating other lifestyle factors that might influence the carcinogenic potential of tobacco (27–29); and examining differences in the types
of cigarettes used by higher- versus lower-risk groups (30–33).

**Mentholated cigarette use**

As noted by Brooks et al. (1), menthol cigarette use is higher both in Blacks and in women. It is a curious historical fact that when menthol brands were first introduced before World War II, Blacks and women evinced a preference for these brands (34). In a classic example of the interaction between marketing and product preference, menthol brands were targeted specifically at Blacks (35). From their introduction through 1955, mentholated brands represented about 3 percent of all cigarette sales, with Blacks and women accounting for a disproportionate share (36). From 1956 to the middle of the 1970s, menthol cigarettes’ share of the market rose rapidly (34, 37). After achieving about 29 percent of market share in the late 1970s, menthol cigarettes’ share of the market began falling in the late 1980s and now accounts for just under 26 percent of total sales (37). Currently, about 75 percent of Black smokers use mentholated brands (vs. 23 percent of Whites), with three brands available only in mentholated form (Newport (Altria Group, Inc., New York, New York (formerly Philip Morris Companies)), Kool (Brown & Williamson Tobacco Corporation, Louisville, Kentucky), and Salem (R. J. Reynolds Tobacco Company, Winston-Salem, North Carolina) accounting for 55 percent of total Black tobacco use (38). The observation that exposure to mentholated cigarettes could explain some of the discrepancy between overall tobacco exposure and rates of lung cancer, and other cancers of the upper aerodigestive tract, led to a number of studies being conducted beginning in the late 1980s (39–43). Generally, the results have been null, with only two of the five studies on lung cancer showing an effect in men (42, 43) and none, including this one (1) and two from the American Health Foundation (using overlapping populations), showing an effect in women (40, 44).

**Measurement and study design issues**

During the probable period of etiologic relevance for this study (1), which would have begun in the 1950s (for the other studies, perhaps up to a couple of decades farther back in time), a large number of ambiguous brands were available on the market; for example, Benson & Hedges, Virginia Slims, and Marlboro (Altria Group); Winston (R. J. Reynolds); and Pall Mall (Brown & Williamson) had menthol subbrands. At the same time, the parent brands accounted for a large part of total cigarette market share (34, 37). Consequently, longer-term estimates of past exposure would tend toward higher levels of misclassification (e.g., by substituting nonmenthol for menthol subbrands). In all of these studies, it is conceivable that subjects did not correctly designate an ambiguous brand, especially given that doing so would have represented a historical exposure. On the basis of the low frequency of exposure (especially in the distant past), even minor misclassification could obscure or distort a menthol cigarette–lung cancer relation. Future studies, particularly among Blacks, who have much stronger loyalty to the major menthol brands (38), may benefit from lower rates of misclassification resulting from concentration of mentholated cigarette exposure in a relatively small number of unambiguous brands. Note also that the Philippines, where mentholated cigarettes account for 62–65 percent of total sales, might provide an interesting opportunity for study (45).

Reported use of mentholated cigarettes by Blacks in all of the studies conducted to date is lower than the prevalence rate in the general population. For example, in the Brooks et al. study (1), ever use of mentholated cigarettes was slightly under 51 percent in Black controls compared with an average prevalence in Blacks ranging from approximately 63 percent over most of the period of etiologic relevance (34, 37) to about 75 percent currently (38). Many of the collaborating hospitals included in existing studies are university teaching facilities. It may be that persons seeking care there are atypical of the general Black population who are at an elevated risk of lung cancer. Although it is doubtful that type of cigarette smoked per se has an important impact on the likelihood of hospitalization, if socioeconomic status is related to the probability of menthol (as opposed to nonmenthol) cigarette smoking, then the types of hospitals used in this study could underrepresent the poor Blacks who might be more likely to smoke menthol brands and also may have higher disease rates. In this study (1), the fact that cases were more likely to be White than were controls suggests that the Black population represented by these hospitals may be different in some relevant way(s) from the general Black population.

It is important to note that the lung cancer incidence rates for Blacks in the NPCR data set (12) are lower than the SEER rates (11). NPCR rates are representative of entire states, whereas Blacks in the SEER data are overrepresented by the urban registries (e.g., Atlanta, Georgia; San Francisco-Oakland Standard Metropolitan Statistical Area (California); Detroit, Michigan; Seattle, Washington). Whole states that are SEER members (Connecticut, Hawaii, Iowa, New Mexico, Utah) are located in the north or west. These states tend to have a low proportion of Black residents, and, unlike the southern states that have the highest proportion of Blacks (55 percent of whom live in this region), most are urban dwellers (46). In spite of having relatively high cancer rates overall and ones that disfavor Blacks in general, southern states tend to have White lung cancer incidence rates above the US average, while rates for Blacks are lower, sometimes much lower, than the national average (12). Studies conducted in the Northeast or in California would tend to concentrate on areas that may be more typical of the SEER urban registries and underestimate a large segment of the US Black population, which is not primarily urban (e.g., 46 percent of all rural residents of South Carolina are Black (47)). This observation calls into question additional issues regarding representativeness but in no way strengthens an argument regarding the role of mentholated cigarettes. Nonetheless, it may provide important clues for future studies.

Menthol could exert an effect through a mechanism related to its topical effects (at first heightening and then attenuating sensations of heat and local irritability), which
could result in increasing exposure to tobacco smoke. Because poor people could have more of an economic impetus to increase their exposure to addictive agents in tobacco by reducing cost per unit exposure, it would be important to have information on compensatory smoking behaviors to help assess risk. Previous studies looking at puff frequency and volume (48–51) did not associate the physical properties of menthol cigarettes with the motivation of socioeconomically disadvantaged menthol smokers to increase tobacco exposure. In future studies, it would be important to relate sociodemographic factors to information on topographic smoking factors such as puff volume, depth of inhalation, frequency, degree of covering of air vents in cigarette filters, and completeness of smoking the cigarette (15, 38). Although Brooks et al. (1) did a good job of adjusting for the conventional measures related to smoking, they acknowledge that some residual confounding may have remained. Clearly, informal compensatory mechanisms (due both to the nature of menthol and the socioeconomic differences between menthol and nonmenthol cigarette smokers noted above) might fall into this category.

Most studies, including this one (1), have not examined effects by histologic site. It is known that tobacco is more strongly related to squamous-cell, small-cell, and large-cell carcinoma than to adenocarcinoma (33). However, use of a filtered cigarette with mild anesthetic properties could increase adenocarcinomas because of increases in small-sized particles being deposited in the periphery of the lung (52). Effects including increased solubility and membrane permeability (53, 54) also could have differential effects according to anatomic site. Clearly, future studies should focus on histologic and anatomic subtypes.

Conclusion

With this paper by Brooks et al. (1), it is becoming clear that if there is an elevation in risk of lung cancer from smoking mentholated cigarettes beyond that from smoking regular, filter-tipped brands, it is either subtle or refractory to smoking mentholated cigarettes beyond that from smoking regular, filter-tipped brands, and it is either subtle or refractory to the methods we have used thus far. Racial disparities in lung cancer incidence figure prominently in the background of this work, and the imperative to determine the cause(s) will necessitate moving beyond the kinds of populations that have been studied thus far, considering disease subtypes, conducting more detailed exploration of smoking habits, and investigating factors that may modify the known carcinogenic effects of tobacco.

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