Review Article

Lung cancer early detection and health disparities: the intersection of epigenetics and ethnicity

Lane Lerner[1], Robert Winn[1], Alicia Hulbert[2]

[1]University of Illinois at Chicago Cancer Center, [2]Department of Surgery/Cancer Center University of Illinois at Chicago Cancer Center, University of Illinois Hospital and Health Sciences System, Chicago, USA

Contributions: (I) Conception and design: A Hubert; (II) Administrative support: L Lerner; (III) Provision of study materials or patients: L Lerner; (IV) Collection and assembly of data: L Lerner, A Hulbert. (V) Data analysis and interpretation: L Lerner, A Hulbert; (V) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Alicia Hulbert, MD. Department of Surgery/Cancer Center University of Illinois at Chicago Cancer Center, University of Illinois Hospital and Health Sciences System, Chicago, USA. Email: ahulbert@uic.edu.

Abstract: Lung cancer is the most prominent cause of cancer-related mortality. Significant disparities in incidence and outcome characterize the disease's manifestations among ethnically and racially diverse populations. Complete surgical resection is the most effective curative treatment. However, success relies on early tumor detection. The National Lung Cancer Screening trial showed that lung cancer related mortality can be reduced by the use of low-dose CT (LDCT) screening. However, this test is plagued by a high false positive rate of 97% and the device itself is limited to designated cancer centers due to its expense and size. This restriction makes it difficult for underserved groups to access LDCT screening, the current standard of care. Highly sensitive and specific epigenetic DNA methylation-based biomarkers have the potential to work independently or in conjunction with LDCT screening to identify early-stage tumors. These tests could reduce unnecessary invasive confirmatory diagnostic tests and their associated morbidity and mortality. These tests also have the opportunity to bring lung cancer screening to the community thereby reducing unequal accessibility. However, epigenetic alterations are closely linked to the interplay between hereditary and environmental factors such as diet, lifestyle, ethnic ancestry, toxin exposure, residential segregation, and disparate community support structures. Despite this, the overwhelming number of early detection DNA methylation biomarker studies to date have either failed to control for ethnicity or have employed heavily Caucasian-biased patient cohorts. This review seeks to summarize the literature related to the early detection of lung cancer through molecular biomarkers among different ethnicities. Ethnical specific epigenetic biomarkers have the potential to be the first step towards an accessible, available personalized medicine approach to cancer through liquid biopsy.

Keywords: Lung cancer; biomarkers; genetics; epigenetics; tumor markers; disparity

Submitted Mar 17, 2018. Accepted for publication Mar 28, 2018.
doi: 10.21037/jtd.2018.04.07
View this article at: http://dx.doi.org/10.21037/jtd.2018.04.07

Introduction

Although rates of tobacco consumption have steadily declined following the 1st Surgeon General's Report in the early 1960's, the total number of daily smokers has risen and lung cancer remains the most common cause of cancer-related mortality in the world and the second most common cause of death in the United States (1,2). 222,500 new domestic diagnoses and 155,870 deaths were expected to be attributed to the disease, in 2017 (1). The narrow margin between these figures reflects lung cancer's abysmal overall 5-year survival rate of 7% for small cell lung cancer and 21% for non-small cell lung cancer (NSCLC) (3). NSCLC makes up the vast majority of lung

cancer diagnoses and is the focus of this review. The low NSCLC survival rate is mainly due to the fact that nearly half of all new cases are identified at stage IV (1,4,5). Patients with pathologic stage IA tumors possess a 73% 5-year survival rate while those with stage IIB and IIIB face 36% and 9%, respectively (4). This emphasizes a need to detect tumors in their early stages in order to provide patients with better treatment options, such as surgical resection, and ultimately to decrease the mortality burden posed by lung cancer, as demonstrated in other cancers such as prostate, breast and colon.

Current diagnostic techniques rely heavily on imaging. In 2011, The National Lung Screening Trial (NLST) demonstrated the efficacy of LDCT scans in detecting lung cancer and reducing disease mortality rates by 20% (6). Since then, several scientific societies have modified their respective diagnostic guidelines to include LDCT screening for high risk patients, a test for which Medicare now reimburses patients (7). However, LDCT is an inefficient diagnostic tool. The test yields a high false positive (FP) rate of 96.6%, which can lead to unnecessary invasive diagnostic procedures and increased deaths from avoidable surgeries (8).

Tumor markers, or cancer biomarkers, have the potential to work independently of or in conjunction with existing LDCT based screening techniques to detect early stage lung cancer. They can increase the proportion of tumors eligible for surgical resections, the most effective curative treatment for local tumors (9). Biomarkers represent a broad category of compounds produced either by a tumor or by a patient in response to a tumor. To function as effective clinical diagnostic or early detection instruments, biomarkers must possess the following features: first, they must be found in a bodily fluid such as blood, sputum or urine; second, they must be quantifiable and reliable; and third, they must be linked to the studied disease with high sensitivity and specificity (10,11). Liquid biopsy techniques have additional advantages over imaging-based screening techniques such as their potential for tracking microscopic disease progression as well as patient responses to treatment (10,12,13). Some proteomic biomarkers are currently used to aid in early lung cancer diagnosis. These include CEACAM, CYFRA 21-1, CA125, ProGRP and several others. Unfortunately, in spite of numerous screening trails with encouraging results, no individual or panel of clinically available lung cancer biomarkers has had high enough specificity and sensitivity for widespread use (14).

Methylation based epigenetic markers have risen to the forefront of early detection strategies. However, most published studies do not include ethnicity or racial controls and the few that do tend to be heavily weighted towards Caucasian patients. The current dearth of studies that test biomarkers in socioeconomically or ethnically inclusive ways could present a missed opportunity to develop personalized lifesaving diagnostic tools for many subsets of patient populations. Ethnic minorities and undeserved groups have higher incidence and mortality rates than Caucasians (1,5). Excluding these groups from studies and trials reduces generalizability of their results and therefore compromises their reproducibility. Additionally, studies that reflect the true nuance of methylation status in NSCLC could find patterns that may pave the way for novel therapy targets for underserved groups. Diverse patient cohorts could provide the scientific community with a better understanding of the interplay between patient backgrounds and optimal care modalities.

Mechanistic description of topics

Gene promoter methylation as lung cancer liquid biopsy biomarkers

Methylation of promoter regions within genomic CpG islands is a common epigenetic method of regulating gene expression, which usually leads to gene silencing (15-17). While DNA methylation is a naturally occurring process required for ordinary cell function, aberrant methylation has been observed in cancer and functions by altering gene regulation to promote oncogenesis (18-20). Methylated genomic regions that are correlated with particular types of cancer have been investigated since the early 1980s (21). However, in 2010, Bailey *et al.* introduced an effective, reproducible method of detecting methylation markers from samples with low DNA copy numbers. This opened the door for new early detection strategies and investigations of circulating DNA from bodily fluids. The technique, known as methylation on beads (MOB), utilizes magnetic nanoparticles in an effort to combine DNA isolation and bisulfite treatment procedures into a single tube thereby increasing sample yield nearly 6-fold relative to the next most efficient kit-based assay (22). Since then, many markers have been identified and validated in bodily fluids with potential for use as independent or collaborative diagnostic tests in tandem with current screening methodologies (23-29).

Ethnicity linked disparities in lung cancer

Particular malignancies differentially impact certain populations. As a whole, cancer disparity investigations try to examine the differences in incidence, prevalence, mortality, and disease burden levied on various racial, ethnic, and underserved groups as compared to the population as a whole. Given the ethnically and genetically heterogeneous nature of the United States, cancer-related health disparities will become ever more pronounced if this diversity is not reflected in our nation's medical research (30,31).

For lung cancer, male populations of African descent have the highest incidence and mortality rates of any racial or ethnic group in the United States (1,3). In 2016, the national age-adjusted incidence and mortality rates for African American (AA) males were 18% and 11% higher than those of whites, respectively (1,5,32). Interestingly, AA are more likely to show familial aggregation of lung cancer and as a group are more likely to develop lung cancer at an earlier age than Caucasians, even though smoking rates among AA adolescents are lower than those among Caucasian adolescents (1,5,32-38). In spite of recent declines in incidence rates among Caucasians and the United States population as a whole, Asian Americans exhibited stable incidence trends between 1990 and 2008 (39). Additionally, lung cancer rates among Asian American women are higher than those of the general population despite their lower smoking rates (39-42). Conversely, groups with Hispanic heritage are 40–50% less likely to be diagnosed with lung cancer when compared with Caucasians (43-46). While a significant portion of this figure may be the result of lower overall smoking rates within the generalized Hispanic community, Haiman *et al.* found that among smokers with a pack-a-day habit or less (≤20 cigarettes), Hispanics' risk of developing lung cancer is 33–50% that of Caucasians' and one third that of AA. The study also found that, of the groups examined, AA and Native Hawaiians had significantly greater risks of lung cancer development than did other ethnicities (45). On the other hand, Dr. Steven Belinsky and his team at the Lovelace Respiratory Research Institute have provided evidence that contradicts this and suggests that Native American ancestry may play an important role within Hispanic lung cancer statistics. After controlling for pack year history, Leng *et al.* found that the New Mexican Hispanic smoking community possesses a higher risk of developing lung cancer as a function of pack years when compared with Caucasians, but this risk was reduced among Hispanics with a high proportion of Native American ancestry (43). Bruse *et al.* found evidence to suggest that smokers with strong Native American ancestry have half the risk of incurring chronic obstructive pulmonary disease (COPD) and significantly reduced odds of developing pulmonary function decline when compared with Caucasians (47).

While disparities in incidence and outcome reflect a complex host of factors including socioeconomic status (SES), differences in life styles, diet, smoking rates, unequal access to care, and disparate community support structures, disparity trends seem to hold constant in some capacity even when these known risk factors are accounted for in regression models, indicating that they do not fully explain the differences between groups (30,32,33,45,48,49). Thus, the growing body of evidence suggests that cancer disparities are more complex than societal discrepancies alone and that interactions between biological mechanisms and environmental factors may underpin many cancer-related health disparities (30,50,51).

Molecular and genetic variation between groups

Somatic mutations failure to explain ethnic disparities in NSCLC

Many research groups have investigated disparities through the lens of somatic mutations that differ between groups. The epidermal growth factor receptor (EGFR) and Kirsten rat sarcoma viral oncogene homolog (KRAS) families have been of particular interest due to their importance in lung carcinogenesis and patient susceptibility to targeted therapy (52). Investigations into somatic differences between AA, the group facing the largest NSCLC disparity burden, and Caucasian populations have revealed inconsistent results (53-56). Bauml *et al.* found decreased rates of EGFR mutations in AA patients compared with Caucasians, but Reinersman *et al.*, previously observed a higher frequency of EGFR mutations among AA lung cancer patients relative to Caucasians, but this difference was not statistically significant (54,56). Confounding factors such as sex and smoking history may contribute to this range of results in these early studies (57). Furthermore, some studies used pooled tumor samples from patients collected in a variety of clinical settings and employed a barrage of genetic testing techniques, thus raising concerns about sample quality, regional smoking rates, and other

factors. To address these issues and expand the scope of research beyond just EGFR and KRAS, both Campbell *et al.* and Bollig-Fischer *et al.* designed studies that controlled for these variables of concern. Ultimately, Bollig-Fischer *et al.* found no discernable evidence for differences in EGFR and KRAS between AA and Caucasian lung cancer populations, with the exception of EGFR exon 19 at p.E746. The deletion occurred solely in women and had a higher frequency among AA (33). Campbell *et al.* examined 504 cancer linked genes, including tyrosine kinase/Ras/Raf, EGFR and KRAS pathways, within a cohort of 509 lung tumors evenly split between AA and Caucasian patients of each gender. The investigators found no significant differences between AA and Caucasian populations in either squamous cell or adenocarcinoma tumor types (53). Araujo *et al.* found similar results to these two studies; however, their data indicated an overall higher frequency of driver gene alteration in Caucasian patients when compared with AA patients (58).

Alternatively, EGFR and KRAS mutations help to explain some of the disparities as well as the increase in lung cancer rates among East Asians and in particular East Asian female never-smokers. Ha *et al.* found EGFR alterations to be the most common driver of mutations (63%) among 124 non-smoking Asian women harboring this subgroup of cancer (59). Overall East Asian patients are over three times more likely to possess EGFR mutations and roughly half as likely to possess KRAS mutations, relative to Caucasian lung cancer patients (60). Groups of Native American heritage display similar trends (61). Gimbrone *et al.* examined over 1,000 genes and noted that a Hispanic/Latino population of 120 lung adenocarcinoma patients exhibited nearly double the mutational frequency of EGFR but decreased prevalence of KRAS and STK11 mutations, relative to Caucasians (62). Other genes assessed in this study did not exhibit significant discrepancies between ethnically based cohorts.

Ultimately, these sparse and inconsistent results cast doubt on the notion that differential somatic mutations alone are responsible for the observed racial disparities in incidence and mortality between various populations indicating a need to explore other avenues of molecular discrepancies such as epigenetics.

Global epigenetic differences between ethnicities

General studies of methylation and histone modifications linked to ethnicity have demonstrated stark differences between groups. An analysis of 26,485 autosomal CpGs within 201 newborns, 107 AA and 94 Caucasian, revealed 3,623 autosomal CpGs with significantly different DNA methylation levels between the two groups. While overall methylation levels were lower in AA newborns, known pathways related to non-small cell lung cancer, corroborated with the Kyoto Encyclopedia of Genes and Genomes (KEGG) database, expressed 2.1 times the level of methylation enrichment when compared to Caucasians in an Infinium Human Methylation 27 Bead Chip Assay (63). Among adults, Terry *et al.*'s 2008 study found that a cohort of AA women possessed significantly lower levels of global DNA methylation when compared with Hispanic (who had the highest levels) and Caucasian women (64). A subsequent LINE-1 methylation study in normal colonic tissue from a cohort of middle-aged male and female patients with a history of benign epithelial tumors revealed similar levels of methylation among Caucasian and AA patients, but increased levels among Hispanics (65).

Studies such as these indicate clearly that a significant frequency of DNA methylation differences exist between ethnic communities and thus more specific analyses could provide insight into particular causal pathways linked to differences in oncogenesis or outcome.

Differences in response to environmental toxins

Emerging evidence suggests that, amongst various ethnic groups, certain epigenetic regulatory pathways respond differentially to exposure to known environmental toxins (66-68). The causal link between tobacco inhalation, the toxin most commonly associated with lung cancer development, and gene promoter methylation has been explored within the context of ethnicity and resulted in inconsistent findings. Sun *et al.* suggested that DNA methylation changes are specifically linked to smoking rather than an interplay between ethnicity and toxin exposure. This group explored 27,578 CpG loci and 15 known smoking-related DNA methylation sites (from studies that previously examined predominantly Caucasian cohorts) in a cohort of 972 AA, and found that the majority of the smoking-related DNA methylation sites remained consistent between the two groups (69). Dogan *et al.*, on the other hand, discovered that GPR15, a chemokine receptor involved in human immunodeficiency virus (HIV) propagation, was significantly differentially methylated in AA smokers when compared with Caucasian smokers. The group also mentioned that this could point towards a causal

pathway for the increased prevalence of HIV within the AA community as the loss of function in the GPR15 gene may leave patients in this demographic subset at increased risk for HIV susceptibility (70).

Exposures to toxins such as *in utero* tobacco particles, diesel exhaust, and psychosocial stress were linked to differential methylation changes within Latino ethnic subgroups in Galanter *et al.'s* investigation of over 450,000 CpG sites among a 573-person patient cohort. In particular, the group found that 27 loci known to be associated with maternal smoking showed significantly different degrees of methylation enrichment amongst different ethnic groups (71). Another study, Leng *et al.*, noted that Native American genetic ancestry helps to safeguard exfoliated lung cells, collected from sputum, from DNA methylation alterations. The group stratified patients by proportion of Native American ancestry, based on genetic markers, and found that smokers with higher levels of Native American heritage had a significantly reduced prevalence of methylation changes in a 12-gene panel of loci associated with lung cancer risk. Methylation alterations of CpG islands in genes DAL1, JPH3, and GATA4 were found to be lowest amongst patients with Native American ancestry (43).

The reason behind these differential hereditary links to gene-specific methylation rates could lie within single-nucleotide polymorphisms or SNPs. As Dawn DeMeo, from Harvard School of Medicine, pointed out in an editorial, a SNP in a promoter region could either be characterized by a C allele creating a CpG site with methylation potential or a T allele and thus neither be a CpG site nor possess methylation potential. The C allele of her example loci, rs61277615, has a 90% frequency within individuals of Caucasian and Asian descent, while the C and T alleles are represented equally among individuals of African heritage. The frequency of these allele variants among Native American groups is unknown (44). This rationale follows for other cases as well considering a differential SNP mutation in rs2230344, a loci within the promoter region of GPR15, was observed within the AA cohort in Dogan *et al.'s* analysis (70).

We must continue to broaden our studies to investigate how environmental factors interact with epigenetic regulatory pathways while keeping in mind that known carcinogenic routes may not reflect the complete range of oncogenic frameworks. While the majority of pathways may remain consistent between groups, it is possible that differential heredity linked SNPs or other mechanisms may lead to a variety of DNA methylation changes between patients and thus different pathways may be important and unique to particular ethnic communities.

Insights from other cancers

Other tumor types have already revealed important epigenetic differences between ethnic groups. Within the context of colorectal cancer (CRC), microsatellite instability (MSI), a condition characterized by a deficient mismatch-repair (MMR) system, is associated with poor differentiation, mucinous histology, lymphoid infiltrate, and poor response to chemotherapy (72-77). MSI typically arises from hypermethylation of the promoter region of the mutL homolog 1 gene (MLH1). MSI can lead to further aberrant methylation across a wide spectrum of genes and general destabilization of the genomic framework within a tumor (78). Some studies have indicated that MSI rates are significantly higher in the AA CRC community, which is already burdened by higher rates of disease and more aggressive forms of CRC, than in the Caucasian population (79). However, a meta-analysis found little statistical difference in overall MSI rates between AA, Caucasians, and Hispanics (80). Regardless, the impact MSI has on various populations is clearly ethnically linked. MSI-derived aberrations in chromosomes 11, 17p, and X are more prominent within the AA population when compared with Caucasians. Additionally, gene specific methylation changes in THRB, RAF1, LPL, DCC, XIST, PCNT, STS, TPD521.2, TOP1, and TNFRSF6B are all observably different between the two groups (11,81,82). These methylation discrepancies indicate that different sets of molecular markers are important in determining patients' susceptibility to various disease states. The biomolecular patterns listed above could have potential as early detection or prognostic biomarkers for CRC among ethnical groups and could lead to novel strategies for personalized care. MSI detection is important for projecting disease course, choosing relevant therapeutics, and identifying patients who might benefit from surgery alone (83).

Similar cases of ethnically linked epigenetic relevance are prevalent in breast cancer. Breast cancer incidence is lower among AA women relative to Caucasians, but the mortality rate is significantly higher in the AA community (1). Additionally, AA women are more likely to be diagnosed with the disease at an early age and express more aggressive phenotypes that are higher-grade and are linked to worse outcomes (84-87). Associations between ancestry and epigenetics have been found within breast cancer. Hypermethylation of BRCA1 and p16, both well-

known tumor suppressor genes, in normal breast tissue from Caucasian and AA patients were associated with a family history of cancer (88). Other studies have shown that tumors from AA breast cancer patients have a higher frequency of methylation in RASSF1A, HIN-1, Twist, Cyclin D2, and RAR-β when compared with Caucasian breast cancer patients (89,90). Of these genes Cyclin D2 exhibited a stark contrast in frequency between AAs (64%) and Caucasians (19%). While some of these genes may not be linked to prognosis, hypermethylation of Cyclin D2 and RASSF1A are both associated with higher relapse rates and poor overall survival (91-93).

Prostate cancer is yet another tumor in which there are significant disparities in terms of disease burden and outcome. Incidence and mortality rates are 60% and 200–300% higher among AA men relative to Caucasians (94). Hypermethylation of GSTP1, a gene that codes for an enzyme involved with the reduction of intracellular chemical carcinogens and reactive oxidative species, has been shown to be an important event in prostate cancer progression. The literature regarding hypermethylation rate differences between ethnicities, however, has been inconsistent (95-98). Nevertheless, GSTP1 functionality plays a significant role in patient susceptibility to the carcinogenic impacts various dietary and lifestyle styles can have, which differ between the two populations and ultimately do play a role in differentiating the groups' overall outcomes (94,99). Other genes such as CD44 and CDH1 have also been reported to exhibit racially-linked differential methylation statuses (95). Additionally, the prostate cancer rate within the United States is 15 times greater than is that of Asian countries. It has been proposed that this difference may be linked to the relative levels of soy consumed by each group and the known demethylating effect soy isoflavone possesses (97,100,101).

The case for diverse cohorts in DNA methylation biomarker studies

Differences in socioeconomic status, life style, diet, smoking rates, access to care, community support structures, and access to diagnostic procedures underpin and reinforce the differential disease incidence and outcome burdens within particular communities. Socioeconomically disadvantaged groups lack access to the current standard of care of lung cancer screening, LDCT imaging. Additionally, the high rate of false positives commonly necessitate that patients return for multiple follow-up appointments in order to monitor lesion progression and to accurately diagnose lung cancer. Methylation biomarker based liquid biopsy techniques rely on bodily fluids and have the potential to bring lung cancer screening to the community thereby reducing unequal accessibility. Blood, sputum, or urine could be collected from patients in a primary care physician's office, community health clinic, or even at home. In addition, DNA methylation can be used to diagnose patients early as well as predict effective treatment strategies.

However, the variation in methylation rates between ethnicities presents a challenge. The factors listed above disproportionately impact ethnic minorities in a negative manner making liquid biopsies indispensable for their communities. While some groups have investigated molecular differences in NSCLC tumors from various ethnic populations, to date, very few publications have controlled for race or ethnicity in their early detection or prognostic DNA methylation biomarker studies. This absence can be seen as a form of unconscious structural violence within medical research and could potentially have serious future ramifications. This review seeks to summarize these findings and open the door for future researchers to study personalized biomarker panels in order to effectively detect NSCLC in its early stages across diverse patient populations. Studies that reflect the true nuance of methylation status in NSCLC among different ethnical groups could find patterns that may pave the way for novel therapy targets. Diverse patient cohorts could provide the scientific community with a better understanding of the interplay between patient backgrounds and optimal care modalities.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017;67:7-30.
2. Ng M, Freeman MK, Fleming TD, et al. Smoking

prevalence and cigarette consumption in 187 countries, 1980-2012. JAMA 2014;311:183-92.
3. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin 2016;66:271-89.
4. Woodard GA, Jones KD, Jablons DM. Lung Cancer Staging and Prognosis. Cancer Treat Res 2016;170:47-75.
5. Howlader NNA, Krapcho M, Miller D, et al, editors. SEER Cancer Statistics Review, 1975-2014. Bethesda, MD: National Cancer Institute; 2017.
6. National Lung Screening Trial Research Team, Aberle DR, Berg CD, et al. The National Lung Screening Trial: overview and study design. Radiology 2011;258:243-53.
7. Hoffman RM, Sanchez R. Lung cancer screening. Med Clin North Am 2017;101:769-85.
8. Tammemagi MC, Katki HA, Hocking WG, et al. Selection criteria for lung-cancer screening. N Engl J Med 2013;368:728-36.
9. Lackey A, Donington JS. Surgical management of lung cancer. Semin Intervent Radiol 2013;30:133-40.
10. Mayeux R. Biomarkers: potential uses and limitations. NeuroRx 2004;1:182-8.
11. Manne U, Jadhav T, Putcha BK, et al. Molecular biomarkers of colorectal cancer and cancer disparities: current status and perspective. Curr Colorectal Cancer Rep 2016;12:332-44.
12. Fleming TR, Powers JH. Biomarkers and surrogate endpoints in clinical trials. Stat Med 2012;31:2973-84.
13. Reid M, Yasko J. The role of biomarkers in cancer clinical trials. Semin Oncol Nurs 2012;28:116-21.
14. Zamay TN, Zamay GS, Kolovskaya OS, et al. Current and prospective protein biomarkers of lung cancer. Cancers (Basel) 2017;9:155.
15. Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. Nat Genet 2003;33 Suppl:245-54.
16. Vaissiere T, Sawan C, Herceg Z. Epigenetic interplay between histone modifications and DNA methylation in gene silencing. Mutat Res 2008;659:40-8.
17. Besser D, Gotz F, Schulze-Forster K, et al. DNA methylation inhibits transcription by RNA polymerase III of a tRNA gene, but not of a 5S rRNA gene. FEBS Lett 1990;269:358-62.
18. Egger G, Liang G, Aparicio A, et al. Epigenetics in human disease and prospects for epigenetic therapy. Nature 2004;429:457-63.
19. Herman JG, Baylin SB. Gene silencing in cancer in association with promoter hypermethylation. N Engl J Med 2003;349:2042-54.
20. Feinberg AP, Tycko B. The history of cancer epigenetics. Nat Rev Cancer 2004;4:143-53.
21. Feinberg AP, Vogelstein B. Hypomethylation distinguishes genes of some human cancers from their normal counterparts. Nature 1983;301:89-92.
22. Bailey VJ, Zhang Y, Keeley BP, et al. Single-tube analysis of DNA methylation with silica superparamagnetic beads. Clin Chem 2010;56:1022-5.
23. Hulbert A, Jusue-Torres I, Stark A, et al. Early Detection of Lung Cancer Using DNA Promoter Hypermethylation in Plasma and Sputum. Clin Cancer Res 2017;23:1998-2005.
24. Gama-Sosa MA, Slagel VA, Trewyn RW, et al. The 5-methylcytosine content of DNA from human tumors. Nucleic Acids Res 1983;11:6883-94.
25. Galusca B, Dumollard JM, Lassandre S, et al. Global DNA methylation evaluation: potential complementary marker in differential diagnosis of thyroid neoplasia. Virchows Arch 2005;447:18-23.
26. Piyathilake CJ, Frost AR, Bell WC, et al. Altered global methylation of DNA: an epigenetic difference in susceptibility for lung cancer is associated with its progression. Hum Pathol 2001;32:856-62.
27. Liu H, Liu W, Wu Y, et al. Loss of epigenetic control of synuclein-gamma gene as a molecular indicator of metastasis in a wide range of human cancers. Cancer Res 2005;65:7635-43.
28. Santourlidis S, Florl A, Ackermann R, et al. High frequency of alterations in DNA methylation in adenocarcinoma of the prostate. Prostate 1999;39:166-74.
29. Park SY, Yoo EJ, Cho NY, et al. Comparison of CpG island hypermethylation and repetitive DNA hypomethylation in premalignant stages of gastric cancer, stratified for Helicobacter pylori infection. J Pathol 2009;219:410-6.
30. Verma M. Cancer epigenetics. New York: Springer; 2014.
31. Albano JD, Ward E, Jemal A, et al. Cancer mortality in the United States by education level and race. J Natl Cancer Inst 2007;99:1384-94.
32. DeSantis CE, Siegel RL, Sauer AG, et al. Cancer statistics for African Americans, 2016: Progress and opportunities in reducing racial disparities. CA Cancer J Clin 2016;66:290-308.
33. Bollig-Fischer A, Chen W, Gadgeel SM, et al. Racial diversity of actionable mutations in non-small cell lung cancer. J Thorac Oncol 2015;10:250-5.
34. Schwartz AG, Swanson GM. Lung carcinoma in African Americans and whites. A population-based study in

metropolitan Detroit, Michigan. Cancer 1997;79:45-52.
35. Gadgeel SM, Severson RK, Kau Y, et al. Impact of race in lung cancer: analysis of temporal trends from a surveillance, epidemiology, and end results database. Chest 2001;120:55-63.
36. Hardy D, Liu CC, Xia R, et al. Racial disparities and treatment trends in a large cohort of elderly black and white patients with nonsmall cell lung cancer. Cancer 2009;115:2199-211.
37. Anderson C, Burns DM. Patterns of adolescent smoking initiation rates by ethnicity and sex. Tob Control 2000;9 Suppl 2:II4-8.
38. Cote ML, Kardia SL, Wenzlaff AS, et al. Risk of lung cancer among white and black relatives of individuals with early-onset lung cancer. JAMA 2005;293:3036-42.
39. Gomez SL, Noone AM, Lichtensztajn DY, et al. Cancer incidence trends among Asian American populations in the United States, 1990-2008. J Natl Cancer Inst 2013;105:1096-110.
40. Raz DJ, Gomez SL, Chang ET, et al. Epidemiology of non-small cell lung cancer in Asian Americans: incidence patterns among six subgroups by nativity. J Thorac Oncol 2008;3:1391-7.
41. Barnoya J, Glantz S. Association of the California tobacco control program with declines in lung cancer incidence. Cancer Causes Control 2004;15:689-95.
42. Centers for Disease C, Prevention. State-specific trends in lung cancer incidence and smoking--United States, 1999-2008. MMWR Morb Mortal Wkly Rep 2011;60:1243-7.
43. Leng S, Liu Y, Thomas CL, et al. Native American ancestry affects the risk for gene methylation in the lungs of Hispanic smokers from New Mexico. Am J Respir Crit Care Med 2013;188:1110-6.
44. DeMeo DL, Rybicki BA. DNA methylation and ancestry. The smoke starts to clear. Am J Respir Crit Care Med 2013;188:1049-51.
45. Haiman CA, Stram DO, Wilkens LR, et al. Ethnic and racial differences in the smoking-related risk of lung cancer. N Engl J Med 2006;354:333-42.
46. Howington JA, Blum MG, Chang AC, et al. Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e278S-313S.
47. Bruse S, Sood A, Petersen H, et al. New Mexican Hispanic smokers have lower odds of chronic obstructive pulmonary disease and less decline in lung function than non-Hispanic whites. Am J Respir Crit Care Med 2011;184:1254-60.
48. Blackstock AW, Herndon JE, 2nd, Paskett ED, et al. Similar outcomes between African American and non-African American patients with extensive-stage small-cell lung carcinoma: report from the Cancer and Leukemia Group B. J Clin Oncol 2006;24:407-12.
49. Bach PB, Schrag D, Brawley OW, et al. Survival of blacks and whites after a cancer diagnosis. JAMA 2002;287:2106-13.
50. Godley SH, Hedges K, Hunter B. Gender and racial differences in treatment process and outcome among participants in the adolescent community reinforcement approach. Psychol Addict Behav 2011;25:143-54.
51. Godley PA, Schenck AP, Amamoo MA, et al. Racial differences in mortality among Medicare recipients after treatment for localized prostate cancer. J Natl Cancer Inst 2003;95:1702-10.
52. Midha A, Dearden S, McCormack R. EGFR mutation incidence in non-small-cell lung cancer of adenocarcinoma histology: a systematic review and global map by ethnicity (mutMapII). Am J Cancer Res 2015;5:2892-911.
53. Campbell JD, Lathan C, Sholl L, et al. Comparison of prevalence and types of mutations in lung cancers among black and white populations. JAMA Oncol 2017;3:801-9.
54. Reinersman JM, Johnson ML, Riely GJ, et al. Frequency of EGFR and KRAS mutations in lung adenocarcinomas in African Americans. J Thorac Oncol 2011;6:28-31.
55. Cote ML, Haddad R, Edwards DJ, et al. Frequency and type of epidermal growth factor receptor mutations in African Americans with non-small cell lung cancer. J Thorac Oncol 2011;6:627-30.
56. Bauml J, Mick R, Zhang Y, et al. Frequency of EGFR and KRAS mutations in patients with non small cell lung cancer by racial background: do disparities exist? Lung Cancer 2013;81:347-53.
57. Toyooka S, Matsuo K, Shigematsu H, et al. The impact of sex and smoking status on the mutational spectrum of epidermal growth factor receptor gene in non small cell lung cancer. Clin Cancer Res 2007;13:5763-8.
58. Araujo LH, Lammers PE, Matthews-Smith V, et al. Somatic mutation spectrum of non-small-cell lung cancer in african americans: a pooled analysis. J Thorac Oncol 2015;10:1430-6.
59. Ha SY, Choi SJ, Cho JH, et al. Lung cancer in never-smoker Asian females is driven by oncogenic mutations, most often involving EGFR. Oncotarget 2015;6:5465-74.
60. Zhou W, Christiani DC. East meets West: ethnic differences in epidemiology and clinical behaviors of lung cancer between East Asians and Caucasians. Chin J Cancer

2011;30:287-92.
61. Cress WD, Chiappori A, Santiago P, et al. Lung cancer mutations and use of targeted agents in Hispanics. Rev Recent Clin Trials 2014;9:225-32.
62. Gimbrone NT, Sarcar B, Gordian ER, et al. Somatic mutations and ancestry markers in hispanic lung cancer patients. J Thorac Oncol 2017;12:1851-6.
63. Adkins RM, Krushkal J, Tylavsky FA, et al. Racial differences in gene-specific DNA methylation levels are present at birth. Birth Defects Res A Clin Mol Teratol 2011;91:728-36.
64. Terry MB, Ferris JS, Pilsner R, et al. Genomic DNA methylation among women in a multiethnic New York City birth cohort. Cancer Epidemiol Biomarkers Prev 2008;17:2306-10.
65. Figueiredo JC, Grau MV, Wallace K, et al. Global DNA hypomethylation (LINE-1) in the normal colon and lifestyle characteristics and dietary and genetic factors. Cancer Epidemiol Biomarkers Prev 2009;18:1041-9.
66. Chen W, Boutaoui N, Brehm JM, et al. ADCYAP1R1 and asthma in Puerto Rican children. Am J Respir Crit Care Med 2013;187:584-8.
67. Jiang R, Jones MJ, Sava F, et al. Short-term diesel exhaust inhalation in a controlled human crossover study is associated with changes in DNA methylation of circulating mononuclear cells in asthmatics. Part Fibre Toxicol 2014;11:71.
68. Joubert BR, Haberg SE, Nilsen RM, et al. 450K epigenome-wide scan identifies differential DNA methylation in newborns related to maternal smoking during pregnancy. Environ Health Perspect 2012;120:1425-31.
69. Sun YV, Smith AK, Conneely KN, et al. Epigenomic association analysis identifies smoking-related DNA methylation sites in African Americans. Hum Genet 2013;132:1027-37.
70. Dogan MV, Xiang J, Beach SR, et al. Ethnicity and Smoking-Associated DNA Methylation Changes at HIV Co-Receptor GPR15. Front Psychiatry 2015;6:132.
71. Galanter JM, Gignoux CR, Oh SS, et al. Differential methylation between ethnic sub-groups reflects the effect of genetic ancestry and environmental exposures. eLife 2017;6:e20532.
72. Lynch HT, Smyrk TC, Watson P, et al. Genetics, natural history, tumor spectrum, and pathology of hereditary nonpolyposis colorectal cancer: an updated review. Gastroenterology 1993;104:1535-49.
73. Niv Y. Microsatellite instability and MLH1 promoter hypermethylation in colorectal cancer. World J Gastroenterol 2007;13:1767-9.
74. Carethers JM, Smith EJ, Behling CA, et al. Use of 5-fluorouracil and survival in patients with microsatellite-unstable colorectal cancer. Gastroenterology 2004;126:394-401.
75. Thibodeau SN, French AJ, Cunningham JM, et al. Microsatellite instability in colorectal cancer: different mutator phenotypes and the principal involvement of hMLH1. Cancer Res 1998;58:1713-8.
76. Thibodeau SN, Bren G, Schaid D. Microsatellite instability in cancer of the proximal colon. Science 1993;260:816-9.
77. Moslein G, Tester DJ, Lindor NM, et al. Microsatellite instability and mutation analysis of hMSH2 and hMLH1 in patients with sporadic, familial and hereditary colorectal cancer. Hum Mol Genet 1996;5:1245-52.
78. Herman JG, Umar A, Polyak K, et al. Incidence and functional consequences of hMLH1 promoter hypermethylation in colorectal carcinoma. Proc Natl Acad Sci U S A 1998;95:6870-5.
79. Ashktorab H, Smoot DT, Carethers JM, et al. High incidence of microsatellite instability in colorectal cancer from African Americans. Clin Cancer Res 2003;9:1112-7.
80. Ashktorab H, Ahuja S, Kannan L, et al. A meta-analysis of MSI frequency and race in colorectal cancer. Oncotarget 2016;7:34546-57.
81. Nayani R, Ashktorab H, Brim H, et al. Genetic Basis for Colorectal Cancer Disparities. Curr Colorectal Cancer Rep 2015;11:408-13.
82. Brim H, Lee E, Abu-Asab MS, et al. Genomic aberrations in an African American colorectal cancer cohort reveals a MSI-specific profile and chromosome X amplification in male patients. PLoS One 2012;7:e40392.
83. Merok MA, Ahlquist T, Royrvik EC, et al. Microsatellite instability has a positive prognostic impact on stage II colorectal cancer after complete resection: results from a large, consecutive Norwegian series. Ann Oncol 2013;24:1274-82.
84. Mohammed SI, Springfield S, Das R. Role of epigenetics in cancer health disparities. Methods Mol Biol 2012;863:395-410.
85. Agurs-Collins T, Dunn BK, Browne D, et al. Epidemiology of health disparities in relation to the biology of estrogen receptor-negative breast cancer. Semin Oncol 2010;37:384-401.
86. Hayanga AJ, Newman LA. Investigating the phenotypes and genotypes of breast cancer in women with African

ancestry: the need for more genetic epidemiology. Surg Clin North Am 2007;87:551-68, xii.
87. Amend K, Hicks D, Ambrosone CB. Breast cancer in African-American women: differences in tumor biology from European-American women. Cancer Res 2006;66:8327-30.
88. Dumitrescu RG, Marian C, Krishnan SS, et al. Familial and racial determinants of tumour suppressor genes promoter hypermethylation in breast tissues from healthy women. J Cell Mol Med 2010;14:1468-75.
89. Fackler MJ, McVeigh M, Evron E, et al. DNA methylation of RASSF1A, HIN-1, RAR-beta, Cyclin D2 and Twist in in situ and invasive lobular breast carcinoma. Int J Cancer 2003;107:970-5.
90. Mehrotra J, Ganpat MM, Kanaan Y, et al. Estrogen receptor/progesterone receptor-negative breast cancers of young African-American women have a higher frequency of methylation of multiple genes than those of Caucasian women. Clin Cancer Res 2004;10:2052-7.
91. Jiang Y, Cui L, Chen WD, et al. The prognostic role of RASSF1A promoter methylation in breast cancer: a meta-analysis of published data. PLoS One 2012;7:e36780.
92. Karray-Chouayekh S, Trifa F, Khabir A, et al. Aberrant methylation of RASSF1A is associated with poor survival in Tunisian breast cancer patients. J Cancer Res Clin Oncol 2010;136:203-10.
93. Truong PK, Lao TD, Doan TP, et al. Loss of expression of cyclin d2 by aberrant DNA methylation: a potential biomarker in vietnamese breast cancer patients. Asian Pac J Cancer Prev 2015;16:2209-13.
94. Powell IJ, Bollig-Fischer A. Minireview: the molecular and genomic basis for prostate cancer health disparities. Mol Endocrinol 2013;27:879-91.
95. Woodson K, Hayes R, Wideroff L, et al. Hypermethylation of GSTP1, CD44, and E-cadherin genes in prostate cancer among US Blacks and Whites. Prostate 2003;55:199-205.
96. Kwabi-Addo B, Wang S, Chung W, et al. Identification of differentially methylated genes in normal prostate tissues from African American and Caucasian men. Clin Cancer Res 2010;16:3539-47.
97. Li LC. Epigenetics of prostate cancer. Front Biosci 2007;12:3377-97.
98. Enokida H, Shiina H, Urakami S, et al. Ethnic group-related differences in CpG hypermethylation of the GSTP1 gene promoter among African-American, Caucasian and Asian patients with prostate cancer. Int J Cancer 2005;116:174-81.
99. Nelson WG, De Marzo AM, Yegnasubramanian S. Epigenetic alterations in human prostate cancers. Endocrinology 2009;150:3991-4002.
100. Varinska L, Gal P, Mojzisova G, et al. Soy and breast cancer: focus on angiogenesis. Int J Mol Sci 2015;16:11728-49.
101. Mahmoud AM, Yang W, Bosland MC. Soy isoflavones and prostate cancer: a review of molecular mechanisms. J Steroid Biochem Mol Biol 2014;140:116-32.

Cite this article as: Lerner L, Winn R, Hulbert A. Lung cancer early detection and health disparities: the intersection of epigenetics and ethnicity. J Thorac Dis 2018;10(4):2498-2507. doi: 10.21037/jtd.2018.04.07

