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***Case Control Study***

**Risk factors for the development of colorectal carcinoma: A case control study from South India**

Iswarya S *et al*. Risk factors of colorectal carcinoma

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**AIM:** To study the association of colorectal carcinoma (CRC) with diet, smoking, alcohol, physical activity, body mass index, family history and diabetes.

**Methods:** All consecutive patients with CRC confirmed by histopathology diagnosis were included. Age (± 5 years) and gender matched controls were selected among the patients admitted in surgery ward for various conditions without any co-existing malignancy. Food Frequency Questionnaire (FFQ) was developed and validated after pretesting by investigator trained in data collection techniques. Cases and controls were interviewed ensuring privacy, in similar interview setting, with same duration of time for both cases and controls without any leading question. Biological variables like family history of CRC in first degree relatives, history of diabetes mellitus; behavioral factors like tobacco use both smoking and smokeless form, alcohol consumption and physical activity were recorded. Dietary details were recorded using a FFQ consisting 29 food items with seven categories. Analysis was done using appropriate statistical methods.

**Results:** Ninety-four histopathologically confirmed cases of CRC and equal number of age and gender matched controls treated over a period of two years were studied. Age distribution, mean age, male to female ratio, education level and socioeconomic status were similar in cases and controls. Intake of food items was categorized into tertile due to skewed distribution of subjects as per recommended cut off for consumption of food item. On univariate analysis red meat [OR = 7.4 (2.935-18.732)], egg [OR = 5.1 (2.26-11.36)], fish, fried food and oil consumption were found to be risk factors for CRC. On multivariate analysis red meat consumption of more than 2-3 times a month (OR = 5.4; 95%CI: 1.55-19.05) and egg consumption of more than 2-3 times a week (OR = 3.67; CI: 1.23-9.35) were found to be independent risk factors for the development of CRC.

**Conclusion:** Egg and red meat consumption found to be independent risk factors for CRC. Smoking, alcohol, physical activity and family history were not associated with increased risk.

**Key words:** Dietary factors; Smoking; Colorectal malignancy; Red meat; Rectal cancer

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**Core tip:** In this hospital based case control study, egg consumption of 2-3 times a week and red meat consumption of 2-3 times a month were found to be independent risk factors for the development of colorectal carcinoma. On the other hand smoking, alcohol, physical activity, diabetes and family history were not associated with an increased risk. There was no conclusive evidence to suggest that fruits and vegetable consumption has protective effect on colorectal carcinoma. Since red meat and egg had an increased risk, the community needs to be educated to reduce the consumption of red meat such as mutton and egg.

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**INTRODUCTION**

Colorectal cancer (CRC) is one amongst the leading cause of cancer related morbidity and mortality. CRC share 10% of the total cancers worldwide and accounts for 8% of all cancer related mortality; caused 608000 deaths worldwide[1-2]. In India data from population based cancer registry at Bangalore, Chennai and Delhi showed significantly increased incidence of CRC from 1982-2006[3].

Epidemiological studies have estimated that up to 70%-80% of CRCs could be ascribed to dietary, environmental and lifestyle factors; suggesting majority of the risk factors are modifiable[4]. It has been demonstrated that diet significantly influences the risk of developing CRC, and up to 70% reduction in the cancer burden can be achieved by changing the food habits[5]. Many Epidemiological studies across the globe have tried to evaluate the role of dietary and life style factors in the development of CRC, however a fair share of controversies exist among the observations[6]. Majority of the studies that investigated the role of high vegetable and fruit diet failed to prove any significant reduction in the incidence of CRC.

For a long time, it was believed that low meat intake and high fiber vegetarian diet by Indian population is the reason for the low incidence of CRC in India. It was found that only two studies have been reported in literature from India regarding factors associated with CRC[7,8]. Identifying the factors associated with decreased CRC incidence among Indian population may help in the prevention of CRC. Hence an attempt was made to study these factors through a case control study. The objective of the study was to find the association of CRC with life style variables (diet, smoking, alcohol, physical activity) and Biological Variables [body mass index (BMI), family history of CRC in 1st -degree relatives, history of diabetes mellitus].

**Materials and methods**

The study was conducted in Department of Preventive and Social Medicine in collaboration with department of Surgery in a tertiary care referral and research institute of India. This study was conducted from period of two years. This study was approved by the institute Ethics Committee. The nature, methodology of the study was explained to the patient and informed consent was obtained. All the information collected was kept confidential and patient was given full freedom to withdraw from the study at any point during the study. All provisions of the Declaration of Helsinki were followed in this study.

All consecutive patients with confirmed histopathology diagnosis were included. Histopathology was done either pre-operatively or postoperatively. Diagnosis of CRC was confirmed by per-rectal sigmoidoscopic or endoscopic biopsy. In case where resection for colorectal malignancy was done as an emergency surgical procedure, the diagnosis was confirmed post operatively. CRC patients with co-existing malignancy were excluded. Age (± 5 years) and gender matched controls were selected among the patients admitted in Surgery ward for various conditions like inguinal hernia, varicose veins, necrotizing fasciitis and diabetic foot.

Patients with co-existing malignancies, familial adenomatous polyposis and patients admitted with any abdominal disorders were excluded from the study. Controls were selected within one week after selecting the case. When more than one control was eligible then control was selected by simple random methods using lots. During initial phase of the study, food frequency questionnaire (FFQ) was developed and face validation was carried out by circulating among the faculty who were involved in the study. Pre-testing was done among 10 patients admitted in the surgery ward by investigator trained in data collection techniques. It helped to estimate the average time taken for questionnaire administration, examination and to check for comprehensibility of participants to the questions.

After pre-testing of questionnaire necessary modifications were carried out. After obtaining informed consent cases and controls were interviewed ensuring privacy, in similar interview setting, with same duration of time for both cases and controls without any leading question. Average time taken for each interview was around 45 min. Anthropometric measurements was taken at the end of the interview. Pre-tested questionnaire which elicited information on demographic parameters like name, age, gender; Social variables like education, occupation, income, presenting complaints; biological variables like family history of CRC in first degree relatives, history of diabetes mellitus; behavioral factors like tobacco use both smoking and smokeless form, alcohol consumption and physical activity.

The alcohol consumption among study participants was measured and classified as per the WHO STEPwise approach to surveillance of non-communicable diseases. The STEPS questionnaires used for the study are available in the internet from: http://www.who.int/ncd\_surviellance/en/steps\_framework­\_dec03.pdf. The alcohol consumption pattern of drinkers (amount, type and frequency) was noted and converted in terms of average alcohol consumed in grams per day. These were further classified as abstainers (who never consumed alcohol in past 12 mo), grade I (< 39.9 g/d), grade 2 (40-59.9 g/d) and grade 3 (> 60 g/d). The physical activity was measured using international physical activity questionnaire- short version. Metabolic equivalent (MET) levels for walking, moderate and vigorous intensity activities were taken as 3.3, 4.0 and 8.0. The activities were measured separately (MET level × minutes of activity/d × days per week) and expressed as total MET min/wk. Based on the total scores, study participants were categorized in to low (< 600 MET min/wk), moderate (600-3000 MET min/wk) and high (> 3000 MET min/wk) level of physical activity.

Dietary details were recorded using a FFQ consisting 29 food items with seven categories (never or hardly ever, once a month, 2-3 times a month, once a week, 2-3 times a week, 4-6 times a week, once a day or more) for egg, chicken, mutton, beef, pork, fruits, vegetables, fried foods, type of oil, type of food, tea, coffee; Anthropometric measurements including weight, height, , hip circumference, waist circumference also were recorded.

Sample size was calculated using n Master software 2.0 for matched case control study , taking exposure in controls for non-vegetarian food as 58% and OR 3.38 at 95%CI, 80% power the minimum sample size was 93[9].

Analysis was done using SPSS version 20[10]. Socio-demographic details and frequency of food intake were expressed in proportions. Univariate analysis for categorical variables (diet, smoking, alcohol, physical activity, BMI, history of diabetes, family history) were done using *χ2* test. Seven frequencies of food item intake were categorized into tertile. Tertile1 corresponds to lowest frequency of intake and tertile 3 corresponds to highest frequency of intake. Odds ratio was calculated for highest tertile of intake relative to lowest tertile by logistic regression. Factors having *p* value < 0.05 in univariate analysis were included as parameter for multivariate analysis using logistic regression. Results of multivariate analysis were given as Odds ratio with 95%CI. All *p* values were two tailed and significant when values were less than 0.05.

**RESULTS**

A total of 94 cases and controls were included in the study. The mean age group of cases and controls were 54.1 ± 11.5 years and 55 ± 11.8 years respectively. Age distribution of cases and controls were in the range of 17-78 years. There was almost equal distribution of males and females 48.9% and 51.1% respectively among the study subjects (Table 1). Around 39.4% cases and 35.1% of controls never attended school. In both cases and controls more than 50% of them belonged to class v socio economic status.

The distribution of subjects as per recommended cut off for consumption of food item was much skewed as shown in (Table 2). Among cases 22.3% consumed egg 2-3 times a week compared to only 8.5% among the controls. In cases about one-fourth 24.5% never or hardly ever consumed mutton compared to 46.8% in controls. Beef consumption was reported to be low among both cases and controls, 72.3% of cases and 86.2% of controls never or hardly ever consumed beef. Similarly more than 80% of cases and controls never or hardly ever consumed pork. Majority of cases 78.7% and controls 89.4% consumed vegetables once a day.

As distribution of subjects as per recommended cut off for consumption of food item was much skewed, intake of food items was categorized into tertile. The frequency cut-off into tertile is not same for all the food items. For certain food items (beef, pork, vegetables, tea, coffee) ranking into tertile was not possible due to its skewed distribution. Univariate logistic regression analysis was done considering these tertile groups as shown in (Table 3). It was observed that consumption of egg for more than 2-3 times a week increases the risk of getting CRC by five times [OR = 5.1 (2.26-11.36)] compared to those who never or hardly consume egg. Mutton consumption of more than 2-3 times a month increases the risk of CRC by 7 times [OR = 7.4 (2.935-18.732)] compared to those never or hardly consumes mutton. Consuming fish and fried foods more than 2-3 times a month increases the risk for CRC. Coffee consumption was not significantly associated with CRC [OR = 1.95 (0.76- 5.43)]. Similarly Tea consumption also did not show any significant association with CRC in the present study [OR = 0.49 (0.22-1.70)].

Compared to never smokers, subjects who smoked < 10 pack years, 10-20 pack years and > 20 pack years were not at increased risk for CRC. Alcohol consumption of < 39.9 g/d, 40-59.9 g/d and > 60 g/d was not associated with increased risk for CRC compared to non-users. High (3000 METs/wk) and moderate (600-3000 METs/wk) level of physical activity was not protective for CRC. BMI greater than 25 is not associated with CRC risk. History of diabetes was not significantly associated with CRC risk (Table 4). Multivariate logistic regression results (Table 5) for those factors found to be statistically significant in univariate analysis (mutton, egg, fish, fried foods and type of oil) showed egg and mutton as independent risk factor.

**DISCUSSION**

Though population based cancer registries showed a statistically significant increase in the incidence of CRC in India from 1982-2006, very few studies have been done in India to document the association of modifiable risk factors with CRC. The present study attempted to identify the modifiable risk factors so that appropriate preventive measures can be planned. Red meat consumption more than 2-3 times a month found to be an independent risk factor in multivariate regression analysis and increased the odds of developing CRC by 5.41 (1.55-19.05) times compared to those never or hardly consume. This was similar to study by Nayak *et al*[7] which reported beef consumption more than once a week has increased risk compared to those who do not consume beef [OR = 4.25 (2.02-8.94)]. A study from Uruguay[9] reported a positive association between CRC and high intake of red meat with OR = 3.38 (2.37-6.20). Similarly Singh *et al*[11] reported red meat intake more than once a week increased the risk compared to non-consumers [RR = 1.90 (1.16-3.11)].

In the western studies red meat consumption included beef, pork and mutton. However, in present study population due to cultural practices and beliefs beef and pork consumption were minimal. Subjects who consumed egg more than 2-3 times a week had 3.6 (1.23-9.35) times higher risk compared to those who never or hardly ever consume egg. This was similar to the study[12] which reported consumption of egg more than 2-3 times/wk is associated with increased risk of CRC compared to those who never or hardly consume egg [OR = 2.95 (1.75-5)]. In the present study fish consumption more than 2-3 times a month is associated with increased risk for CRC in univariate analysis. In contrast Nayak *et al*[7] from Kerala showed 20% decreased risk of CRC with consumption of fish with every meal [OR = 0.32 (0.13-0.98)]. European study reported fish consumption more than 80 g/d was inversely associated with CRC compared to those consuming < 10 g/d [OR = 0.69 (0.54-0.88)][13]. Discrepancy between present study finding and other studies could be due to difference in type of fish consumed, amount of fish consumed, method of cooking and method of preservation.

Fruits and vegetable consumption was not found to be protective for CRC, similar to the findings reported in studies from western countries[14-16]. Frequent intake of fried food a proxy variable for high fat intake was associated with CRC [OR = 2.52 (1.35-4.70)] in univariate analysis but it was not an independent risk factor. In contrast studies reported consuming deep fried foods more than once a month was not associated with increased risk[17,18]. Coffee consumption was not significantly associated with CRC [OR = 1.95 (0.76-5.43)]. A meta-analysis by Je *et al*[19] in 2008 showed no significant association between coffee consumption and colorectal cancer [RR = 0.91 (0.81-1.02)], nevertheless; studies have also shown protective effect of coffee in the development of CRC. Kato *et al*[20] in Japan found daily coffee consumption had protective effect on both colon and rectal carcinoma compared with the non drinkers with RR = 0.43 (0.25-0.73) and RR = 0.53 (0.27-1.03), respectively. Reasons for varying results across studies are due to difference in type of coffee, serving size, brewing method and also cutoffs for high and low exposure categories varies between studies. Tea consumption did not show any significant association with CRC in the present study [OR = 0.49 (0.22-1.70)]. Similar findings were found by Nayak *et al*[7] where highest quartile of tea consumption has not shown any risk difference compared to lowest quartile with OR = 1.03 (0.62-1.71). In 2005, Michels *et al*[14] from United States reported that tea consumption of more than 5 cups per day was not significantly associated with CRC [HR = 1.01 (0.83-1.22).

Smoking and alcohol use was not associated with CRC in contrast to increased risk reported in few studies[21-25]. As smoking and alcohol were considered as undesirable behavior in community people tend to under report the use due to social desirability bias[26]. This could be the reason for no association in the present study. High level of physical activity was not associated with decreased risk for CRC compared to low level of physical activity as reported in other studies[27,28]. BMI was not significantly associated with CRC; in contrast studies reported high BMI increased risk for CRC[29,30]. This could be due to underlying limitation of hospital based case-control study, where cases are ill and admitted to the hospital in late stage of disease. By the time patients seek medical attention they would have lost considerable amount of weight. The weight recorded at the time of admission may not find the true association.

Selection of appropriate controls is crucial to establish the true association between exposure (diet, smoking, alcohol, physical activity) and outcome (CRC). Selection of controls remains a major concern when designing a case-control study due to the issues involved in the internal validity and cost. Scientifically there is scope for introducing bias (selection bias and information bias) while selecting hospital based controls[31]. However there is several advantage of selecting hospital controls such as feasibility, cost, travel time and better recall among hospital controls. Validation studies conducted by Li *et al*[32], Gonzalez *et al*[33], Inoue *et al*[34] showed that hospital based controls elicit similar information to community controls in assessment of dietary risk factors. Hospital controls are preferred in a hospital based case-control study in view of the issues of practicability. It also reduces the cost involved in the travel and decreases the time taken for face-to-face interviews at field. It has also been demonstrated that the capacity to recall and report the exposures are better in those who are actively seeking health care advise than the members randomly selected from the population[35].

Since it measures long term, average and habitual dietary intake; FFQ as a mean of dietary assessment have been found appropriate in many nutritional and epidemiological studies[36]. FFQ captures pattern of food consumption over a period of time ranging from months to years. Pandey *et al*[37] from India reported FFQ had good correlation (0.8) with 5 d diet record and was reproducible. The quantity of food consumed is considered an important factor in estimating the dietary intake of an individual; however, the frequency rather than the serving size has been found to be a better contributor to the variance in the intake of most foods.

Primary limitation of the study was dietary items were not quantified. Though efforts were taken to minimize the recall bias, change in dietary pattern of cases after development of symptoms might have led to biased reporting of their diet.

In conclusion, this hospital based case control study showed egg consumption of 2-3 times a week and mutton consumption 2-3 times a month as independent risk factor. On other hand smoking, alcohol, physical activity, history of diabetes and family history were not associated with increased risk for CRC and no conclusive evidence to suggest fruits and vegetable consumption as protective factor. Cohort study is required to assess the risk associated with commonly consumed dietary items in a given population.

As it was found that persons consuming red meat (mutton) had an increased risk of developing CRC (OR = 5.4), the community needs to be educated to reduce the consumption of red meat such as mutton, so that they can minimize their risk for developing CRC. Similarly, egg consumption was found to increase the odds of developing CRC (OR = 3.6), people especially adults need to be advised to reduce the egg consumption.

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**COMMENTS**

***Background***

Epidemiological studies have shown that significant proportion of colorectal cancer (CRC) incidence could be ascribed to dietary, environmental and lifestyle factors; suggesting majority of the risk factors are modifiable. Regional variation in the dietary and social habit could play a vital role in the causation of CRC and may be responsible for the geographical variations in the occurrence of CRC.

***Research frontiers***

For a long time, it was believed that low meat intake and high fiber vegetarian diet by Indian population is the reason for the low incidence of CRC in India. Only two studies have been reported in literature from India regarding factors associated with CRC and more research studies are require to evaluate or to confirm the risk factors. Identifying the factors associated with decreased CRC incidence among Indian population may help in the primary prevention of CRC across the globe.

***Innovations and breakthrough***

This study found that red meat consumption of more than 2-3 times a month egg consumption of more than 2-3 times a week are independent risk factors for the development of CRC. Contrary to common belief the study showed no association between CRC and smoking, alcohol consumption, physical activity, body mass index or diabetes. Consumption of coffee or tea were also not associated with CRC

***Applications***

As it was found that persons consuming red meat (mutton) had an increased risk of developing CRC (OR = 5.4), the community needs to be educated to reduce the consumption of red meat such as mutton, so that they can minimize their risk for developing CRC. Similarly, egg consumption was found to increase the odds of developing CRC (OR = 3.6), people especially adults need to be advised to reduce the egg consumption.

***Peer-review***

This is a good case control study taken a very relevant and significant problem to be studied. The article evaluated important life style and dietary factors for the possible relationship with colorectal cancer in South Indian population. The study showed significant association between red meat and egg consumption and certainly gives better insight and understandings about the other risk factors including smoking, alcohol consumption, body mass index, diabetes and physical activity *etc*.

**References**

1 **Ferlay J**, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; **127**: 2893-2917 [PMID: 21351269 DOI: 10.1002/ijc.25516]

2 **Jemal A**, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2010; **61**: 69-90 [PMID: 21296855 DOI: 10.3322/caac.20107]

3 **Swaminathan R**, Shanta V, Ferlay J, Balasubramanian S, Bray F, Sankaranarayanan R. Trends in cancer incidence in Chennai city (1982-2006) and statewide predictions of future burden in Tamil Nadu (2007-16). *Natl Med J India* 2011; **24**: 72-77 [PMID: 21668047]

4 **Franco A**, Sikalidis AK, SolísHerruzo JA. Colorectal cancer: influence of diet and lifestyle factors. *Rev EspEnferm Dig* 2005; **97**: 432-448 [PMID: 16011418DOI: 10.4321/S1130-01082005000600006]

5 **Willett WC**. Diet and cancer: an evolving picture. *JAMA* 2005; **293**: 233-234 [PMID: 15644551 DOI: 10.1001/jama.293.2.233]

6 **Mohandas KM**. Colorectal cancer in India: controversies, enigmas and primary prevention. *Indian J Gastroenterol* 2011; **30**: 3-6 [PMID: 21222189 DOI: 10.1007/s12664-010-0076-2]

7 **Nayak SP**, Sasi MP, Sreejayan MP, Mandal S.A case-control study of roles of diet in colorectal carcinoma in a South Indian Population. *Asian Pac J Cancer Prev* 2009; **10**: 565-568 [PMID: 19827870]

8 **Ganesh B**, Talole SD, Dikshit R.A case-control study on diet and colorectal cancer from Mumbai, India. *Cancer Epidemiol*2009;**33**: 189-193 [PMID: 19717354 DOI: 10.1016/j.canep.2009.07.009]

9 **Aune D**, De Stefani E, Ronco A, Boffetta P, Deneo-Pellegrini H, Acosta G, Mendilaharsu M. Meat consumption and cancer risk: a case-control study in Uruguay. *Asian Pac J Cancer Prev*2009; **10**: 429-436 [PMID: 19640186]

10 **IBM Corp.** Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.

11 **Singh PN**, Fraser GE.Dietary risk factors for colon cancer in a low-risk population. *Am J Epidemiol* 1998; **148**: 761-774 [PMID: 9786231 DOI: 10.1093/oxfordjournals.aje.a009697]

12 **SoleraAlbero J**, TárragaLópez PJ, CarbayoHerencia JA, López Cara MA, Celada Rodríguez A, Cerdán Oliver M, OcañaLópez JM. [Influence of diet and lifestyle in colorectal cancer]. *Rev EspEnferm Dig* 2007; **99**: 190-200 [PMID: 17590100]

13 **Norat T**, Bingham S, Ferrari P, Slimani N, Jenab M, Mazuir M, Overvad K, Olsen A, Tjønneland A, Clavel F, Boutron-Ruault MC, Kesse E, Boeing H, Bergmann MM, Nieters A, Linseisen J, Trichopoulou A, Trichopoulos D, Tountas Y, Berrino F, Palli D, Panico S, Tumino R, Vineis P, Bueno-de-Mesquita HB, Peeters PH, Engeset D, Lund E, Skeie G, Ardanaz E, González C, Navarro C, Quirós JR, Sanchez MJ, Berglund G, Mattisson I, Hallmans G, Palmqvist R, Day NE, Khaw KT, Key TJ, San Joaquin M, Hémon B, Saracci R, Kaaks R, Riboli E. Meat, fish, and colorectal cancer risk: the European Prospective Investigation into cancer and nutrition. *J Natl Cancer Inst* 2005; **97**: 906-916 [PMID: 15956652 DOI: 10.1093/jnci/dji164]

14 **Michels KB**, Edward Giovannucci KJ, Rosner BA, Stampfer MJ, Fuchs CS, Colditz GA, Speizer FE, Willett WC. Prospective study of fruit and vegetable consumption and incidence of colon and rectal cancers. *J Natl Cancer Inst* 2000; **92**: 1740-1752 [PMID: 11058617 DOI: 10.1093/jnci/92.21.1740]

15 **van Duijnhoven FJ**, Bueno-De-Mesquita HB, Ferrari P, Jenab M, Boshuizen HC, Ros MM, Casagrande C, Tjønneland A, Olsen A, Overvad K, Thorlacius-Ussing O, Clavel-Chapelon F, Boutron-Ruault MC, Morois S, Kaaks R, Linseisen J, Boeing H, Nöthlings U, Trichopoulou A, Trichopoulos D, Misirli G, Palli D, Sieri S, Panico S, Tumino R, Vineis P, Peeters PH, van Gils CH, Ocké MC, Lund E, Engeset D, Skeie G, Suárez LR, González CA, Sánchez MJ, Dorronsoro M, Navarro C, Barricarte A, Berglund G, Manjer J, Hallmans G, Palmqvist R, Bingham SA, Khaw KT, Key TJ, Allen NE, Boffetta P, Slimani N, Rinaldi S, Gallo V, Norat T, Riboli E. Fruit, vegetables, and colorectal cancer risk: the European Prospective Investigation into Cancer and Nutrition.*Am J ClinNutr*2009;**89**: 1441-1452 [PMID: 19339391 DOI: 10.3945/ajcn.2008.27120]

16 **Koushik A**, Hunter DJ, Spiegelman D, Beeson WL, van den Brandt PA, Buring JE, Calle EE, Cho E, Fraser GE, Freudenheim JL, Fuchs CS, Giovannucci EL, Goldbohm RA, Harnack L, Jacobs DR, Kato I, Krogh V, Larsson SC, Leitzmann MF, Marshall JR, McCullough ML, Miller AB, Pietinen P, Rohan TE, Schatzkin A, Sieri S, Virtanen MJ, Wolk A, Zeleniuch-Jacquotte A, Zhang SM, Smith-Warner SA. Fruits, vegetables, and colon cancer risk in a pooled analysis of 14 cohort studies. *J Natl Cancer Inst* 2007; **99**: 1471-1483 [PMID: 17895473 DOI: 10.1093/jnci/djm155]

17 **Lee SA**, Shu XO, Yang G, Li H, Gao YT, Zheng W. Animal origin foods and colorectal cancer risk: a report from the Shanghai Women's Health Study.*Nutr Cancer*2009;**61**: 194-205 [PMID: 19235035 DOI: 10.1080/01635580802419780]

18 **Galeone C**, Talamini R, Levi F, Pelucchi C, Negri E, Giacosa A, Montella M, Franceschi S, La Vecchia C. Fried foods, olive oil and colorectal cancer. *Ann Oncol* 2007; **18**: 36-39 [PMID: 17018706 DOI: 10.1093/annonc/mdl328]

19 **Je Y**, Liu W, Giovannucci E. Coffee consumption and risk of colorectal cancer: a systematic review and meta-analysis of prospective cohort studies.*Int J Cancer*2009; **124**: 1662-1668 [PMID: 19115212 DOI: 10.1002/ijc.24124]

20 **Kato I**, Tominaga S, Matsuura A, Yoshii Y, Shirai M, Kobayashi S. A comparative case-control study of colorectal cancer and adenoma. *Jpn J Cancer Res*1990;**81**: 1101-1108 [PMID: 2125036 DOI: 10.1111/j.1349-7006.1990.tb02520.x]

21 **Lüchtenborg M**, White KK, Wilkens L, Kolonel LN, Le Marchand L. Smoking and colorectal cancer: different effects by type of cigarettes? *Cancer Epidemiol Biomarkers Prev* 2007; **16**: 1341-1347 [PMID: 17626999 DOI: 10.1158/1055-9965.EPI-06-0519]

22 **Gram IT**, Braaten T, Lund E, Le Marchand L, Weiderpass E. Cigarette smoking and risk of colorectal cancer among Norwegian women. *Cancer Causes Control*2009;**20**: 895-903 [PMID: 19274482 DOI: 10.1007/s10552-009-9327-x]

23 **Nisa H**, Kono S, Yin G, Toyomura K, Nagano J, Mibu R, Tanaka M, Kakeji Y, Maehara Y, Okamura T, Ikejiri K, Futami K, Maekawa T, Yasunami Y, Takenaka K, Ichimiya H, Terasaka R. Cigarette smoking, genetic polymorphisms and colorectal cancer risk: the Fukuoka Colorectal Cancer Study.*BMC Cancer*2010;**10**: 274 [PMID: 20534171 DOI: 10.1186/1471-2407-10-274]

24 **Fedirko V**, Tramacere I, Bagnardi V, Rota M, Scotti L, Islami F, Negri E, Straif K, Romieu I, La Vecchia C, Boffetta P, Jenab M. Alcohol drinking and colorectal cancer risk: an overall and dose-response meta-analysis of published studies. *Ann Oncol* 2011; **22**: 1958-1972 [PMID: 21307158 DOI: 10.1093/annonc/mdq653]

25 **Cho E**, Smith-Warner SA, Ritz J, van den Brandt PA, Colditz GA, Folsom AR, Freudenheim JL, Giovannucci E, Goldbohm RA, Graham S, Holmberg L, Kim DH, Malila N, Miller AB, Pietinen P, Rohan TE, Sellers TA, Speizer FE, Willett WC, Wolk A, Hunter DJ. Alcohol intake and colorectal cancer: a pooled analysis of 8 cohort studies. *Ann Intern Med* 2004; **140**: 603-613 [PMID: 15096331 DOI: 10.7326/0003-4819-140-8-200404200-00007]

26 **Davis CG**, Thake J, Vilhena N. Social desirability biases in self-reported alcohol consumption and harms. *Addict Behav* 2010; **35**: 302-311 [PMID: 19932936 DOI: 10.1016/j.addbeh.2009.11.001]

27 **Satia-Abouta J**, Galanko JA, Potter JD, Ammerman A, Martin CF, Sandler RS. Associations of total energy and macronutrients with colon cancer risk in African Americans and Whites: results from the North Carolina colon cancer study.*Am J Epidemiol*2003;**158**: 951-962 [PMID: 14607803 DOI: 10.1093/aje/kwg248]

28 **Arafa MA**, Waly MI, Jriesat S, Al Khafajei A, Sallam S. Dietary and lifestyle characteristics of colorectal cancer in Jordan: a case-control study. *Asian Pac J Cancer Prev* 2011; **12**: 1931-1936 [PMID: 22292627]

29 **Adams KF**, Leitzmann MF, Albanes D, Kipnis V, Mouw T, Hollenbeck A, Schatzkin A. Body mass and colorectal cancer risk in the NIH-AARP cohort.*Am J Epidemiol* 2007; **166**: 36-45 [PMID: 17449892 DOI: 10.1093/aje/kwm049]

30 **Matsuo K**, Mizoue T, Tanaka K, Tsuji I, Sugawara Y, Sasazuki S, Nagata C, Tamakoshi A, Wakai K, Inoue M, Tsugane S. Association between body mass index and the colorectal cancer risk in Japan: pooled analysis of population-based cohort studies in Japan. *Ann Oncol* 2012; **23**: 479-490 [PMID: 21597097 DOI: 10.1093/annonc/mdr143]

31 **Grimes DA**, Schulz KF. Compared to what? Finding controls for case-control studies. *Lancet* 2005; **365**: 1429-1433 [PMID: 15836892 DOI: 10.1016/S0140-6736(05)66379-9]

32 **Li L**, Zhang M, Holman CD. Hospital outpatients are satisfactory for case-control studies on cancer and diet in China: a comparison of population versus hospital controls. *Asian Pac J Cancer Prev* 2013; **14**: 2723-2729 [PMID: 23803022 DOI: 10.7314/APJCP.2013.14.5.2723]

33 **González CA**, Torrent M, Agudo A, Riboli E. Hospital versus neighbourhood controls in the assessment of dietary risk factors. *Int J Epidemiol*1990; **19**: 354-361 [PMID: 2376447 DOI: 10.1093/ije/19.2.354]

34 **Inoue M**, Tajima K, Hirose K, Hamajima N, Takezaki T, Kuroishi T, Tominaga S. Epidemiological features of first-visit outpatients in Japan: comparison with general population and variation by sex, age, and season. *J ClinEpidemiol*1997;**50**: 69-77 [PMID: 9048692 DOI: 10.1016/S0895-4356(96)00297-1]

35 **Schulz KF**, Grimes DA. Case-control studies: research in reverse.*Lancet*2002; **359**:431-434 [PMID: 11844534 DOI: 10.1016/S0140-6736(02)07605-5]

36**Willett W.** Nutritional epidemiology New York, NY Oxford University Press; 1998

37 **Pandey D**, Bhatia V, Boddula R, Singh HK, Bhatia E. Validation and reproducibility of a food frequency questionnaire to assess energy and fat intake in affluent north Indians. *Natl Med J India* 2005; **18**: 230-235 [PMID: 16433134]

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**Table 1 Socio demographic details of study population *n* (%)**

|  |  |  |
| --- | --- | --- |
| **Variable** | **Cases** | **Controls** |
| Age (yr) |  |  |
| < 40 | 9 (9.6) | 7 (7.4) |
| 40-49 | 21 (22.3) | 18 (19.1) |
| 50-59 | 28 (29.8) | 29 (30.9) |
| 60-69 | 30 (31.9) | 32 (34) |
| ≥ 70 | 6 (6.4) | 8 (8.5) |
| Educational status |  |  |
| Never attended school | 37 (39.4) | 33 (35.1) |
| 1-4 | 23 (24.5) | 34 (36.2) |
| 5-7 | 15 (16) | 10 (10.6) |
| 8-10 | 14 (14.9) | 9 (9.6) |
| 11-12 | 1 (1.1) | 6 (6.4) |
| Graduation | 4 (4.3) | 2 (2.1) |
| Occupation |  |  |
| Non worker | 23 (24.5) | 19 (20.2) |
| Skill I | 44 (46.8) | 59 (62.8) |
| Skill II | 25 (26.6) | 16 (17) |
| Skill III | 2 (2.1) | 0 |
| PCI in Indian Rupees/mo |  |  |
| Class I > 4400 | 1 (1.1) | 0 |
| Class II 2200-4399 | 1 (1.1) | 2 (2.1) |
| Class III 1320-2199 | 5 (5.3) | 6 (6.4) |
| Class IV 660-1319 | 34 (36.2) | 38 (40.4) |
| Class V <660 | 53 (56.4) | 48 (51.1) |

PCI: Per Capita Income (after adjusting for Consumer Price Index of 2011).

**Table 2 Frequency of food intake among cases and controls *n* (%)**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Food item** | | **Never or hardly**  **ever** | **Once a mo** | **2-3 times/mo** | **Once a wk** | **2-3 times/ wk** | **4-6 times/wk** | **Once a day** | **Total** |
| Egg | Case | 7 (7.4) | 17 (18.1) | 6 (6.4) | 28 (29.8) | 21 (22.3) | 7 (7.4) | 8 (8.5) | 94 |
| control | 8 (8.5) | 36 (38.3) | 10 (10.6) | 27 (28.7) | 8 (8.5) | - | 5 (5.3) | 94 |
| Chicken | Case | 13 (13.8) | 31 (33) | 9 (9.6) | 36 (38.3) | 5 (5.3) | - | - | 94 |
| Control | 12 (12.8) | 45 (47.9) | 14 (14.9) | 19 (20.2) | 4 (4.3) | - | - | 94 |
| Mutton | Case | 23 (24.5) | 40 (42.6) | 4 (4.3) | 25 (26.6) | 1 (1.1) | 1 (1.1) | - | 94 |
| Control | 44 (46.8) | 42 (44.7) | 3 (3.2) | 4 (4.3) | 1 (1.1) | - | - | 94 |
| Fish | Case | 26 (27.7) | 49(52.1) | 2 (2.1) | 6 (6.4) | 10 (10.6) | 1 (1.1) | - | 94 |
| Control | 27 (28.7) | 61 (64.9) | 1 (1.1) | 2 (2.1) | 1 (1.1) | 2 (2.1) | - | 94 |
| Beef | Case | 68 (72.3) | 1 (1.1) | 1 (1.1) | 18 (19.1) | 6 (6.4) | - | - | 94 |
| Control | 81 (86.2) | 6 (6.4) | - | 7 (7.4) | - | - | - | 94 |
| Pork | Case | 81 (86.2) | 9 (9.6) | 1 (1.1) | 2 (2.1) | 1 (1.1) | - | - | 94 |
| Control | 87 (92.6) | 5 (5.3) | - | 2 (2.1) | - | - | - | 94 |
| Fried foods | Case | 3 (3.2) | 32 (34.0) | 6 (6.4) | 3 5 (37.2) | 18 (19.1) | - | - | 94 |
| Control | 5 (5.3) | 45 (47.9) | 14 (14.9) | 28 (29.8) | 2 (2.1) | - | - | 94 |
| Fruits | Case | 32 (34.0) | 37 (39.4) | 7 (7.4) | 6 (6.4) | 5 (5.3) | 3 (3.2) | 4 (4.3) | 94 |
| Control | 36 (38.3) | 23 (24.5) | 14 (14.9) | 13 (13.8) | 3 (3.2) | - | 5 (5.3) | 94 |
| Vegetables | Case | - | - | - | - | 13 (13.8) | 7 (7.4) | 74 (78.7) | 94 |
| Control | - | - | - | - | 2 (2.1) | 8 (8.5) | 84 (89.4) | 94 |
| Coffee | Case | 81 (86.2) |  | - | - | - | - | 13 (13.8) | 94 |
|  | Control | 87 (92.6) | - | - | - | - | - | 7 (7.4%) | 94 |
| Tea | Case | 20 (21.2) |  | - | - | - | - | 74 (78.7) | 94 |
|  | Control | 11 (11.7) | - | - | - | - | - | 83 (88.3) | 94 |

**Table 3 Colorectal carcinoma risk associated with individual dietary item**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Food item** | | | **Adjusted OR (CI)** | ***p* value** |
| Egg | Tertile 1 | Never or hardly ever | 1 |  |
| Tertile 2 | Once a month | 1.6 (0.85-3.33) | 0.133 |
| Tertile 3 | > 2-3 times a week | 5.1 (2.26-11.36) | 0.001 |
| Chicken | Tertile 1 | Never or hardly ever | 1 |  |
| Tertile 2 | Once a month | 0.6 (0.25-1.51) | 0.297 |
| Tertile 3 | Once a week | 1.6 (0.64-4.19) | 0.297 |
| Mutton | Tertile 1 | Never or hardly ever | 1 |  |
| Tertile 2 | Once a month | 1.8 (0.93-3.45) | 0.070 |
| Tertile 3 | More than 2-3 times a month | 7.4 (2.93-3.45) | 0.001 |
| Fish | Tertile 1 | Never or hardly ever | 1 |  |
| Tertile 2 | Once a month | 0.8 (0.44-1.60) | 0.588 |
| Tertile 3 | More than 2-3 times a month | 3.2 (1.13-9.53) | 0.028 |
| Beef | Tertile 1 | - | - | - |
| Tertile 2 | Never or hardly ever | 1 |  |
| Tertile 3 | More than once a month | 2.3 (0.13-4.99) | 0.237 |
| Fruits | Tertile 1 | Never or hardly ever | 1 |  |
| Tertile 2 | Once a month | 1.8 (0.89-3.64) | 0.099 |
| Tertile 3 | More than 2-3 times a month | 0.8 (0.39-1.68) | 0.540 |
| Vegetables | Tertile 1 | 2-3 times a week | 1 |  |
| Tertile 2 | Once a day | 0.4 (0.19-1.00) | 0.050 |
| Tertile 3 | - | - | - |
| Fried foods | Tertile 1 | Never or hardly ever | 1 |  |
| Tertile 2 | Once a month | 0.61 (0.21-1.74) | 0.350 |
| Tertile 3 | 2-3 times a month | 2.52(1.35-4.70) | 0.004 |

OR: Odds ratio.

**Table 4 Association of variables with colorectal carcinoma *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Cases** | **Controls** | **OR (CI)** |
| Type of oil |  |  |  |
| Refined | 29 (30.9) | 22 (23.4) | 1 |
| Groundnut | 15 (16) | 42 (44.7) | 0.271 (0.12-0.61) |
| Palm | 50 (53.2) | 30 (31.9) | 1.264 (0.62-2.59) |
| Type of food | | | |
| Moderate spicy | 73 (77.7) | 82 (87.2) | 1 |
| Very spicy | 21 (22.3) | 12 (12.8) | 1.97 (0.91-4.28) |
| Smoking status | | | |
| Non-Smoker | 74 (78.7) | 75 (79.7) | 1 |
| < 10 Pack years | 3 (3.19) | 5 (5.31) | 0.60 (0.14-2.63) |
| 10- 20 Pack years | 5 (5.31) | 10 (10.6) | 0.50 (0.16-1.55) |
| > 20 Pack years | 12 (12.8) | 4 (4.3) | 3.04 (0.93-9.85) |
| Alcohol use | | | |
| Non users | 68 (72.3) | 74 (78.7) | 1 |
| Grade I (< 39.9 g/d) | 19 (20.2) | 10 (10.6) | 2.06 (0.89- 4.75) |
| Grade II (40-59.9 g/d) | 4 (4.2) | 6 (6.3) | 0.72 (0.19-2.68) |
| Grade III (> 60 g/d) | 3 (3.2) | 4 (4.2) | 0.81 (0.17-3.78) |
| Physical activity (METs/wk) | | | |
| Low (< 600) | 18 (19.1) | 24 (25.5) | 1 |
| Moderate (600-3000) | 51 (54.3) | 44 (46.8) | 1.54 (0.74-3.21) |
| High (> 3000) | 25 (26.6) | 26 (27.7) | 1.28 (0.56-2.91) |
| BMI (kg/m2) | | | |
| < 18.5 (underweight) | 19 (20.2) | 10 (10.6) | 1 |
| 18.5-22.99 (Normal) | 47 (50) | 57 (60.6) | 0.43 (0.18-1.02) |
| 23-24.99 (over weight) | 14 (14.9) | 17 (18.1) | 0.43 (0.15-1.22) |
| ≥ 25 (obese) | 14 (14.9) | 10 (10.6) | 0.73 (0.24-2.24) |
| Diabetes Mellitus | | | |
| No | 73 (53.3) | 67 (46.7) | 1 |
| yes | 21 (41.2) | 30 (58.8) | 1.62 (0.85-3.12) |

METs/wk: Metabolic equivalents minutes per week; BMI: Body mass index; OR: Odds ratio.

**Table 5 Factors independently associated with colorectal carcinoma**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Food item** | | | **Adjusted OR (CI)** | ***p* value** |
| Mutton | Tertile 1 | Never or hardly ever | 1 |  |
| Tertile 2 | Once a month | 2.62 (0.08-6.33) | 0.137 |
| Tertile 3 | > 2-3 times a month | 5.41 (1.55-19.05) | 0.008 |
| Egg | Tertile 1 | Never or hardly ever | 1 |  |
| Tertile 2 | Once a month | 1.54 (0.63-3.70) | 0.340 |
| Tertile 3 | > 2-3 times a week | 3.67 (1.23-9.35) | 0.013 |
| Fried foods | Tertile 1 | Never or hardly ever | 1 |  |
| Tertile 2 | Once a month | 0.76 (0.22-2.54) | 0.655 |
| Tertile 3 | > 2-3 times a month | 2.03 (0.95-4.43) | 0.060 |
| Fish | Tertile 1 | Never or hardly ever | 1 |  |
| Tertile 2 | Once a month | 0.02 (0.08-0.58) | 0.195 |
| Tertile 3 | > 2-3 times a month | 0.39 (0.09-1.62) | 0.237 |
| Type of oil | Refined | NA | 1 |  |
| Ground nut | NA | 0.4 (0.15-1.00) | 0.068 |
| Palm | NA | 1.6 (0.75-4.04) | 0.240 |

OR: Odds ratio.