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Racial differences in cancer susceptibility and survival: More than the color of the skin?

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Abstract

Epidemiological studies point to race as a determining factor in cancer susceptibility. In US registries recording cancer incidence and survival by race (distinguishing "*Black versus White*"), individuals of African ancestry have a globally increased risk of malignancies compared to Caucasians and Asian Americans. Differences in socioeconomic status and health care access play a key role. However, the lesser disease susceptibility of Hispanic populations with comparable life-styles and socioeconomic status as African Americans, ("*Hispanic paradox*") points to the concomitant importance of genetic determinants. Here, we overview the molecular basis of racial disparity in cancer susceptibility ranging from genetic polymorphisms and cancer-driver gene mutations to obesity, chronic inflammation and immune responses. We discuss implications for race-adapted cancer screening programs and clinical trials to reduce disparities in cancer burden.

Keywords

Racial disparities; Racial differences; Cancer; African; Asian

Epidemiological evidence for racial differences in cancer susceptibility and survival

Race refers to a population with common genetic and phenotypic features that separates them from other populations. Ethnicity pertains to the different cultural, socioeconomic, religious properties, including customs, language, diet and cultural identity [1]. The association of race with political ideologies and the abuse of science to promote racism have rendered the term race itself problematic. However, since this review deals with the biological basis of disparities in cancer risk we are going to employ the term "race" rather

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than “ethnicity”. Currently the United States Census Bureau defines six race categories: White or Caucasian, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander and “some other race”. Consistent with this, Hispanics refers to people with historical or cultural relationship with Spain, regardless of race, while individuals originating from Middle East or North Africa belong to the “White” race with no further distinction[i]. Epidemiological data highlight large racial disparities in incidence and survival of many cancer types [2, 3]. The most comprehensive data on racial differences are derived from US cancer registries that distinguish among races as indicated above[ii]. According to these, African Americans, referred to as “Black”, have higher incidence and lesser survival of all combined malignancies relative to individuals of the “White” population (Figure 1) [4]. These differences were historically attributed to confounding socio-economical and behavioral factors, such as diet, alcohol abuse, smoking, and access to screening and treatment. However, there is evidence that the survival disparity persists after normalization for these factors and in equal access settings, such as in the US Military Health System [5, 6]. In this context, while differences in incidence of specific cancer types such as head and neck squamous cell carcinoma (HNSCC) disappeared or were even reversed over the last 20 years, the survival gap between “Black and White” people remained, independent of stage at diagnosis and treatment (Figure 2 A, B) [2]. Interestingly, survival differences between Black and White patients in this non sex-related cancer type are limited to the male population, pointing to the interplay between racial and sex determinants of cancer susceptibility. As we previously reviewed, females have a generally lower cancer risk than males [7]. However, the importance of race-related determinants of cancer susceptibility goes beyond sex as indicated by the greater incidence and/or lower survival of Black versus White patients even in sex-specific cancers, such as prostate, breast and cervix (Figure 2 C–F).

Additional epidemiological data show a better outcome in cancer patients with Hispanic versus African American background, in spite of comparable socioeconomic status, a phenomenon known as the “Hispanic paradox” [8]. Besides genetic factors, differences in life styles, specifically diet, have been proposed as a possible explanation for this observation [9]. Asian Americans have also a generally lower cancer risk than all other racial groups [3] and even in this case there is an interplay between genetic differences and a variety of behavioral/environmental risk factors. This review investigates possible molecular determinants of disparity in cancer susceptibility among different races, focusing in particular on African Americans relative to Caucasians and Asians, given the wealth of available information on these three races. We summarize the evidence of racial determinants of different susceptibility to various cancer types, ranging from genetic polymorphisms, epigenetic alterations and cancer-driver gene mutations, to immune/inflammatory responses and obesity, and point to future directions of investigation on as yet poorly explored areas, like cancer initiating cells and tumor microenvironment.

[i] http://census.gov/topics/population/race/about.html
[ii] https://seer.cancer.gov

Genetic diversity

Racial differences in a wide variety of phenotypes and susceptibility to diseases can be attributed in part to genomic diversity. Comparative studies show greater genetic diversity and lower levels of linkage disequilibrium in African populations relative to all other Non-African populations [10]. This has been attributed to the origin of Hominids in Africa >900,000 years ago, with internal migrations and the bottleneck of migrating populations towards the rest of the world about 100'000 years ago ("*Out of Africa*" hypothesis) [11]. In addition, some interbreeding occurred after the spreading of *Homo sapiens* into the Euro-Asian continent with *Neanderthals*, resulting in the presence of 1.5–4% of Neanderthal DNA in the genome of modern Eurasians [12].

Neanderthal alleles have been linked with higher risk for sun-induced skin precancerous lesions (*actinic keratosis*) in population of Caucasian ancestry compared to Africans who develop rarely sun-induced skin cancers. A mutation in the melanocortin 1 receptor (MC1R) that reduces receptor activity and is associated with pale skin color and red hair in individuals of European ancestry has been identified in Neanderthal DNA [13]. Molecular studies revealed that MC1R is implicated in DNA repair and cell survival pathways, which helps explaining the increased melanoma risk of individuals harboring the non-functional "red hair color MC1R" variant [14].

Pigmentation is obviously protective against UV-induced cancers of the skin and can explain the different spectrum of skin tumors arising as a consequence of immunosuppression in organ transplant patients of Caucasian versus African ancestry. In fact, in a large South-African study and data comparison with transplant centers worldwide, the incidence of skin tumors was similar between "White" and "Non-White" (black and mixed-race) patients, while the tumor type was significantly different: squamous cell cancer (SCCs) and basal cell cancer of the skin being the most common malignancies in the "White" population, while Kaposi sarcoma was much more frequent in Black [15]. Four epidemiological forms of Kaposi sarcoma are known: classic (sporadic); African (endemic); AIDS-associated (epidemic); and immunosuppression-associated (iatrogenic). While human herpesvirus-8 infection appears to be the triggering agent in all cases, other determinants of cancer development are likely involved, which may differ among races. These include putative cancer cells of origin, either lymphatic or vascular endothelial progenitors, their microenvironment and, as considered in detail further below, the immune system [17]. Countering the protective role of pigmentation, other, as yet unknown, determinants render Africans more susceptible to aggressive cancer development, even in the skin [18]. In fact, although African American have a much lower incidence of UV-induced cutaneous SCCs, they develop SCCs at sites of wound healing that are much more aggressive than in Caucasians [19]. In addition, African Albinos are disproportionately affected by skin SCCs compared to the general African population [20].

Genetic polymorphisms and cancer gene mutations

Recent advances in genome-wide association studies (GWAS) have provided exciting novel insights into the genetic basis of complex common diseases like cancer. Although many

genetic variants have been linked to predisposition to specific cancer types, the association of most identified variants results only in a marginally increased risk of cancer development. This unaccounted basis of genetic predisposition has been called “genetic dark matter”, in the sense that genetic susceptibility appears like a certainty, while its molecular basis cannot, as yet, be explained [21].

There are many reported single nucleotide polymorphisms (SNPs) [22] and copy number variations (CNVs) [23, 24] associated with racial diversity, potentially affecting non coding RNAs [25], epigenetic regulation [26, 27] and/or posttranslational modifications [28]. However, their biological and clinical significance in most cases is unknown. A notable exception in relation to cancer susceptibility is the TP53 P72R polymorphism, the main P/P allele being preferentially found in African Americans with colon cancer [29] and Asians with gastric cancer [30]. It has been proposed that the TP53 P/P-related cancer susceptibility is due to a faster accumulation of mutations and a larger pool of putative cancer-initiating cells. In fact, the TP53 P72R allele induces transcription of the tumor suppressor gene *PRDM1B* (*BLIMP-1*) that can promote stem cell commitment to differentiation, favoring elimination of cells with DNA-damage induced p53 activation [31].

While the significance of nucleotide differences with possibly subtle regulatory function is difficult to assess, there are also differences in incidence of cancer-driver mutations among races (Table 1). One well-documented example are EGFR mutations, which are significantly more common in Asian lung cancer patients (32–57%) than in those of other races, with important consequences for targeted therapies [32, 33].

In melanoma, the frequency and type of mutation in the main driver oncogenes is also race-dependent. BRAF and NRAS mutations are found in about 30–60% and 30% of Caucasian patients, but only in 8% and 12%, respectively, of those of African ancestry [34]. BRAF mutations are mainly present in melanomas of intermittently sun-exposed skin, such as the trunk, while the occurrence in melanomas of non-exposed or chronically sun exposed skin such as the face and extremities is low [34]. These differences are consistent with a different, sun-independent pathogenesis of melanoma in black skin [34]. In prostate cancer, TMPRSS-ERG fusion is more common in Caucasian men (50%) than African (31%) or Asian (16%) [35]. Similarly, PTEN deletion, leading to increased PI3K activity, is rarely found in African (7%) and Asian (14%) prostate cancer patients but present in 20–40% of Caucasian prostate cancer samples [36, 37]. Given the lower survival of African Americans, the surprisingly lower incidence of PTEN mutations in tumors of these patients points to the possibility of alternative pathways being of greater importance.

Recently, comparison of the mutational landscape of colorectal tumors from Caucasian and African American patients identified two genes, ephrin type A receptor 6 (*EPHA6*) and folliculin (*FLCN*) as cancer driver genes exclusively in African Americans [38]. Overall, these differences in cancer driver mutations can contribute significantly to survival disparity among races and are of relevance in this era of targeted therapies (Table 1).

Epigenetic differences and the transciptome

At the epigenetic level, racial differences in DNA methylation were identified in healthy as well as cancer tissue, in line with the hypothesis that methylation changes are an early predisposing event occurring years before overt cancer development [39]. On the basis of differentially methylated CpG sites, Caucasian Americans, African Americans and Han Chinese-American could also be correctly clustered according to their geographical origins and associated with their distinct phenotypic features, drug metabolism and disease susceptibility [26].

Most epigenetic studies have been focusing on differences between White and Black in breast cancer, with cancer incidence being higher and survival lower in the Black population. Triple negative breast cancer (ER-, PR-, HER2-), probably the most aggressive form of breast cancer, is significantly more frequent in women of African ancestry (20–50%) compared to other races (9–15%) [40, 41], contributing to the racial survival disparities. The reason for this greater incidence is not clear, but could be related to differences in gene expression at various levels as discussed here below. Hypermethylation of *TWIST*, *Cyclin D2*, *RAR-B* and *RASSF1A* genes, implicated in cell proliferation and differentiation is more common in African American premenopausal breast cancer patients than in Caucasians [42]. These findings are difficult to reconcile with the putative tumor promoting function of the *TWIST* and *Cyclin D2* genes. However, it is possible to speculate that the loss of the tumor suppressor gene *RASSF1A* and the gene encoding retinoic acid receptor beta (*RAR-B)* promote more undifferentiated breast tumors in African American women.

Also, gene variants of miRNA processing genes, such as *AGO4*, and SNPs in miRNAs regulating breast carcinogenesis are associated with differences in cancer susceptibility in African American compared to Caucasians [43].

At the transcriptome level, global gene expression analysis of breast tumors from African American and Caucasian patients matched by pathological characteristics revealed diverse molecular profiles. In several studies, two genes, *CRYBB2* (crystallin beta B2) and *PSPHL* (L-3-phosphoserine phosphatase homolog), which have been connected, respectively, with cataract formation and pterygia, a pathological deposition of extracellular matrix of the eye connective tissue, were reported to be highly expressed in tumor epithelium from African American individuals and could be used to correctly cluster specimens according to race [44, 45]. The function of these genes in this context remains enigmatic and possible linkage to other genes of greater significance for cancer development remains to be evaluated.

Limited information is available on gene expression and/or epigenetic differences in prostate cancer of White versus Black patients and even less data exists in other major cancer types such as squamous cell cancer of various organs. In a small study, higher promoter methylation for the genes encoding *SNRPN*, involved in pre-mRNA processing, *MST1R*, a tyrosine kinase related to c-MET and *ABCG5, a* member of the ABC transporter superfamily, was detected in African American prostate cancer samples compared to those from Caucasians [46]. Likewise, the gene motor neuron and pancreas homeobox1 (*MNX1*) was shown to be upregulated to a higher extent in prostate cancer tissue from African

American compared to those from European American men, [47] with the suggestion that it contributes to carcinogenesis through AKT activation and increased lipid synthesis.

Obesity and chronic inflammation

Obesity

The association between metabolic disorders such as obesity and increased incidence and mortality of postmenopausal breast, endometrial, colon, esophagus and kidney cancer has been well documented over the last 20 years [48]. It has been estimated that 14% of cancer-related deaths in men and 20% in women are caused by obesity [49]. The prevalence of obesity in African Americans and Hispanics is significantly higher than in Caucasians and Asians [50]. Black individuals have a lower maximal capacity of aerobic metabolism and greater percentage of fast contracting (type II) skeletal muscle fibers, which, together with a reduced energy consumption, predisposes them to obesity and other metabolic disorders [51]. While African Americans are particularly susceptible to obesity-related cancers, Hispanics seem to be relatively unaffected [48]. As mentioned before, this could be related to genetic but also behavioral differences, specifically diet. Even within the black population, the importance of diet is illustrated by a recent study on colon cancer risk, linking a high-fat and low-fiber western-style versus low-fat and high-fiber, African-style diets to metabolome and microbiota composition [52].

Various mechanisms have been proposed to explain how obesity promotes cancer. One possible mechanism is through insulin signaling pathways. African Americans present higher levels of insulin and after administration of glucose, the increase in serum insulin in African Americans is two to three times higher than in Caucasians [48]. Interestingly, this different insulin response is independent of any differences in body fat distribution and composition or physical activity and is already evident in children [53]. Hyperinsulinemia is caused by both increased β-cells secretion and decreased hepatic clearance in African Americans. In parallel with differences in insulin blood levels, African Americans and Hispanics are more insulin resistant than Caucasians, even after accounting for differences in body mass index (BMI) [54]. Related to the above, insulin-like growth factor 1 (IGF-1) is an important autocrine-paracrine stimulatory factor for adipose tissue growth. IGF-1 levels normally decrease with increasing BMI in Hispanics and Asian, while this decline is diminished in Caucasian and absent in African American [55], pointing to possible cancer-promoting effects of persistently elevated IGF-1 levels. Insulin resistance also increases bioavailability of IGF-1 through decreased synthesis of IGF-binding proteins (IGFBP-1 and IGFBP-2) [48]. Insulin and IGF-1 inhibit the expression of sex-hormone binding globulin (SHBG) at the same time as they stimulate secretion of female sex hormones, which, in breast and endometrial tissue, can promote cellular proliferation and inhibit apoptosis, both of which could also contribute for differences in cancer risk [56]. These complex racial variations in insulin/IGF-1 signaling in obese individuals could help explain the "*Hispanic paradox*", to which we referred above [8].

Chronic Inflammation

The obesity-related cancer risk is also linked to chronic inflammation. Many conditions can trigger chronic inflammation and increase cancer susceptibility. About 15–20% of cancer related deaths are thought to be due to underlying infections and associated inflammatory responses [57].

Significant disparities between Black and White populations have been described in susceptibility and response to HIV infection [58] [59]. This disparity was also reported in a large US military cohort with equal access to health care and similar duration of HIV infection [60]. Also, in chronic hepatitis C virus (HCV) infections, racial differences in response to treatment have been reported [61] [62] [63].

Serum levels of the inflammatory proteins CRP and IL6 are higher in African American compared to various other races and this disparity persists after adjustment for BMI [64]. The G174C polymorphism in the *IL6* gene with higher frequencies of the 174G allele in Non-Caucasians including African, African-American and Mexican (0.87–1.0) compared to Caucasians (0.54–0.62) leads to significantly higher IL-6 serum levels and has been proposed to contribute to racial differences in prevalence and survival of various chronic diseases including cancer [65].

Chronic inflammation results in an imbalance of circulating adipose tissue cytokines or “adipokines”, such as leptin and adiponectin, with levels of the latter decreasing with increasing BMI [66]. While there are conflicting data on leptin, high adiponectin levels are consistently correlated with reduced breast cancer risk [67]. Mechanistically, this could be linked to activation by adiponectin receptors of the antitumorigenic peroxisome proliferator-activated receptor gamma (PPARy) pathway and downstream increase of BRCA1 expression [68]. Importantly, in both Caucasians and African Americans, a SNP rs1501299 in the adiponectin gene, associated with adiponectin serum levels, also correlates with increased breast cancer risk [69].

Immune system

While racial differences in immune related functions are well established, their relationship to cancer susceptibility remains mostly to be investigated. In fact, tumor immunity is a complex phenomenon and a strong inflammatory response against pathogens or increased activity of the immune system as in autoimmune disorders does not necessarily confer protection against cancer development. On the contrary, various studies in different populations have shown an increased cancer risk -especially lymphomas - in individuals suffering from systemic inflammatory autoimmune diseases such lupus erythematodes and rheumatoid arthritis [73] [74] s[75].

Innate immunity

Susceptibility to acute infections as wells as chronic diseases including cancer is determined by genetic variations in the immune system. Genes of the immune system are subject to constant evolutionary pressure, which can vary depending on environmental conditions and relocation of populations. Individuals of African ancestry show inherent differences in their

immune system relative to other races, possibly due to selective pressure in response to endemic infectious diseases in Africa [70].

The number of granzyme B secreting cytotoxic cells has been reported to be significantly lower in African American patients compared to Caucasians, suggesting that the functional activity of inflammatory cells is not identical across races [76]. Two other studies analyzed the response of cultured monocytes and macrophages to bacterial [71] and viral infections [72] in individuals of African and European ancestry. There were significant differences in gene expression before and after infection, African Americans showing stronger inflammatory responses and faster bacterial clearance [71]. Strikingly, many of the genes whose expression was altered in response to infection showed sequences that were very similar between Europeans and Neanderthals, but not Africans, suggesting that a contribution of the Neanderthal genome lead to acquisition of regulatory variants associated with reduced inflammatory responses in Euro-Asian genomes [72].

Several immunity related genes, such as the Toll-like receptor (TLR) *TLR1/TLR6/TLR19* gene cluster, [77] the caspase-12 gene (*CASP12)*, involved in cytokine production upon bacterial lipopolysaccharide stimulation, evolved under strong selective pressure and show racial variation [78].

Various studies have correlated SNPs in TLR genes to alterations in susceptibility to various infectious or inflammatory diseases, which in turn might affect cancer development [79], as described above.

Adaptive immunity

The Th1 immune response (characterized by IL2 and IFNγ secretion) results in cytotoxic CD8 cells with anti-viral and anti-tumor activity [80], while Th2-type immunity (characterized by IL4, IL5, IL9, IL10 and IL13 production, and eosinophil and basophil activation) seems to have evolved in response to parasitic infections. In many cancers, the fraction of Th1 cells is significantly decreased, while the proportion of Th2 cells is increased [80], which, for colorectal cancer, can be of prognostic value [81]. Polymorphisms present in the West African and Asian populations are linked with an increased Th2 response, with lesser acute inflammation [82], but more persistent chronic inflammation and/or suppression of antitumor immunity [80].

Individuals of African ancestry express higher levels of IL2RA, which encodes the IL2-receptor CD25, that is key for proliferation of regulatory T cells (Treg). Underlying this difference, the low-expression variant rs12251836 is common in European, and rare in African and Asian individuals [83].

Genetic variants of adaptive immune response related genes such as *IL4R* (interleukin 4 receptor), *IL15* (interleukin 15), *LTA* (lymphotoxine alpha) and *INFGR2* (interferon gamma receptor 2) have also been associated with enhanced cancer risk in patients of African ancestry [84].

Epigenetically, DNA methylation profiling of naïve CD4 T cells revealed hypomethylation of various genes related to apoptosis and autoimmune disorders in healthy African

Americans, which may account for their greater susceptibility to these diseases than European-Americans [85].

Translational implications for cancer prevention and treatment

In the era of precision medicine, race needs to be recognized as a risk factor independent of environmental dynamics for incidence and mortality of specific cancer types and screening and treatment modalities should be adapted in order to diminish the racial survival disparity.

For instance, there is a significant difference in age-specific increase of colorectal cancer, the incidence beginning to increase at 43 years in African Americans compared to 47 years in European Americans, with a 20% higher stage-adjusted mortality. As a result, some associations recommend to start screening of average-risk African Americans at 45, rather than at 50 years of age as recommended for individuals of all races by other major agencies such as the American Cancer Society and the U.S. Preventive Services Task Force [86]. Rather than screening at an earlier age, it has been suggested that similar beneficial effects would be obtained with a 5–10% increase of total number of African American individuals that undergo the test [87].

Whether earlier initiation of screening or improving the adherence to the existing screening programs is more efficient in decreasing the cancer burden is also a question for other cancer types. In fact, African American race is considered a risk factor for prostate cancer and separate screening guidelines are proposed [88]. Similarly, genetic screening of Jewish women starting at age 25 years of age for BRCA mutations has been advised in order to identify women at high risk for developing breast and ovarian cancers in this population with relatively high BRCA mutation prevalence [89]. Given the higher mortality of breast cancer in African Americans and the higher incidence of gastric cancer in Asian individuals population-based specific screening recommendations should be considered.

In concert with variations in cellular metabolism, polymorphisms for genes encoding detoxifying and drug metabolizing enzymes such as cytochrome P450 and transporters such as P-glycoprotein are present with variable prevalence in different races. Such differences can have multiple effects at the level of conversion of various toxic compounds into DNA damaging carcinogens, steroid hormone processing and pharmacokinetics of various drugs. For instance there is emerging evidence for racial disparities in the incidence of adverse events after chemotherapy, probably as a consequence of differences in body fat composition and distribution and differential function of drug metabolizing enzymes.

It is therefore important to investigate the presence of clinically relevant genetic polymorphisms affecting various drug metabolizing enzymes in order to establish the appropriate drug doses across races and optimize therapy regimens (“pharmacoethnicity”) [90].

In clinical trials, independent of the discipline, there is often a selection bias in terms of age (younger), gender (males) and race with more European/Caucasian patients being included [91], resulting in underrepresentation of African American, Hispanic and Asian patients (<10% of clinical trial participants are minorities) [92]. In addition to improving access to

novel therapies, participation of racial groups in clinical trials is critical to reach robust conclusions about the risks and benefits of drugs and specific interventions in these populations.

Racial minorities could benefit from focused accrual, taking into account their different cultural and religious background. The patient navigation model, where a lay individual is trained to provide support and education for patients enrolled in trials, has been successfully applied to improve health care access and increase participation and retention in clinical trials [92].

The complex interplay between genetic factors, obesity, chronic inflammation and environmental influences on racial disparity in cancer susceptibility and survival is illustrated in Figure 3, Key Figure.

Concluding Remarks

There has been a paradigm shift in the notion of carcinogenesis in the last decades. Cancer is no longer solely considered as an uncontrolled proliferation of genetically altered single cells but rather a consequence of disturbed tumor-stroma interactions, diminished immune surveillance and loss of tissue homeostasis and therefore, as a complex disease occurring in tissues rather than in cells exclusively [93].

However, the impact of race on cancer initiating cell populations and their surrounding stromal environment are only starting to be appreciated (see Outstanding Questions). Therefore, besides identification of race-specific cancer driver mutations, the exploration of variation in the stem cells compartment and the stromal composition in healthy and cancer tissues in diverse races is essential for a thorough understanding of carcinogenesis in different genetic backgrounds.

There is emerging evidence that the tissue composition in normal and tumor tissue differs between races, African ancestry being associated with a significant increase in stem cells populations in healthy breast and colon cancer, compared to Caucasians [94, 95]. It is also tempting to speculate that the different spatial distribution of stem cells might underlie well-known differences in tumor locations, as African American harboring significantly more right-sided colon [96] and anterior prostate tumors [97] than other races.

Recent studies showed significant alterations in the tumor microenvironment in patients of African ancestry, namely in the extent of angiogenesis, immune infiltrate, expression of genes related to epithelial to mesenchymal transition (EMT) and extracellular matrix formation [98, 99].

The interplay between behavioral/environmental factors and genetic determinants needs to be elucidated. Several studies have shown an impact of the microbiome on cancer risk and anticancer immunosurveillance [100]. In this context, the influence of diet-related racial differences on intestinal flora composition remains to be assessed. The importance of the stromal environment is illustrated by the success of immunotherapies, principally in tumors with a strong immune cell infiltrate, so called immunologically “hot tumors”.

Currently, immunotherapies, based on immune checkpoint inhibitors are rapidly becoming a powerful therapeutic tool for various cancer types, with very promising response rates and potentially severe immune related adverse events (irAEs) [101]. Despite the ever-increasing number of clinical trials with thousands of patients, so far subgroup analysis based on race of the enrolled patients have not been reported. Similarly, separate analysis based on sex has been missing. In our view, there is an unmet need to determine to what extent race affects efficacy and tolerance of immune checkpoint inhibitors targeting the CD80/CD86- CTLA4 and PD1-PD-L1 axis, in order to better select for patients who might benefit from such therapies.

However, while we encourage to further explore the contribution of biological factors to racial differences in cancer risk and mortality, we caution against trivializing the role of socio-environmental determinants such as health care access and health literacy. We believe that meaningful scientific and clinical research of racial factors is most likely to be successful using a multidisciplinary approach including geneticists, epidemiologists and social scientists.

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Trends

- Racial disparities in cancer incidence and survival are not solely attributable to environmental factors such as health care access and risk behavior.
- African populations show greater genetic diversity compared to all other Non-African populations. The interbreeding of the migrating population with *Neanderthals* in Euro-Asia resulted in the presence of 1.5–4% of Neanderthal DNA in the genome of modern Eurasians, contributing to the differences in disease susceptibility.
- The prevalence of genetic polymorphisms and mutations shows racial differences for various cancer types.
- The immune response in individuals of African ancestry diverges from the one in Caucasians, presumably due to distinct evolutionary pressure in response to infectious disease.
- The higher cancer susceptibility of African American is linked to genetic predisposition to obesity and chronic inflammation.

Outstanding Questions

1. How do behavioral and environmental factors interact with epigenetic and genetic determinants of cancer susceptibility?
2. How does cancer susceptibility relate to the greater genetic diversity of African populations?
3. Are there racial differences in the gut microbiota, which could contribute to differences in cancer risk and treatment response?
4. What is the contribution of racial differences in cancer stem cells and surrounding stroma in susceptibility to initiation and progression of the neoplastic process?
5. How do racial differences in innate and acquired immune responses affect personalized approaches to cancer therapy, specifically immunotherapy?

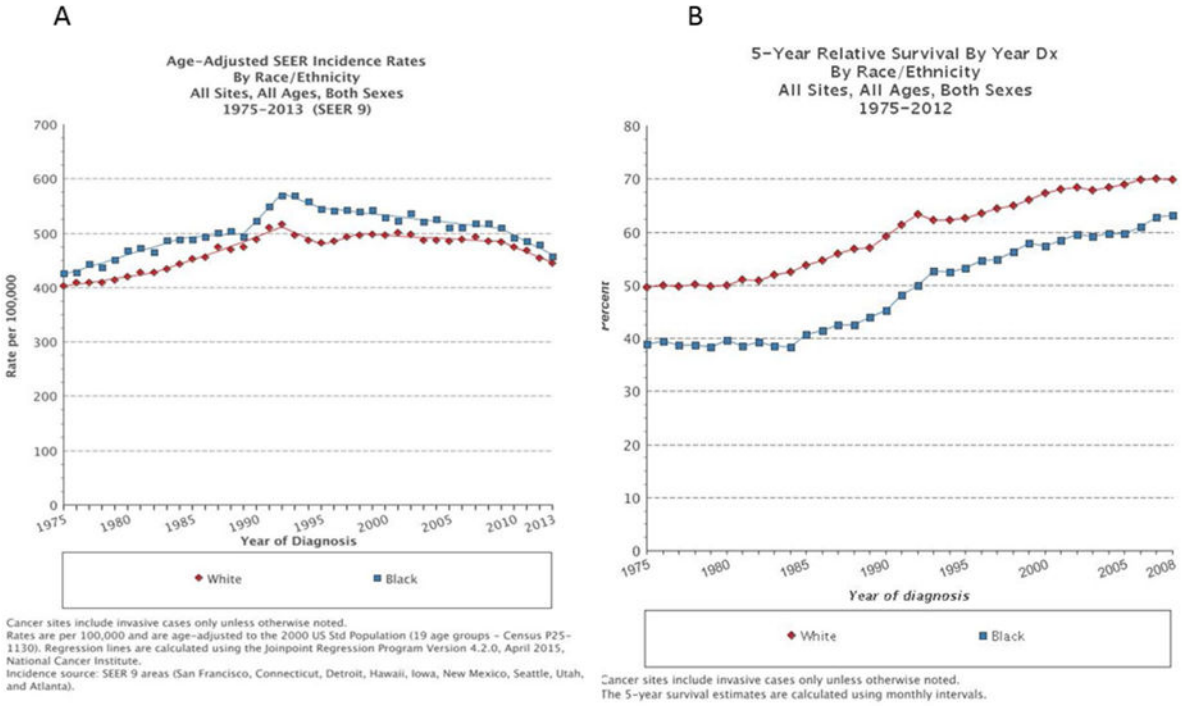
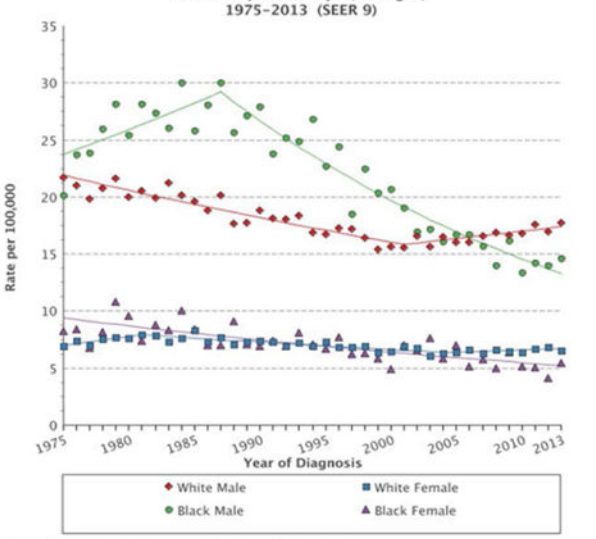


Figure 1. Racial differences in cancer incidence and survival

Incidence (A) and 5-year survival (B) of all cancer registered cancer sites for White and Black, all ages and both sexes, confounded for the years 1975–2013 and 1975–2012, respectively.

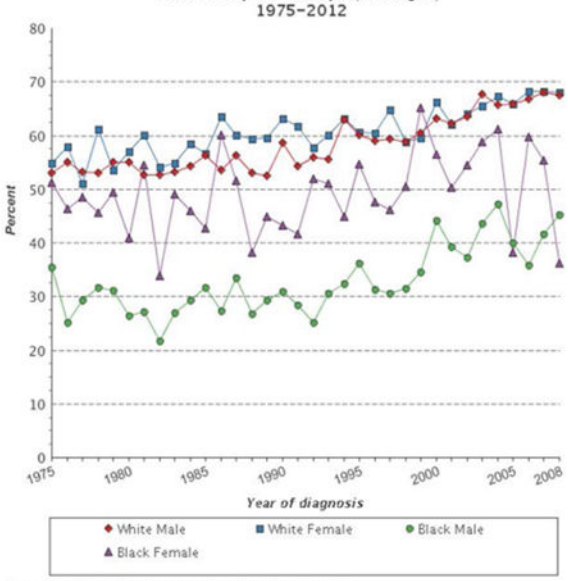
Data retrieved from SEER 2012[ii]

A



Cancer sites include invasive cases only unless otherwise noted.
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 4.2.0, April 2015, National Cancer Institute.
Incidence source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).

B



Cancer sites include invasive cases only unless otherwise noted.
The 5-year survival estimates are calculated using monthly intervals.

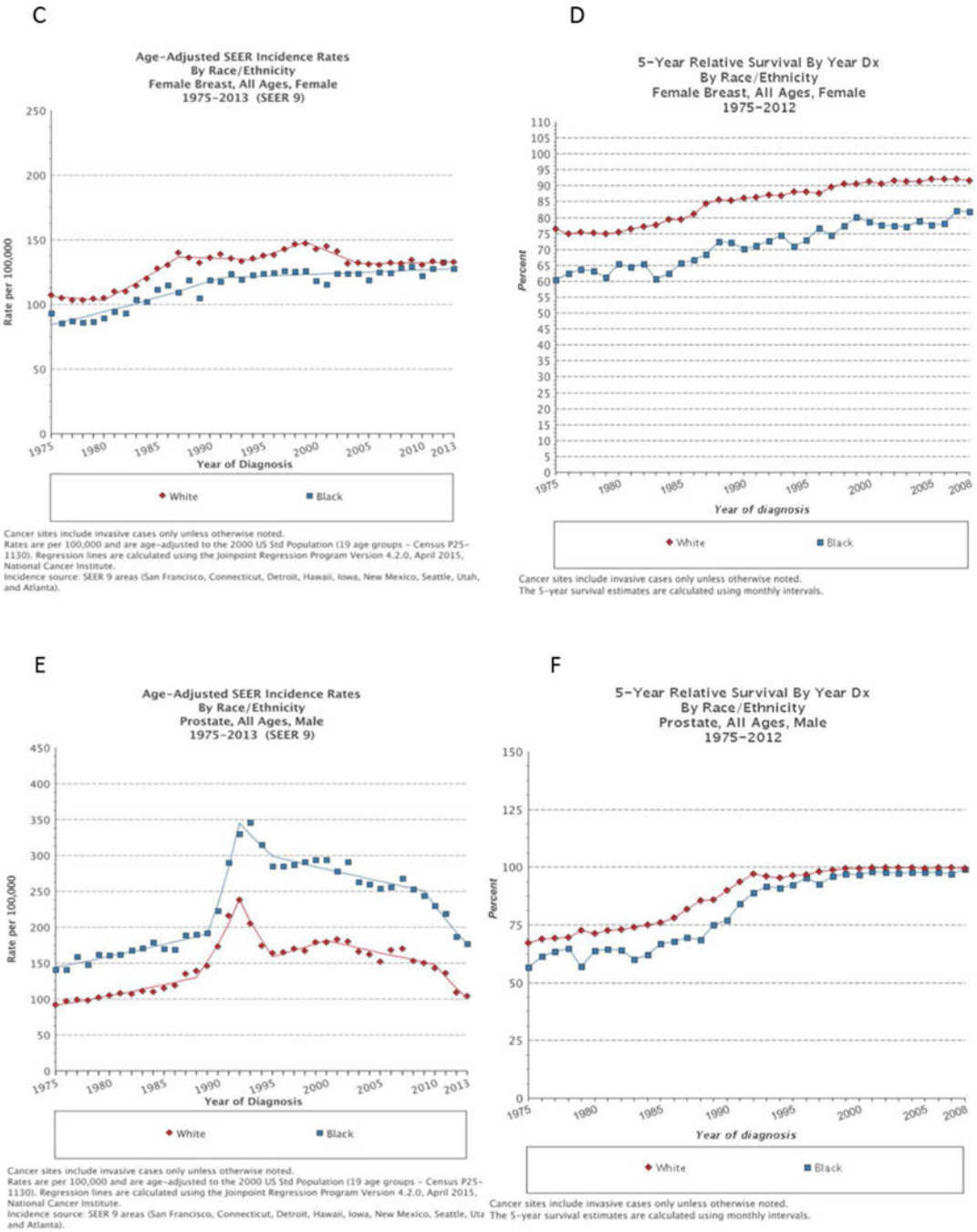


Figure 2. Persistence of survival disparity between Black and White over time

Despite a significant decline in incidence of head and neck squamous cell carcinoma (HNSCC) in Black men compared to White men (A) over the time period of 1975–2013, with currently even lower incidence rates among Black men, the survival disparity remains (B). In Black women the incidence (C) and survival (D) of breast cancer are both lower compared to White women. In prostate cancer, the higher incidence (E) in Black men persists, while the survival (F) differences diminish over time.

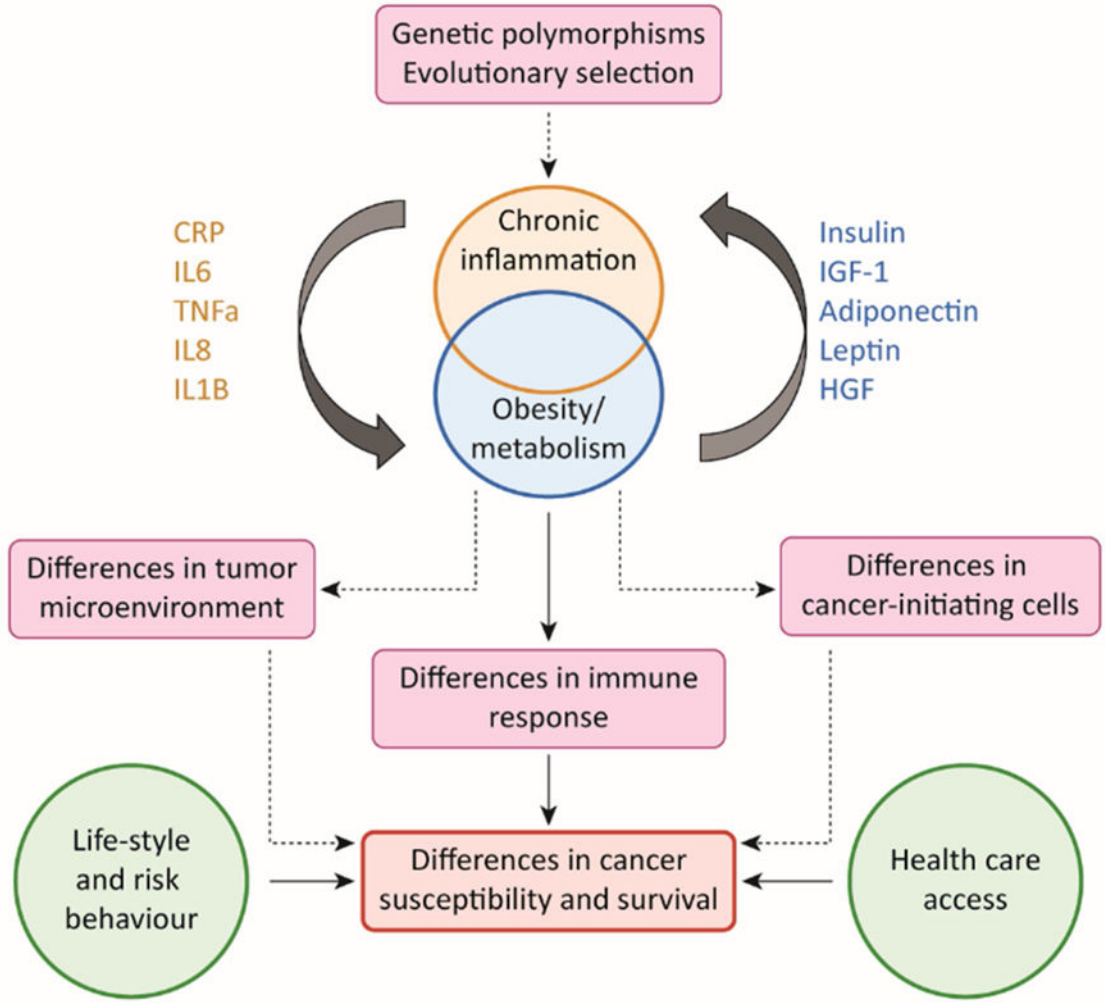


Figure 3. Key Figure. Biological basis of disparity in cancer susceptibility among different races

There is evidence for evolutionary selection of polymorphisms in the Th2 immune response in African populations. The prevalence of obesity in African Americans and Hispanics is significantly higher than in Caucasians and Asians. A major driver of obesity-related cancer is chronic inflammation, which is associated with an increased release of inflammatory cytokines such as TNFα, IL6, IL8, IL1-ß which results in imbalance of circulating adipose tissue cytokines or "adipokines", such as leptin, adiponectin and hepatocyte growth factor (HGF). The racial differences in metabolism and inflammatory response contribute to differences in the immune system, how they affect cancer initiating cells and the tumor microenvironment needs to be explored. The disparity in cancer susceptibility and survival is presumably a consequence of biological and environmental factors, such as differences in life-style, risk behavior and health care access.

Table 1

Differences in clinicopathological characteristics and driver gene mutations in selected cancer types

Cancer type	African American	Caucasian	Asian	Clinical implication	References
Lung cancer					
KRAS mutation	17%	26–31.6%	10.4–11%	Mutation significantly more frequent in smokers.	[32, 101]
EGFR mutation	3–19%	3–20%	32–57%	Mutation significantly more frequent in women and non-smokers. Predicts response to EGFR tyrosine kinase inhibitors.	[32, 101–105]
ALK rearrangement (EML4-ALK fusion)	4%	5.6%	4.9–67%	Associated with younger age, never smoking, advanced clinical stage. Predicts response to ALK inhibitors.	[32, 105–108]
MET mutation	0–1%	2.2–19%	13–14.3%	More frequent in males, smokers.	[101, 102, 109]
Melanoma					
BRAF mutation	8%	21%	24–25.5%	BRAF or NRAS mutation mutually exclusive, more frequently associated with ulceration and poor survival.	[34, 110–112]
N RAS mutation	12%	22%	7.2%		[34, 112]
GNAQ mutation GNA11 mutation		45–49% 32%	18% 20%	Present at all stages of uveal melanoma GNAQ and GNA11 mutations are mutually exclusive.	[110, 113, 114]
Prostate cancer					
Anterior localization	49.2%	20%		Associated with lower androgen receptor signaling.	[115]
ERG rearrangement TMPRSS-ERG fusion	27.6–31.3%	37.4–50%	7.5–15.9%	No correlation with clinicopathological features besides race	[35–37]
PTEN deletion	6.9%	19.8–42.3%	14.3%	Associated with higher Gleason score, androgen independence and worse prognosis. May predict response to PI3K inhibitor.	[36, 37]
SPINK1 overexpression	23.8%	8.2%		SPINK1 overexpression and ERG rearrangements mutually exclusive. Associated with aggressive disease.	[36]
Breast cancer					
Triple negative tumors	19.5–48.1%	9.2–14.5%	9%	Associated with poor survival.	[40, 41, 116]
Basal like tumors -*Premenopausal* -*Postmenopausal*	39% 14%	16% 16%		Significantly more TP53 mutations in basal like vs luminal A tumors (44 vs 15%).	[117]
Luminal A tumors -*Premenopausal* -*Postmenopausal*	36% 59%	51% 58%			[117]

Cancer type	African American	Caucasian	Asian	Clinical implication	References
Luminal B tumors *-Premenopausal* *-Postmenopausal*	9% 16%	18% 16%			[117]
HER2 expression	7–19.5%	6–13%	8.5–20%	No differences between pre-and postmenopausal status. Predicts response to anti- HER2 antibodies.	[40, 41, 116–120]
BRCA1 mutation *All ages* *<35 years*	1.3% 16.7%	2.2% 7.2%	0.5% 2.4%	8.3 % in Ashkenazi Jewish breast cancer patients of all ages, 66.7% in patients <35 years. Associated with poor survival.	[121, 122]
TP53 mutation	42.9%	27 6%		TP53 mutations associated with poorer survival for African Americans but not for Caucasians.	[123, 124]
PIK3CA mutation	20%	33.9%		May predict response to PI3K inhibitors.	[123]
Colorectal cancer					
Proximal localization Cancer stage III, IV Lymphocytic infiltration	49% 52% 29%	34% 37% 12%		Proximal (right-sided) tumors associated with worse outcome.	[125, 126]
KRAS mutation	23–44.1%	15–34.9%	27.8–37.9%	Associated with poor prognosis. Predicts lack of response to EGFR-antibodies.	[125,127–129]
BRAF mutation	4–6.4%	7–13.9%	4.5–6%	Associated with poor prognosis.	[111, 125, 127, 128]
Microsatellite instability (MSI)	9%	9%	9%	MSI associated with favorable outcome. Negative predictor marker for 5-FU based therapy in stage II and III patients.	[125, 128–131]
Gastric cancer					
HER2 expression		23.6%	23.9%	FIER2 expression higher in intestinal vs diffuse-type (31.8 vs 6.1 %), and gastroesophageal junction cancer vs gastric tumors (32.2 vs 21.4%). Predicts response to anti-FlER2 antibodies	[120, 132]
GIST					
c-KIT mutation		78–79% -exon 11: 67–83% -exon 9: 11–14%	90.7% -exon 11: 74% -exon 9: 7.3%	Exon 11 mutations predict better outcome after imatinib treatment.	[133–136]
PDGFRA mutation		6–12%- exon 18: 9%	16%- exon 18: 8%	KIT and PDGFRA mutations mutually exclusive.	[133, 136]
HNSCC					
HPV infection	4–25%	34–71.1%	51.3%	Associated with better outcome.	[137–139]
Papillary Thyroid cancer					
BRAF mutation		48%	75.4–80%	Associated with aggressive clinicopathological features.	[111, 140–142]
TERT promoter mutation		4.7–25.5%	4.4–11.3%	Associated with poor prognosis.	[142, 143]

Cancer type	African American	Caucasian	Asian	Clinical implication	References
Glioblastoma					
IDH1 and 2 mutation		10%	16,1%	Associated with better outcome	[144, 145]
TERT promoter mutation		73.3%		TERT promoter mutation alone associated with poor prognosis, occurring together with IDH1 mutation associated with prolonged survival.	[144]
MGMT promoter méthylation		36%		Associated with better survival.	[146]