



## RESEARCH ARTICLE

### EFFECT OF PELVIC FLOOR EXERCISE ON BOWEL DYSFUNCTION FOR COLORECTAL CANCER PATIENTS

<sup>1</sup>Zakaria Mowafy Emam Mowafy, <sup>2</sup>Ereny Sobhy Wahba, <sup>3</sup>Mahmoud Abd el Atti Hamida  
And <sup>4</sup>Mohamed Ahmed Abd el Aziz

<sup>1</sup>Professor of Physical Therapy for Surgery, Faculty of Physical Therapy, Cairo University

<sup>2</sup>Lecturer of Physical Therapy for Surgery, Faculty of Physical Therapy, Cairo University

<sup>3</sup>Professor of Surgery, Faculty of Medicine, Alexandria University, Egypt

<sup>4</sup>Researcher of Physical Therapy for Surgery, Faculty of Physical Therapy, Cairo University, Egypt

#### ARTICLE INFO

##### Article History:

Received 15<sup>th</sup> June, 2019

Received in revised form

19<sup>th</sup> July, 2019

Accepted 17<sup>th</sup> August, 2019

Published online 30<sup>th</sup> September, 2019

##### Keywords:

Colorectal cancer (CRC), irritable bowel syndrome (IBS), pelvic floor exercise (Kegel exercise), irritable bowel symptoms Severity questionnaire.

#### ABSTRACT

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. It was found that there was a corresponding relationship between cancer as a disease and the general condition of the affected patient as he may suffer from symptoms such as cachexia, abnormal bleeding, prolonged cough, unexplained weight loss and a change in bowel movements. Colorectal cancer (CRC) also called bowel cancer especially was related to bowel dysfunction leading to irritable bowel syndrome (IBS) which may compromise the patient's quality of life. It was found that including a physical activity such as an exercise on regular daily bases in the program of treatment for the cancer patient has a profound effect on the general condition of the patient. The current study aimed to evaluate the effect of pelvic floor exercise training program on the bowel dysfunction for colorectal patients. Furthermore the need of this study was developed from the lack in the quantitative knowledge and information in the published studies about the effect of pelvic floor exercise (Kegel exercise) on the bowel dysfunction in colorectal cancer patients. This study was designed to provide a guideline about the effect of pelvic floor exercise on improving the bowel dysfunction for colorectal patients. Thirty patients (males and females) were diagnosed with colorectal cancer were participated in the study, their ages ranged from (40 – 55) years had been selected randomly from department of oncology Alexandria university hospital, Alexandria, Egypt and were distributed randomly into 2 groups. Group A (study group) conducted pelvic floor exercise for 6 weeks for 3 times per week 3 session per day for 20 minutes beside traditional cancer treatment. Group B only received traditional cancer treatment. Results were assisted by the irritable bowel symptoms severity questionnaire. **Results:** The results of the study showed that there was a statistically significant decrease in bowel dysfunction symptoms after 6 weeks of treatment application of pelvic floor exercise (post-treatment) of group A when compared with the corresponding mean value of the group B which were only treated with traditional treatment of colorectal cancer. It was concluded that the pelvic floor exercise helps in decreasing the bowel dysfunction symptoms in colorectal cancer patients.

#### INTRODUCTION

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. Not all tumors are cancerous; benign tumors do not spread to other parts of the body possible signs and symptoms include a lump, abnormal bleeding, prolonged cough, unexplained weight loss and a change in bowel movements. While these symptoms may indicate cancer, they may have other causes Over 100 cancers affect humans (Kushi *et al.*, 2012). Few symptoms are specific. Many frequently occur in individuals who have other conditions. Cancer is a "great imitator". Thus, it is common, for people diagnosed with cancer to have been treated for other diseases, which were hypothesized to be causing their symptoms (Tolar and Neglia, 2003).

\*Corresponding author: Zakaria Mowafy Emam Mowafy

Professor of Physical Therapy for Surgery, Faculty of Physical Therapy, Cairo University

The classical view of cancer is a set of diseases that are driven by progressive genetic abnormalities that include mutations in tumor-suppressor genes and oncogenes and chromosomal abnormalities. Later epigenetic alterations' role was identified (Baylin *et al.*, 2006). Once it is clear that a patient has a familial form of colorectal cancer, genetic counselling is mandatory and must provide the patient and his or her extended family with important details about their genetic risk of cancer at specific sites, on the basis of the natural history of the hereditary cancer syndrome; the options for surveillance and management; and the availability of genetic testing. Counselling should be face to face, but a session may include multiple family members (Henry *et al.*, 2006). Treatment of advanced colorectal cancer (CRC) increasingly requires a multidisciplinary approach and multiple treatment options add to the complexity of clinical decision-making. Recently novel targeted therapy against angiogenesis and epidermal growth factor receptor completed a plethora of phase III studies (Chau

*et al.*, 2009). The association between inflammatory bowel disease (IBD) and colorectal cancer (CRC) has been recognized since 1925 and still accounts for 10%-15% of death in IBD. IBD-associated CRC (IBD-CRC) affects patients at a younger age than sporadic CRC. The prognosis for sporadic CRC and IBD-CRC is similar, with a 5-year survival of approximately 50%. Identifying at-risk patients and implementing appropriate surveillance for these patients is central to managing the CRC risk in IBD. The increased risk of colorectal cancer in association with IBD is thought to be due to genetic and acquired factors (Jessica K *et al.*, 2012). Bowel cancer may be diagnosed by obtaining a sample of the colon during a sigmoidoscopy or colonoscopy. This is then followed by medical imaging to determine if the disease has spread. Screening is effective in preventing and decreasing deaths from colorectal cancer. Screening is recommended starting from the age of 50 to 75 (Bibbins-Domingo *et al.*, 2016). The irritable bowel syndrome (IBS) is the most widely recognized functional bowel disorder, but is it a disease? The Oxford English Dictionary considers disease to be "absence of ease; uneasiness; discomfort; inconvenience; annoyance; disturbance." Disease has been more specifically defined to infer that something is wrong with bodily function, based on evidence of physiological and/or psychological dysfunction. This is somewhat different from illness, which refers to the subjective state of the person who feels aware of not being well, and from sickness, which is a state of social dysfunction where the individual assumes the illness role. It is our thesis that IBS is a real intestinal disease (Zigheblom and Nicholus, 2008).

Since it is not known whether the symptoms and bowel function of patients with the irritable bowel syndrome are truly abnormal we used diaries and frequent telephone interviews over a 31 day period to assess symptoms, defecation, and stool types in 26 unselected female hospital patients with the irritable bowel syndrome, 27 women who admitted to recurrent colonic pain but had not consulted a doctor, and 27 healthy control subjects. Unexpectedly, abdominal pain and bloating occurred in most of the control subjects. Pain, however, was six times more frequent in the patients and was more often considered severe. Bloating occurred three times more often. Defecation was more frequent, more erratic in timing and stool form, and more likely to produce stools of extreme forms, indicating rapid fluctuations in intestinal transit time (Braddon *et al.*, 2015). The pelvic floor or pelvic diaphragm is composed of muscle fibers of the levatorani, the coccygeus muscle, and associated connective tissue which span the area underneath the pelvis. The pelvic diaphragm is a muscular partition formed by the levatorani and coccygei, with which may be included the parietal pelvic fascia on their upper and lower aspects. (Drake *et al.*, 2005).

## MATERIALS AND METHODS

### Subjects and study design

**Study subjects:** Thirty patients (males and females) were diagnosed with colorectal cancer participated in the study, their ages ranged from (40 – 55) years had been selected randomly from department of oncology Alexandria university hospital, Alexandria, Egypt and were distributed randomly in to 2 groups subjects, design of the patients, groups, equipment used, procedures of the study and the statistical procedures and data analysis. The current study was carried out in accordance with

the ethical committee of faculty of physical therapy, Cairo University, Egypt. They suffer from irritable bowel symptoms secondary to colorectal cancer. Excluded patients with cardiac diseases, Metastasis and mental disease or psychological problems. All 30 subjects were under supervision of the multidisciplinary team.

**Measurement Equipment:** The bowel dysfunction will be assessed by bowel symptoms severity questionnaire.

**Parameters:** The outcome measure used to assess the frequency of bowel symptoms during each one and half month interval of follow up contained the items found by to discriminate between functional and organic causes of abdominal pain. For each symptom, subjects were asked, during the past month, how often you bothered by each of the following symptoms response possibilities were recorded according to score according to the following:

- Score 25-30: the patient is likely suffering from IBS.
- Score 15-24: the patient may suffer from mild IBS.
- Score < 15: the patient is not suffering from IBS.

### Therapeutic Equipment

a) Pelvic floor exercise (**Hay-Smith *et al.*, 2008**): Audiovisual media teaching the pelvic floor exercise beside verbal instructions as follow:

Audiovisual media teaching the pelvic floor exercise beside verbal instructions as follow:

- Sit in a chair with your knees slightly apart and back in erect position
- Imagine you are trying to stop wind escaping from your anus by contracting your muscles for 3-5 seconds.
- Keep your buttocks and legs steady and don't move them during the exercise
- Relieve you anal muscle squeeze after 3-5 seconds
- Rest for 3-6 seconds
- Now repeat the previous movement for 15 times per session.
- Repeat the previous session for 1-3 times per day

**Procedures of the study:** The procedures of the study were classified into two main parts:

**Evaluation Procedures:** Evaluation of both group 6 weeks before treatment and 6 weeks after treatment by the irritable bowel syndrome severity score questionnaire for group A and traditional colorectal cancer treatment for group B.

**Therapeutic Procedures:** A verbal explanation about the treatment procedures of this study explained to every patient. Pelvic floor exercise for 6 weeks for 3 times per week 3 session per day for 20 minutes beside traditional cancer treatment.

**Statistical analysis:** Descriptive statistics and t-test were conducted for comparison of the mean age of both groups. A paired t-test was conducted for comparison between pre and post-treatment mean values of the irritable bowel symptom severity score questionnaire in each group. T-test was conducted for comparison of mean values of the irritable bowel symptom severity score questionnaire between both groups.

The level of significance for all statistical tests was set at  $p < 0.05$ . All statistical measures were performed through the statistical package for social studies (SPSS) version 19 for windows.

## RESULTS

Thirty patients (males and females) were diagnosed with colorectal cancer were participated in the study, their ages ranged from (40 – 55) years had been selected randomly and divided into two equal groups. The mean score post-treatment of study group was  $18.87 \pm 2.75$  and that of control group was  $22.0 \pm 3.63$ . As observed in table (1) the mean difference between both groups was 3.13 points. There was a significant decrease in severity of irritable bowel symptoms in the study group than the control group post-treatment. As observed from table (2), the mean age  $\pm$  SD of the group A was  $48.26 \pm 4.38$  years, with maximum value of 55 years and minimum value of 40 years, while that of the group B was  $48.13 \pm 3.73$  years, with maximum value of 54 years and minimum value of 41 years. It is clear from table (1) that there was non-significant difference in the mean values of age between both groups of the study (A and B groups) ( $p > 0.05$ ).

**Table 1. Comparison between Post treatments mean values of bowel symptoms of both groups (study and control)**

Score	After-treatment		T value	P value
	Study (n=15)	Control (n=15)		
$\bar{x}$	2.75	3.63	2.668	0.013*
Min. – Max.	14.0–25.0	16.0–27.0		
$\pm$ SD.	$18.87 \pm$	$22.0 \pm$		
Median	19.0	22.0		
MD	3.13			
Level of significance	Significant			

- $\bar{x}$  = Mean
- $\pm$ SD = Standard deviation
- MD = Mean difference
- = %Percentage
- P-Value = Probability level\*
- Statistically significant at  $p \leq 0.05$

**Table 2. Demographic data of blood group A**

Item	Age (years)	
	Group A	Group B
$\bar{x}$	48.26	48.13
$\pm$ SD	4.38	3.73
MD	0.13	
T- value	0.09	
p-value	0.92	
Level of significance	NS	

- $\bar{x}$  = Mean
- $\pm$  SD = Standard deviation
- MD = Mean difference
- P-Value = Probability level
- NS= non-significant

## DISCUSSION

Colorectal cancer (CRC): Colorectal cancer is cancer that starts in the colon or the rectum. These cancers can also be named colon cancer or rectal cancer, depending on where they start. Colon cancer and rectal cancer are often grouped together because they have many features in common. Cancer starts

when cells in the body start to grow out of control. Cells in nearly any part of the body can become cancer and can spread to other areas of the body. To learn more about how cancers start and spread (Kozanoglu *et al.*, 2009). This study has dealt with 30 patients (11 female and 19 male) with colorectal cancer, they were divided randomly into two equal groups. Group A (study group) treated with pelvic floor exercise and traditional colorectal cancer treatment and the other group B (control group) treated with traditional colorectal cancer treatment.

- This study was conducted to evaluate the effect of pelvic floor exercise on bowel dysfunction in colorectal cancer patients

In accordance with this study It was found by (Granger and Denehy, 2014), (Kaaks and Bianchini, 2002), (Takizawa and Kojima, 2009), (Akiyama *et al.*, 2009), (Heseltine and Niedzwiecki, 2006) that Pelvic floor muscle training for patients following surgery for colorectal cancer appears to be associated with improvements in bowel function and health-related quality of life (HRQoL) Results from nonrandomized studies are promising but randomized controlled trials with sufficient power are needed to confirm the effectiveness of PFMT in this population. Six prospective non-randomized studies and two retrospective studies were included. The mean (SD) NOS risk of bias score was 4.9 (1.2) out of 9; studies were limited by a lack of non-exposed cohort, lack of independent blinded assessment, heterogeneous treatment protocols, and lack of long-term follow-up. The majority of studies reported significant improvements in stool frequency, incontinence episodes, severity of faecal incontinence, and health-related quality of life (HRQoL).

The present study agreed with (Benninga and Verwijs, 2016), (Doyle and McCullough, 2012), (Harvey, 2003), (Morkved and Fairbrother, 2008) that Constipation and abdominal pain (physicians' diagnoses) and the parent-reported symptoms hard stools and bloating decreased from primary to tertiary healthcare after 2month interval of Kegel exercise. Discrepancies exist between the prevalence's of physicians' diagnoses and parent-reported symptoms. Locomotor problems predominate in all healthcare settings. The aims of this study are to evaluate in a pragmatic cross-sectional study, the clinical characteristics of childhood bladder and/or bowel dysfunctions. The results of present study agreed with recent results obtained by (Emmanuel, 2010) that recent years have seen a major increase in our understanding of bowel dysfunction in people with central neurological diseases or injury. The most commonly studied conditions are spinal cord injury, multiple sclerosis, spina bifida, Parkinson's disease and stroke. The primary symptoms related to constipation, rectal evacuation difficulties, fecal incontinence or some combination of these. Loss of control of gut function is common in neurological disorders. All those symptoms have reacted positively to sustained muscle strengthening program targeting the pelvic floor muscles.

**Conclusion:** It was concluded that the pelvic floor exercise helps in improving the bowel dysfunction symptoms in colorectal cancer patients.

## REFERENCES

A Schneider, P Enck, K Streitberger, C Weiland, S Bagheri, S Witte, H-CFriederich, WHerzog, Zipfel. 2005. Acupuncture treatment in irritable bowel syndrome.

- Alpers, David H., Kalloo, Anthony N., Kaplowitz, Neil, Owyang, Chung, Powell and Don W. 2008. Yamada, Tadataka, ed. Principles of clinical gastroenterology. Chichester, West Sussex: Wiley-Blackwell. p. 381.
- Anguiano L., Mayer DK., Piven ML. and Rosenstein D. (Jul—Aug 2012). "A literature review of suicide in cancer patients". *Cancer Nursing* 35 (4): E14-26
- Ballard-Barbash R., Friedenreich CM, Courneya KS, Siddicij SM., McTiernan A. and Alfano CM. 2012. "Physical Activity, Biomarkers, and Disease Outcomes in Cancer Survivors: A Systematic Review". *JNCI Journal of the National Cancer Institute* 104 (11): 815-840.
- Baylin SB. and Ohm J. (2006). "Epigenetic gene silencing in cancer - a mechanism for early oncogenic pathway addiction?" *Nature Reviews Cancer* 6 (2): 107-16.
- Bibbins-Domingo, Kirsten, Grossman, David C., Curry, Susan J., Davidson, Karina W., Epling, John W., Garcia, Francisco A. R., Gillman, Matthew W., Harper, Diane M., Kemper, Alex R., Krist, Alex H., Kurth, Ann E., Landefeld, C. Seth, Mangione, Carol M., Owens, Douglas K., Phillips, William R., Phipps, Maureen G., Pignone, Michael P., Siu and Albert L. (2016). "Screening for Colorectal Cancer". *JAMA* 315 (23): 2564
- Bo K., Talseth T. and Holme I. (2009) Single-blind, randomised controlled trial of pelvic floor exercises, electrical stimulation, vaginal cones, and no treatment in management of genuine stress incontinence in women. *BMJ* Feb 20; 318(7182):487-93
- Bridgeman, Bruce; Roberts and Steven G. (2010-03-01). "The 4-3-2 method for Kegel exercises". *American Journal of Men's Health* 4 (1): • 75-76.
- Charles D. R. Murray, Joanna Flynn, Laura Ratcliffe, Merona. Jacyna, Michael A. Kamm, and Anton v. Emmanuel. (2004) Effect of Acute Physical and Psychological Stress on Gut Autonomic Innervation in Irritable Bowel Syndrome chemotherapy". *Medicine* 36 (1): 19-23 .
- CK Bomford, IH Kunkler, J. Walter and Miller's (2011) *Textbook of Radiation therapy* (6th Ed), p311
- Courneya, K.S. and Friedeinreich(2001). Relationship between exercise pattern across the cancer experience and current quality of life in colorectal cancer survivors. *Journal of Alternative & Complementary Medicine*, 3,215± 226
- Croce CM. (2008). "Oncogenes and cancer". *N. Engl. J. Med.* 358 (5):.502-11
- Daftary, ShirishChakravarti and Sudip (2011). *Manual of Obstetrics* (3rd Ed.). Elsevier. pp. 1-16
- Danaei G., Vander Hoorn S., Lopez AD., Murray CJ. andEzzatiM. (2005). "Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors".*Lancet* 366 (9499): 1784-93
- Defining Cancer. National Cancer Institute. Retrieved 10 June 2014
- Drake, Richard L. Vogl, Wayne Mitchell and Adam W. M. (2005). *Gray's Anatomy for Students*. p. 391
- Dumoulin C. and Hay-Smith J. (2008). Pelvic floor muscle training versus no treatment for urinary incontinence in women. *A Cochrane*
- Edward B. Blanchard, Barbara Greene, Lisa Scharff, andShirley P. Schwarz-McMorris. (2010) *Relaxation Training as a Treatment for Irritable Bowel Syndrome*
- Elspeth Guthrie, Francis Creed, David Dawson, and Barbaratomenson. (2002) *A Controlled Trial of Psychological Treatment for the Irritable Bowel Syndrome*
- Evans WJ. Morley JE. Argiles J., Bales C., Baracos V. and Guttridge D. (2008). "Cachexia: a new definition". *ClinNutr.* 27: 793-799.
- Fraser G. and Pearce N. (2005) Occupational physical activity and risk of cancer of the colon and rectum in New Zealand males. *Cancer Causes Control* 4:45-50
- Harvey and M. A. (2003). "Pelvic floor exercises during and after pregnancy: A systematic review of their role in preventing pelvic floor dysfunction". *Journal of Obstetrics and Gynaecology Canada* 25 (6): 487-98
- Hay-Smith J., Morkved S. and Fairbrother KA. (2008) Pelvic floor muscle training for prevention and treatment of urinary and faecal incontinence in antenatal and postnatal women. *Cochrane Database Syst Rev.* 2008
- Holmes MD., Chen WY. andFeskanich D.(2005). Physical activity and survival after a breast cancer diagnosis. *JAMA* 293: 2479-2486.
- Hulisz D. (2004). "The burden of illness of irritable bowel syndrome: current challenges and hope for the future". *J Manag Care Pharm.* 10 (4): 299-309
- J. Valenzuela and J. Alvarado,H. Cohen (2004) Un consensolatinoamericanosobre el síndrome del intestino irritable *GastroenterolHepato*l, 27
- Kate V. Grafton, Grad.Dip.Phys, MSc, MCSP, MMACP, Nadine E. Foster, BSc(Hons), Dphil, MCSP, and Christine C. Wright, BSc(Hons), FSS, C.Math MIMA.(2005) *Test-Retest Reliability of the Short-Form McGill Pain Questionnaire*
- Knudson AG. (November 2001). "Two genetic hits (more or less) to cancer". *Nature Reviews Cancer* 1 (2): 157-62
- Kravchenko J. Akushevich I. and Manton KG. (2009). Cancer mortality and morbidity patterns in the U S. population: an interdisciplinary approach
- Kuan-Yin Lin, Catherine L Granger Linda Denehy, and Helena C Frawley.(2014) *Pelvic Floor Muscle Training for Bowel Dysfunction Following Colorectal Cancer Surgery: A Systematic Review*
- Kushi L.H., Doyle C. and McCullough M. (2012): "American Cancer Society Guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity". *CA Cancer J Clin* 62 (1): 30-67
- L.J. Colwell, M.S., C.M. Prather, M.D., S.F. Phillips, M.D., and A.R. Zinsmeister, PhD (2000) *Effects of an Irritable Bowel Syndrome Educational Class on Health-Promoting Behaviors and Symptoms*
- Lind MJ. (2008). *Principles of cytotoxic chemotherapy.* *Medicine* 36:5.
- Lira FS,Neto JC. andSeelaender M. (2014). "Exercise training as treatment in cancer cachexia". *ApplPhysiolNutrMetab* 39 (6): 679-86
- Marieke L. van Engelenburg–van Lonkhuyzen& Esther M.J. Bol&Marc A. Benninga&Wim A. Verwijs& Rob A. de Bie.(2016) *Bladder and bowel dysfunctions in 1748 children referred to pelvic physiotherapy: clinical characteristics and locomotor problems in primary, secondary, and tertiary healthcare settings*
- Mark A Jenkins, Jane R Clarke, John B Carun, Colin F Robertson," John L Hopper, MaritaF Dalton," Diane P Holst," Kevin Choi and Graham G Giles.(2000)*Validation of Questionnaire and bronchial Hyper-responsiveness against Respiratory PhysicianAssessment in the Diagnosis of Asthma*
- Maronna R., Martin R. and Yohai V. (2006):"Robust statistics theory "18; 148(6):459-73. Epub 2008 Feb 11

- Meyerhardt JA., Heseltine D. and Niedzwiecki D. (2006): Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer
- Pavot, W. and Diener, E. (2008). Review of the satisfaction with life scale. *Psychological Assessment*, 5, 164± 172
- Shamliyan TA, Kane RL. and Wyman J.(2008), et al; Systematic review: randomized, controlled trials of nonsurgical treatments for urinary incontinence in women. *Ann Intern Med.* 2008 Mar 18; 148(6):459-73. Epub 2008 Feb 11
- Stampfer MJ, Willett WC. and Speizer FE.(2008) Test of the National Death Index. *Am J Epidemiol* 119:837-839.
- Stampfer MJ., Hu FB., Manson SE., Rimm EB., Willett WC., Hu, Manson, Rimm and Willett (2000). "Primary Prevention of Coronary Heart Disease in Women through Diet and Lifestyle". *New England Journal of Medicine* 343. (1): 16-22
- Stein A., Atanackovic, and Bokemeyer C. (Sep 2011). "Current standards and new trends in the primary treatment of colorectal cancer". *European Journal of Cancer* 47 (Suppl 3): S312-4
- Ted J Kaptchuk, John M Kelley, Lisa A Conboy, Roger B Davis, Catherine E Kerr, Eric E Jacobson, Irving Kirsch, Rosa N Schyner, Bong Hyun Nam, Long T Nguyen, Min Park, Andrea L Rivers, Claire McManus, Efi Kokkotou, Douglas A Drossman, Peter Goldman, Anthony J Lembo.(2008) Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome
- Solar and Neglia JP (June 2003). "Trans placental and other routes of cancer transmission between individuals". *I. Pediatr. Hematol. Oncol.* 25 (6): 430-4
- Vainio H., Kaaks R. and Bianchini F. (2002) Weight control and physical activity in cancer prevention: international evaluation of the evidence. *Eur J Cancer Prev* 11:S94-S100, 2002
- Yuasa Y., Nagasaki H., Akiyama Y., Hashimoto Y., Takizawa T. and Kojima K. (2009). "DNA methylation status is inversely correlated with green tea intake and physical activity in gastric cancer patients". *Int. J. Cancer* 124 (11): 2677-82

\*\*\*\*\*