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Perspective

Oropharyngeal Cancer, Race, and the Human Papillomavirus

Perspective on Settle et al., p. 776

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Abstract This perspective on Settle et al. (beginning on p. 776 in this issue of the journal) discusses the racial disparity in oropharyngeal cancer survival in relation to the biological factor human papillomavirus and its association with sexual behavior. This discussion is expanded to a more general consideration of biological and nonbiological (e.g., socioeconomic and cultural) factors affecting racial disparities in disease.

Head and neck cancer is a group of diseases that have a higher incidence and cause higher mortality in blacks or African-Americans. Compared with whites, blacks are more likely to have an advanced stage of disease at diagnosis and to have inferior outcomes (shorter survival) within the same stage. The higher incidence of head and neck cancer among blacks has been attributed to a variety of factors, including differences in diet, alcoholic beverages, and tobacco use. Head and neck cancer occurs more frequently in men than in women (1, 2).

In this issue of the journal, Settle et al. (3) report a significant study of black-white outcomes in head and neck cancer, which, like any significant article, asks perhaps as many questions as it answers. This article makes one think about what race really means in the medical literature, population categorizations, gene-environment interactions, and disparities in cancer incidence and outcome.

Settle et al. show that, despite having disparate outcomes in head and neck cancer overall, black and white patients have similar outcomes for most head and neck cancer sites when they receive the same high-quality care. This finding confirms the premise that a major reason for black-white disparities in head and neck cancer outcomes in the United States is disparities in the quality and timeliness of cancer care, which have been documented in numerous studies (4). This difference in care is especially true of head and neck cancer (5). The key to solving most racial health disparities in the United States is for us to understand that equal treatment yields equal outcome among equal patients, and equal treatment has not been achieved.

Much to their credit, these investigators took the important step of searching for the reason for the overall head and neck difference they observed, finding that it was entirely due to differences in oropharyngeal cancer outcomes. Searching further, they found that the oropharyngeal difference was attributable to racial differences in the prevalence of human papillomavirus (HPV)–positive tumors. Black and white patients with HPV-negative oropharyngeal tumors had similar outcomes.

These findings are complemented by and consistent with the results of another study reported in this issue of the journal [Chen et al. (6)]. These investigators performed very detailed matching of African-American or Hispanic American head and neck cancer patients with non-Hispanic white patients by age, sex, smoking status, site, tumor stage, nodal status, and treatment. African-American patients had a significantly worse survival from cancer of the oropharynx but not of other head and neck sites. Therefore, two independent research groups using different methods found the same pronounced racial disparity in outcomes of oropharyngeal cancer (but not of other head and neck cancers) among patients receiving the same high-quality care.

The role of HPV, specifically HPV-16, in oropharyngeal cancer is well established (7–9). Patients with HPV-positive oropharyngeal tumors have a better prognosis compared with HPV-negative oropharyngeal patients (10). The reasons for this better prognosis are not understood.

At first glance, it seems surprising that the white population of oropharyngeal patients would have such a higher rate (~9-fold) of HPV-positive cancers (3). Could there have been a selection or sampling bias in the trial population of HPV-tested patients? No such bias was apparent, however, because these patients were prospectively accrued to a well-designed clinical trial. Therefore, could a race-related biological difference make whites more susceptible than blacks to HPV infection?

The subject of biological differences among races is politically charged, harking back to the "biological difference" justification for slavery and segregation. The issue of biological differences, race, and infectious disease is especially sensitive. The atrocity known as the Tuskegee syphilis study was founded on the now discredited principle that an infectious disease (e.g., syphilis) behaves differently in blacks versus whites (11).

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Many people have strongly argued that the medical profession should not use race as a biological categorization (12, 13). Anthropologists recognize race as a sociopolitical construct that is not based on biological taxonomy. This is not to say there are no biological differences, which indeed do exist between various populations and can result from gene-environment interactions. These influences cause changes in biology that can be immutable over generations or mutable within a lifetime (13).

Geographic area of origin is a legitimate scientific categorization and is associated with a higher prevalence of certain genetic markers (14, 15). For example, the sickle cell mutation, which is found in sub-Saharan and North Africa, the Middle East, and European Mediterranean countries (16), exists because of evolutionary pressures due to endemic malaria, an environmental influence lasting generations. Although this is an excellent example of a biological difference based on geographic origin, most Americans mistakenly think that sickle cell disease is a black disease attributable to racial, and not geographic, differences.

An example of a gene-environment interaction that can affect a population within a generation is the association of poverty with genetically more aggressive breast cancers. Estrogen receptor–negative breast tumors tend to be more frequent in poor than in more affluent breast cancer patients of the same race (17, 18). Diet, birthing habits, and other environmental influences likely cause this disparity.

Several neoplasms are associated with infectious agents, such as the EBV, which disproportionately affect certain populations and may provide insight into HPV and its behavior. EBV is very common worldwide and is associated with nasopharyngeal carcinoma. Although nasopharyngeal carcinoma is relatively rare in most populations, it is one of the most common cancers in southern China (19). A large body of evidence supports the role of EBV as the primary etiologic agent in the pathogenesis of nasopharyngeal carcinoma in both low- and high-incidence areas, although the great majority of EBV-infected patients, even in China, do not develop this tumor (20).

The higher prevalence of nasopharyngeal carcinoma in southern China may be due to environmental and genetic influences on biology. There is some evidence that a diet high in salt-cured foods may promote nasopharyngeal carcinoma in this region (21). One case-control study of nasopharyngeal carcinoma (with age- and geography-matched controls) showed that having a first-degree relative with nasopharyngeal carcinoma increases the risk of this disease by 7.6-fold (22). Nasopharyngeal carcinoma is associated with certain *human leukocyte antigen* haplotypes, which also could explain a genetic predisposition, at least in some populations (4, 23).

Burkitt lymphoma, also associated with EBV, is the most common childhood malignancy in equatorial Africa (24). The etiology of this disease is an example of a socioeconomic combined with an environmental influence. More than 95% of African children are infected with EBV by the age of 3 years, whereas a primary infection with this agent in affluent countries is often delayed until adolescence (25). EBV by itself is not sufficient for developing Burkitt lymphoma because geographic regions neighboring the Burkitt "belt" have as high a prevalence of EBV but not relatively high incidences of Burkitt lymphoma. Malaria, which is endemic in equatorial Africa, and EBV infection are considered cofactors in the genesis of Burkitt lymphoma (26, 27). Other infections of interest are *Helicobacter pylori*, which is a major risk factor for gastric cancer and is more prevalent in U.S. blacks and Hispanics than in whites (28–31), and chronic hepatitis C, which is more prevalent and associated with increased liver cancer in U.S. blacks than in whites (32). A fascinating inverse association between *H. pylori* and esophageal cancer (33) may be worth investigating for racial differences. It has been speculated that a higher frequency of i.v. drug use by black soldiers during the Vietnam War contributed to the current racial disparity in chronic hepatitis C infection and liver cancer.

HPV is the most common sexually transmitted infection in the world. In the United States, ~20 million people currently have an active HPV infection, and estimates are that another 6.2 million will become infected in 2009. Seroprevalence studies suggest that 75% to 80% of sexually active adults will acquire a HPV infection before the age of 50 years (34, 35). There is no known difference in how populations defined by whatever criteria respond to this infectious agent. This issue was extensively discussed when the HPV vaccine was approved by the U.S. Food and Drug Administration for preventing cervical cancer. Much of the data supporting this approval came from studies in South America.

HPV is spread through direct contact of HPV-infected fluid with a susceptible tissue, some sites of which are more susceptible to infection than the others. HPV has been detected in the epithelium of the penis, scrotum, anal canal, cervix, vulva, and perianal area (36). Certain mucous membranes, especially the squamocolumnar junction of the cervix, crypts of the tonsils, and the oropharynx, are especially susceptible. HPV infections are spread by unprotected penetrative intercourse, close physical contact (including digital/anal, oral/anal, deep oral, and digital/vaginal), and by fomites (37).

The annual HPV infection rate in the United States is unknown. In one small survey, 4.8% of all adults and 2.9% of college-aged men had an active oral HPV infection (37). Surveys have shown that the risk of oral HPV infection was significantly elevated among current tobacco smokers and individuals who reported having had either >10 oral or >25 vaginal lifetime sex partners.

Could the racial difference Settle et al. discovered in HPV-positive oropharyngeal cancers be explained by socioeconomic or sociocultural factors and the biology of the virus? A search of literature that oncologists normally do not read shows that sexual practices can differ by race (as defined socioculturally). Oropharyngeal cancer has an increasing incidence, which has been linked to an increase in the number of people who perform oral-genital sex acts (37).

There are racial differences in the prevalence of certain sexual acts. The U.S. Centers for Disease Control and Prevention–sponsored and NIH-sponsored 1995 National Survey of Adolescent Males showed that >80% of black and >80% of white males ages 15 to 19 years were sexually active (38). Compared with black males, however, white males were 2.7 times more likely to engage in oral sexual activity with a female and were 1.4 times more likely to receive oral sex from a female. Compared with white males, black males were 1.35 times more likely to engage in genital-to-genital sex with a female. The 2002 National Survey of Family Growth[1] showed

[1] http://www.cdc.gov/nchs/NSFG.htm

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that white females ages 15 to 19 years were twice as likely as black females to have engaged in oral-genital sex. There are no good surveys of youth-aged sexual behaviors in earlier periods when patients currently being diagnosed and treated for oropharyngeal cancer might have been exposed initially to HPV. The 1995 and 2002 data cited above, however, suggest that a higher proportion of whites engaging in oral-genital sexual behavior, especially as initial sexual behavior, might explain the higher rate of HPV-positive oropharyngeal cancers in whites (versus blacks) reported by Settle et al. (3).

A genital HPV infection acquired before HPV exposure through oral sex may evoke an immune response that decreases the risk of an oral HPV infection (13). When HPV exposures in years past initiated the oropharyngeal tumors presenting today, it is plausible that an initial genital infection was more likely among blacks, and an initial oral infection more likely among whites. This difference may be an important factor underlying the lower prevalence of HPV-positive oropharyngeal cancer in blacks.

In addition to differences in sexual behavior patterns, various pieces of the puzzle of racial disparity in oropharyngeal cancer include reports of Gillison and colleagues showing molecular evidence for the role of HPV in the etiology of oropharyngeal cancer (8), confirming this role and showing its association with sexual activity (39), establishing the prognostic benefit of HPV-positive oropharyngeal cancer in a prospective clinical trial (10), and showing that racial oropharyngeal cancer incidence trends began in 1985 to 1990 to descend for African-American men, to rise for white men, and crossed in 2004 (oropharyngeal cancer develops three times more often in men than women; ref. 40). These trends are consistent with decreasing tobacco use and a rarity of HPV positivity among black male patients and with dramatically increasing HPV positivity among white male patients (notwithstanding their decreasing use of tobacco). The HPV-16 results of Settle et al. in oropharyngeal cancer tissue from black and white patients are the last piece of this puzzle.

The better outcomes of white (versus black) oropharyngeal cancer patients in an equal-care setting can be explained by the larger proportion of white patients with better-prognosis HPV-positive tumors. One cannot say with certainty that this racial difference is due to a cultural difference in the prevalence of a sexual behavior, but this is a very plausible explanation. Socioeconomic, cultural, and other environmental influences can have a significant influence on the etiology and behavior of cancer. The thorough work of Settle et al. in this issue of the journal serves as a reminder that we should approach racial disparities with a broad and open mind. The HPV findings also have important prevention implications for the use of HPV vaccines and behavioral modification through sex education among young Americans of any descent.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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