

Localization and upregulation of survivin in cancer health disparities: a clinical perspective

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Abstract: Survivin is one of the most important members of the inhibitors of apoptosis protein family, as it is expressed in most human cancers but is absent in normal, differentiated tissues. Lending to its importance, survivin has proven associations with apoptosis and cell cycle control, and has more recently been shown to modulate the tumor microenvironment and immune evasion as a result of its extracellular localization. Upregulation of survivin has been found in many cancers including breast, prostate, pancreatic, and hematological malignancies, and it may prove to be associated with the advanced presentation, poorer prognosis, and lower survival rates observed in ethnically diverse populations.

Keywords: survivin, cancer, exosomes, health disparity

Introduction

Cancer is a major public health problem in the United States and the world. Recent epidemiological statistics indicate that cancer will develop in one in three women and one in two men in the US over their lifetime.¹ The three most common cancers among males are prostate, colorectal, and melanoma of the skin; and among females, breast, uterine corpus, and colorectal.² Although deaths attributed to cancer have declined among both Caucasians and African Americans, the latter continue to suffer a greater burden for each of the most common types of cancer.¹ This discrepancy recorded among cancer patients from different ethnicities is termed cancer health disparity. The National Cancer Institute defines cancer health disparity as an adverse difference in cancer incidence (new cases), cancer prevalence (all existing cases), cancer death (mortality), cancer survivorship, and burden of cancer or related health conditions that exist among specific population groups.¹ When investigating the factors that contribute to cancer health disparities, the most obvious are access to health care and socioeconomic status.³⁻⁵ However, evidence exists that dietary fat can influence carcinogenesis.⁶ In 1982, the US National Academy of Sciences committee on Diet, Nutrition, and Cancer, using both epidemiological and experimental data, concluded that a causal relationship between fat intake and the occurrence of cancer exists.⁷ However, the strongest evidence that environmental factors give rise to an etiology of cancer comes from the studies of cancer incidence in different ethnic populations and their migrations and lifestyle habits. Specifically, the adoption of a Westernized diet appears causal in the significant increase in annual deaths in native Japanese from colon,⁸ breast,⁹ and pancreatic cancers¹⁰ upon their moving from Japan to the US. In addition, experimental animal studies agree that both specific and nonspecific evidence

exists for the occurrence of cancer being strongly associated with the consumption of a diet high in fat.¹¹ Contradictory studies also exist in which lifestyle factors in cancer incidence have been described. Whereas years of smoking and number of cigarettes smoked had a correlation with an increased incidence of pancreatic cancer, there was no correlation with pancreatic cancer and body mass index, physical activity, alcohol, coffee, and green tea consumption.¹²

Early detection is important in cancer discovery, treatment, and survival. In order to better understand cancer incidence and mortality in diverse populations, it has become imperative that we identify and then characterize markers of cancer development and progression to include both pathways and molecular mechanisms associated with these disparities. Given the strong link between cancer incidence, oxidative stress, and diets high in fat,¹³ we must map these associations and identify the survival entities and pathways as potential targets. A long-term goal in health disparities research is to understand how an increase in oxidative stress will ultimately promote cancer cell resistance to therapy-induced death and how to overcome this resistance.

Survivin is an important member of the inhibitors of apoptosis (IAP) protein family because its tumor-specific expression is unique out of all of the human gene products.¹⁴ Survivin expression is evident during embryonic and fetal development, but not in terminally differentiated tissue.¹⁵ It is expressed in virtually all of the different types of human cancers (Table 1), making survivin an alluring protein in the study of carcinogenesis.¹⁶ Survivin is referred to as a bifunctional protein, having essential roles in inhibiting apoptosis and controlling proper cell division.¹⁷ In our most recent work, we have begun to refer to survivin as a multifunctional protein as it does much more, to include controlling diverse cellular functions, including surveillance checkpoints, suppression of cell death, the regulation of mitosis, and adaptation to unfavorable environments.^{17,18}

Localization of survivin

The multifaceted functionality of survivin is still being intensely scrutinized, and it appears that protein compartmentalization may be important. Survivin has been shown to localize in mitochondria, where it modulates tumor cell apoptosis similar to the Bcl-2 family.¹⁹ Its localization to the nucleus and cytosol confers its role in mitosis regulation and apoptosis inhibition, respectively.²⁰ Furthermore, we have identified the existence of survivin extracellularly, contained in small membrane-bound vesicles known as exosomes (Figure 1), and have shown that the exosome-bound survivin

Table 1 Influence of survivin on clinical prognosis

Cancer type	On prognosis/staging of the disease	Survivin expression	Reference
Breast cancer	Good to poor	Moderate to high	Kalla Singh et al, 2010 ⁶⁶ , Adamkov et al, 2012 ⁶⁷ , Rexhepaj et al, 2010 ⁶⁸ , Xu et al, 2012 ⁶⁹ , Dedić Plavetić et al, 2013 ⁷⁰ , Span et al, 2006 ⁷¹ , Li, 2005 ⁷² , Boidot et al, 2009 ⁷⁴ , Khan et al, 2014 ⁷⁵
Prostate cancer	Fair to poor	Moderate to high	Zaffaroni et al, 2005 ⁸⁰ , Shariat et al, 2004 ⁸¹ , Koike et al, 2008 ⁸² , Zhang et al, 2009 ⁸³
Pancreatic cancer	Poor	High	Xie et al, 2013 ⁹³
Leukemia	Good to poor	Low to high	Fulda, 2009 ¹⁰⁰ , Kamihira et al, 2001 ¹⁰² , Park et al, 2011 ¹⁰⁴ , Kelly et al, 2011 ¹⁰⁵ , Troeger et al, 2007 ¹⁰⁶ , Esh et al, 2011 ¹⁰⁷ , Tyner et al, 2012 ¹⁰⁸ , Ahmed et al, 2012 ¹⁰⁹ , Morrison et al, 2012 ¹¹⁰ , Grzybowska-Izydorczyk et al, 2010 ¹¹² , Carter et al, 2012 ¹¹³ , Small et al, 2010 ¹¹⁴
Other cancers	Good to poor	Moderate to high	Waligorska-Stachura et al, 2012 ⁹⁹

protein can be secreted by cancer cells to be taken up by surrounding cells, producing a field effect that confers a general stress-survival phenotype.^{21–23} Consistent with survivin's association with unfavorable clinicopathological parameters, extracellular trafficking of survivin throughout the tumor microenvironment could be responsible for augmenting the aggressive status of a tumor, while prohibiting or minimizing therapeutic results.^{21,24,25} This review focuses on the multifaceted roles of survivin in cancer biology, its cellular localization, and its cancer health disparity-specific upregulation, specifically in breast, prostate, pancreas, and hematological cancers.

Nuclear survivin as a cell cycle regulator

Nuclear survivin is known to be a cell-cycle-associated protein. Investigations of cell division regulation during the depletion of survivin by small interfering (si)RNA demonstrated an increase in mitotic arrest and chromosomal misalignment. Furthermore, this study confirmed that survivin is involved in microtubule assembly and centromere stabilization during mitosis.²⁶ Survivin's role in mitosis regulation is associated with its involvement in the chromosomal

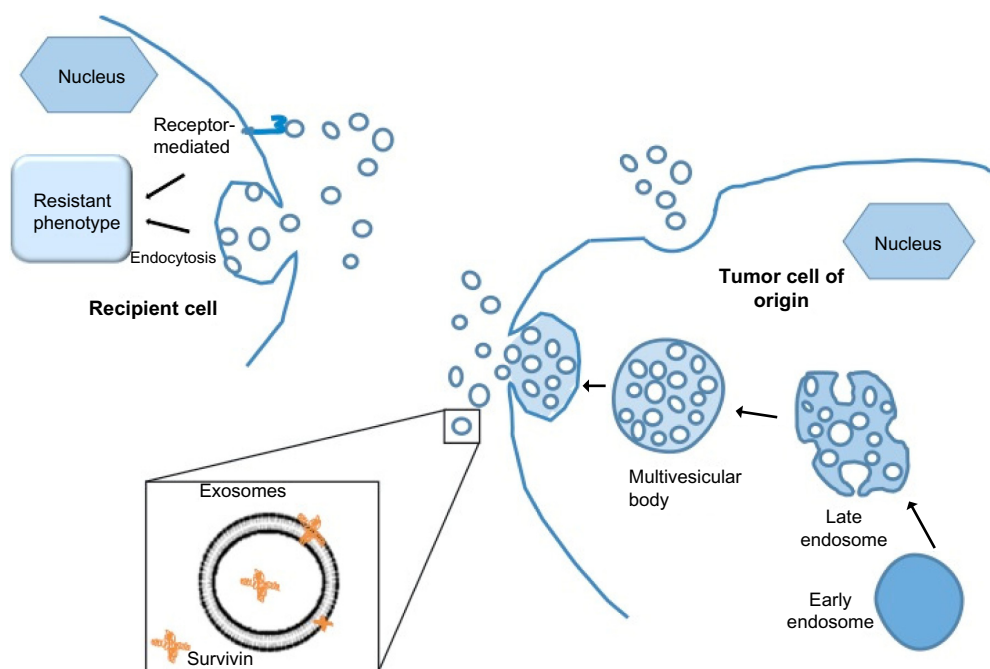


Figure 1 Exosomes play important roles in intercellular communication.

Notes: A tumor cell communicates with the tumor microenvironment and may be able to affect cancer cell aggressiveness as a result of the protein, RNA, and/or microRNA payload found within. One potentially important protein to the proliferative, invasive, or therapy-resistant nature of the tumor is survivin, which has been found released from cancer cells in exosomes.

packaging complex and its contribution to the formation of the mitotic spindle.^{27,28} IAP family proteins cIAP2 and survivin have been shown to dramatically increase upon exposure to hypoxia.^{29,30} Furthermore, survivin's promoter has been shown to contain three putative HIF-1 binding or response elements.³¹ Nuclear survivin was found to be distinctly involved in the prognosis of different cancers, as will be discussed in our specific cancers section.

Cytoplasmic/mitochondrial survivin as an apoptosis inhibitor

Survivin's ability to interfere with cellular death pathways appears to reside in the cell's cytoplasm. Survivin localizes to the mitochondria¹⁹ and therefore may provide, like Bcl-2, a role in mitochondrial stability. Cellular stress was shown to modulate the expression and localization of surviving, with hypoxia-induced survivin found exclusively in the mitochondria. Furthermore, upon apoptotic stimulation, mitochondrial survivin is rapidly released to the cytosol where its cytoprotective effects prevent the activation of the initiator caspase 9.¹⁹

Early studies showed that survivin and XIAP protected cells from undergoing caspase-dependent apoptosis. Subsequently, *in vitro* binding experiments showed that survivin, like XIAP and other IAPs, bound to the terminal

effector cell death proteases, caspases 3 and 7, but not to initiator caspase 8.³² Controversy in the field arose when a study by Banks et al³³ showed that survivin did not inhibit caspase 3 activity, and where recombinant survivin failed to decrease recombinant caspase 3 activity *in vitro*. Current evidence suggests that survivin acts on caspases in an indirect manner by binding to the hepatitis B X-interacting protein (HBXIP) and forming a complex with procaspase 9, inhibiting the apoptosome formation.³⁴ This survivin–HBXIP complex, not individual survivin or HBXIP proteins, binds to procaspase 9 and works to prevent recruitment of apoptosis activating factor 1 (Apaf1), thus suppressing intrinsic apoptosis. In addition, survivin binds to and regulates the stability of XIAP, which is a direct caspase 3 and 9 inhibitor.²⁷ More specifically, the formation of a survivin–XIAP complex promotes increased XIAP stability, protecting XIAP from proteasomal degradation, resulting in a facilitated inhibition of caspase-dependent cell death.³⁰

Extracellular survivin as a modulator of tumor microenvironment

Survivin has recently been shown to exist in the extracellular space,²¹ via 40–100 nm membrane vesicles called exosomes.²² Various cell types, such as B- and T-lymphocytes, dendritic cells, neurons, intestinal epithelial cells, as well as

tumor cells, release exosomes.^{35–38} In particular, it has been shown that both human and mouse tumor cells release tumor cell-derived exosomes (TEX) constitutively.³⁹ Additionally, specific protein content found both on and within TEX give an indication of their functional and biological roles, and their cell of origin, making TEX excellent biomarkers.^{40–43} Early detection, aggressive determination, and therapeutic efficacy may 1 day be possible through the use of these exosomes and their contents.

Our lab has shown that the extracellular pool of survivin has the ability to cause neighboring cancer cells to increase resistance to therapy, rapidly proliferate, and acquire an increased potential to become invasive *in vitro*,²¹ providing a protective role to the neighboring tumor cells.²² The ability of extracellular survivin to cause these effects in the surrounding cancer cells correlates with the fact that survivin overexpression is observed in virtually every human cancer type.⁴⁴ TEX may also be used as a tool to detect malignant conditions.⁴³ Serum taken from cancer patients has an increased level of TEX,^{45,46} which has a positive correlation with the progression of the tumor.²² In addition to serum, TEX were shown to be isolated from malignant tumor fluids, urine,^{47,48} ascites fluids,^{49,50} and pleural effusions.^{40,51} We have recently shown that exosomal survivin may be a useful tool for early detection, diagnosis, and even monitoring of prostate cancer (PCa) progression.⁵² Newly diagnosed and advanced PCa patients with high- or low-grade cancer had significantly higher levels of exosomal survivin compared to control subjects or patients with preinflammatory benign prostatic hyperplasia (BPH).⁵²

Survivin in cancer immunity evasion

Survivin has been ascribed multiple roles not only in malignancy but also in immunity and differentiation.⁵³ Survivin has been shown to be essential for T-cell maturation, homeostasis, and proliferation at various stages of development.⁵⁴ It has also been shown to modulate peripheral blood leukocytes when in the extracellular space by binding to leukocytes, thereby inducing molecular processes implicated in the pathogenesis of inflammation.⁵⁵ On the basis of the literature and our data, survivin may be said to exhibit duplicity in cancer immunity, as it can act as a tumor-associated antigen, or modulate the immune environment to permit tumor growth.^{53–62}

Recently, an artificial antigen-presenting cell, developed to study anti-survivin CD4⁺ T-cell responses in cancer patients, was shown to elicit both Th1 and Th2 responses against survivin.⁵⁶ The level of avidity was appropriate to

recognize tumor cells.⁵⁶ Previously, constructed DNA–peptide complexes (mimovirus) of survivin epitopes have been shown to stimulate strong cytotoxic T-lymphocyte-mediated long-term memory of murine immune response and exact a high antitumor effect in BALB/c mice.⁵⁷ Furthermore, a DNA construct encoding a secreted version of survivin, along with a plasmid coding for murine granulocyte-macrophage colony-stimulating factor as a molecular adjuvant, was observed to elicit humoral responses against survivin in sera collected from mice.⁵⁷ The immunoglobulin G2a antibody was the prevalent antibody subclass, thereby implicating the induction of a Th1–CD4⁺ cellular response.⁵⁸

We have recently shown that when T-cell cultures were incubated with survivin, surface binding and intracellular uptake of survivin by these T-cells occurred.⁶³ Upon further investigation, a survivin-associated decreased proliferation was observed in these T-cells. In addition, analysis of cytotoxic T-lymphocytes revealed a reduction in their functional cytotoxicity. However, T-regulatory cell function remained unaltered. Importantly, the numbers of Th1 and Tc1 cells were significantly reduced, together with the cytokines associated with them (interferon- γ and interleukin [IL]-2), while an increase in IL-4⁺, IL-5⁺, and IL-13⁺ T-cells was observed. These results suggest a skewing from a type 1 response, which mediates immunity with cytokines that enhance cellular cytolytic activity and can elicit an effective antitumor response to a type 2 T-cell response, which does not lead to tumor rejection and is frequently observed in cancer patients.^{59–62} The verification and molecular mechanism underlying this Th-cell plasticity is yet to be fully elucidated.

Cancer-specific upregulation of survivin: breast cancer

Breast cancer is the second most common cancer type (following lung cancer) and the most common cancer among women worldwide.¹ It is estimated that in the US alone there are nearly 3 million women with diagnosed breast cancer and approximately 227,000 more will be added to that number this year.¹ African American women are more likely than all other women to die from breast cancer, as their tumors often are discovered at a later, more advanced stage, leaving them fewer treatment options.^{63,64} There are several pathways involved in breast cancer pathogenesis with pathways of tumor cell death playing an important role in its development and maintenance. Among the proteins involved in cell death/survival pathways, survivin is one of the most studied. Using serial analysis of gene expression, survivin

was found to be the fourth highest expressed transcript in a number of common cancers including breast cancers.⁶⁵ In a study examining the interaction of the insulin-like growth factor (IGF)-II and survivin, Kalla Singh et al⁶⁶ found that high IGF-II expression–regulation of survivin correlated and was significantly higher in African Americans than in Caucasians. In this study, it was shown that IGF-II regulates survivin, leading to the inhibition of mitochondrial membrane depolarization, cell survival, and chemoresistance. Furthermore, the effect of IGF-II and IGF-II siRNA on the expression of Bcl-2, Bcl-XL, and survivin in African American and Caucasian breast cancer cells was measured. IGF-II expression was shown to be causative in the upregulation of these antiapoptotic proteins, while IGF-II siRNA was prohibitive.⁶⁶ This intriguing observation will require further investigation.

The different subcellular pools of survivin in breast cancer appear to have distinct functions. Adamkov et al⁶⁷ suggested that nuclear staining of the survivin antigen could be used as a marker of the degree of neoplasia, while Rexhepaj et al⁶⁸ suggested that increased levels of nuclear survivin are associated with a proliferative phenotype. One thing that is clear is that survivin plays a key role in the initiation and progression of breast cancer. High messenger (m)RNA expression was found to be an independent prognostic marker in breast cancer patients⁶⁹ and survivin upregulation significantly correlated to lymph node involvement,

tumor stage, and histological type.⁷⁰ By contrast, others have shown that high levels of its expression are associated with a beneficial response to chemotherapy.⁷¹ This could be due to alternative splicing of survivin. Multiple studies demonstrate that alternative splicing patterns are altered during cancer progression.⁷² Several different mechanisms contribute to changes in the regulation of alternative splicing including stress, stimulation of receptors by growth factors, cytokines, hormones, etc. Survivin, to date, has six different described variants with different apoptotic properties and intracellular localization (Figure 2).⁷³ Protein and mRNA levels of the pro- and antiapoptotic isoforms of survivin correlate with cancer prognosis.⁷⁴

Early diagnosis of breast cancer is challenging due to a lack of serum biomarkers and, inadequate as it is, performed through invasive means such as needle biopsy, scanning, and invasive pathological examination. Despite the availability of numerous diagnostic and prognostic methods, there remains a need for an easy, sensitive, and noninvasive way to track tumor activity. We propose that through analysis of tumor exosomes and by specifically assaying these exosomes for tumor-specific antigens such as survivin, XIAP, cIAP1/2, and chaperone proteins such as HSP70 and HSP90, just such a biomarker discovery may 1 day be realized. We have found an extracellular survivin pool in serum exosomes in prostate⁵² and breast cancers.⁷⁵ In these breast cancer patients' sera, we found

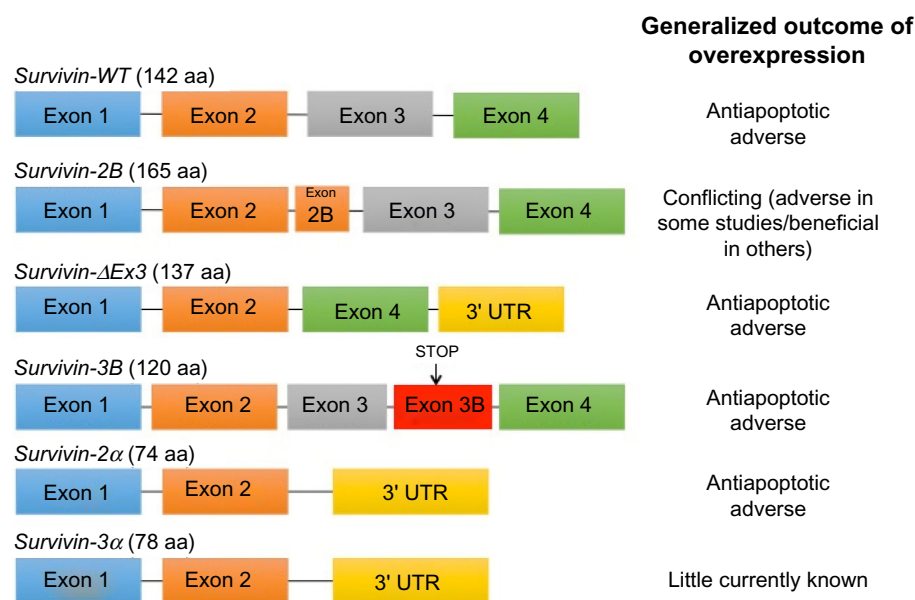


Figure 2 Splicing of the human survivin pre-messenger RNA produces six different splice variants.

Notes: With the exception of *survivin-3α* and *survivin-2B*, *survivin-WT*, *survivin-ΔEx3*, *survivin-3B*, and *survivin-2α* are all associated with unfavorable antiapoptotic phenotypes. *Survivin-2B* has been shown to have either a favorable or unfavorable association, depending upon the cancer type it is expressed in, and *survivin-3α* has yet to be determined.

Abbreviations: WT, wild type; UTR, untranslated region.

survivin levels and exosome numbers to be significantly increased over controls with a disparate expression of the survivin splice variants similar to that observed in tissues. It is important though that we recognize the possible confounding factors such as comorbidities, psychological complications, genetics, and environmental exposures that could affect these results.

Cancer-specific upregulation of survivin: prostate cancer

PCa is the most frequently diagnosed nonskin cancer in men and the second leading cause of male cancer deaths in the US, accounting for 238,590 new cases and 29,720 deaths in 2013.^{1,76} These statistics have undergone minimal changes despite advances in screening and early diagnosis, and therefore still require a significant investment if PCa is to be defeated. As has recently been described by our colleagues, African American men have a growing disparity in their PCa incidence and mortality compared to other ethnic groups,⁷⁷ and they present with the disease at a much younger age than do Caucasian men, which is a trait common in more aggressive cancers.^{78,79}

Survivin is expressed in PCa and has been shown to be upregulated in order to protect the PCa microenvironment against apoptosis and oxidative stress-induced damage.⁸⁰ Survivin, therefore, directly and/or indirectly influences cell survival and death. Shariat et al, using immunohistochemistry, compared survivin protein expression in normal and malignant prostate tissue and lymph node tissue from PCa patients. There appeared to be a gradual but consistent rise of survivin expression from normal prostate specimens (36%) to PCa (71%), with the highest expression found in metastatic lymph nodes (81%).⁸¹ Survivin expression therefore seemed to correlate with the degree of transition from normal prostate epithelia to a more aggressive form of PCa (metastatic PCa).

Our group recently looked at relative levels of survivin in the sera of PCa patients and compared it to that of patients with BPH and from subjects with no diagnosis of cancer or BPH.⁵² Survivin levels proved to exhibit a stronger correlation in our hands than prostate-specific antigen when it came to distinguishing the two clinical conditions. We therefore propose that exosomal survivin evaluation should be given serious consideration as a plausible biomarker for the early detection of PCa and perhaps could be used to monitor treatment efficacy and disease recurrence. Higher levels of not only survivin but its splice variants 2B and 2 α , both in vitro and in tissue, seem to correlate with PCa cell proliferation

and a more aggressive phenotype.⁸² The intracellular compartment localization of survivin has been suggested to be of prognostic value. When tissues of patients with locally advanced PCa were stained and examined for survivin, patients with higher levels of intranuclear survivin exhibited improved survival, whereas those with higher levels of cytoplasmic survivin exhibited a poorer prognosis.⁸³

In summary, survivin, in PCa has a dual role as an inhibitor of apoptosis and cell cycle mediator. Its level of expression appears to correlate with the progression from normal to indolent and to a more aggressive form of PCa. Our demonstration of exosomal survivin in the plasma of patients with newly diagnosed low-grade PCa⁵² provides a rationale for studies to investigate the utility of exosomal survivin as an early, easily measured biomarker for PCa diagnosis, as well as a marker to monitor treatment efficacy and tumor recurrence.

Cancer-specific upregulation of survivin: pancreatic cancer

Cancer of the pancreas is the fourth most common cause of cancer death in men and women in the US. In 2013, an estimated 45,220 new cases and 38,460 deaths from pancreatic cancer occurred.¹ It is a highly malignant disease and lacks clear early warning signs or symptoms thus remaining silent in its victims until it is well advanced. The vast majority of patients are not diagnosed until stage III or IV, and once diagnosed, exhibit a median survival of 4–8 months with a 5-year survival rate being <5%.⁸⁴ Risk factors include sex, age, diabetes, chronic pancreatitis, family history, smoking, alcohol abuse, and possibly diets high in fat.⁸⁴ Early diagnosis continues to be the greatest obstacle and there is an urgent need for screening biomarkers.

Pancreatic cancer incidence in the US is higher in African Americans and Hispanics than in Caucasians.^{85,86} In a number of recent studies, the risk factors in men (cigarette smoking and diabetes mellitus) and women (moderate/heavy alcohol consumption and an elevated body mass index [obesity]), explain almost the entire African American/non-Hispanic White disparity in incidence.^{85,86} In the absence of these risk factors, pancreatic adenocarcinoma incidence rates among African Americans do not exceed those of Caucasians from either men or women.^{87–89} In 2003, a group at the Barbara Ann Karmanos Cancer Institute analyzed a group of pancreatic cancer patients (166 African American, 244 Caucasian) for clinicopathologic characteristics of the disease, as well as for immunohistochemical expression of commonly found pancreatic cancer biomarkers: Fas, FasL, p21/waf-1, p27,

p53, and Her2. They also investigated the presence and types of K-ras mutations at codon 12.⁹⁰ African Americans were found to have significantly higher rates of K-ras mutations than did Caucasians, and their treatment with chemotherapy or radiation therapy was also much less effective than that recorded in Caucasians. African Americans more frequently than Caucasians were found with positive surgical margins and many clinicopathologic variables such as median survival, 5-year survival, and stage at presentation were different. African Americans were less immunoreactive to Fas expression and had a much stronger Her2 expression than did Caucasians.⁹⁰

As in prostate and breast cancer, as previously discussed, epidemiological evidence exists for a strong association between pancreatic cancer and a high consumption of dietary fat. Dietary fat is made up of fatty acids and lipids that are metabolized into arachidonic acid. The key enzymes for arachidonic acid metabolism are lipoxygenases (LOXs) and cyclooxygenases (COXs) which, outside of dietary fat research, have been shown to be associated with the development and progression of pancreatic cancer.⁹¹ LOX and COX inhibitors prohibit the continued progression of pancreatic cancer and induce intrinsic mitochondria-associated apoptotic cell death.⁹²

There have been numerous studies performed on the prognostic implications of survivin in pancreatic cancer. A high expression of survivin was found to be related to shorter survival in patients with resected pancreatic adenocarcinoma.⁹³ In contrast, high nuclear levels of survivin predicted better prognosis than cytoplasmic survivin.⁹⁴ Furthermore, Sagol et al⁹⁵ and Sun et al⁹⁶ showed no significant association between survivin and long-term survival. Targeting survivin early on in the process could play an invaluable role in preventing the progression to malignancy. In addition, a screening biomarker that could potentially detect early stages of the disease is of utmost importance.

Cancer-specific upregulation of survivin: hematological malignancies

Hematological malignancies such as leukemia, lymphoma, myeloma, and myelodysplastic syndromes affect the bone marrow, the blood cells, the lymph nodes, and other parts of the lymphatic system. These pathologies are interrelated, likely the result of acquired changes to the DNA of a single stem cell. Approximately 140,000 people will be diagnosed with leukemia, lymphoma, or myeloma, accounting for approximately 9% of all new cancers diagnosed each year in the US.⁹⁷ Of particular interest is multiple myeloma, which

accounts for ~10% of all hematologic malignancies diagnosed in the US annually.⁹⁸ Among the hematological malignancies, multiple myeloma is known to affect individuals from ethnically diverse populations in a disparate manner.

In accordance with reports for many types of solid tumors,^{27,99} cancer-specific upregulation of survivin also occurs in hematological malignancies,^{100,101} though to date, there have been no published reports taking ethnicity into account. In hematological cancers, expression of survivin is associated with poor clinical outcomes and resistance to chemotherapy.^{102–105} Survivin expression levels are linked to risk of early relapse in pediatric B-cell acute lymphoblastic leukemia,^{106–108} and to tumor aggressiveness¹⁰⁹ and chemoresistance in adult acute lymphoblastic leukemia.¹¹⁰

High levels of survivin expression have also been linked to cell proliferation and antiapoptotic characteristics in chronic myelogenous leukemia¹¹¹ and chronic lymphocytic leukemia.¹¹² In acute myeloid leukemia, levels of survivin expression were found to be significantly predictive of shorter overall and event-free survival.¹¹³ In addition, the highest survivin expression levels are detected in the CD34(+)CD38(–) acute myeloid leukemia stem/progenitor cell populations,¹¹³ further validating survivin's potential as a prognostic biomarker and therapeutic target. Overexpression of survivin in CD34+ hematopoietic cells has been found to induce hematological malignancies *in vivo*, suggesting that it has a role in the development of these diseases.¹¹⁴

Localization of survivin to the nucleus versus the cytoplasm is very important because the functional dynamics of survivin are dependent on the site of survivin expression.¹¹⁵ Using chemotherapeutic drugs in hematologic cancer, Bernardo et al¹¹⁶ reported that cytoplasmic survivin was more relevant to the apoptotic index than that associated with nuclear survivin. Investigating survivin's cellular locations, alternative splice variant profiles within the context of cancer health disparities and novel therapeutic modalities will continue to be important areas of study.

Liquid biopsy

The tumor microenvironment is being increasingly recognized as providing many key factors necessary for many of the stages of disease progression including local resistance, immune escape, and distant metastasis. Understanding this tumor microenvironment, including the cells involved and the communications ongoing between them, will continue to prove instrumental in our understanding of cancer and eventually our ability to control it, if not terminate it. In order to fully “learn the language”, there is a need for new

biomarker discovery. Specifically, biomarkers that are easily isolated and identified from blood, urine, saliva, cerebral spinal fluid, ascites, etc, as well as from tissue biopsies, will need to be identified. The term “liquid biopsy” has been used recently to describe the source of these biomarkers and could be defined as broadly as circulating tumor cells, circulating tumor DNA, exosomes, and secretomes.⁴⁸ Differential expression of exosomal survivin may serve as a diagnostic and/or prognostic marker in early cancer patients, and it may soon lead to the development of potential therapeutics for the treatment of these diseases.

Conclusion

Most efforts on the identification of candidate cancer biomarkers, and on analyzing differences in the cancer biology that exists between African Americans and Caucasian patients, have focused on gene expression differentials in tumor tissues, epigenetic issues (such as methylation patterns), and on single nucleotide polymorphisms (SNPs). While these efforts have been necessary in providing important clues for understanding the biochemical mechanisms associated with cancer health disparities, it is also imperative to develop noninvasive approaches that analyze, indirectly and early in the disease process, the molecular profiles of tumors. One recent study has investigated the -31G>C *survivin* promoter polymorphism across approximately 7,500 cancer cases and 9,000 controls.¹¹⁷ This polymorphism was significantly associated with an increased cancer risk in colorectal, gastric, and urothelial cancers. In contrast, this SNP was remarkably decreased in patients with hepatocellular carcinoma. With regard to ethnic diversity, this SNP was shown to increase cancer risk in Asian populations,¹¹⁷ as well as a higher Wilms' tumor risk in Serbian children.¹¹⁸ Findings such as these encourage us to not only look at the overall abundance of gene or protein products in racial disparities and cancer but also look deeper into the minutia that may have been historically overlooked and may provide important insights not before recognized as factors in cancer development and resistance.

Recent studies have shown that small membrane-bound vesicles called exosomes constitute the latest mode of intercellular information transfer or communication. This exchange of molecular information is facilitated by their unique composition, which is enriched with enzymes, structural proteins, adhesion molecules, lipid rafts, microRNA, and RNA. Importantly, cancer cells have been shown to secrete more exosomes than do their normal counterparts, indicating that exosomes can be used as diagnostic markers and their

active secretion has functional implications. In addition, recent studies revealed that genes involved in inflammation and autoimmune responses are differentially upregulated in cancer patients compared to controls. This could imply that differences in antitumor immune responses may exist between racial groups in tumors.

It is very important to specifically target survivin in a defined location for therapeutic purposes. Survivin is a unique inhibitor of apoptosis with triple functionality: in cell cycle regulation when it is present in the nucleus; inhibition of apoptosis when it is in the mitochondria; and resistance to chemotherapy when it exists in the tumor microenvironment packaged in exosomes. Survivin's upregulation in specific cancers, in addition to its presence in serum exosomes, makes it an important molecule as a diagnostic as well as prognostic marker. Unfortunately, controversy exists as to whether survivin expression is favorable or unfavorable in the outcome of cancer. Survivin expression is an unfavorable prognostic indicator in esophageal, hepatocellular, and ovarian cancers, cholangiocarcinoma, and endometrial cancers, but it has associated favorable outcomes in gastric, bladder, breast, ependymoma osteosarcoma, and pancreatic ductal adenocarcinomas.^{113,119} To validate its role, a large number of case-control studies need to be adapted. Subsequent studies exploiting the exosomal packaging of survivin may also 1 day be used in cancer therapeutics.

In conclusion, this review addresses an urgent need in the fight against cancer health disparities: the need to identify and evaluate novel serum biomarkers such as survivin and its alternative splice variants for the noninvasive, early detection of cancer in interventions that can be tailored to Americans of different ethnicities, ultimately paving the way for future studies focused on analyzing these biomarkers in larger cohorts of ethnically diverse cancer patients.

Informed consent and animal studies

No animal or human studies were carried out by the authors for this article.

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Disclosure

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