COMMENTARY

GYNECOLOGICAL CANCER AND NUTRITION IN PAKISTAN
IN THE 21ST CENTURY

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In the 21st century, society medicine, obstetrics and gynecology, cancer and nutrition have all changed. The United Nation (UN) and World Health Organization (WHO) approach to healthcare has failed. Flawed Millennium Development Goals (MDGs) developed into the sustainable development goals after the 4P’s – prediction, prevention, personalization and participation of Hood and Flores\textsuperscript{1}. This applies particularly to cancer and human reproduction where advances in cancer therapy have led to an overall apparent cure rate of 90% in hormone dependent breast cancer, whatever the stage\textsuperscript{3}. These changed concepts are easily applicable to Pakistan, so late presentation and deprivation is no longer adequate justifications for suboptimal outcome. These changed concepts also point the way forward. They have been achieved by individualizing breast cancer according to its receptor metabolism. The most therapy resistant cancers are so called triple negatives lacking estrogen, progestogen and human endothelial to receptor (HER), where we do not know the canonical pathways supporting the cancer at the expense of the host. The case of ovarian cancer is less satisfactory because associations are combined to produce all stemming from Ca125, a protein product of active cells, without considering the canonical preferred and preserved pathways necessary for cancer persistence and metastasis\textsuperscript{3}. The mechanisms whereby these pathways act are usually by tyrosine kinases (e.g. brutinib and imatinib) whereas serine kinases are generally protective and inhibitory although inhibition of a reactive protective protein also helps cancer progression. These canonical pathways cover the entire spectrum of cell function such as\textsuperscript{4}:

1. Initiating genomic factors (e.g. Wnt, NOD, SOX, CMYC), which are preserved across species and persist in adult life as canonical pathways and are genomic in origin.
2. Metabolic dominant pathways – inisitol AKT transforming growth factor (TGF) alpha and beta balance), mesenchymal transition to epithelium (extra cellular growth factors), Ras, hypoxia inducible factor (HIF).
3. Growth factors – insulin, insulin like growth factors (ILGF) and their receptors, human epidermal growth factor receptor (HER), vascular endothelial growth factor (VEGF).
4. Cell cycle and DNA repair mechanisms (e.g. P53, BRCA1 and 2).

This incomplete development in gynecological canonical pathways demonstrates the way forward. This is how cancers bypass the normal immunological defense mechanisms and divert cellular metabolism to preserve cancer survival at the expense of the host most often by inefficient use of increased mitochondrial glycolysis\textsuperscript{5}. This opens up a huge 21st century field for individualization as no cancer is identical. This individualization has been successfully applied making breast cancer a chronic curable disease in 90% cases using technology that is available in Pakistan today, e.g. cytotoxic agent given at night to minimize damage to normal cells and cell marker directed therapy to individuals after baseline treatment.

Gynecological management of cancer as usual lags in searching for magic bullets and associations instead of integrating management with genome wide association studies (GWAS) demonstrated many actionable associations. This together with other management blunders justified the Wooden Spoon award for ineffectiveness by Archie Cochrane himself to Obstetrics and Gynecology. The long term UK collaborative trial of screening has produced a 25% reduction in ovarian cancer in the long term\textsuperscript{6}.

In Sind, gynecological cancer is the 3rd commonest presentation with 9.6% of over 2000 cases at the
regional centre at Jamshoro\textsuperscript{7}. Karachi oncologists have made a concerted effort to define urban incidence of cancer. Overall, it appears that cancer is more common in deprived communities worldwide. Ovarian cancer over a wide age distribution is commonest at Jamshoro followed by cervical, with endometrial surprisingly relegated to third, although there may be a selection bias by early hysterectomies for high risk patients. In the modern world, a woman with ovarian cancer below the age of 40 may want to preserve fertility. These large germ cell cancers are highly malignant and spread rapidly but paradoxically are curable with 66\% subsequently producing children\textsuperscript{8}. The process required is fertility preserving surgery and the addition of a DNA gyrase inhibitor such as etopside. This area has been neglected by gynecologists. Similarly, gonadotropin releasing hormone (GnRH) is known to protect ova during cytotoxic administration in young patient\textsuperscript{9}. It is clear that human reproductive biology input needs to be upgraded as oncologists are not up to the task of modern complexity.

Nutrition also needs updating in Pakistan, as in many other countries it is dominated by dietetics, strongly assisted by the food and advertising industries and concerned with what people eat rather than the hard outcomes of BMI (<23 in Asia) and weight distribution (e.g. waist <50 of height in Pakistan). I have yet to see a single gynecologist measure these components. The limitation of the present day obesity (and oncogenic) epidemic is to be sought in percent reduction of intake rather than a complicated diet that is unsustainable because it does not fit into the patient lifestyle. Failure to lose weight means that there is a metabolic component which requires a different management. Genetic screening for familial cancers such as the Lynch syndrome, breast cancer markers (Lynch BRCA 1 and 2 syndrome), Li-Fraumeni syndrome should be kept in mind.

Food is the most important drug of all because a simple calculation reveals that the average person for good or bad eats at least 25 tons of food in their lifetime. As everyone is an expert in nutrition but very few actually have verifiable knowledge. It comes as no surprise that magic bullets of nutritional intervention have very little impact although nutritional metabolism is surprisingly sensitive to intervention. We know what the correct diet is\textsuperscript{10,11} – South Asian Mediterranean using locally available food sources – dal (a legume) is the godsend to Pakistan. This diet includes 5 vegetables + fruits, five times per week whole grains (white rice is an expensive sick joke) low fat milk or yogurt, fatty fish and (a fat American addition) 10\% discretionary (i.e. cheating) for variety. Heme containing meat, fatty meat and processed meat should be limited. It should be remembered that food deserts available at convenience stores and supermarkets do not contain fresh foods because of salt preservation and dehydration increasing calorific density, also contains coloring agents and other preservatives. Overriding all of this is that a diet limited to 60-70\% of ad libitum eating will lead to a long healthy life free of disease and cancer\textsuperscript{12} – the Hunza in Pakistan are our local example although even they are being Coca colonized. It should be the task of every health worker in Pakistan to reverse coca colonization as far as possible to prevent cancer among other objectives.

The other concept about food in the 21st century is the life cycle approach with prevention rather than cure being the objective (Sustainable Development Goals). Gynecologists have ignored intrauterine programming although adult disease (especially cardiovascular and cancer) is clearly dependant on this\textsuperscript{13}. The Barker hypothesis is now no longer a hypothesis and affects both Pakistan and now China, with a double disease load. Intrauterine programming\textsuperscript{14} and post natal excess without exercise leading to a 40\% of incidence of carcinogenic diabetes in midlife. In our country this makes insulin resistance (not blood sugar) and polycystic ovaries an ideal opportunity for long term prevention after subfertility is treated, particularly as the diet prescribed is meant for insulin using type 1 diabetics. Insulin being a growth hormone is associated with the development of cancer\textsuperscript{15} whereas metformin affecting the canonical AKT pathway\textsuperscript{16} is protective.
against cancer and is now in a huge multinational trial centered in Mount Sinai, NY to delay ageing. The European polycystic ovary syndrome (PCOS) are largely fat related and a randomized double blind trial beloved of gynecologists for a syndrome such as PCOS is a statistical joke because of differing components in South Asia. It is sad to see the continuing production of articles on blood hormones designed to clarify the clinical syndrome. The central 21st century concept is that PCOS with a major nutritional component is an ideal early marker for preventing cancer, but both patients and doctors think only of the immediate complaints of infertility or hirsutes rather than the life cycle effects which are critical in the 21st century.

Having established the changed concepts of the 21st century before we go into clinical management, we should know what is the connection between cancer and nutrition? The answer was provided by German pathologist, Otto Warburg, more than 70 years ago (Warburg Phenomenon). He noted that cancer required a high rate of glycolysis for inefficient initiative of energy production and hence sugar to prosper even after bypassing the immunological and growth defenses of the host. This means that cancer hijacks the host resources to the extent that cachexia ultimately supervenes with weight loss. This catabolism is lethal in its own right as branched chain amino acids are broken down from muscle. Cachexia also occurs in old age, following diseases such as coronary artery thrombosis and parainflammation such as chronic obstructive pulmonary disease (COPD). In cancer, treatment of cachexia is, therefore, a prime objective – 80% of the patients are dead within 1 to 2 years whether the cancer is cured or not. The management is to reverse catabolism. This is accomplished by an elemental diet which limits the metabolic work especially of the liver by using simple components which do not require energy to break down food for metabolic use by the cancer cells in this case. These may include:

1. Branched chain amino acids particularly cysteine at doses of 4-6 g/kg/day. These are easily and cheaply obtained from whey (liquid remaining after milk has been curdled and strained), as is well known to body builders.
2. Sugar <100 g per day leads to hepatic necrosis whereas >300 g per day lead to fatty degeneration of the liver in adults.
3. The critical short and medium chain fatty acids which are competitively produced by humans (omega 3 and fatty acids) are probably best supplied by a tablespoonful of cod liver oil.
4. Micronutrients should be supplied as a balanced combination in these nutritionally deprived people. In general, magic bullets (e.g. calcium) by mouth are nutritional nonsense. Of 1200 mg daily, often prescribed to prevent osteoporosis, only a maximum of 3% is absorbed by slow turnover bone whereas the high blood levels deposit in other tissues including coronary arteries leading to a 20-40% increase in heart attacks in big controlled series, which is not mentioned by pharmaceutical salesman.
5. Of course anabolic agents can be used but in cancer these may aggravate the situation. A notable exception is megesterol for endometrial cancer (and COPD). Similarly, the 6 isomers human chorionic gonadotropin (hCG) are being explored because of their unique function of controlled growth.

The other issue about cancer is the major place of surgery, which is often required. The majority of patients are in poor nutritional condition and if not corrected the death rate is double a least and serious complications such as severe infections are trebled irrespective of the quality of surgery or the surgeon. The MUST (Malnutrition Universal Screening Tool) guidelines should always be assessed and, if negative, up to two weeks can be spent to correct this in the patients’ best interests. The rather poor clinical marker that is widely used is a serum albumin of less than 3.6 g%. This simple approach to the nutrition of cancer has, I hope, established the very changed concepts of standard of care required in the 21st century and attainable in Karachi.

I have not covered subjects such as carcinogens (e.g.
Bisphenol A banned in the Emirates but widely used in water bottles in Karachi) and the huge field of the metabolome. We are born human and die bacterial with 10 to 100 times more bacteria and viruses in our bodies than cells, but most of them are “old friends” and protective. Disturbance of this can be carcinogenic especially bowel cancer but also as the Swedes have noted, prolonged bacterial vaginosis is associated with abnormal cervical cytology24.

REFERENCES


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