Harnessing genomics to improve outcomes for women with cancer in India: key priorities for research

Sundar, S; Khetrapal-Singh, P; Frampton, J; Trimble, E; Rajaraman, P; Mehrotra, R; Hariprasad, R; Maitra, A; Gill, P; Suri, V; Srinivasan, R; Singh, G; Cazier, JB

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Harnessing genomics to improve outcomes from women's cancer in India – key priorities for research

Sudha Sundar MBBS[1], Poonam Khetrapal-Singh PhD[3], Professor Jon Frampton PhD[1], Edward Trimble MD[4], Preetha Rajaraman PhD[4], Professor Ravi Mehrotra MD[5], Roopa Hariprasad PhD[5], Arindam Maitra PhD[6], Professor Paramjit Gill MD[7], Professor Vanita Suri MD[8], Professor Radhika Srinivasan PhD[9], Professor Gurpreet Singh MS[10], Professor JS Thakur MD[11], Preet Dhillon PhD[12], Professor Jean-Baptiste Cazier PhD[1,2]

1- Institute of Cancer and Genomic Sciences, University of Birmingham, United Kingdom
2- Centre for Computational Biology, University of Birmingham, United Kingdom
3- Regional Director for South-East Asia, World Health Organisation
4- National Cancer Institute, United States
5- National Institute of Cancer Prevention and Research, India
6- National Institute of Biomedical Genomics, India
7- Institute of Applied Health, University of Birmingham, United Kingdom
8- Department of Obstetrics and Gynaecology, Postgraduate Institute of Medical Education and Research, India
9- Department of Pathology and Cytology, Postgraduate Institute of Medical Education and Research, India
10- Department of Surgery, Postgraduate Institute of Medical Education and Research, India
11- Department of Public Health, Postgraduate Institute of Medical Education and Research, India
12- Public Health Foundation of India, India

Author for correspondence

Dr Sudha Sundar MBBS, MPhil, MRCOG
Senior Lecturer/Consultant in Gynecological Oncology
Pan Birmingham gynecological cancer center, City Hospital and
Institute of Cancer and Genomic Sciences, University of Birmingham, B152TT, United Kingdom
s.s.sundar@bham.ac.uk

Summary

Cumulatively, breast, cervical, ovarian and uterine cancer account for more than 50% of cancers in women in India. Distinct differences in phenotype (clinical presentation) suggest underlying differences in cancer biology and genetics - the peak age of onset of breast and ovarian cancer appears to be a decade earlier in India (45- 50yrs) than developed nations (> 60 years). Understanding these differences through research to derive India-specific paradigms for diagnosis, screening, prevention and treatment is critical and essential to improving women's health in India. Since the sequencing of the human genome in 2001, applications of advancing technologies such as massively parallel sequencing have transformed our understanding of the genetic and environmental drivers of cancer. The $1000 dollar whole genome sequence is now a reality. How can these technologies be best harnessed to provide health care solutions at scale and at budget for a country of 1.2 billion people? What research programs are necessary to answer India specific questions and build capacity for innovative solutions using these technologies? We performed a systematic review and convened a workshop with key stakeholders to address these issues. We highlight challenges, ongoing genomics research, developments in infrastructure and suggests key priorities for research.

Introduction

Women's cancer (breast, cervical, ovarian and uterine cancers) cause in excess of 1 million deaths each year worldwide; about three times more deaths each year than maternal mortality. [1] The majority of these cancer deaths will occur in Low and middle income countries. [1] India's cancer burden, currently estimated at over 1.5 million new cases is predicted to nearly double in the next 20 years , with age-adjusted mortality rates of 64.5 per 100,000 (GLOBOCAN 2012).[2] [3]The burden among Indian women is higher than men, in marked contrast with the worldwide picture of cancer in which the overall age standardized cancer incidence rate is almost 25% higher in men than in women.[4] Cumulatively, breast, cervical, ovarian and uterine cancer account for more than 50% of cancers in women in India. (Figure 1)

Whilst cancer incidence rates are relatively low in India, cancer mortality rate is very high, at 68% of the annual incidence. This ratio indicates that fewer than 30% of Indian patients with cancer survive 5 years or longer after diagnosis.[5] In view of the limitations in the available data, (including low coverage, particularly in rural areas), the true proportion could be significantly lower. By contrast, in North America and Western Europe, overall 5 year survival for all cancers is about 60%. Delayed diagnosis and inadequate, incorrect or suboptimum treatment (including patient inability to access or complete appropriate therapies) are significant causes of poor cancer survival in India.[6] [7] Hitherto unidentified differences in tumour biology may also contribute to poorer survival. The delivery of affordable and equitable cancer care is thus one of India's greatest public health challenges.[8]

Since the sequencing of the human genome in 2001,[9] [10] applications of advancing technologies such as massively parallel sequencing have transformed our understanding of the genetic and environmental drivers of cancer. [11-13]The under $1000 dollar whole genome sequence is now a reality. Insightful applications of this technology have the potential to transform health by delivery of 'precision medicine' or 'individualized medicine'. How can these technologies be best harnessed to provide health care solutions at scale and at budget for a country of 1.2 billion people that has huge diversity and a fragmented healthcare system? What research programs are necessary to answer India specific questions and build capacity for innovative solutions using these technologies?

Search strategy and Selection criteria

We performed a systematic search of published literature in English using the terms 'India', 'cancer', 'genomics', 'Genome-wide association studies' (GWAS), search date any published to December 2016. We searched Pubmed and Google. Papers were selected for inclusion if they were reviews or original research with data relevant to the application of genomics in women's cancer (breast/cervical/ovarian/uterine) in India. We convened a workshop drawing together stakeholders from the World Health Organization, India's National Institute of Cancer Prevention and Research, United States National Cancer Institute, Department of Biotechnology, India, Chandigarh Research Innovation Cluster, Postgraduate Institute of Medical Education and Research, National Institute of Biomedical Genomics, Public Health Foundation of India, Research Councils UK, British Council, Wellcome Trust India alliance, and Illumina.

Challenges from women's cancer in India

Changing demographics in India including rapid economic growth, increasing life expectancy, declining mortality from communicable diseases and changes in lifestyle are mirrored by a change in cancer profiles. [14] Breast cancer is now the most common cancer diagnosed in women with an Age standardized rate (ASR) of 25/100,000 and 27% of cancers in women, followed by cervical cancer, ASR of 22/100,000 and 22.9% of cancers diagnosed in women. [15] However, there is variation within the country, with cervical cancer still being the leading cause of cancer in many rural registries as demonstrated in the National cancer registry programme. [2] Ovarian cancer is the 4th most common cancer accounting for 5%, ASR of 4.9/100,000. [3]

India's National Cancer Control Programme was launched in 1976, and has been incorporated as part of the National Program for the Prevention of Cancer, Diabetes, Cardiovascular Disease and Stroke (NPCDS) since 2010. Large scale implementation of cancer prevention and control strategies has yet to take place, and public expenditures on cancer remain low at 1.2% of GDP.[8] Currently, there is no national organized screening program in India. However the NPCDS has introduced opportunistic screening for breast and cervical cancers alongside screening for Diabetes and Hypertension in a 100 selected districts in 21 states. [16] The Ministry of Health & Family Welfare, Government of India has recently launched the operational guidelines for screening and

prevention of three common cancers oral, breast and cervical cancer.[17] There are also substantial variations in health systems, access and coverage between the various states in India.

Rationale for cancer genomics research in India - differences in cancer biology and epidemiology

Significant clinical differences in cancer behaviour demonstrate that data derived in the West cannot be applied without modification to India. For instance, oral cancer occurs more frequently in Indian populations; nearly 73.4% of Head and neck cancer in India is from gingivobuccal origin as compared to 22% of cancer in the West and is associated with extensive tobacco and betel nut chewing practices. [18] For breast and ovarian cancers, the peak age of onset in Asian countries appears to be a decade younger (45-50 years) than the peak age in the west (> 60). [19] By contrast almost half of all breast and ovarian cancers in the UK will be diagnosed in women over the age of 65 years. [20] These epidemiological differences may be underpinned by a difference in biology – incidence of triple negative breast cancer has been reported as higher in India. [19 21] Multicenter large scale studies with standardized histopathology are needed to confirm these observations (Box1)

These findings have social and economic ramifications but also practical implications for diagnosis and management. For instance, the accuracy of mammography in Indian women as a screening tool may be lower due to differences in breast architecture in younger women. A key deficit previously highlighted is the lack of cancer research to guide early detection, prevention, and treatment strategies tailored to India rather than international guidelines suited to implementation in high income countries. [22]

Significant regional differences also exist within India with variations in cancer type and distribution between the different Indian states. Total cancer rates in population-based registries vary by more than 6-fold across the country , and more than 30-fold differences for sites such as the oesophagus (East Khasi Hills, North East India at 71.2 per 100,000 males versus Barshi, Western India at 2.7 per 100,000 males).[2] For women, a comparison of incidence rates for Breast cancer shows a 10-fold variation between the highest, Delhi at Age adjusted rate (AAR) of 41 to Naharlagun (excluding Papumpare) in the North-East of India at AAR 4.4. (Figure 2) [2] For Cervical cancer, a fivefold difference is seen with the highest incidence in the North East of India, Papumpare at AAR 30.2 with the lowest in Dibrugarh, also in the North East of India with AAR of 4.9. [2] (Figure 3)

These epidemiological differences may well be underpinned by a difference in cancer genomics and biology, differences in prevalence of cancer risk factors, or both, and efforts to unravel these will be absolutely vital to effective cancer control and prevention efforts. (Box-1)

Applications of cancer genomics

Population Diversity and Cancer Genomics

India is the sixth largest country in size and is the second most populous country in the world at 1.2 billion. (http://www.censusindia.gov.in). The majority of the modern Indian population comprises a mix of two large genetically divergent and heterogeneous population groups that mixed in ancient times (about 1200–3500 BC), known as Ancestral North Indians (ANI) or the Caucasoids and Ancestral South Indians (ASI) or the Australoids.[23] Overall there are more than 4000 anthropologically distinct groups and 22 languages with various dialects in this diverse nation. [24] This diversity is enhanced by caste and religion based boundaries and consanguinity, making clusters of specific diseases and founder mutations a possibility.[23]

This genetic diversity is represented in an extremely limited way in current bioinformatics databases, posing challenges for research and meaningful clinical interpretation. For instance the Exome Aggregation Consortium which seeks to aggregate and harmonize exome sequencing data has limited representation of population of Indian origin.[25] An excellent resource is the Indian Genome Variation Consortium project which has studied polymorphisms in 900 genes from 55 different population groups (http://www.igvdb.res.in/). This forms an important database for design of further studies of multifactorial as well as single gene disorders. [26] Another excellent advance is the TMC-SNPdb: an Indian germline variant database derived from whole exome sequences representing 114 309 unique germline variants-generated from whole exome data of 62 normal samples derived from cancer patients of Indian origin. [27]

Even with these advances, population level sequencing or genotyping data for India is quite limited at present, with only a few hundred whole genome datasets among various institutions, and some larger array-type studies to draw upon. The 100,000 Asian Genomes Project will give access to the largest amount of India Sequence data in future and is in planning stages. [28] A truly representative pan Indian genomic variant data resource across diverse ethnic groups is a key challenge to be

overcome if implementation of genomics to improve clinical care in India is to be a reality. [29] (Box-1)

Cancer being a disease at a genome level, every patient has a unique profile, at both pathological and molecular levels. However, shared germline mutations are known to confer susceptibility risk. This has inspired the design of linkage analysis studies to identify regions of the genome shared across families carrying the same phenotype, most successful in the identification of the BRCA1 and BRCA2 genes. [30 31] Such approaches however cannot explain the entire incidence, and the focus has since shifted to association studies of common variants, with potentially modest effect. These genome-wide association studies (GWAS) are based on more, albeit less informative, markers, shared further generations back than in linkage studies. This allows for the analysis of larger cohorts without the need to collect familial information and has led to hundreds of studies being performed across the world resulting in the association of thousands of genetic loci with numerous phenotypes. Famously genetic background could link up geographical information, especially across the numerous GWAS performed in Europe.[32] This underlying structure of the data admirably reflects population diversity at a genetic level; conversely this also raises concerns about the validity of GWAS findings in populations distinct from the original region of discovery and undermines associations where cases and controls had different backgrounds.

Carefully elucidating the effect of population diversity in India through well planned GWAS studies is likely to yield valuable fresh insights into disease aetiology and responses to drug therapy. Recently the first such study in an Indian population to examine a large number of GWAS-identified breast cancer risk loci has been published. [33] Using such cohorts especially enriched for a given phenotype, may maximize the information and find valuable associations with key genes even with limited cohort size. [34] Furthermore, if appropriately recognized, limited population heterogeneity is an opportunity to increase the power of discovery. [35] Finally, the larger scale of analysis enables the creation of cohorts sharing predisposition beyond the molecular susceptibility, such as response to environmental factors. (Box -1)

Studies comparing genotype-phenotype interactions are of particular interest in populations where it is possible to compare between Indian groups in India and Indian groups settled elsewhere, say the West. For instance, the Punjab region in India has deep cultural, family links at multiple levels with the West Midlands region of the UK. The Indian Punjabi diaspora came to the UK in the 1950s and have settled in the major conurbations including Birmingham.[36] Large scale parallel studies in

women's cancer patients in Punjab and the Punjabi diaspora in the UK may offer the unique opportunity to compare and contrast genetic and environmental influences in cancer behavior in genetically related populations subject to very different environmental milieu and can provide insight into cancer prevention. (Box 1) Punjab state benefits from a robust population based registry covering both the urban area of Chandigarh UT as well as Sangrur, Mansa and SAS Nagar districts. (http://www.canceratlaspunjab.org/) Apart from known epidemiological risk factors driving cancer incidence such as visceral obesity, tobacco and alcohol consumption, increased pesticide use in agriculture and higher levels of heavy metal in water and food have been postulated as drivers specific to Punjab.[37]

Familial cancer in women

Approximately 10% of women with breast cancer, 20% with ovarian cancer and up to 9% with uterine cancer display inherited mutations in germline DNA as reported in studies performed in the West. [38-40] Importantly, these mutations are also identified in 'unselected women' with cancer that is those without a family history of cancer or early age of onset. [41]The autosomal dominant disorders, hereditary breast and ovarian cancer (HBOC) with mutations in the BRCA 1 and 2 genes and Lynch syndrome (formerly referred to as hereditary nonpolyposis colorectal carcinoma, HNPCC) with mutations in the mismatch repair genes underlie the majority of this inherited susceptibility. Women with a BRCA1 mutation have a lifetime risk of ovarian cancer by age 70 years of up to 63% and of breast cancer by age 70 years of up to 85%. Risks of ovarian and breast cancers in women by age 70 years among BRCA2 carriers are reported to be up to 27% and 84% respectively. [42 43] Mutations are in high prevalence genes BRCA 1 and 2, PALB2, TP53, PTEN, CDH1, STK11, genes with moderate prevalence CHEK2, BRIP1, RAD51, and ATM as well as in the Lynch syndrome family of genes MLH1, MSH2, MSH6, PMS2 and EPCAM. Identifying families at risk and characterization of risk can enable evidence based large scale targeted prevention and screening efforts to reduce mortality from these cancers. Risk reducing interventions such as prophylactic mastectomy, bilateral salpingo- oophorectomy in in women with a familial risk of cancer in developed countries have robustly demonstrated reductions in cancer incidence and mortality. [44-46] While population-based mammography screening is unlikely to be useful in India at present, targeted screening efforts using mammography in these 'at risk' populations, with careful age constraints on publically available programs may prove cost effective and reduce mortality. [47]

We also highlight a note of caution here – that screen-detected cancers may have a different genomic and phenotypic presentation than clinically detected cancers. Cancers that present clinically are more commonly biologically aggressive cancers, more commonly basal or triple-negative tumours, which screen detected (clinically occult) cancers are more commonly ER+ more biologically favourable variants.

In this context, it would be helpful to investigate the differences between screen detected cancers and clinically detected cancers in the South Asian populations who have migrated to high income countries. (Box1) Data on this is currently limited, as unfortunately, South Asian immigrants settled in the United Kingdom and North America have lower screening uptake rates for breast, cervical and colorectal cancers [48]

Furthermore, considerable diversity in mutation profiles by ethnicity exists in the BRCA 1 and 2 genes.[49] Whilst substantial information about the prevalence and spectrum of BRCA mutations exists in European and North American populations information is lacking in other populations, including the Indian population. Using data from Caucasian populations to interpret data from non – Caucasian populations can be highly misleading and lead to misdiagnosis.[50] In addition, the inherited risk of breast and ovarian cancer risks vary by type and location of BRCA1/2 mutations, making it vital to characterise the spectrum of mutations by ethnicity. [51]

Current data on the prevalence and nature of BRCA mutations and other inherited cancer predisposing genes in the Indian population is valuable but limited to single centre studies, relatively small sample sizes, restricted to selected women with strong family history of cancer, using older technologies e.g. Sanger sequencing. [52 53] More recently two pivotal studies using panel testing and Next generation sequencing have been published. [54 55] The first study screened 91 patients with family history of Hereditary breast or ovarian cancer or early onset of cancer from Southern India, previously tested negative by an earlier PCR-dHPLC (PCR-denaturing high performance liquid chromatography)-based, by targeted resequencing of a multi-gene panel and reported a mutation rate of 26.4% (24/91). The second study identifies up to 36% prevalence of pathogenic mutations in breast and ovarian cancer susceptibility genes in women tested with a private provider, including some sporadic patients. [54 55]

There is an urgent unmet need for large scale studies recruiting unselected women with Breast, ovarian and uterine cancer from across the different regions of India, from both urban and rural

distributions, carefully annotated with clinical, pathological, survival data, tested with pan cancer panels using NGS to characterize the prevalence and spectrum of mutations and variants of uncertain significance in Indian women. In order to tease apart intrinsic biological differences from environmental factors, and to assess the interplay of the two, it is essential that data should be also collected on epidemiological characteristics and environmental exposures to potential carcinogens. (Box1)

Human Papilloma virus (HPV) infection and Cervical cancer

As previously discussed, Cervical cancer incidence rates differs widely across regions in India. Furthermore, HPV variants differ in oncogenic potential, because of differences in biological, biochemical effects. [56] The oncogenicity of distinct HPV variants may also differ between geographical regions because of differences in the population related to the distribution of HLA alleles. [57] Efforts to understand the natural history of HPV infection and the development of cervical cancer across regions of varying incidence of cancer; establishing type and infection rates of HPV through population based cohort studies and characterization of India-wide HPV genome variants will be critical to the development of India specific low cost vaccines and HPV diagnostics (Box 1). Recently complete genome sequences of HPV 16 isolates from lesions in Indian women have been published. [58]

Influence of environmental risk factors

Genetic heterogeneity between endogamous groups within India is at least 3-fold higher than that observed between European populations, which is attributable to different waves of migration and admixture. Further, the genetic variants interact with the diverse environmental factors within India and exhibit such diverse effects across different geographic regions and ethnic groups.
Wide variations in cancer types and incidence between various regions in India maybe due to genetic variations in a proportion of patients, however it is also highly likely that environmental factors, lifestyle and habits play a bigger role.

For instance, significant variations in the cancer type and presentation are found in the Indian subcontinent compared to the rest of the world some of which can be related to specific differences in environmental exposure e.g. in case of oral cancer , which is the predominant cancer type in men

in India. Oral cancer predominantly presents as tongue cancer in the West, while in India it predominantly affects the gingivo-buccal region, comprising buccal mucosa, retro-molar trigone and lower gum. This might be related to the chewing betel-quid comprising betel leaf (Piper betle), areca nut (Areca catechu) and slaked lime (predominantly calcium hydroxide), with or without tobacco, is traditional and popular in India and is known to cause oral cancer. [59] Human papilloma virus (HPV) infection is also an established risk factor, with prevalence in oral cancer ranging between 20 and 50% across geographical regions. [60]

Ongoing efforts in cancer genomics in India

A recent Global cancer genomics consortium conference at Mumbai showcased the vibrant cancer genomics research field in India, with progress in several cancers, including oral cancer, lung cancer, cervical cancer and gliomas. [61] The National Institute of Biomedical genomics, Kolkata (NIBMG) has had significant infrastructural funding from the Department of Biotechnology, Govt of India to address some of the questions key to Indian cancer.

The International Cancer Genome Consortium (ICGC) has been launched to generate high resolution catalogues of genomic and other biological alterations in tumours of more than 50 different cancer types/subtypes that have clinical and societal importance across the globe. Oral cancer occurs more frequently in Indian populations; nearly 73.4% of Head and neck cancer in India is from gingivobuccal origin as compared to 22% of cancer in the West and is associated with extensive tobacco and betel nut chewing practices. [18] In view of the high prevalence and existence of possible interacting environmental factors, India, a founder member of ICGC, is focusing on oral squamous cell cancer – gingivo-buccal – in the Indian component of the project. NIBMG, along with Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Mumbai as the clinical partner, is spearheading the Indian initiative in ICGC which is funded by Department of Biotechnology, Govt. of India. The key objective of this initiative is to identify genomic, epigenomic and transcriptomic landscapes of alterations that drive OSCC-GB. NIBMG has developed substantial infrastructure and expertise in genomic analysis of cancer and is generating and analyzing genomic, epigenomic and transcriptomic data in the project. The OSCC-GB data in ICGC is available on http://dcc.icgc.org/projects/ORCA-IN. [62] [63] In addition, NIBMG is engaged in studies on genomics, epigenomics and transcriptomics of oropharyngeal cancer and gastric cancer in specific populations in the North Eastern region of India (Meghalaya and Mizoram respectively), genomic studies on cervical, breast and pancreatic cancer as well as whole genome sequencing studies to catalogue the genomic variation of different populations of the Indian subcontinent.

Institutions actively engaged in capacity building in India for genomics include the National Institute of Biomedical genomics, Institute of Genomics and Integrative Biology, Council of Scientific & Industrial Research, India and others. Indian research funders Department of Biotechnology, Indian Council of Medical Research have initiated Infrastructure Development at institutes for advanced Genomic Research and pharmacogenomics implementation across several sites in India. [64] A national Bioethics committee has established regulatory guidelines for Genomic medicine techniques, research activities and harmonization with international ethical guidelines.

Capacity building for research in genomics in India

Capacity building for research in genomics in India will require a multipronged approach, with the need to train scientists in next generation sequencing, bioinformatics and health care providers including clinicians, nurses and counsellors in engaging with informed consenting of patients, nuanced interpretation and communications of results. Ongoing efforts such as the infrastructure to collect large scale prospective clinical, pathological, therapy and survival data such as the National cancer grid will also be vital to this effort.[8] Patient – public engagement by researchers and effective advocacy through patient groups will be pivotal. All these efforts may be enhanced by public-private partnerships.

India's standing as a leader in Information technology, the large pool of graduates trained in the traditionally valued science disciplines and India's demographic dividend may be fortuitous in creating the right conditions to create a genomic powerhouse. The Government of India has launched ambitious initiatives to improve online infrastructure and internet connectivity with 'Digital India' and a commitment to making India the skills capital of the world, 'Skills India' which may facilitate the skilling up of graduates in the relevant disciplines. [65] [66] The Government of India has also launched a massive project, called Aadhar, to provide a digital identity based on an individual's fingerprints and retina scans. As of 2016, the program had issued 12-digit identification numbers to 1.1 billion people. [67] These initiatives are pivotal in imagining a future where individuals can carry health data in conjunction with a digital identity.

Whilst advances in massively parallel sequencing have revolutionized our understanding of disease genomics and personalized medicine, it has also unleashed an enormous amount of data, both structured and unstructured, prompting experts and scientists to coin the term "BIG DATA". These huge data sets have challenged the community to devise new sets of analytical and data access tools. It is important to highlight the lack of experience and expertise in bioinformatics while dealing with analysis of big data in India. There are currently very few islands of excellence where expertise exists to evaluate and meaningfully analyse big data from genomics research. Other areas of deficit include the lack of expertise in statistical genetics, systematic data management, data management of array data and a lack of basic computational facilities required to store and manage huge databases. Institutions such as NIBMG and ACTREC conduct capacity building workshops focusing on focused on cutting edge experimental and computational tools of contemporary genomics. International collaborations with ongoing training efforts such as those established by Health Education England for UK health care system workers as part of the UK 100,000 genome sequencing efforts may potentiate capacity building. [68]

Need for efficient research networks

Integrated research systems that can prevent duplication of research efforts, optimize research reach, impact and output by creating clusters that can work synergistically and work well together. A provocative questions workshop between the US NCI and DBT, India identified key issues regarding cancer research in India, including the need for increased cancer research funding, and a focus on providing relevant human resource training and technology sharing platforms. Continued open debate between researchers, funders and policymakers will be essential to effectively strengthen the cancer research portfolio in India.[69]

Clusters of research collaborations results in greater synergy, effective use of administrative costs. For instance, the AMPATH partnership has resulted in collaborators from > 19 universities and academic institutions in Africa, Europe, and North America working synergistically across Kenya, resulting in more than 275 publications in 17 years in over 90 active research projects securing more than $83.4M in research funding. (http://www.ampathkenya.org/) Indian clusters such as the Chandigarh Research and Innovation cluster (CRIKC), bringing together research active organizations across a wide range of expertise can facilitate effective research delivery. (http://crikc.puchd.ac.in/) Other models include innovative partnerships, such as the successful collaboration between the University of Cambridge, the National Centre for Biological Sciences

and Institute for Stem Cell Biology and Regenerative Medicine (inStem), Bangalore CBS resulting in the establishment of the multidisciplinary Centre for Chemical Biology and Therapeutics, Bangalore. A landmark initiative, the Indian National Cancer Grid now links more than 85 major cancer centers to build a platform that will enable development and dissemination of Indian guidelines, uniformity in training in training in cancer care and establish Pan India cancer research networks. [8] This development is a key step to enabling the delivery of clinical and translational research at scale.

Increased research capacity and training, protected time for clinical researchers; enhanced collaborative funding programs and development of infrastructures across a range of domains including clinical trials and tissue banking have been identified as cancer research priorities in India. [22] Research capacity building for manpower to staff biobanks, animal house laboratories, genomics and bioinformatics will also add to the skills base development in India as championed by the Skills Development agenda (http://www.makeinindia.com/home) from the Government of India.

Initiatives from funders such as the Wellcome trust – Department of Biotechnology India alliance fellowships for clinical and non-clinical researchers will contribute significantly to capacity building for research. (http://www.wellcomedbt.org/). The Newton fund was launched in 2014 and commits to £ 75 million pounds each year of research spending with global partners. This is set to increase to £150 million by 2021. (http://www.newtonfund.ac.uk/). A significant funding stream for UK-India relevant research is the Newton-Bhabha funding stream, delivered jointly between the Research Councils UK and the Department of Biotechnology India.

Public Health Implications

Cancer accounts for 12% of premature deaths in Low and middle income countries (LMIC's) with 7.6% of Disability adjusted Life years (DALY) lost due to cancer.[70] The WHO has also set an ambitious target of reduction of death from non-communicable disease including cancer by 25% by 2025 in its recent global monitoring framework. [71]

There are a range of socio-economic and socio-cultural factors that can also play a role in the variation in site-specific incidence and survival that is observed globally, and by region and race/ethnicity within countries such as India. [72] [73] Specifically, barriers to early detection in India

stem from factors including low cancer literacy, stigma, fear, health care access and cost of care.[74] A recent review found low literacy for breast cancer awareness in Indian women, including nursing professionals, whose knowledge of risk factors was not aligned with the importance/strength of a risk factor.[75] Cancer mortality patterns reveal the importance of socio-economic determinants including geographical location such as the Northeast or living in rural areas for women or infectious-related cancers, low education and religion. [74] Individual- and societal-level social barriers for breast cancer in Indian women include cancer stigma, fear, fatalism and financial constraint. [76] Global evidence shows the importance of health-systems constraints for women's cancers related to development of health services, availability of health insurance, distance to cancer services as well as gender equity and human development. [77] Thus, sociocultural barriers to cancer control are key challenges in India. [78]

Public health measures to tackle cancer control include the Package of essential NCD interventions championed by the World Health Organisation (WHO) for primary health care addressing cancer, diabetes, heart disease and stroke, chronic respiratory disease; a conceptual framework for strengthening equity and efficiency of primary health care in low-resource settings; it identifies core technologies, medicines and risk prediction tools; discusses protocols required for implementation of a set of essential NCD interventions; develops technical and operational outline for integration of essential NCD interventions into primary care and for evaluation of impact. (http://www.who.int/cardiovascular_diseases/publications/pen2010/en/)

In addition, there is a substantial knowledge deficit on cultural attitudes to genetic testing amongst patients and caregivers as well as the awareness of inherited cancer risk in Indian women. Shyness, fear of cancer, stigma, financial constraints are some of the barriers to early detection of cancer. [79] Qualitative studies to assess the type and magnitude of the various barriers will be important; to ensure that insight gained by cutting edge genomic technologies translates into real benefit in screening, prevention for family members at risk. Studies that promote cancer literacy and understanding social and cultural barriers to cancer prevention will also be important. [80] (Box-1)
Thus, whilst genomics based research may enable a better understanding of ethnic variations in cancer patients in India and enable India specific cost effective interventions, it is only one factor in a much broader framework of cancer control and not likely to be a universal panacea.

Genomics and improving Outcomes from womens cancers

How might a better understanding of Genomics improve outcomes from women's cancer in India given such prevalent sociocultural barriers? Population based screening methods for India may not be affordable or cost effective, given equally competing demands for universal education, sanitation amongst others. However understanding India specific differences through genomics may enable the identification of women at high risk of development of cancer where targeted screening may be cost effective. We need to urgently identify Indian specific genetic/epigenetic biomarkers related to intermediates of breast cancer like mammographic density. These may have potential to be used as biomarkers for early detection at screening stage. Equally a greater understanding of the oncogenicity of HPV variants in Indian woman will help the development of low cost vaccines for cervix cancer. Treatment regimens developed using evidence generated from trials performed on Caucasian women may not be applicable or as effective in a population with such distinct phenotypical differences. Developing evidence based India specific paradigms of screening and management are therefore essential to improving outcomes.

Conclusions

We envisage that genomics technologies harnessed to understand India specific differences in the presentation, epidemiology and clinical behaviour of women's cancer may lead to the development of appropriate cost effective, targeted screening and prevention for women at risk of development of Breast and ovarian cancer, new strategies for prevention in Cervix cancer as well as effective cancer treatment paradigms.

Strong multidisciplinary research teams comprising expertise in clinical studies, genomics, bioinformatics, modeling, qualitative research and public health will need to work collaboratively to harness the immense potential offered by novel next generation sequencing technologies. This will ensure that the benefits from these technologies are harnessed in an evidence based and cost effective way to improve women's health and alleviate cancer burden in India.

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Conflicts of interest

We have no conflicts of interest to declare

Contributors statement

SS and JB-C conceived the manuscript and wrote the paper, PKS, JF, ET, PR, RM, RH, AM, PG, VS, RS, GS, JST wrote sections of the manuscript and critically reviewed the manuscript.

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