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OBESITY AND COLORECTAL CANCER

The increased body fat (overweight and obesity) has been implicated as a cause of morbidity and mortality for several non-communicable diseases including cardiovascular diseases, diabetes, hypertension, kidney failure, degenerative osteo-arthritis and cancer[1]. Epidemiological evidences strongly support that weight gain in adult life with or without physical activity is associated with increased incidence of cancers in men and women[2]. Studies have revealed that obesity is a major risk factor for several cancers such as colon, breast (post-menopausal), endometrium, kidney and oesophagus[3]. Some studies have also reported links between obesity and cancers of the gallbladder, ovaries and pancreas[4]. A prospective cohort study on cancer prevention in the USA estimated that overweight and obesity accounted for 14 % of all cancer deaths in men and 20 % of those in women. Significant positive associations have been found between obesity and higher death rates for cancers such as oesophagus, colon and rectum, liver, gallbladder, pancreas, kidney, stomach, prostate, breast, uterus, cervix, and ovary[5]. Universally accepted, suggested ideal body mass index (BMI) is 20-24.9 kg/m^2 for both sexes. A BMI between 25 and 29.9 kg/m^2 is considered overweight; and that of 30 kg/m^2 and above defines obesity. This applies to adults, aged 18 years and above. In view of Asian Indians being at a higher risk of developing atherosclerosis and related complications, the cut off limit for over weight has been suggested at a BMI of 23.0 kg/m^2 , with those above a BMI of 25 kg/m^2 being cosndiered as obese[6].

Some researchers have argued that overall body mass is less important in determining colon cancer risk than the distribution of body fat. In men, a high BMI tends to be associated with fat that is distributed abdominally, whereas in women fat is more likely to be distributed in the hips, thighs and buttocks. Thus, waist-to-hip ratios, a measure of abdominal adiposity, may be a better predictor as well as indicator of colon cancer risk. This review will focus on association between colorectal cancer and obesity, and also attempt to summarize the results of some major trials carried-out for prevention of colorectal cancer.

The contribution of diet and nutrition status to cancer risk has been a major focus of research as well as public health policy. An increased amount of fat or adipose tissue in an overweight or obese person probably influences the development of cancer by releasing several hormone-like factors or adipokines. Chemoprevention intervention studies have been carried-out to evaluate the effect of various strategies such as dietary modifications, vitamins and antioxidants, folate, fiber, calcium supplementation, aspirin therapy, *etc.* on the adenoma recurrence, adenoma

growth or on incidence of colorectal cancers[7]. There are convincing evidences to show that colon cancer arises from adenomas, which are considered to be potential pre-cancerous lesions, with specific factors involved in the development of adenomas and further progression to invasive cancer[1]. A number of studies have focused not only on the primary prevention of, but also on the secondary prevention of adenoma recurrence and growth. The early detection and removal of these lesions are presumed to reduce the incidence and mortality of colorectal cancer[4].

Cancer of colon and rectum is the fourth most common incident cancer and the cause of death from cancer, throughout the world. An estimated 1,023,152 colorectal cancer cases occurred in 2002[8], accounting to 9.42 per cent of all new cases of cancer. Incidence and deaths from this cancer are generally increasing, most of all in the developed world and urban areas of the developing world. In India, although the incidence rate of colorectal cancer is very low, and rectal cancer remains more common, a significant increase in its incidence has been reported for both men and women over the last two decades. The age adjusted annual incidence rates (AAR) of colorectal cancers per 100,000 persons during the year 2004-05/ 2005-06 in the various population based cancer registries operating under Indian Council of Medical Research was found to range from 1.5 to 6.9 and 2.5 to 7.4 amongst males and females in urban areas respectively. Similarly, in the rural areas the rates were 1.6 and 2.4 and 1.1 to 1.3 amongst males and females respectively[9-10] (Table). The trend analysis for seven Population Based Cancer Registries (PBCRs) of the country during 1968-72 to 1998-2002 was estimated as an annual percentage change (APC) using relative difference between recent and the earliest AARs. Out of the seven PBCRs an increasing trend AAR in the colorectal cancer was observed in three registries ranging from 0.63% to 1.8% and 0.11% to 0.69 % in various registries amongst males and females respectively. An estimated 35635 new cases of colorectal cancer occurred in 2006[11], accounting to 3.9 per cent of all new cases of cancer.

Table. Age adjusted incidence rate (AAR) per 100,000 person years of colorectal cancer in various population based cancer registries

Registry	Period	Colorectal	
		Males	Females
Urban			
Bangalore	2004-05	6.3	4.7
Mumbai	2004-05	5.9	4.6
Bhopal	2004-05	4.1	2.8
Delhi	2004-05	5	3.7
Chennai	2004-05	5.8	4.1
Kolkata	2005	3.1	3.2
North Eastern Region			
Dibrugarh	2005-06	4.6	3.4
Kamrup urban District.	2005-06	4.9	3.6
Silchar Town	2005-06	1.5	3.6
Imphal West District.	2005-06	6.9	5.5
Mizoram	2005-06	5.6	7.4
Sikkim	2005-06	4	2.5
Rural			
Ahmedabad	2004-05	2.4	1.1
Barshi	2004-05	1.6	1.3

Source: Based on data from National Cancer Registry Programme (ICMR) for Population based cancer registries for the years 2004-05 for Bangalore, Barshi, Bhopal, Chennai, Delhi, Mumbai, Ahmedabad, and 2005 data for Kolkatta and 2005-2006 data for North Eastern Region (NER) registries viz. Dibrugarh , Kamrup urban District, Silchar Town, Imphal West District, Mizoram State, Sikkim State.

The prevalence of obesity in India is 2-15 per cent in urban, and 0-6 per cent in rural population by using current definition of obesity[12] (BMI > 30 kg/m^2). In India women suffer from a dual burden of malnutrition with nearly half of them being either too thin or overweight. National Family Health Survey-3 (NFHS-3) study undertaken at the National level during the year 2006, revealed that the percentage of ever-married women in the age group of 15-49 years who are overweight or obese increased from 11 per cent in NFHS-2 to 15 in the NFHS-3 study. Overweight and obesity were found to be more than 3 times higher in urban than in rural areas[13].

Epidemiological evidences strongly support a relationship between dietary constituents and risk of colorectal cancers. It is commonly agreed that the risk

of colorectal cancer can be modified by food and dietary habits. High red meat and animal fat consumption have been associated with an increased risk of colorectal cancer[14-15]. Obesity, greater adult height, frequent eating, and diets high in sugar, total and saturated fat, eggs, high alcohol intake, and processed meat, all possibly increase the risk[1]. Contrary to this, diet rich in fruits and vegetables, dietary fiber, and certain micronutrients appear to be protective against colorectal cancer. A joint report by the World Cancer Research Fund and American Institute for Cancer Research found convincing evidence that a high fruit and vegetables diet would reduce cancer of colon and rectum[1]. Fruits and vegetables possibly offer protection against colorectal cancer through anti-carcinogenic components such as antioxidants, folic acid, flavonoids, organosulfides, isothiocyanates, and protease inhibitors as well as fermentable fibre. Donaldson in his publication "Nutrition and cancer: A review of the evidence for an anti-cancer diet" reported that of the 26 reports of human studies investigating the link between diet and colon or colorectal cancer, 21 reported a significant positive relationship between red meat and colon or colorectal cancer[16]. Contrary to this, however, many reports from prospective population based studies on diet and cancer did not find protective effect in fruits and vegetables against colorectal cancer.

A case-control study was carried-out at the National Naval Medical Centre, USA to investigate the possible associations between dietary factors and colorectal adenomas diagnosed by sigmoidoscopy or colonoscopy[17]. Dietary variables were assessed by a 100 item food frequency questionnaire containing detailed information on fat and its subtypes, fiber and its subtypes, fruits and vegetables and their subtypes. Fat intake was adjusted for red meat intake. The findings of the study revealed an increased risk of 7% (odds ratio: 1.07, 95%CI: 0.94-1.22) per 5% energy/day from total fat. Every additional 5%unit of oleic acid intake/day significantly increased the adenoma risk by 115% (OR: 2.15; 95%CI: 1.05-4.39). Red meat fat increased the risk by 20% (OR: 1.20; 95%CI: 0.71-2.04), and white meat fat decreased the risk by 67% (OR:3.3; 95%CI: 0.19-0.95) for every additional 5% unit of respective intake per day. Risk decreased by 41% (OR: 0.59, 95% CI: 0.41-0.86) for every additional 5% unit of fiber intake/day. Vegetable (OR per 100 g of vegetable intake/day: 0.83; 95%CI: 0.67-1.04) and fruit (OR per 100 g of fruit intake/day: 0.92; 95%CI: 0.82-1.03) intake showed an inverse association. The study showed a strong positive association between oleic acid intake and colorectal adenoma risk. Increased intake of dietary fiber was associated with a moderately decreased risk of adenomas.

Another study attempted to establish association between consumption of total fat, major dietary fatty acids, cholesterol, consumption of meat and eggs, and the incidence of colorectal cancer in a cohort of Finnish population[18]. The study revealed that high colesterol intake was associated with increased risk for colorectal cancers (OR: 3.26, 95%CI: 1.54-6.88) between the highest and lowest quartiles of dietary cholesterol. Non-significant associations were found between consumption of meat and eggs and colorectal cancer risk.

Women's Health Initiative Randomized Controlled Dietary Modification Trial carried out on 48,835 postmenopausal women aged 50 to 79 years to evaluate the effects of a low fat eating pattern on risk of colorectal cancer revealed that low fat dietary pattern intervention did not reduce the risk of colorectal cancer in postmenopausal women during a follow-up of 8 years[19]. Similarly, the Polyp Prevention Trial (PPT) on Dietary Intervention carried out to evaluate the effect of a high-fiber, high fruit and vegetables and low fat diet on recurrence of adenomatous polyps did not reveal any protective effect[20]. The PPT study failed to show any effect of a low fat, high fibre, high fruit and vegetables eating pattern on adenoma recurrence even with 8 years of follow-up, where as the high intake of fish was found to be associated with lower risk of adenoma recurrence[21]. The Health Professionals Follow-up study (data from 47 328 males' health professionals) is a prospectively investigated study to evaluate the association of fruit and vegetable consumption with the incidence of colon and rectal cancers in large cohort. The incidence of newly diagnosed cancer of the colon and rectum was confirmed by review of medical records and pathology reports while the diet was assessed using a detailed food frequency questionnaire (FFQ). This longitudinal study, with repeated diet assessment over time did not show any association between fruit and vegetable consumption and incidence of colon or rectal cancer[22]. However, it had also been indicated that assessment of diet might have been affected by measurement error and has to be kept in mind while interpreting the results.

Many studies have found a significant reduction in colon and rectal cancers with higher intakes of folic acid and their related nutrients (vitamin B-6, and B-12)[16]. Folate, a micro-nutrient highly abundant in fruits and vegetables, has gained a great deal of attention in the prevention of

colorectal cancer. In the Nurses Health Study, supplementation of folic acid, was found protective against colon cancer and became statistically significant after 15 years of use, suggesting that folate may act early in the carcinogenic process[23]. Calcium is hypothesized to prevent carcinogenesis in the colon by either binding bile acids and or fatty acids in the lumen or by having a direct inhibitory effect of the proliferation of the epithelial cells in the colon. The randomized controlled trial which assessed the efficacy of calcium supplementation on the risk of new colon adenoma formation amongst individuals with history of adenomas has revealed reduced incidence of adenomas apparent after just 1 year of supplementation[24].

A population based case-control study was conducted with 1993 incident colon cancer cases and 2410 controls to evaluate the association between colon cancer and dietary fat as well as specific dietary fatty acids[25]. The study revealed that neither total dietary fat nor specific fatty acids were associated with the risk of colon cancer. However, among older women, fats from food preparation were associated with risk of colon cancer. Women who consumed a diet high in mono-unsaturated fatty acids (MFAs) and poly-unsaturated fatty acids (PFAs) and who had a family history of colorectal cancer were at a greater risk of colon cancer than those with similar intakes but without a family history of colorectal cancer. Similar associations of colorectal cancer with family history were noted among men diagnosed at younger ages for MFA, linolenic acid and 20-carbon PFA.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been widely studied for a number of mechanisms through which these agents might prevent colon cancer. But the Women's Health Initiative randomized controlled trial, did not find any protective effect of low dose aspirin on the incidence of colorectal cancer[26]. However, the recent clinical guidelines prepared for US preventive services concludes that aspirin appears to be effective at reducing the incidence of colonic adenoma and colorectal cancer, especially if used in high doses for more than 10 years. Further, it has been stated that the possible harms of such practice require careful consideration. The analysis of data showed that regular use of aspirin reduced the incidence of colonic adenomas in randomized controlled trials (RR:0.82, 95%CI:0.7-.0.95) and case-control studies (RR:0.87, 95%CI:0.77-.0.98). In cohort studies, regular use of aspirin was associated with RR reductions of 22% for incidence of colorectal cancer[27].

Conclusions

Diet has the greatest impact on the development of human cancers. Within the broad category 'diet', the consumption of fruits and vegetables apparently plays a dominant role. However, the studies on Seventh Day Adventist suggest that early start of such dietary habit may be more important

Considerable efforts have been made to prove the preventive effect of different kinds of fruits and vegetables but randomized chemoprevention trials have failed to prove this presumed effectiveness of any single ingredient. Until the results of definitive studies of chemopreventive agents are available, the most effective ways of preventing colorectal cancer are consumption of diets high in vegetables and regular physical activity and low consumption of red and processed meat. Possible means of preventing this cancer are maintenance of body weight within recommended level throughout life, and consumption of diets high in non-starch polysaccharides, starch and carotenoids and low in sugar, fat and eggs. Overweight and obesity will keep increasing in the country due to increasing affluence of people. Preventing obesity and related chronic diseases should be a priority in various National Health Programmes. Fat intake, especially saturated fat, is increasing in the middle and upper income group population in India. Dietary modification programme for weight control has met with variable success in developed countries. Implementing such a programme in a country like India is a big challenge. Considerable effort has to be made to increase the public awareness and interests on health issues associated with obesity, its causes and management.

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This write-up has been contributed by Dr.N.S. Murthy, Professor & Research Coordinator, Dept. Community Medicine, MS Ramaiah Medical College & Teaching Hospital, Bangalore (Formerly Scientist F, Institute of Cytology and Preventive Oncology, Noida), Dr.Usha Agarwal, Assistant Director, Institute of Pathology, New Delhi, Dr. B.S. Nandakumar, Lecturer, Community Medicine, MS Ramaiah Medical College & Teaching Hospitals, Bangalore, Dr. S. Prutvish, Professor. and I/C Head, Dept. of Community Medicine, MS Ramaiah Medical College & Teaching Hospitals, Bangalore, and Dr. K. Chaudhary, Scientist F, ICMR Headquarters, New Delhi.

ICMR NEWS

The following meetings of various technical groups/ committees of ICMR were held:

Meeting of Scientific Advisory Group (SAG)

SAG of the Division of Non-Communicable Disease	July 28-29,2009 (at New Delhi)

Meetings of Task Forces (TFs)/Expert Groups (EGs) held at New Delhi

TF on Establishment and Characterization of Cell Line from Primary Breast Cancer	June 18, 2009
TF on Jai Vigyan Mission Mode Project on RF/RHD	June 23, 2009
TF on Asthma	July 20, 2009
EG on India Diabetes (INDIAB) Study	July 22, 2009
TF on Development of Biomarkers for Cardiovascular Disease	August 6, 2009
Advisory Committee to Look into Various Aspects of Bhopal Gas Disaster Victims	August 13, 2009

Meetings of Project Review Committees (PRCs):

PRC on Obesity and Metabolic Syndrome	June 15, 2009
PRC on Gastroenterology	June 15, 2009
PRC on Cardiovascular Diseases	June 19, 2009
PRC on Projects for North-East Region	June 22, 2009
PRC on Oncology	June 25, 2009
PRC on Neurology	July 10, 2009
PRC on Orthopaedics	July 27, 2009

Appointments

Dr. S.D. Kholkute took over as the Director of the Council's National Institute for Research in Reproductive Health, Mumbai w.e.f. forenoon of July 14, 2009.

Participation of ICMR Scientists in Scientific Events

Dr. Sunita Saxena, Director, Institute of Pathology (IOP), New Delhi, participated in I Symposium on HPV Vaccination in Asia-Pacific and Middle East Regions at Seoul (June 1-2, 2009).

Dr. J. Bhattacharya, Scientist D, National AIDS Research Institute (NARI), Pune, participated in the International Symposium on Neurovirology at Miami (June 2-6, 2009).

Dr. Suman Kanungo, , Scientist B, National Institute of Cholera and Enteric Diseases (NICED), Kolkata, and Dr. Provash C. Sadhukhan, Scientist D, ICMR Virus Unit, Kolkata, participated in the V PDVI Field Site Consortium Investigators Meeting at California (June 3-5, 2009).

Dr. S.K. Niyogi, Scientist E, NICED, Kolkata, participated in the meeting and discussion in connection with the Joint Collaborative Research Work on Development and Evaluation of Typhi Carrier DNA Kit for the Rapid Detection of *Salmonella typhi* at Kelantan, Malaysia (June 6-12, 2009).

Dr. M.M. Gore, Scientist F, National Institute of Virology (NIV), Pune, participated in the Bioregional Workshop on JE Prevention and Control at Bangkok (June 8-9, 2009).

Dr. Pradeep Das, Director and Dr. Vijay Kumar, Scientist C, Rajendra Memorial Research Institute of Medical Sciences (RMRIMS), Patna, participated in the Workshop on Kala-azar Control at Dhaka (June 8-10, 2009).

Dr. Narendra Kumar, Scientist E, RMRIMS, Patna, participated in the Data Analysis Meeting of Multi-centre Studies on Treatment Strategies of Kala-azar at Dhaka (June 10-12, 2009).

Dr. Deepak Modi, and Dr. Srabani Mukherjee, Scientists C, National Institute for Research in Reproductive Health (NIRRH), Mumbai, participated in the XII Annual Symposium of Frontiers in Reproduction – 2009 at Woods Hole (June 11-13, 2009).

Dr. Amit Pal, Scientist - D, NICED, Kolkata, participated in the Symposium on Bacterial Cell Biology and Pathogenesis at Umea, Sweden (June 14-18, 2009).

Dr. J.M. Deshpande, Director, Enterovirus Research Centre, Mumbai, participated in the XV Informal Consultation of WHO on the Global Polio Laboratory Network at Geneva (June 23-25, 2009).

Dr. A.C. Mishra, Director, NIV, Pune, participated in the Workshop on Asia Pacific Strategy for Strengthening Health Laboratory Services (2010-2015) at Bali (June 23-25, 2009).

Dr. Poonam Salotra, Scientist E, IOP, New Delhi, participated in the Meeting of the Steering Committee of RAPSODI Project at Madrid (June 24-26, 2009).

Dr. S.P. Tripathy, Scientist F, NARI, Pune, participated in the AIDS Clinical Trials Group Network Meeting at Washington D.C. (June 24-28, 2009).

Dr. G.B. Nair, Director, NICED, Kolkata, participated in the WHO meeting "To Lead the 2nd more broader consultation on the newly formed Cholera and Diarrhoeal Infections Network (CHOLDINet) to define the terms of reference for CHOLDINet and develop its plan of work" at Geneva (June 28-30, 2009).

Dr. K.D. Ramaiah, Scientist F, Vector Control Research Centre (VCRC), Pondicherry, participated in the Meeting on MDA Impact, Identifying Critical Research Questions on Stopping MDA and Post MDA Surveillance of Lymphatic Filariasis at Georgia (June 30 - July 2, 2009).

Dr. D.S. Dinesh, Scientist B, RMRIMS, Patna, participated in the VI Kalnet Consoritum Meeting at Geneva (July 9-10, 2009).

Dr. Y. Venkata Ramana, Scientist D, National Institute of Nutrition (NIN), Hyderabad, participated in the IV Asia Pacific Conference and VIII International Sports Science Conference at Kota Bharu, Malaysia (July 15-17, 2009).

Dr. Vrinda V. Khole, Scientist F and Dr. Geeta R. Vanage, Scientist E, NIRRH, Mumbai, participated in the XLII Annual Meeting of the Society for Study of Reproduction at Pittsburgh (July 18-22, 2009).

Dr. K.V.R. Reddy, Scientist C, NIRRH, Mumbai and Dr. C.P. Girish Kumar, Scientist C, National Institute of Epidemiology (NIE), Chennai, participated in the V International Conference on HIV Pathogenesis, Treatment and Prevention at Cape Town (July 19-22, 2009).

Dr. Neeta Mawar, Scientist F, NARI, Pune, participated in the International Union of Anthropological and Entomological Sciences Congress at Kunnings, China (July 27-31, 209).

Dr. R.M. Bhat, Scientist E, National Institute of Malaria Research (NIMR) Field Station, Raipur, participated in the WHO Pesticide Evaluation Scheme Committee Meeting at Geneva (July 28-30, 2009).

Dr. A.C. Mishra, Director, NIV, Pune and Dr. P. Vijayachari, Director, Regional Medical Research Centre (RMRC), Port Blair, participated in the WHO Regional Workshop on Networking of Laboratories for Emerging Infectious Diseases at Colombo (July 28-31, 2009).

Dr. Mausumi Bhardwaj, and Dr. A.C. Bharati, Scientists D, Institute of Cytology and Preventive Oncology (ICPO), NOIDA, participated in the HPV Labnet Workshop on HPV Genotyping and Serology at Bangkok (August 3-7, 2009).

Dr. V. Kumaraswami, Scientist F and Officer-in-charge, Tuberculosis Research Centre (TRC), Chennai, participated in the TB-HIV Working Group Meeting at Bali (August 8-9, 2009).

Dr. K. Narain, Scientist D and Dr. D. Rekha Devi, Scientist C, RMRC, Dibrugarh, participated in the XXII World

Association of the Advancement of Veterinary Parasitology Conference at Calgary, Canada (August 8-13, 2009).

Dr. A.C. Mishra, Director, and Dr. M.S. Chadha, Scientist E, NIV, Pune, participated in the III meeting of National Influenza Centres in the Western Pacific and South East Asia Region and International Symposium on Influenza Pandemic Response and Preparedness at Beijing (August 18-20 and 21-22, 2009 respectively). Dr. Chadha also participated in the CDC Influenza Burden of Disease Workshop and Vaccine Effectiveness Meeting at Bangkok (August 26-28, 2009).

Dr. N. Arunachalam, Scientist F, Centre for Research in Medical Entomology (CRME), Madurai, participated in the I Meeting of the WHO-TDR Disease Reference Group on Dengue and Other Viral Diseases of Major Public Health Importance at Havana (August 19-20, 2009).

Dr. B.K. Tyagi, Scientist F and Officer-in-charge, CRME, Madurai; Dr. S.L. Hoti, Scientist F, VCRC, Pondicherry and Dr. D.T. Mourya, Scientist F , NIV, Pune, participated in the Technical Consultative Meeting on Re-emergence of Chikungunya at Phuket (August 26-28, 2009).

Trainings/Workshops/Fellowships

Dr. V. Vijayalakshmi Venkateshan, Scientist D, NIN, Hyderabad availed Training on Lelca TCS SP5 Confocal Laser Scan Microscope Imaging System at Manheim, Germany (June 15-19, 2009).

Dr. M.B. Singh, Scientist E, Desert Medicine Research Centre, Jodhpur, availed WHO Fellowship for Training in Food Safety at Mahidol University, Institute of Nutrition, Bangkok (July 13-31, 2009).

Dr. Tarun Bhatnagar, Scientist C, NIE, Chennai, availed Training on Methods for Sic Estimation of Most-at-Risk Populations in Asia Pacific Region at Bangkok (July 14-17, 2009).

Dr. Kaushiki Kadam, Scientist C, NIRRH, Mumbai, participated in the Proteomics Workshop conducted by Cold Spring Harbor Laboratory at New York (July 17 - August 1, 2009).

Dr. P.S. Shah, Scientist C, NIV, Pune, availed Pandemic Influenza Diagnostic Training at National Public Health Laboratory, Kathmandu (August 3-9, 2009).

Dr. G.N. Sapkal, Scientist B, NIV, Pune, availed Training on Standard Protocols and Testing of PMS Samples Using PRNT Procedures at Mahidol University, Bangkok (August 16-30, 2009).

Dr. R.K. Nandy, Scientist C, NICED, Kolkata, availed Wet Lab Training at Cleveland (August 17-21, 2009).

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