



To cite: Agnihotri AK, Bahorun T, Aruoma OI. Cancer: global health perspectives. *Arch Med Biomed Res.* 2014;1(1):1-9

Publication history

Received: February 7, 2014
Revised: March 18, 2014
Accepted: March 20, 2014

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Cancer: Global Health Perspectives

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ABSTRACT

Chemotherapy to patients with cancer remains an effective mode of treatment of the disease, but it is associated with many side effects including mild or dose-limiting toxicities such as alopecia, myelosuppression, gastrointestinal dysfunctions, neurologic toxicities, and immune suppression which results in infections and cancer cell proliferation. Although economic analysis of treatment in health care systems may be applied to the full range of interventions that make up a cancer service, the economic impact of cancer in health care systems remains one where much attention, in the context of complementary medicine, needs to be directed. Predicting the cost-effectiveness of developing prevention, screening and treatment strategies continue to be the focus strategies to optimize cancer care.

KEY WORDS: *Cancer; Global health perspectives; Palliative care; Stem cell cancer; Dietary components and chemoprevention*

INTRODUCTION

Cancer is a leading cause of disease worldwide. The International Agency for Research on Cancer released the GLOBOCAN 2012 data on cancer incidence, prevalence and mortality worldwide¹. According to GLOBOCAN 2012, there are 14.1 million new cancer cases, 8.2 million cancer deaths and 32.6 million people living with cancer (within 5 years of diagnosis) in 2012 worldwide including the most commonly diagnosed cancers in the lung (1.8 million, 13.0% of the total), breast (1.7 million, 11.9%) and colorectum (1.4 million, 9.7%), and the most common causes of deaths due to the cancer of the lung (1.6 million, 19.4% of the total), liver (0.8 million, 9.1%) and stomach (0.7 million, 8.8%)¹. The GLOBOCAN 2012 estimates predict substantive increase in new cancer cases per year through to 2025 that is pegged on the growth and aging of the global population (**Figure 1**). Several unique concerns arise in the older adult with cancer as with increasing age, physiologic reserve decreases at a pace that varies with each individual. This is true also for the variations in functional status, cognition, and comorbidity that accompany increased age, and may affect life expectancy, risk of subsequent functional decline, hospitalization, and other morbidity. These age-related changes can influence tolerance to cancer therapy, as well as the overall risk-benefit ratio of cancer treatment.

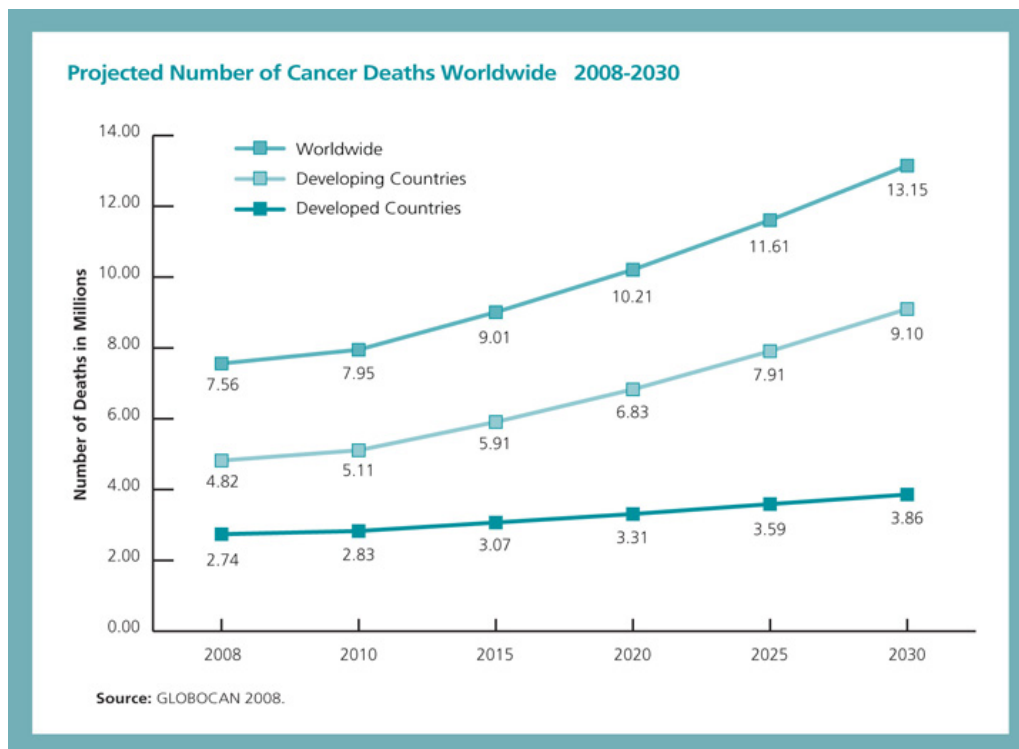


Figure 1: Key factors in these rising rates are the lack of access to information, prevention, early detection, and treatment in developing countries, as well as inadequate medical and public health infrastructure. Cancers are often diagnosed at a late stage, and people suffer needlessly from inadequate palliative care.

The GLOBOCAN report also reveals that 57% (8 million) of new cancer cases and 65% (5.3 million) of the cancer deaths occurred in the less developed regions. The key factors in these rising rates could be due to the lack of access to information, early detection and inadequate medical and public health infrastructure in developing countries. As a result, cancers are often diagnosed at a late stage and people suffer from inadequate palliative care. Heredity, immunity, chemical, physical, viral, bacterial and lifestyle are some factors related to cancer risk. Only 5–10% of all cancer cases can be attributed to genetic defects, whereas the remaining 90–95% may have their roots in the environment and lifestyle². Cancer is commonly believed to be a preventable disease that requires major lifestyle changes. The disease can be prevented by smoking cessation, having a healthy diet – moderate in calories, salt and fat, and low

in alcohol, increases ingestion of fresh fruits and vegetables several times a day, avoiding obesity, to be physically active, avoiding exposure to known carcinogens including aflatoxin, asbestos and UV light, having vaccination against infections causing cancer and regular check-up.

Jean-Marc Nabholz, from the Jean Perrin Comprehensive Cancer Centre of Auvergne, Clermont-Ferrand, France eminently discussed breast cancer management: from empiric approaches to biology-orientated individualized therapies. Despite the fact that the incidence and epidemiology of breast cancer appear different in many countries, the lessons drawn from the experience in developed countries point out the importance of screening programs and improved therapeutic strategies based upon a better understanding of the biology of breast cancer. *Jean-Marc* pointed out that one of the major challenge today is the setting up of proper

infrastructures to improve the transfer of technology from developed countries to developing countries, through the implementation of standardized management strategies globally simpler and cost effective. Indeed the transformation from empiric approaches with traditional chemotherapy and endocrine therapy to the use of targeted therapies has been possible thanks to a better understanding of the tumor not only from a histopathological point of view, but on a further level with molecular biology.

GLOBAL BURDEN ON CANCER: TRENDS AND STRATEGIES

Although the biological behavior of tumor cells and their characteristics are being understood due to advances in pathological techniques, the natural history of cancer continues to change with increasing life expectancy compounded with environmental and hereditary risk factors. *Nicolas Magne, from the Jean Monnet Saint Etienne University, France* further commented on other risk factors that continues to prevail namely age, gender, reproductive factors, endogenous hormones, exogenous hormones, hormone replacement therapy, breast density, previous breast disease and family history. Predicting the cost-effectiveness of developing prevention, screening and treatment strategies continues to be the focus strategies to optimize cancer care.

The drug treatment of cancer has entered the era of “targeted therapy” embracing molecular strategies that exploit the differences between the cancer cells, and normal cells^{3,4}. In the main, molecular process begins with the study of the cancer cells themselves, attempting to identify areas of difference from normal cells, and then to develop new drugs to exploit these differences. As *John Crown from the St. Vincent’s University Hospital, Ireland* observed, “Not only do molecular therapeutics pose serious challenges for the field of therapy, they also will

necessitate dramatic changes in the way the clinical evaluation of new treatments is assessed. With conventional cytotoxic chemotherapy where molecularly unselected patients with disease of a particular histologic type were being studied, it would often be necessary to randomize hundreds or even thousands of patients per arm in a study to detect small but meaningful differences in outcomes such as survival and disease-free survival.” Selecting patients on the basis of molecular selection from the earliest phase one trials should also be looking for hints of efficacy at an early stage of the trials process. Another major challenge, which will face molecular therapeutics, is the possibility that they may end up not working as anticipated. The heterogeneity of tumors was one of the principle reasons why most chemotherapy drugs failed to cure most common cancers. However, it also poses a substantial hurdle to molecular therapeutics.

There is a need to optimize cancer care in the elderly. Older patients commonly have health status issues that can affect cancer outcomes. Indeed cancer patients require assistance with independent activities of daily living, which measure the ability for an older person to complete tasks necessary to live independently in the community. Traditionally in clinical medicine the older population is a neglected group in terms of clinical research, for reasons including comorbidities and practicalities but is now receiving wider attention. The specialty of onco-geriatrics is now embraced by a multi-disciplinary approach involving both the oncologist and the geriatrician. There is also a significant emphasis on clinical research being designed for older patients, more relevant patient and public information, and ongoing improvement in training for healthcare professionals. One of the approaches being used is the comprehensive geriatric assessment (CGA) as discussed by *Mohun R K Bahadoor, from the Jean Perrin*

Comprehensive Cancer Centre, France. The CGA is an evaluation tool utilized by geriatricians to assess overall health status. The CGA includes validated tools of functional status, comorbidities, cognition, social support system, nutrition and medication review. In community-dwelling older adults, impairments in these domains predict morbidity and mortality. In cancer patients, measures within geriatric assessment can predict postoperative morbidity, toxicity of chemotherapy, and mortality^{5,6}. Assessment of frailty is also important in considering options in cancer care for older patients. The involvement of a geriatrician in cancer management decision-making is hence of great benefit, and it may improve in the quality of care for the older patients with cancer.

CANCER - CHALLENGES AND OPPORTUNITIES

The understanding of molecular changes that underlie cancer development offers the prospect of utilizing functional supplements from traditional medicinal plants to augment therapies that can specifically target malfunctioned genes and signaling pathways in cancer. Chemoprevention strategies are increasingly advocated and involve the use of phytochemicals, functional foods, nutraceuticals, and even whole plant extracts to prevent, arrest or reverse the cellular and molecular processes of carcinogenesis. Tobacco smoke and nitrosatable foods containing N-methyl N-nitrosourea (MNU) are among the primary causes of liver cancer. A 40-week MNU treatment induced increased expressions of inflammatory cytokines (IL-1 β , IL-6) of Bcl-2 at mRNA level and NF κ B and IL-1 β at protein level in Balb/c mice involves alteration in hepatocytes compared to control. MNU primed liver DNA samples revealed an interference of MNU in nucleic acid bases and structure, reflected by a peak shift at 1456 cm⁻¹ and shoulder formation at 1357 cm⁻¹ compared to control DNA samples. The

leaf extract of *Aegle marmelos* (L.) Corrêa (Rutaceae) has been studied and shown to have hepatoprotective potential when using the MNU induced hepatocarcinogenesis Balb/c mice model⁷. The protective effect was confirmed by Raman spectroscopy where the MNU induced peak at 1252 cm⁻¹ was normalized. DNA fragmentation data suggest apoptosis as one of the protective mechanisms of HEAM. The hepatoprotective, anti-carcinogenic and immunomodulatory effects of *A. marmelos* extract indicate potential beneficial effects in cancer therapy.

Chronic infections together with other factors like obesity, alcohol, tobacco, radiation, environmental pollutants, and high calorie diet have been recognized as major risk factors for the most chronic diseases including cancer. All these risk factors are linked to chronic diseases through inflammation. *Bharat Agarwal from the MD Anderson Cancer Centre, University of Texas, Houston, USA* highlighted the strong association between cancer and inflammation by numerous lines of evidence and indicate that the suppression of proinflammatory pathways by dietary agents derived from fruits, vegetables, spices and traditional medicine may provide potent opportunities for both prevention and treatment of cancer.

15-Hydroxyprostaglandin dehydrogenase (15-PGDH) is the key enzyme that catalyzes the first step in the inactivation of PGE₂ and is known to be as a physiological antagonist of COX-2. *Hye-Kyung Na from the the Sungshin Women's University, Seoul, South Korea* discussed the role of 15-Hydroxyprostaglandin Dehydrogenase as a novel target for chemoprevention of inflammation-associated carcinogenesis reporting that oral administration of celecoxib increased the 15-PGDH expression while the same treatment decreased COX-2 expression in DSS-treated mouse colon. Moreover, 15-PGDH expression in colonic mucosa following treatment with AOM plus DSS

was more prominent in COX-2 knockout mice than that observed in COX-2 wild type animals. Likewise, levels of constitutively expressed 15-PGDH were higher in COX-2 knockout mice. In patients with colon tumors, the expression of 15-PGDH was markedly reduced in adenomas and carcinomas, compared with normal surrounding tissues. Thus the expression of 15-PGDH is negatively regulated by COX-2, which may contribute to the inflammation-associated colon carcinogenesis.

Ethan Will Taylor, University of North Carolina, USA, advanced the question Can tobacco the use promote HCV-induced miR-122 hijacking and carcinogenesis? Chronic hepatitis C virus (HCV) infection is a well-recognized risk factor for hepatocellular carcinoma (HCC). As a co-risk factor, the role of tobacco use in HCV-driven carcinogenesis and relevant underlying mechanisms remain largely unclear. The latest discoveries about HCV replication have shown that HCV RNA hijacks cellular miRNA-122 by forming an Ago2-HCV-miR-122 complex that stabilizes the HCV genome and enhances HCV replication. Our previous work has demonstrated that aqueous tobacco smoke extract (TSE) is a potent activator of HIV replication via TSE-mediated viral protection from oxidative stress and activation of a set of genes that facilitate HIV, such as DDX3. Since HCV is, like HIV, an enveloped virus that should be equally susceptible to lipid peroxidation, and since one of the TSE-upregulated genes, the DDX3 helicase, is known to facilitate HCV replication, we hypothesize that 1) tobacco use can similarly enhance HCV viability and replication, and promote HCC progression by up-regulation of DDX3, and 2) by competing for binding with miR-122 as a competing endogenous RNA (ceRNA), HCV replication can liberate miR-122's direct target, oncogenic gene cyclin G1 (CCNG1); furthermore, simultaneous tobacco use can synergistically enhance this competing effect via HCV upregulation. Disrupting the HCV ceRNA

effect could be the basis of a new strategy for designing anti-HCV/HCC drugs⁸.

"Challenges and opportunities in head and neck cancer exist" says *BS Tuli* from *SSR Medical College, Mauritius*. Head and neck cancers are the most visible cancers and produce early symptoms. Tobacco smoking is unequivocally associated with a variety of cancers mainly those of the lungs, mouth and throat. The development of oral cavity like uterine cervix cancer in women is related to sexual lifestyles and the Human Papilloma virus. Many cancers are curable, e.g. uterine cervix, breast, colon, mouth and throat, blood cancers and many childhood cancers, if they are diagnosed early. For this to be a reality, it is necessary that the public is made aware of early symptoms and signs, health professionals are educated about cancer, and treatment facilities are provided to enable effective therapy. Palliative care provision, which includes the control of pain and relief of symptoms, needs to be structured and patient-centered.

This aspect of cancer control costs little and yet is important in improving the quality of life of cancer patients. The impact of nutrition and palliative care in the management of cancer remains paramount. Palliative care provided by a specialist who works with a team of other health care professionals, such as doctors, nurses, registered dietitians, pharmacists, and social workers, is comfort care given to a patient who has a serious or life-threatening disease, such as cancer, from the time of diagnosis and throughout the course of illness. Palliative care begins at diagnosis and continues during cancer treatment and beyond advocating the principles of comfort and support. It is now increasingly recognized that palliative care improves the quality of life of patients and family members, as well as the physical and emotional symptoms of cancer and its treatment. In the main, the goal of palliative care is to prevent or treat, as early as possible, the symptoms and side effects of the disease and its

treatment, in addition to the related psychological, social, and spiritual problems. The physical symptoms such as pain, fatigue, loss of appetite, nausea, vomiting, shortness of breath, and insomnia can be relieved with medicines or by using other methods involving palliative care, such as nutrition therapy, physical therapy, or deep breathing techniques. Palliative care can help patients address depression, anxiety, and fear. Here it is imperative for care experts to provide counseling, recommend support groups, hold family meetings, or make referrals to mental health professionals in support of patients. The palliative care team may direct patients and families to resources that can help with financial counseling, understanding medical forms or legal advice, or identifying local and national resources, such as transportation or housing agencies. With a cancer diagnosis, patients and families often look more deeply for meaning in their lives. There is the question that cancer brings patients more faith but patients may also question their faith as they struggle to understand why cancer happened to them. Indeed palliative care experts can help patients explore their beliefs and values so that they can find a sense of peace or reach a point of acceptance that is appropriate for their situation. Ultimately, nutrition therapy may help patients recover more quickly and spend less time in the hospital. Nutrition in palliative care and at the end of life should be one of the goals for improving quality of life. It is important to address issues of food and feeding in order to assist in the management of troublesome symptoms as well as to enhance the remaining life for a cancer patient.

RISK FACTORS AND MANAGEMENT OF CANCER: ROLE OF BIOACTIVE NATURAL PRODUCTS IN CHEMOPREVENTION STRATEGIES

A number of the dietary biofactors has the capacity to interact with multiple

molecular targets and appears to be relatively nontoxic, at least at the doses tested. Since cancer has a long latency period, the role of diet and diet-derived components has gained considerable attention. Despite the global cognizance of the cancer chemopreventive effects of dietary biofactors, most of the claims about their beneficial effects in humans have been based on biochemical in vitro tests or animal experiments with limited data from human studies, thus questioning their potential in the management of cancer. *Nassera Chalabi* from the *Jean Perrin Cancer Centre, Clermond-Ferrand, France* discussed the potential role of nutrigenomics in nutrition research personalized medicine. Cancer stem cells are a small population of cells within the tumor that have the ability to self renew and give rise to mature daughter cells. Within the normal intestine, multiple markers were identified to enrich for a population of cells that have stem-like properties including Bmi 1, LGR 5 and hTERT. *Shrikant Anant and his team at the The University of Kansas Cancer Center, USA*, identified a novel quiescent stem cell maker, DCLK 1. Also DCLK+ cells isolated from colon cancer form colonospheres, and form tumors in nude mice. Notch signaling, an important factor in stem cell renewal is also upregulated in DCLK+ cells. Notch-1 is a cell membrane associated protein, and upon ligand engagement, goes through a series of cleavage activities, including an intracellular event catalyzed by the γ -secretase complex, releasing the intracellular domain of the transmembrane receptor Notch (NICD). NICD translocates to the nucleus, where it interacts with cofactor CBF-1 and activate transcription of target genes. Both curcumin and honokiol inhibited DCLK1-driven colonosphere formation and tumor growth in nude mice. In addition, the compounds inhibited DCLK1 expression in colon cancer cells.

It remains of interest that varying number of patients diagnosed with localized

indolent and asymptomatic disease are not treated initially to avoid treatment side effects such as hair loss, pain, urinary incontinence, and permanent impotence etc. Preventing or inhibiting the growth and progression of prostate cancer through non-toxic chemopreventive agents could be an ideal strategy considering the fact that prostate carcinogenesis involves multiple processes and usually requires more than a decade for the development of clinically significant disease. *Rajesh Agarwal and his research* team at the University of Colorado, USA, have continued to probe the chemopreventive efficacy and utility of silibinin isolated from the seeds of *Silybum marianum* (L.) Gaertn (Family Asteraceae). The molecular mechanisms that describe the silibinin' broad spectrum cancer chemopreventive action includes the induction of cyclin dependent kinase inhibitors and E-cadherin as well as inhibition of epidermal growth factor receptor and NF- κ B pathways. Silibinin targets several tumor microenvironment components including endothelial cells, cancer-associated fibroblasts, macrophages, osteoclasts, etc. to exert its cancer chemopreventive, angiopreventive and anti-metastatic efficacy against prostate cancer.

The association of hepatocellular carcinoma with hepatitis viral infections and the consumption of mycotoxins contaminated food especially aflatoxins with contributing risk factors such as alcohol intake and cigarette smoking (incidence is 23-26% in Africa) is widely documented. The diet of the majority of African populations consists indeed largely of maize, cassava flour and other cereals prone to fungal infestation and thus to contamination by mycotoxins. *Kensese Mossanda from the Walter Sisulu University, South Africa* discussed the potential role of African diet in the occurrence of digestive and liver cancer. Current interest is invested in assessing African diet and beverage consumed in areas with low risk of cancer with a view

to the identification of anti-oxidative, anti-mutagenic and anti-inflammatory/chemopreventive activities for adoption in areas with high risk of cancer. A variety of food plants from households, which include: Maize (*Zea mays*), Ligusha (*Corchorystridens*), Calabash (*Lagenariasiceraria*), Bambara groundnut (*Vigna subterranean*), are widely investigated for mycotoxin contamination. Rooibos tea (*Aspalathus linearis*), Cancer bush (*Sutherlandia frutescens*), Devil's claw (*Harpagophytum procumbens*), African potato (*Hypoxis hemerocallidea*), Pumpkin leaves (*Cucurbita maxima*), Sorghum beverage (*Sorghum bicolor*) are among the staple foods associated with the Southern African areas with low risk of cancer. These food plants could be recommended in the diet of populations living in areas with high risk of digestive and liver cancers for reducing their incidence.

The chemopreventive effects that most edible phytochemicals exert are likely to be the sum of several distinct mechanisms. These include blockage of metabolic activation and DNA binding of carcinogens, stimulation of detoxification, repair of DNA damage, suppression of cell proliferation and metastasis or angiogenesis, induction of differentiation or apoptosis of precancerous or malignant cells, etc. The common dietary chemicals may act on the human genome, either directly or epigenetically, to alter gene expression, thereby regulating carcinogenic processes. *Young-Joon Surh from the Seoul National University, Seoul, South Korea* discussed the notion that the cellular signal transduction pathways that are subjected to fine-tuning has paved the way to unveiling the molecular milieu of cellular homeostasis. Cancer arises when such sophisticated cellular growth-signaling network is deregulated or disrupted. Since the cellular signaling network often goes awry in carcinogenesis, it is fairly rational to target intracellular signaling cascades for

achieving chemoprevention. Targeted modulation or restoration of the intracellular signaling network by use of phytochemicals thus offers a unique strategy for preventing abnormal cell proliferation and other malfunctions.

CANCER NANOTECHNOLOGY, STEM CELL AND DRUG DEVELOPMENT

Nanoparticles are now commonly used in commercial products such as sunscreens, tires, sport-equipment and toner powder for printing devices. Furthermore, it is anticipated that in future nanoparticles will play a central role in medicine as drug delivery systems. However, the toxicity of nanoparticles and their mechanisms of interaction with biological systems are not yet well understood. Some of the emerging technologies in nanomedicine include liposomes (80-200 nm), nanoparticles and nanocapsules (20-1000 nm), polymer-drug conjugates, polymer-protein conjugates, antibody-drug conjugates, albumin-drug conjugates and block copolymer micelles (50-200 nm). Current chemotherapeutic drugs such as paclitaxel and doxorubicin suffer from low solubility, chemoresistance and nonselective cytotoxicity towards both cancerous and normal cells, causing severe side effects. Several drug conjugates are currently on the market to fight cancer more efficiently. Drug conjugates consist of antibodies to which a highly potent toxin is attached via a linker and generally administered intravenously. *Dhanjay Jhurry from the ANDI Centre of Excellence for Biomedical and Biomaterials Research, University of Mauritius*, discussed advent of anti-cancer nanodrugs. Nanodrugs in cancer chemotherapy (cisplatin, carboplatin, 5-fluorouracil, doxorubicin, paclitaxel, dactinomycin, etc.) also seem to be effective providing low side effects and targeted action on cancer cells. The nano drugs are target selective and specific towards tumors only resulting into better treatment^{9,10}.

CONCLUDING COMMENTS

Although our understanding of cancer is unprecedented, cancer continues to be a leading cause of death largely because of lack of application of known interventions. A comprehensive response that promotes prevention, early detection, treatment, and pain control is critical to saving lives and alleviating needless suffering, and will expedite the control of cancer earlier in this century. Elderly patients differ greatly in age-related physiologic changes that can affect the safety and efficacy of chemotherapy. Embracing this will benefit from setting up a centralized specialized clinics covering diagnostic tools, pathology and clinical, medical, surgical and radiation oncology. Also the challenge of clinical research can be met within an organized setting thus facilitating the selection of biologically defined subgroups to optimize research. The major challenge today is the setting up of proper infrastructures to improve the transfer of technology from developed countries to developing countries, through the implementation of standardized management strategies globally simpler and cost effective.

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Acknowledgements: This commentary articulates the views of several eminent scientist who convened to share their thoughts on the global burden of cancer at the second annual symposium on 'CANCER – PRESENT AND FUTURE PERSPECTIVE' on September 16-18, 2013 that was organized by SSR Medical College, Mauritius and International Association of Medical and Biomedical Researchers. The authors acknowledge the participation of the following

scientist whose contribution made the conference a major success:

Nicolas Magne, Jean Monnet Saint Etienne University, France

Shyam S. Manraj, Ministry of Health and Quality of Life, Mauritius

John Crown, St. Vincent's University Hospital, Ireland

Mohun R K Bahadoor, Jean Perrin Comprehensive Cancer Centre, France

Hye-Kyung Na, Sungshin Women's University, Seoul, South Korea

Vidushi S N-Bhujun, ANDI Centre of Excellence for Biomedical and Biomaterials Research, University of Mauritius, Mauritius

B S Tuli, Department , SSR Medical College, Mauritius

Nassera Chalabi, Jean Perrin Comprehensive Cancer Center, France

Jean-Marc Nabholtz, Jean Perrin Comprehensive Cancer Centre, France

Shrikant Anant, The University of Kansas Cancer Center, USA

Ethan Will Taylor, Professor, University of North Carolina, USA

Rajesh Agarwal, University of Colorado School of Pharmacy, USA

Kensese S. Mossanda, Walter Sisulu University, South Africa

Bharat Aggarwal, MD Anderson, Cancer Center, University of Texas, USA

Young-Joon Surh, Seoul National University, Seoul, South Korea

Anupam Bishayee, American University of Health Sciences, CA, USA

Dhanjay Jhurry, ANDI Centre of Excellence for Biomedical and Biomaterials Research, University of Mauritius, Mauritius

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