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The influence of race and ethnicity on the biology of cancer

Brian E. Henderson,
The Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Norris Comprehensive Cancer Center, Los Angeles, California 90033-0804, USA

Norman H. Lee,
The George Washington University Medical Center, Washington, DC, Department of Pharmacology & Physiology, 2300 I Street Northwest, Ross Hall, Washington, DC 20037, USA

Victoria Seewaldt, and
Department of Medicine, Duke University, BOX 2628, Room 221A MSRB, DUMC, Durham, North Carolina 27710, USA

Hongbing Shen
Department of Epidemiology and Biostatistics and Ministry of Education (MOE) Key Lab for Modern Toxicology, School of Public Health, Nanjing Medical University, 140 Hanzhong Rd., Nanjing 210029, Jiangsu, China; is also at The Section of Clinical Epidemiology, Jiangsu Key Laboratory of Cancer Biomarkers, Prevention and Treatment, Cancer Center, Nanjing Medical University, Nanjing 210029, Jiangsu, China

Brian E. Henderson: behender@med.usc.edu; Norman H. Lee: nhlee@gwu.edu; Victoria Seewaldt: seewa001@mc.duke.edu; Hongbing Shen: hbshen@njmu.edu.cn

Abstract

It is becoming clear that some of the differences in cancer risk, incidence and survival among people of different racial and ethnic backgrounds can be attributed to biological factors. However, identifying these factors and exploiting them to help eliminate cancer disparities has proved challenging. With this in mind, we asked four scientists for their opinions on the most crucial advances, as well as the challenges and what the future holds for this important emerging area of research.

In your opinion, what have been the most crucial advances in this field over the past 5 years?

Brian E. Henderson

A few years ago, my colleagues and I published an article in this journal outlining the rationale for the search for germline genetic variants that might provide insight into the aetiology of common cancers. At the time, we hypothesized that such genetic variants might reside within candidate genes in pathways thought to be aetio logically relevant[1]. We based our approach on the known variation in cancer incidence in different racial and ethnic groups. The Multiethnic Cohort Study (MEC), based in Hawaii and California, USA, had been established to use such variations in the specific rates of cancers in different ethnic groups to attempt to disentangle the environmental from the genetic contributions to cancers[2]. Thus, in the MEC, as in the general population of the United States, the rates of

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prostate cancer were much higher in populations of African descent and the rates of breast cancer were highest in native Hawaiians and Japanese populations[1]. In the intervening years, we have observed additional examples of such discrepancies in cancer risk, including a higher incidence of oestrogen receptor (ER)-negative breast cancer in women of African descent[3], and a higher risk of lung cancer among moderate smokers for men of African descent and native Hawaiians[4].

In large part, the candidate gene approach was not successful in explaining the differences in cancer risk within or between racial groups. However, the rapid evolution of genotyping technology created the opportunity for 'agnostic' genome-wide association studies (GWASs) in individuals with a particular cancer and in controls. In 2006, Amundadottir and colleagues published the first evidence of a prostate cancer risk locus at chromosomal location 8q24 (REF. 5). The frequency of the risk allele was higher in a small series of African American prostate cancer cases than in their European counterparts. Using admixture scanning with more detailed fine mapping, my colleagues and I published confirmatory evidence of the original locus in 8q24 (REF. 6), and Haiman *et al.* extended this work to demonstrate that there were multiple independent risk loci within a large 3 Mb span of 8q24, many of which were most common in men of African descent[7]. We concluded that these 8q24 loci could collectively explain up to 50% of the increased risk in men of African descent. Of additional interest, subsequent work has demonstrated that independent, but occasionally overlapping, loci within the 8q24 region are also associated with other cancers, including cancers of the breast, ovary, colorectum and bladder, in multiple ethnic groups.

More recently, Haiman *et al.* have published evidence of a prostate cancer susceptibility locus at 17q21 that is more specific to an African population[8] in that the frequency of the risk allele at this locus is about 5% in African men but is quite rare (<1%) in Europeans and Asians. The authors suggested that close to 10% of the increased risk of prostate cancer in men of African descent could be attributed to this risk locus.

Several susceptibility loci for breast cancer have been discovered in women, and one of these has been specifically linked to women of African descent. A common variant at the TERT-CLPTM1L locus has been associated with ER-negative breast cancer, and the risk allele is twice as common in African American women as in their European counterparts[9].

Additional GWASs of African American, Japanese and Chinese cancer cases and controls have been published or are currently underway. Undoubtedly, additional genetic variants will be identified with allelic frequencies that vary with the cancer risk between different populations.

Norman H. Lee

The implementation of genomic approaches (for example, GWASs, gene expression and epigenomic profiling, and next-generation sequencing) over the past 5 years has reinvigorated attention into the biological component of cancer health disparities. There are striking population (race and ethnicity) disparities in risk and survival outcome borne out of current health statistics data for many cancers, including cancers of the prostate, colon and breast[10]. An overarching theme of the American Cancer Society 2015 challenge goals has been the elimination of disparities in cancer burden.

One particularly prominent example is the study of African American patients with prostate cancer and their Caucasian counterparts. The African American population is 1.6 times more likely to develop prostate cancer and 2.5 times more likely to die from this disease than Caucasians[10]. On the basis of epidemiological studies, multiple socioeconomic and

environmental factors have been advanced to explain the observed prostate cancer health disparities between African Americans and Caucasians, including access to health care, attitudes to health care, socioeconomic differences, diet, and differences in type and aggressiveness of treatment. Whereas socioeconomic factors do contribute to this health disparity, they do not fully explain the differences in prostate cancer incidence, aggressiveness and mortality among different race and ethnic groups[11]. Studies still reveal higher risk of, and mortality owing to, prostate cancer in African American versus Caucasian men even after adjustment for socioeconomic status, environmental factors and access to health care[12,13]. Thus, intrinsic biological factors must partly account for the observed cancer health disparities.

The contributors*

Brian E. Henderson is a professor of preventive medicine at the Keck School of Medicine at the University of Southern California, USA. He has served as Dean of the Keck School of Medicine and President of the Salk Institute for Biological Sciences. Together with Dr. L. Kolonel (University of Hawaii, USA), he initiated the Multiethnic Cohort Study in 1993. His research focuses on genetic susceptibility to breast, prostate and colorectal cancer arising from mutations in hormone and growth factor pathways, and he is the Principal Investigator of a genome-wide association study examining 10,000 prostate cancer cases and controls in African Americans. He has a long standing interest in the health disparities of the Latin American and African American populations of California, USA.

Norman H. Lee is Professor of Pharmacology and Physiology at the George Washington University (GWU) Medical Center, USA. He also serves as Director of the Molecular Medicine Graduate Program and the Molecular Oncology Graduate Concentration at the GWU Institute for Biomedical Sciences. He received a Ph.D. in pharmacology from the University of Maryland, USA, and carried out his postdoctoral training in molecular cell signalling at the US National Institute on Alcohol Abuse and Alcoholism. Afterwards he joined the Institute for Genomic Research, USA, focusing on functional cancer genomics. His current research includes the genomics of cancer health disparities, and gene network circuitry involved in cancer metastasis.

Victoria Seewaldt is a professor of medicine at Duke University, USA, where she leads the Breast Cancer Early Detection Program and a Durham community outreach programme for underserved women. Her research investigates the origins of triple-negative breast cancer. Biomarkers identified in the laboratory are tested as predictors of short-term breast cancer risk in the high-risk women who partner in her clinical trials. She works with her Navigator team and the Durham community to provide breast cancer education, free breast cancer screening and treatment, mentorship of young ethnic minority scholars, and a forum for community-partnered trials.

Hongbing Shen is a molecular epidemiologist of cancer focusing on genetic polymorphisms and environmental determinants of different types of cancers in Chinese populations. He is the Principal Investigator of the Chinese lung and gastric cancer genome-wide association studies and discovered several new susceptibility loci associated with these cancers in the Chinese population. He is also collaborating with researchers in the United States as a co-Principal Investigator of two US National Institutes of Health grants to study genetic determinants of lung cancer development and prognosis in both Chinese and Caucasian populations. He has published more than 150 papers in international peer-reviewed journals including *Nature Genetics, The Journal of Clinical Investigation, The Journal of Clinical Oncology* and *Cancer Research*.

* Listed in alphabetical order.

Traditional investigative approaches (that is, those of the pre-genomics and pre-high-throughput era) have implicated a number of molecular factors as contributing to prostate cancer health disparities, such as differences in the hormonal milieu of the tumour (genetic mutations contributing to higher dihydrotestosterone to testosterone ratio)[14], decreased apoptosis due to lower BCL-2 levels[15] and oncogenic activation as a consequence of overexpressed epidermal growth factor receptor (EGFR)[16]. With the availability of high-throughput-scale technologies and the growing sophistication of computational tools, systematic genomics analysis of prostate cancer has further enhanced our overall understanding of the genetic risk factors that account for prostate cancer health disparities. GWASs have become increasingly popular in studies of population-based cancer health disparities. Although the search for common germline risk variants has been daunting, compelling evidence implicates alleles in 8q24 and 17q21 as susceptibility loci for prostate cancer in men of African ancestry[7,8,17]. Hybridization-based genome-wide expression analysis (that is, DNA microarrays) has identified autoimmunity and inflammation as common themes of differentially expressed genes that distinguish prostate cancer in African Americans from that in Caucasians[18]. In another study, prostate cancer gene expression profiles in African Americans and Caucasians have revealed that at least four candidate genes — transcription elongation factor S-II protein-like 7 (*TCEAL7*), histone deacetylase 11 (*HDAC11*), interferon-regulatory factor 4 (*IRF4*) and *PGR* (encoding progesterone receptor (PR)), which are all downregulated in African Americans — may partially account for the observed prostate cancer health disparities[19]. Although the above-mentioned genomics studies are certainly intriguing, their findings have been association-based (‘guilt by association’), and direct causal links of these genes or loci to cancer health disparities have not yet been firmly established.

Victoria Seewaldt

Race and ethnicity are predictors of poor survival for many cancers, including cancer of the breast, colon and prostate[20,21]. Lack of access to health care clearly affects clinical stage and prognosis. However, it has also been long suspected that a complex and synergistic interaction between biology and economic and social disparities also contributes to racial and ethnic differences in cancer survival.

It is now recognized that cancer is not a single disease, but is instead a heterogeneous collection of diseases, each with its own distinct biological behaviour and prognosis. Genomic profiling of primary breast cancers has identified molecular subtypes, including the poor prognosis basal-like subtype (ER^-, PR^-, HER2 (also known as ERBB2)$^-$ and cytokeratin 5 and cytokeratin 6^+)[22,23]. The Carolina Breast Cancer Study showed that basal-like breast tumours occurred at a higher prevalence among premenopausal African American women[24]. A higher prevalence of basal-like breast tumours and a lower prevalence of good prognosis subtypes are hypothesized to contribute to the poor overall prognosis of premenopausal African American women with breast cancer. However, a higher frequency of poor prognosis subtypes does not fully explain differences in survival. The 5-year survival of premenopausal African American women with stage III/IV basal-type breast cancer was significantly worse than that of non-Hispanic Caucasian and Hispanic premenopausal women (14% versus 37% and 38%, respectively)[24].

Numerous studies provide evidence that many aggressive human cancers (such as breast, colon, ovarian, pancreas and prostate cancer and leukaemia) may contain self-renewing cells with progenitor cell features, called tumour-initiating cells (TICs) or cancer stem cells (CSCs)[25,26]. Increasing evidence links the self-renewing properties of TICs to aggressive

tumour biology and chemotherapy resistance[27–30]. It is hypothesized that TICs may have a role in determining why some populations can have a more aggressive cancer than another, or higher rates of disease recurrence, resistance to treatment and increased metastasis. The mechanistic relationship between TICs and racial and ethnic differences in cancer survival is not yet well defined, but is likely to be an area of key discovery in the next 5 to 10 years.

As obesity rates continue to rise for many racial and ethnic groups, there is a need to better understand the impact of obesity on the initiation of aggressive cancers[31]. First, it is important to understand how obesity may differ in specific racial and ethnic groups. For example, an Asian woman with a body mass index (BMI) of 25 kg per m^2, may be obese and pre-diabetic, whereas an African American woman with a BMI of 25 may be of normal weight. Second, it is important to understand how obesity may affect cancer initiation, particularly aggressive cancers that could be linked to TICs. The tumour microenvironment has recently been found to play an important part in linking obesity and inflammation to cancer initiation and progression[32]. Obesity has been shown to increase tissue inflammation and cytokine production. There is evidence that tissue cytokines such as leptin, interleukin-6 (IL-6) and IL-8, may be drivers of TICs, promote epithelial to mesenchymal transition (EMT), and potentially increase the rate of cancer death, particularly in obese ethnic minority men and women in the United States[33].

The emerging field of epigenetics has provided important insights into the role of poor early nutrition and environmental exposures in potentiating racial and ethnic disparities in cancer survival. Gene imprinting is the silencing of a specific allele resulting in a functionally haploid state[34]. This functionally haploid state eliminates the protection that diploidy normally confers against the deleterious effects of recessive mutations[34]. If an imprinted gene codes for a crucial developmental gene or tumour suppressor, the result can be cancer initiation. Imprinting is modulated by nutrition and exposure to carcinogens[35,36], providing a potential mechanism by which economic and social disparities early in life can affect adult susceptibility to obesity, cardiac disease and cancer.

Hongbing Shen

Incidence and mortality rates vary markedly by race and ethnicity for cancers around the world[37]. The difference represents a multitude of factors, including social and cultural experience, shared behaviours, environmental exposures and genetic backgrounds. In the past century, many environmental factors have been identified as risk factors for cancers, and these factors can also affect the disparity of cancers between races and ethnicities. For example, persistent infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) is a well-established risk factor for hepatocellular carcinoma (HCC), with a coherent distribution of the prevalence of both HBV or HCV and HCC[38]. However, as we begin the twenty-first century less is known about the genetic determinants for cancers.

Following the publication of the human genome sequence draft in 2001, the progression of the International HapMap Project and the advances of genotyping technologies, scanning the entire genome for common variations is now feasible for a large sample size at a sufficiently low cost. In the past 5 years, GWASs have made great progress into understanding the genetic determinants of common diseases[39], and more than 150 susceptibility loci have been discovered for over 20 cancer types[40]. These findings have advanced our current idea of the biology of cancer, especially of previously unanticipated regions and genes, and have provided new insights into the identification of therapeutic targets and developing targeted interventions. At the same time, the results from GWASs have also demonstrated race- and ethnicity-specific cancer susceptibility.

Many GWAS-discovered cancer risk loci have shown substantial heterogeneity between populations of different ancestries. The variations of allele frequency and locus effect may contribute to the difference of cancers between races and ethnicities, though true biologically relevant variants (causal variants) have not been determined for most identified loci. For example, the common variants rs8034191, rs1051730 and rs16969968 — which represent the cholinergic receptor-encoding *CHRNA5-CHRNA3-CHRNB4* locus on chromosome 15q25 and have been associated with lung cancer risk in populations of European ancestry[41–43] — are extremely rare in Asians and have not been replicated in studies of eastern Asian populations[44,45]. Furthermore, a stronger effect of the *ESR1* locus (which encodes ER) at 6q25.1 was observed for breast cancer susceptibility in Chinese women compared with women of European and African ancestries[46].

What are the major challenges or hurdles in understanding how racial and ethnic differences affect cancer risk and outcomes?

B.E.H

The lack of availability of large numbers of germline DNA samples from populations with a higher or lower risk of specific cancers continues to be a major limitation in furthering our understanding of racial and ethnic differences and cancer risk and outcomes. The major source of germline DNA samples for very large studies of common cancers has come from European-derived populations consolidated together in large consortia. Such consortia have been under development in African American, Japanese and Chinese populations, as well as in some other ethnic groups (for example, Latin Americans and native Hawaiians) but the sample sizes are still much lower and the studies thus underpowered compared with those in their European counterparts.

Most of the genetic loci discovered by GWASs in European populations do replicate to some extent in non-European populations. However, there is considerable locus and allelic heterogeneity, and the assessment of risk variants across populations needs to be based on unbiased GWAS findings from each population[47,48]. GWASs use tag-single nucleotide polymorphisms (SNPs) to identify regions containing risk loci but such tag-SNPs generally seem to be proxies of the true causal locus. The GWAS platforms are actually designed for optimal use in European populations and are less sensitive to non-European populations.

The vast majority of the cancer risk loci discovered so far are not in coding regions of genes, but are in intronic or intergenic regions. Few of these risk loci are located in a gene region that had a known or suspected relationship to the particular cancer. Although these findings from agnostic GWASs were unexpected, they have led to an expansion of our knowledge of pathways that may be relevant to cancers and have reinforced the need for a systematic evaluation of the biological and clinical implications of these novel cancer loci[49,50].

Even with the discovery of multiple risk loci in many common cancers, our knowledge of the impact of heredity on cancer risk remains limited. Not only are we not certain of the true causal SNP or SNPs in most instances, nor of the biological implications of the locus, but taken together the 50 or so SNPs already identified in prostate cancer, for example, only seem to explain 20–30% of the heritability. The explanation of the ‘missing’ heritability may be clarified to some extent by the current search for less common or rare variants[51,52]. However, such rare variants will probably be population-specific and may be less informative than the more common variation that has already been described. An alternative, and complementary, approach suggests that the missing heritability could be due to genetic interactions (epistasis)[53].

N.H.L

The definition of race and/or how to go about defining race remains a potential major hurdle in health disparities research[54]. Self-reported race and ethnicity has been the norm for health disparities research, but it is well established that self-reporting serves as a moderate to weak proxy for ancestral genotyping[55]. Consequently, conclusions drawn from results from patients that have self-reported may be partially flawed (but that is not to say uninformative), rendering medical interventions and practices derived from these findings less than optimal.

V.S

The first major challenge is the lack of representation of ethnic and racial minorities in clinical trials in the United States. Community participation in clinical trial design, patient navigators, mentorship of young investigators from US ethnic minority populations, and access to health care are important for increasing trial enrolment and improving cancer survival.

The second major challenge is the difficulty in separating the effect of lack of access to health care and economic disparities from aggressive tumour biology. For example, poor access to health care, co-morbid conditions and treatment differences contribute to poor survival in different racial and ethnic groups. Co-morbid conditions such as obesity, diabetes, hypertension and poor nutrition are linked to poverty, lack of education, exposure to environmental carcinogens, lack of access to health care and economic disparities. Women who are obese are often unable to complete therapy for breast cancer owing to infection and general poor physical health. However, each of these co-morbid conditions also has the potential to contribute to aggressive biology. For example, obesity and diabetes increase the levels of tissue cytokines such as leptin, insulin and interleukins. These tissue cytokines can in turn promote EMT, TIC turnover, and invasion and metastasis.

H.S

GWASs have opened a door to uncovering the genetic factors that are responsible for the cancer risk disparities among races and ethnicities. However, our knowledge of genetic susceptibilities to cancer in different ethnicities is still scarce. The gap of research resources among different countries leads to the disparity of cancer research between populations and has severely stunted our understanding of the influence of race and ethnicity on the biology of cancer. Most GWASs have been conducted in populations of European ancestry[56], although the budgets available for carrying out these studies have been increasing in some developing countries, such as China[57]. Furthermore, cancer profiles differ from one population to another. For example, Chinese researchers may be prone to studying upper digestive tract tumours (such as oesophageal and gastric cancer) instead of prostate or colorectal cancers because upper digestive tract tumours are more common than prostate or colorectal cancers in China.

In spite of these external scientific environments, several internal scientific issues are important influencing factors for unlocking the differences among populations. First, GWASs have been designed for operation in diverse populations, but the existing factors, such as population admixture, marker ascertainment bias, high heterozygosity and sample availability, are challenging the feasibility and efficiency of these analyses in specific populations[56,58]. Second, the common, low-penetrance variants identified thus far by GWASs can only explain a small proportion of the heritability of cancer risk, and are not likely to completely account for the differences in cancer biology among diverse populations. It is still an open topic to find the missing genetic factors that are related to cancer risk, and there is a trend towards identifying rare or structural variants[59–61]. Third, it

is challenging to determine causal variants and to evaluate their biological relevance. Biologically relevant variants may prove to have more direct value with regard to the interpretation of racial and ethnic differences. Fourth, the epistasis or gene–gene interaction of multiple loci and interplay between hereditary and environmental factors may contribute to a large proportion of racial and ethnic disparities in cancer risk. However, the difficulties in epidemiological study design, exposure assessment, methods of analysis and implementation of consortia make successful examples rare, so a second wave of GWASs that are based on well-designed epidemiological studies in different populations might be required.

In what direction do you envision this field moving over the next 5–10 years?

B.E.H

The ultimate goal of studying the common, less common and rare variations in germline DNA is to comprehensively understand their contribution to the risk of individual cancers and the degree to which they explain, alone or in conjunction with environmental variables, the observed variation in cancer risk by race and ethnicity. A prerequisite to such understanding is the revelation of their biological meaning and clinical application.

Over the next 5–10 years the complete genome will be sequenced in large numbers of individuals with and without cancer and from different racial and ethnic groups. Major inroads will have been made on understanding heretofore unknown links between specific biological processes and cancers. By comparing germline and somatic cancer genomes there will be even more novel pathways discovered, which will give rise to new approaches to individualized cancer screening and therapy[62].

N.H.L

Future advances in cancer health disparities research will probably reflect the latest advances in sequencing technologies and computational approaches in the field of genomics[63]. The Cancer Genome Atlas and the International Cancer Genome Consortium projects plan to sequence hundreds of cancer specimens per cancer type. Early genome-sequencing efforts based on capillary sequencing technology have demonstrated that genes (for example, *RAS, PTEN, TP53, PI3K* and *APC*) that exhibit frequent mutational hits in cancers can be found primarily residing in three to five major signalling pathways[64–66]. Massively parallel (next-generation) sequencing efforts directed towards different cancers promise to provide or have already afforded an unprecedented view of the cancer-driver gene mutation and translocation, DNA copy number, epigenomic, mRNA, microRNA and large intergenic non-coding RNA (lincRNA) landscapes. As a consequence, new pharmaceuticals directed against novel cancer targets are anticipated. Given the power and throughput of next-generation sequencing, it is easy to envision the application of this new technology for studying cancer health disparities, representing a natural extension of our current and more generalized efforts to define the cancer genome. Next-generation sequencing efforts have identified complex genomic rearrangements that may facilitate gain-of-function and loss-of-function driver events in prostate carcinogenesis[67]. It will be extremely informative to determine via next-generation sequencing whether prostate cancers from African American and Caucasian men exhibit different genomic rearrangements, which may help to explain the observed cancer disparities.

Perhaps underappreciated is the role of alternative splicing in cancer health disparities, and cancer development in general. Alternative splicing dramatically expands the protein-coding repertoire of the cell. Current estimates suggest that greater than 60% of all human genes

have more than one isoform or splice variant. The expression of specific variants is regulated in a developmentally specific and tissue-specific manner. Alternative spliced isoforms from the same gene can produce proteins with drastically different properties. For example, the *BCLXL* (also known as *BCL2L1*) gene uses different 5′ splice sites, resulting in proteins that have antagonistic functions. The short form of *BCLXL* promotes apoptosis, and the long form inhibits cell death[68]. We have investigated the splicing pattern of open reading frame genes in African American and Caucasian prostate cancer specimens. Our early findings indicate that splice variants expressed in African American prostate cancer specimens seem to encode more aggressive versions of oncogenes (for example, *EGFR*, *MET*, *RASGRP2* (which encodes a RAS guanine nucleotide exchange factor), *PI3K* and *MDM2*), leading to greater proliferation and invasion in prostate cancer cell lines, compared with the variant counter parts found in Caucasian prostate cancer specimens (B.-D. Wang, S.R. Patierno, N.H.L., unpublished observations). An over-arching hypothesis is that the biological component of prostate cancer health disparities may be due, in part, to population-dependent differences in the splicing of cancer-driver genes. Why population-dependent differential splicing is occurring in cancer specimens remains to be elucidated, and perhaps next-generation sequencing will help to resolve this issue (for example, are population-specific mutations occurring at the splice junction of genes, thus leading to exon skipping and population-specific splice variants?).

V.S

The stochastic model of tumour progression postulates that cancer progression occurs through somatically acquired point mutations and chromosomal rearrangements that gradually accumulate over time. However, this model may not apply to a subset of highly aggressive cancers that occur most notably in young African American men and women, as well as in other racial and ethnic populations.

Emerging models of cancer evolution postulate that bursts of somatic mutation may accrue in fairly short periods of time. Such genomic alterations can drive the development of cancer through the deletion of tumour suppressor genes, increased copy number (amplification) of genes promoting malignant cellular processes and the juxta-position of an intact gene with the regulatory machinery of another gene, causing deregulated gene expression[69].

It is also possible that rapid cancer progression may be an inherent property of the tumour microenvironment. There is evidence that the dynamic and reciprocal interaction between tissue tensile forces and pre-malignant epithelial cells create an ‘at-risk’ microenvironment that promotes rapid non-stochastic progression to invasive cancer[70]. In order to address cancer risk and to effectively prevent the development of aggressive cancers that contribute to ethnic and racial disparities, it may be necessary to consider the tissue microenvironment, as well as the epithelium.

H.S

With effort to comprehensively map genetic variants that contribute to human cancers, multiple approaches may be applied that would allow for new discoveries into the disparity of cancers between races and ethnicities. As mentioned above, rare variants have not been examined to the same extent as common variants, and have been proposed as a focus for the next-generation GWASs[71]. These rare variants, if implicated in cancer risk, are more likely to be responsible for the difference in the incidence of different cancer between diverse races and ethnicities, because they are more restricted to a specific population than common variants. Other approaches include comparing multiple populations of diverse ancestries to identify loci that are present in some populations, but that are absent or that only have modest effects in European populations.

In the next couple of years, the introduction and widespread use of massively parallel sequencing might make it possible for individual laboratories to sequence a whole human genome in a multitude of samples. This should enable us to more extensively investigate the genomic alterations of cancers, including single nucleotide changes, small insertions and deletions, copy number alterations and chromosomal rearrangements. Moreover, next-generation sequencing has revolutionized our knowledge of epigenetic alterations in tumours[72] and will provide new opportunities for understanding the disparity of cancers that are attributable to the cancer epigenome.

Cancer is more complicated than we can imagine. In the GWAS era, large-scale consortia allowed a low-cost approach to map modest effect loci with a bigger sample size. Collaborations between different areas and countries have accelerated the shift of successful research experiences towards non-Caucasian populations[56]. In the next step, more comprehensive, closer collaborations are required to initiate primary, systematic studies instead of confirmative studies. In this regard, procedures should be standardized among different study groups, including study design, sample collection, exposure examination and interview questionnaires. Clearly, these collaborations might provide further direct insights into the heterogeneity of cancer biology between populations.

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