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Mentholated cigarettes and smoking-related cancers revisited: An ecologic examination

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Abstract

The US Food and Drug Administration is assessing whether menthol should be banned as an additive to cigarettes. An important part of this determination concerns the health effects of mentholated relative to non-mentholated cigarettes. We examined the ecologic association between sales of mentholated cigarettes for the period 1950–2007, menthol preference by race and sex, and incidence rates of four tobacco-related cancers during 1973–2007. Total sales of mentholated cigarettes (market share) increased from about 3% in 1950 to slightly less than 30% in 1980 and remained fairly stable thereafter. Additional data show consistently that, compared to White smokers, Black smokers favor mentholated cigarettes by roughly a 3-fold margin. Differences in the incidence of lung cancer, squamous cell cancer of the esophagus, oropharyngeal cancer, and laryngeal cancer by race and sex and trends over a 35-year period, during which menthol sales were relatively stable and during which Black smokers were much more likely to smoke mentholated cigarettes compared to Whites, are not consistent with a large contribution of menthol, over and above the effect of smoking *per se*.

Keywords

Mentholated cigarettes; Sales; Prevalence; Esophageal cancer; Lung cancer; Oropharyngeal cancer; Laryngeal cancer; Ecologic study

1. Introduction

The US Food and Drug Administration has been charged with determining whether the use of mentholated cigarettes is more harmful to health compared to use of non-mentholated cigarettes (Menthol Report, 2011). The idea that smoking mentholated cigarettes might pose a health risk arose in the late 1980s, when epidemiologists brought together two striking facts. First, incidence rates of classically tobacco-related cancers were elevated in African Americans compared to Whites: for lung cancer the rate was ~50% higher in African-

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GK declares that he has served as a consultant to a law firm and to a consulting firm on the health effects of menthol cigarettes. NS and JH have no potential conflicts of interest.

American (i.e., Black) males compared to White males and for esophageal cancer the difference was even more extreme, ~3-fold higher in Black males and females compared to Whites. Second, African-American smokers strongly favored mentholated cigarettes compared to Whites: as of the mid-1980s, approximately 62% of African-American smokers smoked mentholated cigarettes compared to 23% of Whites (Hebert and Kabat, 1988, 1989).

Hebert and Kabat showed that the age-adjusted mortality from esophageal cancer in Blacks increased in parallel with the rise in sales of mentholated cigarettes between 1950 and 1984 (Hebert and Kabat, 1988, 1989). They noted that the large excess of esophageal cancer in Blacks had not been explained by differences in overall rates of cigarette smoking; i.e., disease rates 3–4 times higher in Blacks than Whites are inconsistent with Blacks' significantly lower rates of tobacco use (Hebert and Kabat, 1988, 1989); and therefore, they suggested that alcohol consumption, diet, and exposure to mentholated cigarettes should be investigated among other possible factors. A recent review underlines that, compared to Whites, Blacks tend to be lighter smokers, smoke cigarettes with higher tar content, start smoking at later age, are less likely to quit, and have higher cotinine levels (Lee, 2011). A number of studies suggest that compared to White smokers Black smokers of both sexes have lower overall exposure to tobacco smoke as indicated either by pack-years of smoking (Chatila et al., 2004; Stellman et al., 2003) or both amount and duration of smoking (Blot et al., 2011).

Hebert and Kabat further presented data from a case-control study that, with the exception of a marginally significant elevated risk in female smokers of mentholated cigarettes, did not support their hypothesis (Hebert and Kabat, 1988, 1989). Similarly, the results of case-control studies of lung and oropharyngeal cancers were null (Kabat and Hebert, 1991, 1994). However, based on the limitations of their studies, they concluded that further research was warranted.

Besides Kabat and Hebert's work on esophageal, lung, and oropharyngeal cancers, over the past two decades a number of studies have examined the association of use of mentholated cigarettes with risk of lung and other tobacco-related cancers (Blot et al., 2011; Brooks et al., 2003; Carpenter et al., 1999; Etzel et al., 2008; Friedman et al., 1998; Hebert, 2003; Kabat, 1996; Murray et al., 2007; Muscat et al., 2009; Richie et al., 1997; Sidney et al., 1995; Stellman et al., 2003). With few exceptions, these studies have indicated that the risk of disease associated with smoking mentholated cigarettes is no greater than that associated with smoking non-mentholated cigarettes. Based on a meta-analysis of eight studies Lee et al. (2011) concluded that the epidemiologic evidence was consistent with no effect of using mentholated cigarettes on risk of lung cancer.

Analytic epidemiologic studies that have examined mentholated cigarette use in relation to cancer risk have a number of limitations. In case-control studies, the most common design, biased recall, particularly of behaviors in the distant past, and selection bias are potential issues. In cohort studies, information on smoking habits may be limited and information on changes in exposure over the follow-up period is usually not available. Additionally, few analytic studies have focused on cancers other than lung cancer. Finally, as discussed below, these studies are not representative of the US Black population.

Given that ecologic data suggesting a possible association between mentholated cigarette use and rates of certain tobacco-related cancers first drew attention to the possible health effects of menthol cigarettes and initiated this line of inquiry, it is of interest to examine changes in the rates of the major smoking-related cancers in relation to sales and prevalence of mentholated cigarette exposure by race and sex with the addition of 20 years' worth of data. Cancers of particular interest are: lung cancer, squamous cell carcinoma of the

esophagus (ESCC), oropharyngeal cancer, and laryngeal cancer. All four of these cancers are strongly related to tobacco smoking, and all except lung cancer are also associated with alcohol consumption.

2. Materials and methods

Data on mentholated cigarette sales were obtained from Maxwell Reports (Statistical Survey of the Cigarette Industry) for the years 1950–2007. For nearly a century, the Maxwell Reports have been the authoritative source on sales of tobacco products in the US (FERRETT, 2011; Hebert and Kabat, 1988, 1989; Maxwell Reports, 2009, 2011). To obtain estimates of mentholated cigarette use by race and sex we used a variety of additional surveys that collect tobacco use data from nationally representative samples (Cubbin et al., 2010; FERRETT, 2011; Giovino et al., 2004; Lawrence et al., 2010; Rock et al., 2010; Roper Organization, 1986). Because of the large racial disparities that exist in rates of tobacco-related cancers (Chu et al., 2007; Gadageel and Kalemkerian, 2003; Ward et al., 2004) we sought to identify sources of data on tobacco use that specify race. We used “Black” (or African American) or “White” (or European American) as the main categories of interest, which are the self-reported race categories reported to vital status and other registries (Finkenauer et al., 2009; Jemal et al., 2008; Kant et al., 2007; Rock et al., 2010).

Age-adjusted incidence rates per 100,000 population/year were obtained from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute for the following cancer sites: lung, ESCC, oropharyngeal cancer, and laryngeal cancer. Begun in 1973, the SEER program is a widely cited source of information on cancer incidence and survival in the United States. For most of its history SEER collected cancer incidence data from 15% of the population (Ries et al., 2001). SEER currently collects and publishes cancer incidence data from population-based cancer registries covering approximately 28 percent of the US population, with oversampling of minority populations (Howlader et al., 2011). Annual incidence rates were available for these cancers for the years 1973–2007, for which we also present data for these 5-year periods by race and sex: 1973–77, 1978–82, 1983–87, 1988–92, 1993–97, 1998–2002, and 2003–2007. (Howlader et al., 2011; Ries et al., 2006) We used 5-year intervals in order to obtain more stable estimates (i.e., annual incidence rates are less stable, particularly for ESCC, oropharyngeal cancer, and laryngeal cancer and in Blacks generally). Because we were interested in time trends over the period from 1973 to 2007, we were constrained to using the smaller SEER dataset that excludes many of the current registry areas.

3. Results

3.1. Prevalence of menthol use

Starting in 1950 menthol’s relative share of the tobacco market increased from about 3% to nearly 30% in 1980 before leveling off (Fig. 1). During the past two decades overall smoking rates have decreased, while the proportion of menthol’s share of the market has remained stable (Cropsey et al., 2009; Murphy-Hoefer et al., 2008). Since World War II the percentage of Blacks smoking mentholated cigarettes has been consistently very high. As of the mid-1980s, about 62 percent of cigarettes purchased by Blacks were mentholated, compared to only 23 percent of cigarettes purchased by Whites (Maxwell Reports, 1977a, b, 1986). This has increased to about 70% for total sales and 85% for product preference, which represent higher percentages than when we first examined the data in the 1980s (Maxwell Reports, 2009, 2011).

Data from surveys of cigarette preference conducted in representative populations are not available for the entire second half of the twentieth century. However, because of the

mounting interest in the health effects of mentholated cigarettes, starting in 2000 data on menthol prevalence by race and sex from a number of large, representative national surveys have been published. These include the 2000 National Survey on Drug Abuse (Giovino et al., 2004), the 2005 National Health Interview Survey (Cubbin et al., 2010), the 2003 and 2006/07 Tobacco Use Supplements survey, and the 2004–2008 National Survey on Drug Use and Health (Rock et al., 2010). These cross-sectional surveys were designed to obtain representative data on smoking and other health habits in the non-institutionalized US population. These data are consistent in showing that adult Black current smokers of both sexes are more likely to report smoking mentholated cigarettes compared to White current smokers by a margin of 3- to 4-fold, with prevalence of menthol use being somewhat higher in women compared to men (Fig. 2). Data from the National Survey on Drug Use and Health for the years 2004–2008 indicate that the rates in each race/sex group remained fairly stable over this five-year period (Rock et al., 2010). Cross-sectional data from the National Health Interview Study (NHIS) further indicate that among former smokers, Black females favored menthol by a 2.5-fold margin and Black males favored menthol by 4-fold over their White counterparts (Cubbin et al., 2010).

In addition to their preference for mentholated brands, compared to White smokers, Black smokers also tend to smoke fewer cigarettes per day, to start smoking at a later age, to smoke higher tar cigarettes, to have greater difficulty in quitting, and to have higher cotinine levels (Gandhi et al., 2009; Kabat et al., 1991; Lee, 2011; Morgan et al., 2007). In terms of overall exposure to tobacco smoke, a number of studies indicate that compared to White smokers Black smokers have lower overall exposure to tobacco smoke as indicated by pack-years of smoking (Chatila et al., 2004; Stellman et al., 2003) or the combination of amount and duration of smoking (Blot et al., 2011).

3.2. Changes in lung cancer incidence

In the SEER data (Howlader et al., 2011) in 1973–77 the age-adjusted lung cancer incidence per 100,000 was 122.0 in Black males compared to 90.0 in White males (26% excess in Black males) (Fig. 3). Incidence rates peaked in both Black and White males in 1983–87: at 152.0 and 98.5, respectively, and thereafter declined in both Black and White males to 103.6 and 74.5, respectively, by 2003–07. The decline from 1983–87 to 2003–07 was 32% and 24%, respectively. As of 2003–07, the excess in Black males was 35%.

In contrast to the pattern in males, lung cancer incidence was only slightly higher in Black compared to White women in 1973–77 (27.8 vs. 24.8 – an 11% excess in Black females). Lung cancer incidence increased monotonically in both Black and White females over the period 1973–77 to 2003–2007. As of 2003–07, Black women had an excess lung cancer incidence of 4%. Fig. 3 presents age-adjusted lung cancer incidence rates by race and sex for the period 1973–2007.

3.3. Changes in esophageal cancer incidence

The esophagus is the anatomic site that attracted the earliest and most intense attention with respect to the menthol hypothesis (Hebert and Kabat, 1988, 1989). It also is the site for which the largest Black–White differentials exist. In our publications from the 1980's we presented age-adjusted esophageal cancer mortality rates for Whites and Blacks. At that time almost all cases of esophageal cancer were squamous cell carcinomas (ESCC). However, over the past two decades the incidence of adenocarcinoma of the esophagus (AEC) has increased rapidly from a very low level, and mainly in Whites (Ries et al., 2005, 2006; US Cancer Statistics Working Group, 2009). At present, the rates of the two cell types are nearly equal in Whites. ESCC in Blacks is about 4-fold higher than in Whites, while in some southern states the racial difference is nearly 8-fold (Hebert et al., 2006). Unlike ESCC,

AEC is not strongly related to smoking and alcohol consumption. For these reasons, in order to examine the contrast between esophageal cancer rates and the role of smoking (and in the present instance, mentholated cigarette use) in explaining these differences, it is necessary to focus on ESCC.

In the period 1973–1977 the age-adjusted incidence of ESCC was 16.5 per 100,000 in Black males compared to 3.8 in White males (or 4.3-fold greater) and 4.3 in Black females compared to 1.4 in White females (or 3.1-fold greater). Rates in Black males peaked in 1983–1987 at 19.6 and in Black females in 1978–82 at 5.4. In the period 2002–2007 ESCC incidence was 7.1 in Black males (a 64% decrease from the peak incidence) and 1.7 in White males (a 50% decrease from the peak incidence). In Black females, ESCC incidence had declined to 2.6 (a 49% decrease) and in White females to 0.9 (a 40% decrease). Fig. 4 presents age-adjusted incidence rates of ESCC from 1973 to 2007 by race and sex.

3.4. Changes in the incidence of oropharyngeal cancer

Incidence rates of oropharyngeal cancer are very low compared to lung and esophageal cancers, and the rates are correspondingly less stable. As in other tobacco- and tobacco + alcohol-related cancers, males have higher rates compared to females; however, only in Black males have rates risen discernibly compared to their White counterparts: in 1973–77 incidence was 0.8 per 100,000/year in Black men compared to 0.5 in White men; in 2003–07 incidence was 1.3 in Black men compared to 0.4 in White men. In women, the rates were higher in Black women in the period from 1993–97 to 2003–07 but not earlier. There was no clear trend in incidence rates from 1973–77 to 2003–07 in White males or females, or in Black females. Fig. 5 presents incidence rates of oropharyngeal cancer by race and sex for the period 1973–2007.

3.5. Changes in the incidence of laryngeal cancer

Blacks have consistently higher incidence of laryngeal cancer compared to Whites and males have consistently higher rates compared to females. In 1973–77 Black males had an incidence of rate of 13.5 per 100,000/year compared to 9.6 in White males – a 29% excess. Incidence declined in White males from 9.6 in 1973–77 to 5.8 in 2003–2007 (a 40% decrease) and in Black males from 13.5 in 1973–77 to 10.3 in 2003–07 (a 24% decrease). There was no clear trend in the rates in Black or White females. Fig. 6 presents age-adjusted incidence rates for laryngeal cancer by race and sex for the period 1973–2007.

4. Discussion

We have documented dramatic changes in the incidence of four tobacco-related cancers by race and sex over a 35-year period during which menthol sales remained essentially stable. None of the observed trends is consistent with a strong independent effect of menthol use.

Given the large differences in exposure to mentholated cigarettes by race and sex, if menthol had a discernible effect on the risk of smoking-related cancers, one might expect to see one or both of the following patterns: (1) higher incidence rates among Blacks of both sexes compared to their White counterparts; (2) differences in the temporal trends between Blacks and Whites of both sexes. We address each of these patterns for each cancer site. Lung cancer incidence is consistently higher in Black males than in White males, consistent with a possible effect of menthol; however, no difference is seen in women. Furthermore, since 1983–87, lung cancer incidence declined at a steeper rate in Black males compared to White males. For ESCC, Blacks of both sexes have higher incidence over the 35-year time period compared their White counterparts, consistent with a possible contribution of menthol; however, greater declines are also seen for Blacks of both sexes compared to Whites.

For oropharyngeal cancer, Black males have higher incidence compared to White males, whereas there is little difference between the rates in Black and White females. There is an increase in incidence in Black males, whereas incidence in the other three groups remains basically stable. Finally, Blacks of both sexes have higher laryngeal cancer incidence compared to their White counterparts; however, the differential is much greater among males, whose incidence is declining. Incidence in Black women is declining at a lower rate, whereas incidence in White females is stable.

The results of analytic epidemiologic studies to date provide little support for the hypothesis that mentholated cigarette use increases the risk of lung cancer over and above the effect of smoking (Lee, 2011). Unlike ecologic studies, these studies were able to adjust for important confounding factors. The lack of a consistent correlation between mentholated cigarette prevalence and lung cancer incidence in both sexes (Fig. 3) is consistent with the results of the epidemiologic studies. However, few epidemiologic studies have addressed the remaining three tobacco-related cancers, and the number of cases is comparatively small, particularly in Blacks. The pattern of ESCC incidence (Fig. 4) is compatible with a small contribution of menthol, since incidence is higher in Blacks of both sexes compared to Whites. However, prevalence of mentholated cigarette smoking cannot explain the much larger differential in incidence between Black and White males as compared to that between Black and White females. A similar observation applies to oropharyngeal and laryngeal cancers (Figs. 5 and 6).

The different patterns observed over time in the four race/sex groups for the four tobacco-related cancers suggest that, while smoking is strong risk factor for lung cancer and while smoking and alcohol consumption are strong risk factors for ESCC, oropharyngeal, and laryngeal cancers, other risk factors are likely to play an important role in the etiology of these different cancers, as we see in other populations (Castellsague et al., 2000; Ghadirian, 1985; Victora et al., 1987; Zaridze et al., 1985a, b). The dramatic decline in ESCC in all race/sex groups suggests that some other important risk factor for ESCC in addition to cigarette smoking and alcohol intake decreased in the general population, or that some protective factor increased in prevalence. It is important to note that at the time of the original publications there was some indication that total alcohol consumption was actually lower in Blacks than Whites (Harford, 1986; Tollefson, 1985) and this appears to still be true (Dubowitz et al., 2011; Sloan and Grossman, 2011).

Although the apparent correlation between menthol sales and esophageal cancer death rates observed in the late 1980s was striking, that ecological observation, as well as the present one, are subject to the well-documented limitations of ecologic analyses. First and foremost, both exposure and mortality data are aggregates for population groups. Therefore, many important parameters of an individual's exposure (other than mentholated cigarettes) could not be taken into account. Most importantly, these include smoking status, intensity of smoking, duration of smoking, age of initiation, whether one had quit and, if so, when, and tar-level of the cigarette. Second, information on important confounding factors, such as socioeconomic status, and effect modifiers, such as alcohol consumption, was not available. Finally, the depiction of time trends in the ecological data presented at that time did not make allowance for a lag period between exposure and the manifestation of disease.

While ecologic studies are subject to well-known limitations (Rothman and Greenland, 1998), in the present case the ecologic approach is justified by the large differences by race and sex in the incidence of smoking-related cancers and the large contrasts in use of mentholated cigarettes by race and sex. Furthermore, the fact that Black smokers appear to have lower cumulative tobacco exposure compared to White smokers and that Blacks also appear to have lower alcohol consumption suggests that these established factors are

unlikely to obscure a positive association of mentholated cigarettes with disease, were one to exist.

Although at present the SEER data represent the best available population-based resource for examining changes in cancer incidence rates over time, it is important to realize its limitations. Blacks in the SEER population are mostly from urban areas, such as Detroit and Atlanta and the northeastern United States. Thus, SEER excludes the largest portion of the African-American population, over half of which lives in the southeastern US. We know from examining data in a very high-risk state in the southeast, South Carolina, that the differential in ESCC incidence between Blacks and Whites is nearly 8-fold, about twice that seen in the SEER data (Hebert et al., 2006). Unfortunately, these more representative data go back only to the mid-1990s because that is when legislation enabling these National Program of Cancer Registries (NPCR) registries to collect data went into effect.

Most analytic studies examining the association of mentholated cigarette with tobacco-related cancers were conducted in teaching hospitals in the Northern US and may therefore represent a portion of the population at lower risk for tobacco-related cancers than the entire US population, which provided the basis for cancer mortality statistics at the time – through the 1980s (Hebert and Kabat, 1988, 1989; National Cancer Institute, 1991). The fact that the prevalence of mentholated cigarette smoking among African Americans in this and similar populations used in studies on the subject (Brooks et al., 2003) was much lower than that observed in the general Black population at the time (Maxwell Reports, 1977a,b, 1986) suggests that using these populations to address hypotheses related to mentholated cigarette exposure and aerodigestive tract cancers might attenuate large contrasts in mentholated cigarette use and in rates of these cancers between Blacks and Whites. Other, more recent, case-control studies have failed to account for large Black–White differences in rates of ESCC, the cancer evincing the largest racial disparity (Brown et al., 2001, 1994).

In the future, the data resource represented by the NPCR will make possible both ecologic and analytic epidemiologic studies that can exploit the larger contrasts in incidence as well as exposures between different racial groups, sexes, and regions, thereby increasing the power to detect effects and to tease apart the roles of different risk factors.

5. Conclusion: Where we are and future directions

In contrast to the striking positive correlation between mentholated cigarette sales and mortality from esophageal cancer in Blacks observed in the late 1980s, temporal trends in incidence rates of major tobacco-related cancers in Blacks and Whites in the SEER data over the 35-year period to 2007 are not consistent with an important contribution of use of mentholated cigarettes to risk, beyond that due to smoking *per se*. For lung cancer, which has the highest incidence, Black–White differences in incidence at different points in time and trends over time are not correlated with the prevalence of menthol by race and sex. For ESCC, the higher prevalence of menthol in Blacks of both sexes compared to Whites is compatible with a contribution of menthol; however, there has been a dramatic decline in ESCC rates, particularly in males, during a period when mentholated cigarette sales and prevalence have remained stable.

The evidence presented here, which is inconsistent with a major effect of menthol in cigarettes as a cause of the upper aerodigestive tract cancers, brings us no closer to understanding the reason for extreme racial disparities in these cancers. Epidemiologists and others are left to ask: Why do Blacks have rates of tobacco-related cancers, and ESCC in particular, that are incongruent with their exposure to tobacco?

The concept of “mixing,” conventionally thought of as a nuisance (i.e., confounding) in epidemiology, may lie at the heart of understanding the etiology of upper aerodigestive tract cancers (and cancer more generally). Complex mixtures, including those containing nitrosamines, are known to produce dramatic effects on modifying risk (Preston-Martin and Correa, 1989). We would expect that mixing in aqueous solution would be minimal in the lung (where modest racial disparities exist) and maximal in the proximal esophagus (where we see the largest unexplained racial differences of any cancer in ESCC) (Bartsch et al., 1993; Pratt et al., 2011; Preston-Martin and Correa, 1989). Indeed, this observation is consistent with the findings reported by Zaridze et al. for esophageal vs. oral cancer in the Caspian Littoral nearly 30 years ago (Zaridze et al., 1985a). It also forms the basis for the mechanism by which ethanol modifies the effect of tobacco (Castellsague et al., 1999). We now know that menthol affects membrane permeation of many compounds, including tobacco carcinogens (Azzi et al., 2006; Squier et al., 2010), and may alter both tobacco uptake and cessation (Cubbin et al., 2010; Okuyemi et al., 2007). So, though a strong main effect of menthol is doubtful, menthol could play an important role in modifying the effect of tobacco carcinogens. Ecological studies of this kind are incapable of detecting effect modification implied by these laboratory-based studies or adequately controlling for epidemiologic confounding. Future work must focus on combinations of factors, including menthol, to explain these unresolved racial differences.

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Fig. 1.
Sales of mentholated cigarettes (%), 1950–2007.

Fig. 2.
Prevalence of menthol use (%) by race and sex in representative surveys.

Fig. 3.
Age-adjusted incidence of lung cancer by race and sex, for the period 1973–2007.

Fig. 4.
Age-adjusted incidence of ESCC by race and sex, for the period 1973–2007.

Fig. 5. Age-adjusted incidence of oropharyngeal cancer by race and sex, for the period 1973–2007.

Fig. 6. Age-adjusted incidence of laryngeal cancer by race and sex, for the period 1973–2007.