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Review

Molecular basis of sex differences in cancer: Perspective from Asia

Eric David Ornos,[1,2,*] Leslie Faye Cando,[2] Charlene Divine Catral,[2] Elgin Paul Quebral,[2,3,4] Ourlad Alzeus Tantengco,[2,5,6] Ma. Veronica Pia Arevalo,[2] and Edward Christopher Dee[7,*]

SUMMARY

Cancer is a leading cause of mortality and morbidity globally. Sex differences in cancer are evident in death rates and treatment responses in several cancers. Asian patients have unique cancer epidemiology influenced by their genetic ancestry and sociocultural factors in the region. In this review, we show molecular associations that potentially mediate sex disparities observed in cancer in Asian populations. Differences in sex characteristics are evident at the cytogenetic, genetic, and epigenetic levels mediating processes that include cell cycle, oncogenesis, and metastasis. Larger clinical and *in vitro* studies that explore mechanisms can confirm the associations of these molecular markers. In-depth studies of these markers can reveal their importance as diagnostics, prognostics, and therapeutic efficacy markers. Sex differences should be considered in designing novel cancer therapeutics in this era of precision medicine.

INTRODUCTION

Globally, cancer is a leading cause of morbidity and mortality.[1] Cancer's contribution to global morbidity and mortality is also expected to rise in the coming decades, attributed to aging populations and an increasing role in highly populated regions, many of which are lower-middle-income countries.[2] Critically, sex differences in cancer may manifest at all levels of the cancer continuum, from genetic predisposition and behavioral risk factors to access to treatment and treatment response.

Broadly, cancers originating from non-reproductive organs occur more commonly among males than females; the mortality rate among men is also approximately twice that among women.[3] Furthermore, response to treatment may be differential among the sexes: prior work suggests, for example, that women experience improved overall survival (OS) compared to men after surgery for lung cancer.[4]

The etiologies of these differences are multifactorial (Figure 1). Work has shown, for example, that differential rates of smoking, obesity, and chronic inflammation contribute to sex differences in cancer epidemiology.[3] For instance, in the United States, smoking accounted for approximately 30% of cancer deaths; but of these smoking-related deaths, about two-thirds occurred in men.[5] Obesity is similarly associated with cancer risk and is broadly more common among men.[6] Lastly, chronic inflammation, associated with cancer risk, occurs more frequently in males.[7] These factors are deeply intertwined with social risk factors such as poverty, lack of access to care, and adverse social experiences that lead to differential smoking rates, obesity, and chronic inflammation, among other factors.[8,9]

It is important to note that the epidemiology of cancer in Asia is unique and is influenced by the genetic ancestry of the diverse populations in the region and the unique sociocultural fabric that impacts behavioral decisions made by individuals (Table 1). For example, Asia has the greatest incidence and mortality associated with colorectal cancer.[10] However, the globally increasing incidence is more pronounced among men than women in Asia.[11] Similarly, liver cancer incidence is highest in Asian countries, particularly in Mongolia and China.[2,12] Males are disproportionately affected, as hepatocellular carcinoma rates are 2–4 times higher in men compared to women.[12] Lung cancer among non-smoking women in Asia is also on the rise, more so than in other parts of the world.[13] China is particularly affected, given that lung cancer has become the country's leading cause of cancer death among women.[2,14] While leukemia cases are declining in Western Europe, incidence rates are increasing in East Asia.[15] Gastric cancer is the leading cause of cancer death among men in some South Central Asian countries such as Iran, Afghanistan, and

[1]Department of Medical Microbiology, College of Public Health, University of the Philippines Manila, Manila 1000, Philippines

[2]College of Medicine, University of the Philippines Manila, Manila, 1000, Philippines

[3]Virology Laboratory, Department of Medical Microbiology, College of Public Health, University of the Philippines Manila, Manila 1000, Philippines

[4]Hawaii Center for AIDS, John A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu, HI 96813, USA

[5]Department of Physiology, College of Medicine, University of the Philippines Manila, Manila 1000, Philippines

[6]Department of Biology, College of Science, De La Salle University, Manila 0922, Philippines

[7]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY 10028, USA

*Correspondence: ebornos@up.edu.ph (E.D.O.), deee1@mskcc.org (E.C.D.)

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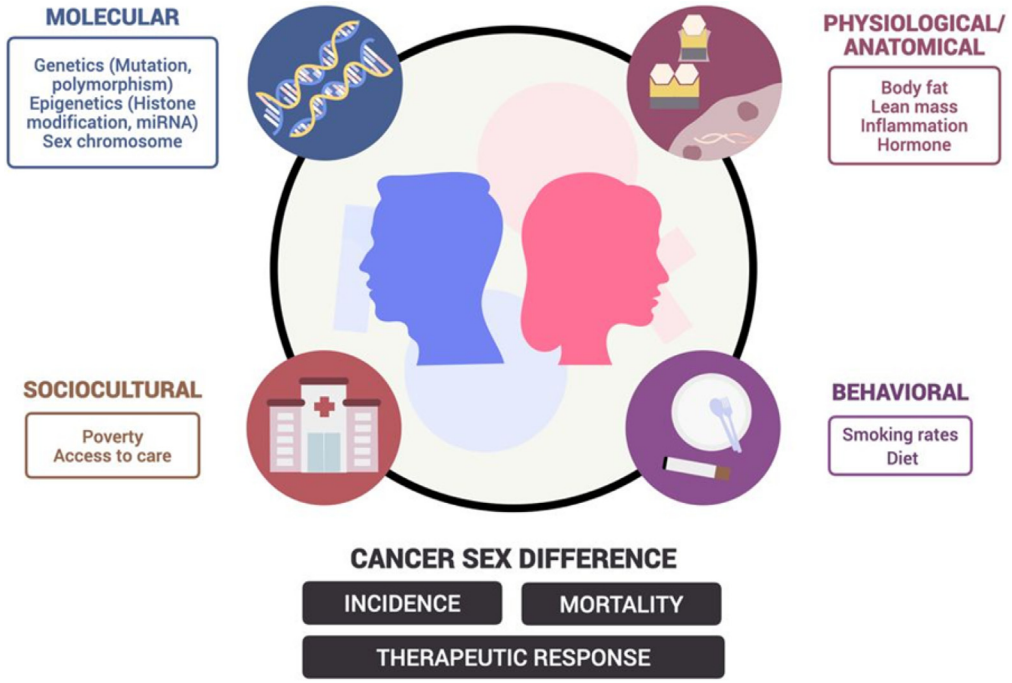

Figure 1. Factors affecting sex differences in cancer

Turkmenistan.[2] Lip and oral cancer incidence in South Asian countries, including India, Sri Lanka, and Pakistan, are among the highest in the world, especially among males.[2] Asians also have the highest incidence and mortality of thyroid cancer.[16] The incidence and mortality rates of thyroid cancer are higher among women than men.[2] These differences are attributed to a mixed picture of genomic predisposition and environmental exposures that merit further exploration.

Given the unique genomic and social context of Asian patients, in this narrative review, we focus on work exploring sex differences in cancer among Asian patients. Additionally, the current review focuses on data exploring molecular associations that may mediate sex differences in cancer. The present review is accompanied by another piece that focuses on sex differences in social determinants of health and cancer epidemiology, focusing on Asian cohorts. These complementary pieces are meant to demonstrate the multifactorial and interlinked modes by which sex differences in cancer are made manifest to contribute toward informing interventions that may mitigate cancer incidence and mortality worldwide.

MOLECULAR DIFFERENCES

The differences in prevalence, treatment response, and cancer outcomes between men and women are attributed to many factors. More studies are revealing how the sex disparity is not only attributed to the differences brought about by the sex chromosomes and hormone regulation but also to differences in genetics, epigenetics, gene regulation, and gene expression.[17] However, there is still limited data that investigate these factors and their underlying mechanisms, especially in the Asian population. Here we discuss the current data on the molecular basis of the sex disparities seen in the Asian population.

Gene differences

Changes in the genetic sequence brought by mutation are the leading cause of variation in organisms. Genomic variability can occur in various ways, such as single nucleotide polymorphisms (SNPs), variable number of tandem repeats (VNTRs), copy number variants (CNVs), and structural alterations (i.e., deletions, duplication, and inversions).[18] These genetic variations account for the normal phenotypic variation of every individual, making everyone genetically distinct and unique. Furthermore, somatic mutations are changes in the DNA sequence found in cells of a multicellular organism's reproductive cells (e.g., gametes). Certain somatic mutations involve those found in the human cancer genome, where most malignancies are caused by point mutations, copy number increase or decrease, chromosome translocation, and loss of

Table 1. Cancer features in Asian Population

Cancer	Features in Asian Population
Colorectal cancer	• Greatest incidence and mortality is in Asian population. • More pronounced rise in incidence among men than women
Liver cancer	• Highest incidence in Asian countries, particularly Mongolia and China • Males have 2–4x rate in men compared to women
Lung cancer	• Rising incidence among non-smoking women, particularly in China • Lung cancer is leading cause of cancer death among women in China
Leukemia	• Increasing incidence rates in East Asia
Gastric cancer	• Leading cause of cancer death among men in some South-Central Asian countries (i.e., Iran, Afghanistan, and Turkmenistan)
Lip and oral cancer	• Among the highest incidence in the world, especially among males, in South Asian countries
Thyroid cancer	• Highest incidence and mortality are in Asian population • Incidence and mortality rates higher among women than men

allelic heterozygosity.[19] Most human malignancies are due to somatic mutations that lead to the activation of oncogenes or the inactivation of tumor suppressor genes. As discussed in the following sections, several studies about genetic differences and their association with sex disparities in cancer in Asian populations have been done (Table 2). However, despite numerous studies on these differences, many only show associations of somatic mutations, which is a major limitation.

Cell survival and repair pathways

DNA damage is at the heart of cancer. While mutagens regularly damage DNA, things go awry once physiologic measures fail to recognize, repair, and eliminate these damages before replication occurs. Several cellular checkpoints are in place to prevent replication in the presence of genetic errors to maintain the integrity of the genome every single time cells replicate. In addition to these cellular checkpoints, DNA repair pathways act depending on the type of DNA damage. These include base-excision repair (BER), nucleotide excision repair (NER), mismatch repair, and double-stranded break repair pathways. As the DNA damage accumulates in the cells, another way that the cells prevent genomic instability is by undergoing cellular senescence, the permanent state of cell-cycle arrest.[31] And as a last line of defense, if the DNA cannot be repaired, protective mechanisms signal the cell to stop dividing and undergo apoptosis. When all these systems fail, it may lead to unregulated cell growth and cancer.[32]

Tumor suppressor genes, which play a fundamental role in oncogenesis, represent a means through which sex differences in cancer may be mediated. TP63 is a part of the TP53 family of tumor suppressor genes with considerable sequence identity in their DNA-binding, activation, and tetramerization domains. They are hypothesized to work by inducing p63-responsive genes, which are part of the p53 family and are said to have a significant role in the development of epithelia by inhibiting cell proliferation, and promoting apoptosis.[33] Other studies have shown that TP63 does in fact cause cancer development in lung cancer upon gene rearrangement, particularly when TP63 is amplified and p63 is expressed in high-grade squamous cell carcinomas.[34] Similarly, p63 has been found to play an early role in lung tumorigenesis as it was found to be amplified in lung cancer.[35] In a case-control study by Tang and colleagues (2016) genotyping SNPs of the intron 9 of TP63 rs6790167 (g243059A>G) in the non-smoking Chinese Han population, they

Table 2. Genes with a sex-specific association in cancer among the Asian population

Gene	Cancer (Population)	Sex bias	Remarks	Reference
TP53	Lung cancer (China)	Females with the CC genotype have a higher risk of lung adenocarcinoma (OR = 4.67 (95% CI: 1.49–14.59) Males with the GC genotype have a higher risk of lung adenocarcinoma (OR = 6.00 (95% CI: 2.20–16.36)	Cell survival pathways Tumor suppressor gene Inhibit cell proliferation and apoptosis	Tang et al., 2016[20]
APE1	Colorectal cancer (Taiwan)	Increased risk for colorectal cancer in females with APE1 148Glu allele (OR = 1.41, 95% CI: 1.02–1.96)	DNA repair gene	Lai et al., 2016[21]
XRCC4	Colorectal cancer (China)	Decreased risk of colorectal cancer with XRCC4 G-1394 genotype in females (OR = 0.113, 95% CI 0.014–0.932) This decreased risk is not seen in males	DNA ligation	Zhang and Hu, 2011[22]
XPC	Acute myeloid leukemia (China)	CC genotype of XPC rs2228001 is higher in males compared to females (p = 0.03) and responds better to cytosine Arabinoside chemotherapy	DNA repair gene	Xu et al., 2012[23]
NRF2	Lung cancer (Taiwan)	NRF2 rs6721961 homozygous frequency was higher in female compared to male lung cancer patients (p = 0.004)	Reactive cxygen species defense	Okano et al., 2013[24]
CD95L (FASL)	Oral cancer (India)	T>C polymorphism in FASL -844 increases the risk for females but not in males (OR = 2.11, 95% CI = 1.17–3.79)	Apoptosis	Daripally et al., 2015[25]
PCNXL2	Thyroid cancer (China)	PCNXL2 r6424270 and rs12129938 polymorphism decreased susceptibility to thyroid cancer among females PCNXL2 rs10910660 polymorphism increased susceptibility among males	Notch signaling pathway	Hao et al., 2021[26]
TLR4	Gallbladder cancer (India)	Ex4+936C>T TLR4 polymorphism higher risk of cancer in females (OR = 2.85, 95% CI = 1.29–6.28)	Antigen recognition in the immune system Toll-like receptors	Srivastava et al., 2010[27]
MPO	Gastric cancer (China)	MPO AA genotype is protective in males (OR = 0.51, 95% CI = 0.26–0.98) but not in females (OR = 0.68, 95% CI = 0.24–1.94)	Oxidative stress response	Zhu et al., 2006[28]
CCDH1	Colorectal cancer (Bangladesh)	CDH1 rs16260 polymorphism higher risk of cancer in females compared to males (OR = 1.83, 95% CI = 1.13–2.92)	Epithelial to mesenchymal transition	Rivu et al., 2017[29]
IL-6 promoter region	Liver cancer (China)	−572C>G (rs1800796) polymorphism has a higher risk of cancer in males compared to females (OR = 1.68, 95% CI = 1.15–2.42)	Inflammation	Tang et al., 2014[30]

found that the frequency of the CC genotype of rs1535045 was significantly higher in non-smoking lung cancer female patients, while the GG genotype of rs6790167 was significantly higher in non-smoking lung cancer male patients.[20] Lung cancer has the second-highest incidence among males and females, but there is a higher incidence among males, with a male-to-female ratio of 1.5–2.0. Interestingly, it has been noticed that lung cancer mortality is decreasing among males while it continues to increase among females.[36] This may indicate that having a different frequency of genotypes may differentially affect the role of TP63 in males and females.

Non-truncating polymorphisms in DNA repair genes have been identified throughout the years and have been implicated in playing a role in carcinogenesis. These polymorphisms were thought to alter the functional properties of DNA repair enzymes.[32] Several factors are involved in these pathways,

including apurinic-apyrimidinic endonuclease 1 (apyrimidinic endonuclease 1 [APE1]), a part of the BER gene family. In a case-control study by Lai and colleagues (2016) in the Taiwanese population, they observed sex-specific increased risk for colorectal cancer in females containing the APE1 148Glu allele.[21] The APE1 gene product directly interacts with error-prone DNA polymerase and is responsible for digesting both matched and mismatched 3′ terminal of a duplex DNA through its 3′–5′ exonuclease activity for proofreading and correcting mistakes during DNA synthesis.[37] Thus, this polymorphism may increase susceptibility among females. To our knowledge, there exists no study specific for Asian populations explaining the sex-specific differences in DNA repair mechanisms.[38] However, somatic mutations and mRNA expression from Asian and non-Asian lung adenocarcinoma (LUAD) patients were assessed for their sex-biased differences and results showed that the Asian population had a male-biased mutation. Regardless, as compared to non-Asians, Asian counterparts rarely showed any significant sex-specific genetic differences in DNA repair mechanisms. Genes specific for immune related pathways were found more prominent in females while males had greater involvement in DNA repair pathways.[39] Examples of this were found in a study conducted on hepatocellular carcinoma where females were found to have increased peroxisome proliferator-activated receptors (PPAR) pathway expression which mostly focuses on activation of ligand binding activity while males had greater expression of PI3K, PI3K/AKT, FGFR, EGFR, and IL-2 signaling pathway which play roles on DNA repair pathway and when affected causes DNA damage response overactivation.[40,41] In contrast, other studies have stated that disparities in DNA repair mechanisms (specifically on DNA strand breaks) between sexes is not evident in studies done on human peripheral blood mononuclear cells and meta-analysis of DNA damage emphasizing the lack of evidence to indicate that DNA repair effectiveness varies between sexes.[42,43] Other studies from outside Asia focusing on DNA repair provided evidence that females had reduced ability to repair tobacco-induced DNA damages by NER, therefore, increasing the risk to develop lung and non-melanoma skin cancer.[44] Another study that utilized comet assay for its analysis of DNA repair mechanisms showed that the fast component of SSBs repair, DNA ligation and polymerization steps of BER, were lower in females than in males.[45] These results show that BER and NER pathways influence the reduced efficiency of DNA repair mechanisms in women compared to men. XRCC4 protein complexes with DNA ligase IV rejoin the two ends of DNA during the last step of variability, diversity, and joining (VDJ) recombination and non-homologous DNA end joining in the double-strand break repair pathway.[46] Results showed a significantly decreased risk of colorectal cancer with the XRCC4 G-1394T genotype in females compared to the control group, but this was not seen in males.[22] Contrary to the previously mentioned study, this polymorphism may instead be protective against colorectal cancer in females.

Another study regarding DNA repair genes was done by Xu and colleagues (2012) among Han Chinese patients diagnosed with acute myeloid leukemia (AML). This time, they investigated six SNPs within the NER pathway that have been reported to be associated with cancer development. Their results showed that the CC genotype of xeroderma pigmentosum group C gene (XPC) rs2228001 was significantly higher in male patients than in female patients ($p = 0.03$), and those that harbored at least one variant allele of XPC rs2228001 were more likely to respond better to cytosine arabinoside (Ara-c)-based chemotherapy than those who did not carry a variant. Ara-C is one of the cornerstones of AML chemotherapy, which acts by introducing DNA lesions. Thus, it is expected that variabilities in the repair pathways can impact the effectiveness of chemotherapy in AML.[23] Interestingly, there are known sex disparities in the incidence and prognosis of AML with higher incidence and significantly inferior outcomes in males compared to females.[47]

Some pathways allow cells to respond to various stresses from toxic exposures. This includes the NRF2 gene, which has an antioxidant response against reactive oxygen species (ROS)-mediated damage that affects cell survival and contributes to the induction of tumorigenesis.[48] A study by Okano and colleagues (2013) in Japanese patients with LUAD investigated the association of SNPs in the NRF2 gene with their prognosis. Their results showed that females with homozygous alleles of NRF2 rs6721961 found in the ARE-like loci had a markedly higher incidence of adenocarcinoma compared to males with the same genotype. Interestingly, it is postulated that the SNP rs6721961 in the ARE-like loci decreases the binding affinity to the transcription factors of NRF2, thus significantly attenuating the positive feedback loop of NRF2 gene transcriptional activation. In relation to this, NRF2 has been reported to regulate the basal expression of the oncogene MDM2, an E3 ubiquitin ligase that targets p53 to suppress its tumor suppressor activity. Thus, this study may imply that SNP in the ARE-like loci of NRF2, which is associated with females, may predispose them by attenuating NRF2 gene transcriptional activation hence affecting the antioxidant response of cells against ROS and affecting the regulation of MDM2.[24] This is interesting because lung

cancer has a male-to-female ratio of 1.5–20 and has a higher mutation burden among males.[17,33] This may be one factor that differentially affects females compared to males. ROS generation and management are known to differ between male and female cells primarily as a consequence of mitochondrial function in male versus female cells.[49] Mitochondria are primarily maternally inherited which explains its strong sex-specific predisposition while paternal mitochondria regulate the mitochondria inherited by the offspring from the mother. Regitz-Zargrosek and colleagues suggested that sex hormones play a role in signaling in the dynamics of the mitochondria as well as the cellular redox biology.[49,50] This was supported by findings in a study on heart failure where female hearts had more efficient maintenance of energy during energy metabolism as compared to males; this was related to the presence of downregulated genes that contribute to energy metabolism in males as compared to those present in females.[50] As an example, estrogen and estrogen-related receptors have been found to play a role in fatty acid oxidation, respiratory chain activity and mitochondrial dynamics where estrogen plays a role in the mitochondrial fission and fusion, providing evidence that during mitochondrial respiration females have a lower reactive oxygen species level than males.[51]

Apoptosis is one of the last lines of defense in ensuring that aberrant cells do not multiply.[32] Thus, dysregulation of the apoptotic pathway is one of the mechanisms by which cancer cells override the body's physiologic checks and balances, ensuring that abnormal cells are sequestered and stopped from reproducing.[52] FAS and FAS ligand (FASL) are critical mediators of apoptosis, and their dysregulation has been implicated in cancer pathogenesis.[53,54] Genetic polymorphisms in FAS and FASL have been shown to confer variable cancer risks, potentially due to differences in the function of cytotoxic T cells and natural killer cells.[25,53] A case-control study in India studied the association of polymorphisms in CD95 (FAS/APO-1) and its ligand, CD95L (FASL), with oral cancers among males and females.[25] $CD95^{-}CD95L$ is part of a receptor and death ligand system that mediates apoptosis which is important in the maintenance of immune cell homeostasis and immune elimination of cancer cells.[52] Their results showed that a T>C polymorphism in FASL-844 increased the risk for buccal mucosa cancer in females but not in males, and FAS genotypes did not alter the risk in either males or females. They also noted that the co-occurrence of combined genotypes of FAS and FAS/FASL altered male susceptibility to tongue cancer. The findings imply that SNPs of FAS and FASL and combined genotypes of these two molecules differentially change the risk of tongue and buccal mucosa cancers in males and females.[25]

Finally, cellular senescence is the state of stable cell-cycle arrest, while remaining metabolically active, which is a strategy to prevent genomic instability. Cells enter this state as a stress response triggered by mechanisms such as DNA damage, telomere shortening, oncogene activation, and tumor suppressor loss.[55] Additionally, it causes increased expression of inflammatory response that promotes immune-mediated tumor clearance.[56] Thus, any sex differences in the factors that promote senescence will ultimately affect its induction as well as its downstream effects. For example, males have shorter telomere lengths and have a faster rate of telomere attrition compared to age-matched females.[57] A study by Liu et al. (2009) in Chinese Han patients showed that shorter telomere length is associated with gastric cancer and females had a significantly longer average telomere length than male. Second, male cells are said to encounter telomere dysfunction sooner than females.[58] Third, male cells are at greater risk for accumulating somatic mutations and undergoing oxidative stress compared to female cells.[57] Ultimately, these mechanisms allow the cells to stop the propagation of deleterious mutations thus cellular senescence has been widely considered to be a protective mechanism against cancer. However, this is being challenged, as recent studies have shown that senescence can paradoxically promote cancer stemness and aggressiveness.[59] Interestingly, a Genome-Wide Association Studies (GWAS) study involving female Asian non-smokers from mainland China, South Korea, Japan, Singapore, Taiwan, and Hong Kong showed that seven telomere-length associated genetic variants which predicted longer telomere length were associated with increased lung cancer risk.[60] Although the relationship of longer telomeres to lung carcinogenesis is unclear, it is possible that while shorter telomeres lead to faster telomere attrition, hence resulting in faster replicative senescence and apoptosis, longer telomeres may result in immortalized cells with unlimited potential for cellular and tumor growth.[60,61] However, much remains to be elucidated as there are still limited studies that investigate the sex-differences in genetic control of cellular senescence especially among Asian populations.

Oncogenes

Cooper and Sunderland (2000) discussed how oncogenes—genes whose aberrant upregulation leads to oncogenesis—can elicit responses that transform the cell into its rather pathogenic counterpart, a cancer

cell. Most oncogenes arise from one's exposure to radiation or chemical carcinogens rather than viral infection; however, it is without a question that viral oncogenes also significantly affect the quality of life of many individuals.[62]

Proto-oncogenes are normal genes that, when mutated, influence the growth of normal cells to be cancerous.[63,64] The mutated proto-oncogene can also be understood as an oncogene where a gene that used to be viable for normal human function becomes overexpressed, causing continuous and uncontrollable growth of cells, thereby leading to cancer. The primary function of proto-oncogenes revolves around cellular division and inhibition of cell differentiation and apoptosis. Therefore, when mutated, it would lead to uncontrollable cellular division and continuous inhibition of cellular death, which may promote cancer development and metastasis.[65]

Complementary to proto-oncogenes are tumor suppressor genes that encode proteins that provide a negative feedback mechanism on cell growth, providing signals for cell regulation, including promoting cell-cycle arrest and inducing apoptosis.[66] Tumor suppressor genes become inactivated by point mutations or deletions of two copies of the tumor suppressor gene, causing the activation of oncogenes. This would result in the loss of function of tumor suppressor genes, disabling their ability to regulate cellular growth and inducing cancer cell growth and malignancy.

An example of a tumor suppressor gene is PCNXL2 or protein pecanex-like protein 2 *Homo sapiens* that encodes multi-pass transmembrane proteins that regulate the Notch signaling pathway.[67] Its activity to regulate Notch signaling occurs when protons are transported across the membrane thereby providing adequate membrane potential that would be enough to activate y-secretase. Y-Secretase then liberates the Notch intracellular domain (NICD) from its receptor to the inside of the cell. With the talk on Notch growing abundant, it is only fair to characterize its importance in the cell. Notch acts as a receptor in a signaling pathway that is highly conserved and is essential in the development and transformation of cells.[68] It plays a role in proteolytic cleavage, where intracellular fragments are released, thereby regulating transcription. Should there be a mutation in the PCNXL2 gene that regulates Notch receptor activity, the development and transformation of cancer cells would be difficult to control.

A case-control study by Hao and colleagues (2021) in a Chinese population focused on the influence of PCNXL2 polymorphisms on thyroid cancer. Based on their findings, the rs10910660 polymorphism in the PCNXL2 gene puts Chinese individuals at greater risk of thyroid cancer, while the rs12129938 polymorphism is protective against thyroid cancer susceptibility.[26] Despite the initial protective role of rs1219938, upon reaching the age of 45 and beyond, it provides a greater risk of thyroid cancer, which was in contrast with the r4649295 polymorphism that decreased thyroid cancer susceptibility at 45 years of age and older. The r6424270 and rs12129938 showed a decreased susceptibility of women to thyroid cancer compared to males, with rs10910660 having an increased susceptibility. This shows that the following PCNXL2 polymorphisms are potential biomarkers that may signify one's risk for cancer depending on age, sex, and race.

Immune-related genes

Cancer development depends not only on DNA aberrations in cells and the complex ecosystems that support these neoplastic cells. Also known as the tumor microenvironment, tumors develop around it a complex and specialized tissue architecture characterized by chronic inflammation and corrupted extracellular matrix that supports the tumor and furthers disease progression.[69] In the updated core hallmarks of cancer, both tumor-promoting inflammation and avoiding immune destruction are now included as core hallmarks of cancer.[70]

Toll-like receptors (TLRs) are found in the immune cells that recognize self and non-self antigens with numerous immune functions.[71] Due to their ability to distinguish self and non-self antigens, they can detect invasive pathogens through their molecular motifs, such as pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs). They can also bridge the innate and adaptive systems as they induce dendritic cell maturation, which initiates adaptive immune responses upon antigen presentation. This, therefore, explains their role in regulating cytokine production, immune cell proliferation, and survival. Numerous studies have cited the influence of TLR gene polymorphisms in the increasing risk of certain cancers of individuals (e.g., prostate cancer, gastric cancer, and colorectal cancer). A study in

India examined the association of polymorphisms in the TLR2 and TLR4 genes with risks of contracting gallbladder cancer (GBC).[27] Based on their results, the wt//del and del/del genotypes of the TLR2(Δ22) polymorphism were associated with an increased risk of GBC. Furthermore, those with a combined genotype of the wt/del+del/del had a significant increase in risk for GBC compared to the w/w genotype. Therefore, this indicates that individuals carrying the *del* allele are at a predominant risk of having GBC. For TLR4 polymorphisms, Ex4+936C>T polymorphism (g.14143CT; rs4986791) showed a significant association with risks of GBC. This polymorphism is under a dominant mode of inheritance. When checked for sex disparities in their risk of GBC, females were found to have a higher risk upon possessing this Ex4+935C>T polymorphism than males. This indicates that low-penetrating variants found in the TLR genes greatly influence susceptibility to GBC. North India had long since been high in the incidence of GBC, consistent with these results where women (10.1 per 100,000 women) had a higher prevalence than men (4.5 per 100,000 men).[72] Previous studies have discussed how bacteria such as *Helicobacter* and *Salmonella* likely influence their susceptibility to GBC. However, current evidence entails no sufficient rationale for the progression of the disease.[73,74] With the continuously growing increase in TLR gene studies associated with cancer progression, this study provides evidence from an Indian perspective that further supports the role of TLR polymorphisms in cancer and the increased risk of women contracting GBC. They also selected good TLRs, such as TLR2 and TLR4, which recognize bacteria and are stimulated by the presence of lipopolysaccharides (LPS) from Gram-negative bacteria. These are the most common TLRs used in studies, providing several supporting evidence for their results.

Another molecule related to innate immunity is myeloperoxidase (MPO), an enzyme that plays a role in oxidative stress response found in neutrophils and monocytes. It catalyzes a reaction that produces hypochlorous acid, which can damage DNA and lead to mutations of oncogenes and tumor suppressors. A case-control study by Zhu and colleagues (2006) in Chinese populations investigated the association between the risk of gastric cancer and MPO G–463A polymorphism. They found that those with GA and AA genotypes of MPO had a 44% reduced risk of gastric cancer compared to the GG genotype. Furthermore, the A allele was protective among males but not in females. It is known that men are at a higher risk of developing gastric cancer than women.[28] Furthermore, the relative sex difference in the incidence of gastric cancer has an increasing trend, with male-to-female ratios rising from 1.86 in 1990 to 2.20 in 2017.[75] However, a study by Kim and colleagues (2016) showed that the female sex is a poor prognostic factor for advanced gastric cancer.[76] Additionally, females also have an inferior 5-year relative survival.[77] The selective protective effect of MPO polymorphism on males but not on females may be one of the mechanisms that cause poorer prognosis in females by maintaining the catalytic function of MPO in the context of gastric cancer.

Invasion and metastasis

In the initial stages of cancer, neoplastic cells are confined to their primary sites. However, as the disease advances, tumor cells can penetrate the membranes surrounding them, and the microenvironment changes, causing these cells to spill over. They may directly invade nearby tissues or may spread by hematogenous or lymphatic routes. Invasion and metastasis are important prognostic factors in cancer patients, as diffusely spread tumors are more difficult to control and treat. Metastasis is also the leading cause of mortality in patients with cancer as they invade the target organs and start to affect their bodily functions. Various mechanisms lead to invasion and metastasis.[78]

One of these mechanisms is the epithelial-to-mesenchymal transition (EMT) process. This developmental process mimicked by tumor cells causes fully differentiated epithelial cells to assume a mesenchymal phenotype with enhanced abilities to migrate and invade other tissues.[78] One molecule is CDH1, another term for E-cadherin, which is responsible for mediating cell signaling, adhesion of intercellular surfaces, as well as the differentiation of cells. The genetic variations in the CDH1 gene also influence a change in the polarity and adhesion of cells, which contribute to tumorigenesis and metastasis.[79,80] A case-control study by Rivu and colleagues found that CDH1 rs16260 polymorphism was found to have a higher risk of colorectal cancer in female patients compared to male patients.[29] Compared with other populations, only the Bangladesh population had an association with an increased risk of colorectal cancer in the presence of CDH1 rs16260 SNP with colorectal cancer compared to Western countries like the United Kingdom, Iran, and Turkey.[79,80] This study reveals another facet of sex disparities in colorectal cancer, as we previously saw how polymorphisms in genes related to the repair pathways affected males and females differently: APE1(148Glu) was found to have an increased risk for colorectal cancer. In contrast, polymorphisms in XRCC4 decreased the risk in Chinese females.[21,22]

Non-coding regions

As technology improved over the years and better understood the human genome, we arrived at a surprising discovery that only 1.5% of the human genome contains coding DNA. The rest of the genome is long non-coding regions, which were once thought to be of no function, and are now known to play vital regulatory roles.[81] Thus, it is expected that polymorphisms in these regulatory regions may be associated with the pathogenesis of different diseases.

One example of non-coding regions includes the promoter sequences of genes located upstream of the initiation site. Promoters are essential in regulating gene expression by binding to transcription factors. Polymorphisms in these regulatory regions may modify the binding of transcription factors leading to differential gene expression.[82] A case-control study in the Han Chinese population investigated the association of −572C>G (rs1800796) polymorphism located within the promoter region of IL-6 with hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC). Their study showed that male patients carrying the G allele were associated with a significantly higher risk of HBV-related HCC, but this was not observed in females.[30] The frequency of HCC among male patients is notably much higher and is considered a risk factor for developing HCC, especially in HBV carriers.[83,84] Thus, Asians are particularly prone to HCC due to the high incidence of HBV in the region.[83] This may also explain why HCC is the third most common cause of cancer-related death in Asia-Pacific.[85] Overall, these results suggest that G allele polymorphisms in the IL-6 promoter region among male patients may alter the expression of IL-6, a crucial factor in the development of HCC. A report by Terry and colleagues showed that the variant in this locus was associated with increased transcription efficiency of IL-6, which is consistent with the findings of high serum IL-6 levels in the development of HCC in chronic hepatitis B patients.[86,87] Tang and colleagues surmise protective estrogenic pathways may counteract this mechanism in females.[30]

Epigenetic difference

Gene sequence mutations and polymorphisms incompletely explain the phenotypic variation observed in the population. Epigenetics, defined as heritable changes in gene expression not attributable to gene sequences, offers a partial explanation for these variabilities.[88,89] Epigenetics mediate gene expression by controlling genetic information that can be accessed by cellular machinery. Aberrance in epigenetics may lead to inappropriate activation or inhibition of cellular processes, leading to disease states such as cancer. DNA methylation, histone modifications, microRNAs, and long non-coding RNAs (lncRNA) are epigenetic mechanisms that are well-described for oncogenesis.[90] Moreover, epigenetics also mediate the mechanisms for sexual differentiation.[91,92] Chromosomal and hormonal signals rely on epigenetic mechanisms in the complex process of sexual development.[91] Thus, epigenetic processes may also mediate sex differences in cancer phenotype in Asia.

Methylation

DNA methylation and histone modifications affect the access and binding of transcription factors to DNA and chromatin, thus playing an essential role in gene expression. These modifications have documented roles in the hallmarks of cancer.[90]

Sex-biased methylation and histone modification have been observed in the Asian population.[93,94] Inoue and colleagues reported sex-biased differences in methylation of long interspersed element (LINE-1) in a healthy Chinese population.[93] Similarly, Cash and colleagues documented different levels of LINE-1 methylation between healthy male and female Chinese.[95] LINE-1 is a repetitive sequence in the human genome, and its differential methylation may impact chromosomal rearrangement and genetic stability.[96,97] Methylation of this repetitive sequence is implicated in the development of cancer. Song and colleagues (2016) reported differential methylation of LINE-1 between sexes in gastric cancer. Methylation of LINE-1 was also associated with invasiveness and prognosis of patients.[94] These findings imply that differential methylation of repetitive sequences in the human genome might explain sex differences in cancer in the Asian population.

Environment and sex may interact through DNA methylation and histone modification for cancer development. Arsenic differentially affects males and females in its carcinogenicity.[98] For instance, in the Bangladeshi population, males are more susceptible to developing skin lesions and malignancies from arsenic exposure.[99,100] Epigenetic mechanisms may play a role in the sex variable effects of arsenic health outcomes. Arsenic exposure has been shown to influence epigenetic mechanisms such as DNA methylation.

Moreover, these epigenetic modifications may mediate the toxicity and carcinogenic effects of arsenic.[101–105] Additionally, mutations in epigenetic modifiers affect the prognosis of acute promyelocytic patients treated with arsenic trioxide and all-trans retinoic acid.[106] Sex differences in global DNA methylation and histone modification have been demonstrated in the Bangladeshi population exposed to arsenic.[107,108] Furthermore, the differential effect of arsenic on epigenetic modification in different sexes might be present at birth.[109]

Interaction between hormonal pathways and epigenetics might account for Asian sex differences in cancer. Methylation of estrogen receptor alpha (ER-alpha) affects the prognosis of several cancers.[110–112] The sex-biased difference in methylation of ER-alpha has been demonstrated in Taiwanese lung cancer patients.[111] In this population, ER hypermethylation is significantly higher in males than in females. There is evidence showing methylation differences between sexes are present at birth.[113] Estrogen hormone might mediate differences in ER-alpha methylation between males and females. Treatment of estradiol was demonstrated to inhibit the methylation of ER-alpha in lung cancer and osteosarcoma cell lines.[111,114] This illustrates that ER-alpha methylation might partially account for differences in cancer prognosis in Asian male and female populations.

Sex differences in methylation are also evident in tumor suppressor genes. MGMT is a DNA repair protein that protects cells from an unstable gene mutation, cell death, and tumorigenesis.[115,116] MGMT gene expression is primarily regulated by epigenetic mechanisms such as DNA methylation and histone modifications.[116,117] Differences in methylation of the MGMT promoter region between sexes have been demonstrated in a healthy Singaporean-Chinese population.[118] In this cohort, the males were associated with higher MGMT promoter methylation. Moreover, several cancers, such as lung, gastric, and colon, also demonstrated sex-biased differences in MGMT methylation.[119–123] Wu and colleagues showed that MGMT promoter methylation is associated with increased p53 mutations in Taiwanese lung cancer patients. This difference is more pronounced in males compared to females.[122] Gastrointestinal cancers also showed sex-biased differences in MGMT promoter methylation.[119,120,123] Estrogen hormones might mediate these differences. Estradiol decreased the expression of methylation proteins DNMT and HDAC1 and attenuated their binding activity to MGMT promoters in a lung cancer cell line. This mechanism might account for the different levels of MGMT methylation between sexes in Asian cancer patients.[121]

FHIT, another tumor suppressor gene, was found to be significantly hypermethylated in Asian patients with non-small cell lung cancer. Moreover, FHIT showed differential methylation in different sexes.[124] This tumor suppressor gene has several functions, including cell-cycle arrest, apoptosis, inhibition of cell proliferation, and protection from DNA-damaging agents.[125] Other tumor suppressor genes that showed differential methylation between sexes in the Asian population include Caveolin 1 in colorectal cancer and TSLC1, TIMP2, and DBC1 in lung cancer.[126–128]

Another plausible mechanism for the sex differences in Asians is the expression and methylation of X-linked tumor suppressor genes. Since females have two copies of X chromosomes, inactivation of the extra chromosome equalizes the gene expression for males and females.[129] However, around 15% of X chromosomes normally escape this inactivation.[106,130] Some of these escapees include tumor suppressor genes (aka. EXIT—escape from X-inactivation tumor suppressor), epigenetic modifiers (e.g., KDM6A), immune genes (e.g., TLR7), and some alleles that interact with p53 pathway.[131–133] Methylation of several X-linked tumor suppressor genes demonstrated an association with an increased risk of cancer in Asians. For instance, Lee and colleagues showed that hypermethylation of BEX-1 and LDOC-1 are significantly associated with oral cell squamous cell carcinoma in a Taiwanese population.[134] Hypermethylation of CHST7, another X-linked tumor suppressor gene, increased colorectal cancer risk in Chinese patients, which is more evident in females.[135]

Sex differences in DNA methylation and histone modifications are evident in Asian cancer patients. These epigenetic mechanisms may mediate the effects of environment and hormones on sex differences.

miRNA

MicroRNAs (miRNAs) are oligonucleotides (20–30 bp) with essential roles in regulating gene expression.[136] They bind to the 3′ untranslated region (3′ UTR) of mRNAs transcript to mediate its degradation or translational repression.[137] miRNAs play a role in oncogenesis-related cellular processes, including cell cycle progression, apoptosis, and cell differentiation.[90]

Table 3. MicroRNAs with sex association in cancer among Asian population

MicroRNA	Cancer (Population)	Sex Bias	Reference
miR-122	Liver cancer (China)	Lower levels of miR-122 in males compared to females with HCC (mean expression 0.44 ± 1.34 males vs. 1.32 ± 0.98 females)	Luo et al., 2013[138]
miR-196b, miR-106a	Gastric cancer (China)	Associated with sex (miR-196: $p = 0.014$; miR-106a: $p = 0.035$), poor differentiation of gastric cancer patients (miR-196: $p < 0.001$; miR-106a: $p = 0.001$)	Yu et al., 2012[139]
miR-135, miR-203, miR-10b	Bone metastasis from primary lung or breast cancer (China)	Differential levels between female and male patients with metastasis (miR-135, $p < 0.05$; miR-203, $p < 0.01$, miR-10b $p < 0.01$)	Xu et al., 2021[140]
miR-18a	Liver cancer (Taiwan)	Elevated in female HCC tissues compared to male (female/male ratio, 4.58)	Liu et al., 2009[141]
miR-22	Liver cancer (China)	Elevated in male-adjacent HCC tumor tissues compared with normal tissues ($p = 0.027$)	Jiang et al., 2011[142]
miR-299-5p	Thyroid cancer (China)	Higher expression in male compared to female papillary thyroid cancer patient (Relative expression 0.79 [0.37–1.69] male vs. 0.37 [0.20–0.74])	Wang et al., 2018[143]
miR-27	Gastric cancer (China)	hsa-miR-27 (rs895819) associated with increased gastric cancer susceptibility in males (OR = 1.56, 95% CI = 1.08–2.27)	Sun et al., 2010[144]
miR-196a	Lung cancer (Korea)	miR-196a (rs11614913) associated with increased susceptibility of non-small cell lung cancer in males (OR = 1.53, 95% CI = 1.09–2.16)	Hong et al., 2011[145]

miRNAs were shown to be differentially expressed between Asian male and female cancer patients (Table 3). Male HCC patients have lower levels of miR-122 than females in a Chinese population.[138] This parallels the lower expression of miR-122 in tumors compared to normal tissues and the lower HCC incidence in females. Expression of miR-196b and miR-106b was shown to be associated with sex and poor differentiation in Chinese gastric cancer patients.[139] Levels of miR-135, miR-203, and miR-10b were higher in females than male patients with bone metastasis from a Chinese lung cancer cohort.[140]

miRNAs' interaction with the estrogen-mediated signaling pathway might be a potential mechanism for regulating cancer sex disparities in Asians. Estrogen is proposed to protect women from HCC development.[146] Liu and colleagues demonstrated that miR-18a is significantly elevated in female HCC tissues. MiR-18a targets 3'UTR of ER-alpha and is correlated with its decreased expression in HCC tissues. Their results suggested that miR-18a attenuates the potential protective role of estrogen through the downregulation of ER-alpha.[141]

Jiang and colleagues showed that miR-22 is significantly elevated in male-adjacent tumor tissues in a Chinese HCC cohort.[142] MiR-22 was associated with decreased expression of ER-alpha by targeting its 3' UTR. Furthermore, they demonstrated that IL-1 alpha is negatively regulated by estrogen through ER-alpha. Increased IL-1 alpha may potentially lead to compensatory proliferation and tumorigenesis. This study suggested that miR-22 downregulation of ER-alpha might lead to increased IL-1 alpha expression and eventually increased cancer risk in males.

Wang and colleagues showed that miR-299-5p expression is associated with sex and extrathyroidal extension in Chinese patients with papillary thyroid cancer (PTC). Mir-299-5p has lower expression in cancer tissues and was shown to inhibit migration and invasion of cancer cell lines.[143] This inhibition was mediated by the miRNA's interaction with ER-alpha and Glil protein. Their results suggest that miR-299-5p is differentially expressed between sexes and regulates the invasiveness and migration of PTC through its interaction with an estrogen receptor.

Polymorphisms in miRNA genes have also been demonstrated in several Asian populations. For instance, hsa-miR-27 (rs895819) variant is associated with gastric cancer susceptibility.[144] These effects are more pronounced in male, older, and nonsmoker patients. Another polymorphism, hsa-miR-196a (rs11614913), was associated with increased susceptibility to non-small cell lung cancer in a Korean population.[145] This increased susceptibility persisted in male, older, and nonsmoker patients.

Genetic variation in the miRNA binding region (3′ UTR) also affected the risk of cancer between different sexes. A group of lipoma preferred partner (LPP) polymorphism genes (rs1064607, rs3796283, and rs2378456) increased susceptibility to lung cancer among male patients, while another LPP (rs2378456) polymorphism weakened the risk for female patients.[147] Differential expression of miRNAs and its interaction with sex hormone pathways might be a possible mechanism for sex differences in cancer. Moreover, polymorphism on the miRNA gene and binding sites may also affect the sex differences observed in Asian patients.

Long non-coding RNAs

LncRNAs are RNAs greater than 200 nucleotides that cannot be translated into proteins.[148] They are involved in gene regulation and various biological processes, including oncogenesis. A study in Zhenjiang, China, by Sang and colleagues enrolling 949 patients with esophageal cancer and 1369 healthy controls investigated the genetic susceptibility of having functional SNPs in the lncRNA CASC8 to developing esophageal squamous cell carcinoma (ESCC).[149] CASC8 is found in the 8q24 region and plays a role in regulating MYC, a proto-oncogene.[150] Furthermore, SNPs in CASC8 have been correlated with the risk of prostate, breast, colorectal, and gastric cancers. This study showed that polymorphism rs1562430 was significantly associated with an increased risk of ESCC, with a much higher risk in males than females.

Cytogenetic differences on the Y chromosome

The most significant cytogenetic difference between males and females is their respective sex chromosome composition, that is, XY and XX, respectively. The Y chromosome contains male-specific genes which play vital roles in germ cell differentiation, male sex determination, and tissue masculinization. Structurally, the acrocentric Y chromosome includes three distinct regions: (1) the euchromatic pseudoautosomal regions (PAR) 1 and 2, located on the telomeric ends of the short arm (Yp) and long arm (Yq), respectively; (2) the heterochromatic region in Yq, apposed to PAR2; and (3) the euchromatic male-specific region of the Y chromosome (MSY), juxtaposed with the centromere and encompassing the proximal regions of the Yp and Yq[151] (Figure 1). Several studies have shown that mutations in and/or ectopic expressions of Y-linked genes were remarkably associated with several male-biased diseases, including various types of cancers.[152] The MSY harbors sex-determining region Y (SRY) and RNA-binding motif (RRM) on the Y chromosome (RBMY), both demonstrated to influence increased cancer predisposition in males.

SRY region

SRY is the key gene that determines maleness in humans.[153] SRY protein, the gene product of *SRY*, has a 79-amino acid high-mobility group (HMG) box. These HMG boxes regulate the binding of *SRY*-related HMG-box (SOX) factors to particular DNA regions.[154] SOX has been demonstrated to affect cancer progression.[155–157]

In 2018, SOX2 was shown to promote tumor aggressiveness and epithelial-mesenchymal transition in Chinese patients with tongue squamous cell carcinoma (TSCC).[155] Liu and colleagues found that TSCC tissue samples (83.6%, 51/61) had remarkably higher Sox2 expression than their corresponding adjacent non-cancerous tissue samples (63.9%, 39/61). Clinically, this study also revealed that SOX2 expression was markedly associated with the pathological tumor-node-metastasis (pTNM) stage, tumor differentiation, and survival. Interestingly, the expression of SOX2 was demonstrated to be the only independent predictor of poor prognosis.[155]

Similar cancer in the head and neck region suggested the potential role of SOX11 in 1196 male Taiwanese oral cancer patients.[156] Results indicated that SOX11 rs77996007 variants were remarkably associated with larger tumor size but not with tumor clinical stage, lymph node metastasis, distant metastasis, and cell differentiation grade. Cancer Genome Atlas database analysis also revealed high SOX11 mRNA expression during tumor development.[156]

In contrast, unlike other SOX genes where an increased SOX expression leads to tumorigenesis, inactivation of SOX30 was associated with malignant potential in Chinese human bladder and myeloid cancer patients.[155,157] Liu and colleagues (2018) found that SOX30 mRNA and protein levels were significantly lower in adjacent noncancerous tissues compared to bladder cancer tissues. Their clinicopathological analyses also demonstrated that low SOX30 expression was significantly associated with higher TNM stages and poor survival rates.[155]

Similarly, Zhou and colleagues (2018) suggested that SOX30 inactivation through methylation was negatively correlated with leukemia-free survival (LFS) and OS in Chinese AML patients.[157] This study classified AML patients into hypermethylated and non-hypermethylated groups based on the methylation level cut-off point (1.024) determined by the ROC curve analysis. SOX30 non-hypermethylated patients had markedly higher SOX30 expression compared to the SOX30 hypermethylated patients. Interestingly, myelodysplastic syndromes (MDS)-derived AML had significantly higher SOX30 methylation levels than *de novo* AML patients. This result suggests that the risk of MDS to AML transformation is increased by SOX30 hypermethylation. Furthermore, MDS patients with high International Prognostic Scoring System (IPSS) risks had significantly higher SOX30 methylation than the control and low/intermediate IPSS risk groups. Moreover, SOX30 hypermethylation was associated with higher bone marrow (BM) blast and lower hemoglobin in MDS patients. Overall, SOX30 methylation was an independent prognostic and predictive biomarker in AML and was associated with MDS disease progression.[157]

RNA-binding motif (RRM) gene on the Y chromosome (RBMY)

RBMY encodes the male germ cell-specific RNA-binding protein associated with spermatogenesis.[158,159] RBMY has been suggested to contribute a vital role in developing hepatocellular carcinoma (HCC) and has been demonstrated to explain HCC male predisposition.[158–161] Kido, Tabatabai, Chen & Lau (2020) stated that RBMY is commonly activated in HCC and suggested to stimulate hepatocarcinogenesis.[162]

RBMY transcripts are normally only expressed in typical human testis but were detected in Taiwanese HCC patients.[159] Interestingly, the different types of RBMY transcripts (wild type, C-terminal SRGY boxes deletion variant, N-terminal RRM deletion variant, and deletion of both variants) were detected in male HCC/hepatoblastoma (HB) tissue samples and testis. Furthermore, RBMY transcripts were not detected in paired-matched adjacent non-cancerous tissues, cirrhotic liver tissues from pediatric patients with biliary atresia, and six other types of cancers (prostate, colon, bile duct, stomach, kidney, lung). RBMY seemed to be a good candidate for HCC and HB biomarkers. However, the molecular mechanisms by which RBMY promotes hepatocarcinogenesis and its possible link to HCC male predominance are not yet fully elucidated.

To further investigate the role of RBMY in hepatocarcinogenesis and HCC male predominance, Tsuei and colleagues (2011) examined the expression of RBMY, androgen receptor (AR), and its inhibitory variant AR45 using quantitative RT-PCR. In RBMY-knockdown HepG2 cell lines, AR *trans*-activation was diminished, but an increased AR45 expression was noted. In contrast, overexpression of RBMY in Hep3B and Huh7 cell lines showed decreased AR45 expression. This trend was consistent with AR45 expression in Taiwanese RBMY-positive and RBMY-negative HCC patients. Hence, the role of RBMY in hepatocarcinogenesis and HCC male predominance may partially be explained by RBMY association with AR regulation through AR45, the inhibitor of AR.[161] However, further studies should be done to confirm these findings.

In another Taiwanese study, Chua and colleagues investigated one mechanism for RBMY's hepatocarcinogenesis. Their RBMY immunohistochemistry (IHC) staining showed four distinct patterns in human male HCC tissues: (1) both nucleus-positive and cytoplasm-positive (N^+C^+; 37.6%, 77/205 cases); (2) only nucleus-positive (N^+; 21.9%, 45/205 cases); (3) only cytoplasm-positive (C^+; 12.7%, 26/205 cases); and (4) both negative (N^-C^-; 27.8%, 57/205 cases). Analyses revealed that RBMY N^+C^+ and C^+ were independent predictors of larger tumor size and late-stage Barcelona Clinic Liver Cancer (BCLC) stage. Notably, RBMY C+ was also significantly associated with early (<1 year) recurrence and metastasis. RBMY N^+C^+ and C^+ also had poorer 5-year survival and 5-year clinical disease-free rates than the $RBMY^-$ and N^+ cases.[130] To determine whether the expression of RBMY or the hormonal effect of AR had a larger influence on HCC male predominance, male childhood (5–10 years old) HCC patients (n = 6) were also examined by Chua and colleagues (2015). These male pediatric patients had negative AR staining, suggesting they had the typical undetectable androgenic activity for their age.[160] Albeit with a low sample size, these findings may suggest

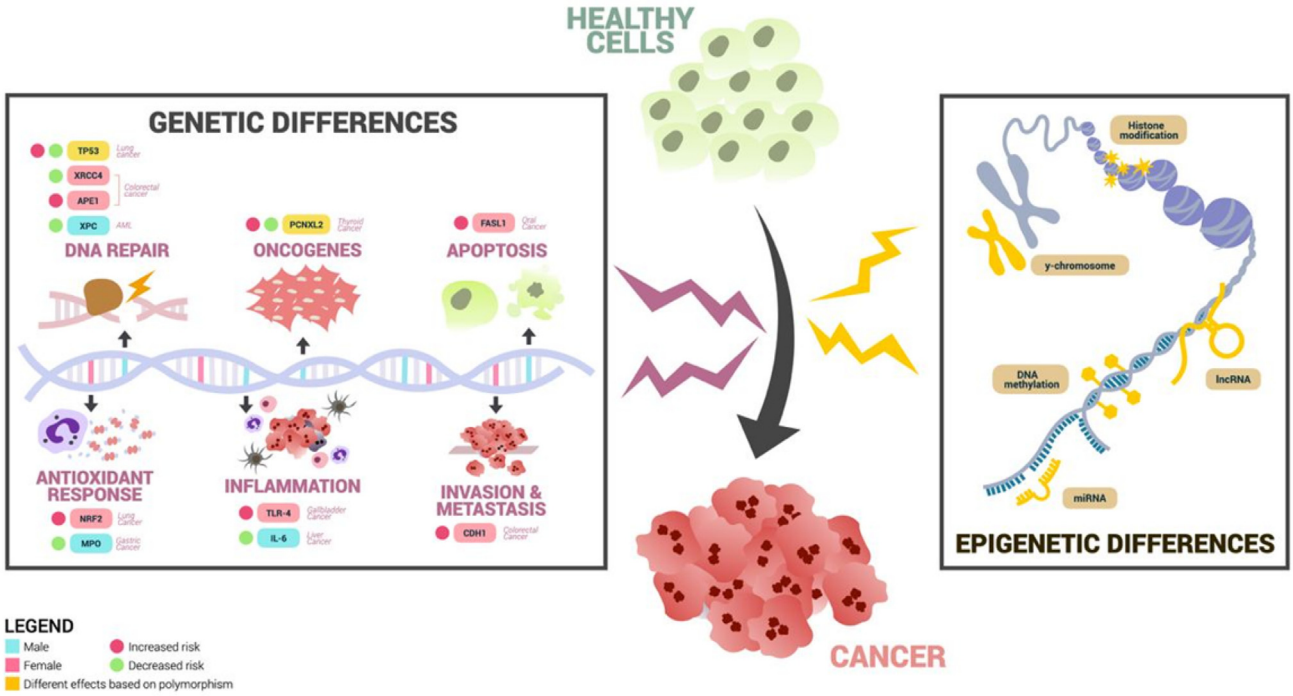

Figure 2. Molecular sex differences among cancer patients in Asia

that RBMY expression has a more crucial role than the androgenic activity in justifying the observed epidemiological HCC male predisposition.

The observed clinical differences in these HCC patients were explored further by determining possible molecular pathways that may unravel key hepatocarcinogenetic mechanisms. Chua and colleagues (2015) reported that the spatial cytoplasmic RBMY localization and its noted association with worse HCC outcomes were, to some extent, accounted for by the RBMY-glycogen synthase kinase 3β regulation via the Wnt/β-catenin signaling pathway. Mechanistically, RBMY inhibits glycogen synthase kinase 3beta activity through Ser9-mediated phosphorylation, preventing β-catenin degradation. Eventually, β-catenin will enter the nucleus and promote transcriptional activation of downstream oncogenes. Furthermore, stimulation of Wnt-3a also leads to increased cytoplasmic RBMY localization.[160] Taken together, the aberrant Wnt/β-catenin signaling pathway, in some ways, explains the role of RBMY in the malignant hepatic stemness in HCC through its interaction with glycogen synthase kinase 3β.

CONCLUSION

Our review showed molecular characteristics that potentially mediate sex disparities found among patients with cancer in Asia (Figure 2). Differences in sex characteristics are evident in genetic sequencing in biological processes, including cell survival, immune function, oncogenesis, and metastasis. Epigenetic differences in DNA and chromosome methylation, miRNA, and lncRNA are also present. Furthermore, the Y chromosome elements SRY and RBMY might influence the male predisposition for some cancers.

As most studies discussed described merely associations, more in-depth research is necessary. Studies designed to identify sex differences with large patient cohorts can confirm relationships between molecular markers to sex disparities in cancer. Moreover, research that utilizes appropriate cellular and animal models can elucidate mechanisms and pathways that bridge sex and cancer. These studies can clarify intricacies in the relationship between sex, race, and cancer and may lead to targetable mechanisms to reduce cancer risk and improve cancer outcomes.

It is important to note that the majority of studies exploring sex differences in Asian patients make use of data from a limited number of Asian countries, mainly in East Asia. Much less is known about sex differences in cancer in the population and the molecular levels in people from less-resourced parts of Asia, including Central Asia, Southeast Asia, and many parts of South Asia.[163] To promote both generalizability of findings and foster the ethical imperative of epistemic equity, multinational research collaborations that explore data more representative of the global population are necessary.[164,165]

Molecular sex differences found in Asian patients with cancer have implications for improving the management of patients. Several studies indicated that genes and gene products might act as markers for diagnosis, prognosis, and effectiveness of therapy. Moreover, sex and racial differences are essential in designing cancer therapeutics in the era of precision medicine. Molecular markers in sex can help guide the development and trials of novel therapeutics in cancer. More studies are required to investigate the role of molecular markers in diagnostics, prognostics, and therapy, to improve the health outcomes of patients.

AUTHOR CONTRIBUTIONS

All authors wrote and edited this review article.

DECLARATION OF INTERESTS

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