

The Trend of Colorectal Cancers at Korle-Bu Teaching Hospital: A Retrospective Histopathological Study

E. M. Der^{1,2*} and R. K. Gyasi¹

¹Department of Pathology, School of Biomedical Sciences, Korle-Bu Teaching Hospital, Accra, Ghana.

²Department of Pathology, School of Medicine and Health Sciences, UDS, Tamale, Ghana.

Authors' contributions

This work was carried out in collaboration between both authors. Authors EMD and RKG designed the research concept. Author EMD did the collection, assembled, interpretation and analysis of data. Authors EMD and RKG wrote the article, read thoroughly and corrected. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JCTI/2016/24745

Editor(s):

- (1) William C. S. Cho, Queen Elizabeth Hospital, Hong Kong.
- (2) Nicole Riddle, Clinical Sciences Division, Alabama College of Osteopathic Medicine, USA.
- (3) Rafael Roesler, Cancer Research Laboratory, University Hospital Research Center, Federal University of Rio Grande do Sul, Brazil.
- (4) Dragos C. Luca, Department of Pathology, Children's National Medical Center/George Washington University, USA.
- (5) Sung-Chul Lim, Industry-Academic Cooperation Foundation, Chosun University, South Korea.
- (6) Lingbing Zhang, Department of Surgery, Stanford School of Medicine, USA.
- (7) Jeng-Shing Wang, Vice-Superintendent, Antai Medical Care Cooperation Antai Tian-Sheng Memorial Hospital, Taiwan and Internal Medicine Department, Taipei Medical University, Taiwan.

Reviewers:

- (1) Georgios Tsoufias, Aristotle University of Thessaloniki, Greece.
 - (2) Bing Yan, Hainan Branch of PLA General Hospital, Sanya, Hainan province, China.
- Complete Peer review History: <http://sciencedomain.org/review-history/15402>

Original Research Article

Received 30th January 2016
Accepted 9th May 2016
Published 14th July 2016

ABSTRACT

Background: Colorectal cancers (CRCs) are common malignancies in Ghana. The aim of the study was to describe the trend and the clinico-pathological characteristics of CRCs in our institution by a retrospective study.

Materials and Methods: This was a retrospective study in the Department of Pathology, from January 2002 to December 2012.

Results: A total of 521 (50.1%) out of 1,040 gastrointestinal malignancies diagnosed during the period of study period were CRCs. Total of 100 (19.2%) of the patients were less than 40 years old. Many (53.2%) were females. The great majority (93.9%) of the patients had stated symptoms

*Corresponding author: Email: maadelle@yahoo.com;

at presentation of which 37.8% were bleeding per rectum. About half (50.0%) of the CRCs were diagnosed in small mucosal biopsies. Approximately 60.8% of the patients reported to a health facility after 3 month of onset of symptoms. Majority (62.2%) of the cancers were located on the left side of the colon particularly the rectosigmoid region (57.4%). The five common CRCs diagnosed in this study were: Conventional adenocarcinoma (80.8%), mucinous adenocarcinoma (6.9%), signet ring adenocarcinoma (3.8%) lymphomas (2.1%) and GIST (1.3%). Of the 199 cases that had Duke's staging, 40.7% were stage C.

Conclusion: There was a rise in the mean age at diagnosis and the number of colorectal cancers over the period of study. Close to 19.2% of the cancers were patients younger than 40 years. Patient presented late with symptoms of advanced disease, most being in Duke's stage C.

Keywords: Colorectal cancer; advanced stage; younger age; Ghana.

1. INTRODUCTION

Colorectal cancers (CRCs) are common causes of morbidity and mortality world-wide and in some developing countries such as Ghana [1-5]. Studies have shown a decreasing trend in the incidence and mortality rates of colorectal cancers (CRCs) in the more developed countries [6,7].

The decline in the trend of CRCs in the higher income countries is attributed to the modification of diet, increased awareness of the disease, early detection and treatment of precancerous lesions [7-10]. Previous studies in Ghana and some other parts of the world have showed rapid rise in the incidence of CRCs [11-18]. On the other hand, the rising trend in the developing countries is attributed to limited resources for screening at risk population and the adoption of the western life styles that are associated with increased incidence of colorectal cancers [19-23].

Although studies in Ghana have shown CRCs are common causes of morbidity and mortality the trend of the disease over the years has not been described. The aim of this study was to use a descriptive histopathological data to determine the trend of colorectal cancers in our institution.

2. MATERIALS AND METHODS

2.1 Study Design

This was a descriptive retrospective histopathological study.

2.2 Study Site

The data were collected from the Department of Pathology, University of Ghana Medical School, which reports between 5,000 and 8,000 histologies per year. This Department receives surgical specimens from the Korle-Bu Teaching

Hospital, the largest referral hospital in Ghana. The department also receives specimens from other health facilities within the Accra metropolis, the greater Accra region, and the 4 other southern regions of Ghana: Central, Western, Eastern, and Volta regions. Although this is a single institutional experience, the sample size of 573 is adequate and may reflect the trend in the general Ghanaian population.

2.3 Data Collection and Analysis

All histopathology request forms and slides of confirmed GI tract malignancies in the Department of Pathology from January 2002 through December 2012 were reviewed independently (by Der EM and cross checked by Gyasi RK) for clinical characteristics (age, main complaints, anatomic location, duration and type of specimen) and histological features (type of cancer, differentiation and Duke's Stage). The data were entered into a computer spreadsheet and analyzed using SPSS version 18 (SPSS, Chicago, IL). The trend in the mean age at diagnosis and the number of colorectal cancers diagnosed during the study period were determined and represented by scatter graphs. The age distribution, symptoms of colorectal cancers, surgical specimens, histological types of colorectal cancers, anatomic location and the Duke's stage at histological diagnosis were determined and presented using tables, bar and pie charts. In this study, the pathological stage of the colorectal cancers was based on the Duke's staging system, as recommended by the American Joint Committee on Cancer, which takes into account the depth of invasion, the number of cancerous lymph nodes, and whether the cancer has spread to other pelvic structures.

3. RESULTS

There were 1,040 histologically confirmed cases of gastrointestinal malignancies diagnosed in our

institution from 2002 to 2012. Of these 521 (50.1%) were colorectal cancers (CRCs), with an incidence rate of 47.4 cases. There was a gradual rise in numbers of colorectal cases over the period of study. For instance, there was a relative rise of 6.2 cases per year between 2008 and 2012 (Table 1, Fig. 1).

The ages of patients ranged from 14 to 92 years with a mean of 54.0±16.1 years. There was a gradual rise in the mean age at diagnosis during the period particularly in the more recent years. For instance from 2002 to 2007, the relative rise in mean age was 0.76 years, compared to 1.14 years relative rise between 2008 and 2012 (Table 1). The modal age group was 50 -59 years (24.0%). About 80.8% of the patients were aged 40 years and above, while 19.2% were below 40 years (Fig. 2). Furthermore from the Table 1, it is cleared that increasing number of colorectal cases were diagnosed in the patients aged 40 years and above in the more recent years. Approximately 53.2% were females with 46.8% males respectively.

The majority (93.9%) of the patients had stated symptoms of CRCs at the time of presentation.

These were bleeding per rectum (37.8%) followed by abdominal mass (28.2%) (Table 2).

The duration of symptoms as stated on the pathology request form was available for only 120 (23.0%) of the cases. Of these 60.8% reported after 3 months of onset of the illness (Table 2).

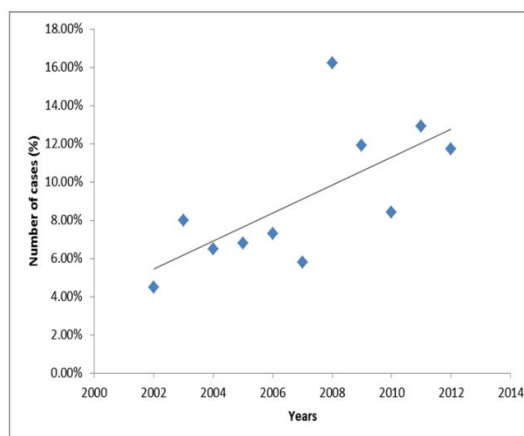


Fig. 1. Trend in colorectal cancers at the KBTH from 2002 – 2012

The commonest surgical specimens from which CRCs was small mucosa biopsies 255 (50.0%) followed by hemicolectomy (25.3%). Majority (62.2%) of the cancers were located on the left side of the large bowel particularly the rectosigmoid region (57.4%) (Fig. 3).

The great majority (80.8%) of the CRCs were invasive conventional adenocarcinomas (consisting of 45.6% moderate, 40.2% well and 14.2% poorly differentiated type). A total of 199 (74.8%) of the large specimens (resected specimens) from which CRCs were diagnosed had Duke's staging done; of these 40.7% were stage C with 39.2% being stage B1 (Table 3).

Table 1. Age characteristics of colorectal cancers diagnosed in the department of pathology in KBTH (2002 – 2012)

Year	Age range (years)	Mean age (SD)	Age< 40 years	Age≥ 40 years	Total number cancers n (%)
2002	23 - 90	47.1 (18.5)	10	13	23 (4.4)
2003	22 – 81	55.3 (16.6)	8	33	41 (8.0)
2004	21 – 90	51.9 (16.7)	8	25	33 (6.3)
2005	25 – 85	53.0 (17.4)	7	19	26 (5.0)
2006	17 – 76	53.5 (14.4)	6	33	39 (7.5)
2007	23 – 86	50.9 (15.5)	9	22	31 (6.0)
2008	14 – 84	55.8 (14.8)	12	77	89 (17.1)
2009	14 – 82	49.4 (18.1)	21	39	60 (11.5)
2010	18 – 91	58.1 (16.0)	6	37	43 (8.5)
2011	25 – 92	55.4 (16.0)	17	57	74 (14.2)
2012	20 - 83	56.6 (14.3)	8	54	62 (11.9)
Total			117	409	521 (100.0)

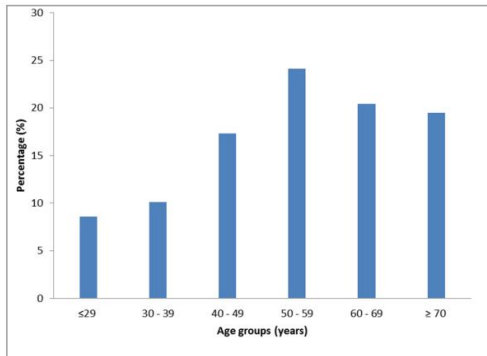


Fig. 2. Age distribution of patients diagnosed with colorectal cancers at the KBTH

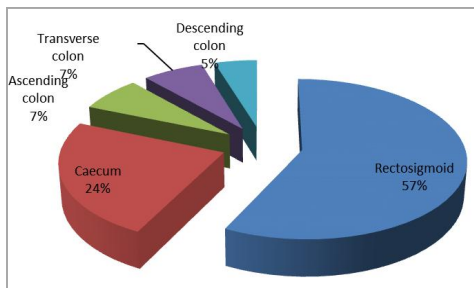


Fig. 3. Anatomic distribution of colorectal cancers

Table 2. Symptoms and duration of colorectal cancers at presentation

Variable symptoms	Frequency (n)	Percentage (%)
Bleeding per rectum	185	37.8
Abdominal mass	138	28.2
Intestinal obstruction	58	11.8
Altered bowel habits	56	11.5
Abdominal pain	28	5.7
Anaemia	12	2.5
Weight loss	10	2.1
Others	2	0.4
Total	489	100.0
Duration of symptoms (months)		
≤ 3	47	39.2
4 - 6	29	24.2
7 - 9	31	25.8
10 - 12	9	7.5
>12	4	3.3
Total	120	100.0
Type of surgical specimens obtained		
Small mucosa biopsies	255	50.0
Hemicolectomy	132	25.3
Resections/ colectomy	119	22.8
Polypectomy	15	2.9
Total	521	100.0

Table 3. Histological characteristics of colorectal cancers diagnosed at the KBTH (2002 – 2012)

Histologic type	Frequency (n)	Percentage (%)
Conventional adenocarcinoma	421	80.8
Mucinous adenocarcinoma	36	6.9
Squamous cell carcinoma	4	0.8
Signet ring adenocarcinoma	20	3.8
Lymphoma (high grade 7 and low grade 4)	11	2.1
GIST	7	1.3
Carcinoid	5	1.0
Neuroendocrine carcinoma	4	0.8
Sarcoma	4	0.8
Anaplastic	2	0.4
Adenosquamous carcinoma	2	0.4
Metastases	3	0.6
Total	521	100.0
Duke's staging		
A	19	9.5
B1	78	39.2
B2	21	10.6
C	81	40.7
Total	199	100.0

4. DISCUSSION

Colorectal cancers (CRCs) are common causes of morbidity and mortality world-wide and in Ghana [1,2,3,4,5]. The current institution-based study found a gradual rise (approximately 6.2 cases per year) in the incidence of colorectal cancers (CRCs) over the period 2002 to 2012. This finding differs significantly from studies in some developed countries where there is a decrease in trend due to increased awareness of the disease, early detection and treatment of precancerous lesion [6,7,8,9,10]. This however supports previous clinical studies in this same institution where the current study was conducted [11,12,13,14]. The findings of this current study are also in accord with reports from North America, Europe [15] and Asia [16,17,18] where CRCs are found to be on a rapid rise. The

rising trend in this current study may be attributed to certain life-style changes associated with westernization of our societies, such as the consumption of calorie-dense food, physical inactivity, obesity and the absence of population-based (CRCs) screening methods such as stool for occult blood and colonoscopy in Ghana and other developing countries [19,20,21,22,23].

Colorectal cancers were commonly diagnosed in relatively older individuals with a mean age of 54.0 ± 16.1 . A significant finding in this study is the gradual rise in the mean at which CRCs were diagnosed in Ghana. The population of Ghana from 1970 to date from the Ghana statistical Service is that of an aging population [24,25,26,27,28] and supports the age pattern in this study. This is also similar to studies in other parts of the world such as Canada, where colorectal cancers are found to be commoner in older individuals aged 50-years and above [14,29,30]. However in this study, 19.2% of the patients were younger than 40 years, with the youngest being 14 year old. This finding is significant and may seem to suggest genetic predisposition in these individuals and thus requires molecular studies to identify the genes involved in these Ghanaians. This is particularly so because younger age at diagnosis has been found to be associated with poor prognosis [31,32,33,34].

Colorectal cancers were commoner in the female gender (53.2%), similar to previous studies by Naaeder et al. [13] and Der et al. [35] in Ghana., This however differs from other studies that found these cancers to be commoner in males [30,36,37]. Many of the patients with colorectal cancers presented with symptoms of advanced disease such as bleeding per rectum, abdominal masses, intestinal obstruction and altered bowel habits. This is in accord with previous studies in Ghana [13,14] and outside Ghana [38] where more than half of colorectal adenocarcinomas are still diagnosed only when the disease involves regional or distant structures. The study found that colorectal cancers were commoner on the left site of the large bowel, particularly, the recto-sigmoid region (57.4%). This anatomic distribution supports previous studies in Ghana, [13] Great Britain [39,40] and other parts of the world, [41] that found the left side of the large bowel to be common anatomic location of colorectal cancers.

Histologically, a majority of the cancers were moderately differentiated conventional adenocarcinoma and this is in accord with other studies on colorectal cancers [14,42]. The prognosis of colorectal cancers depends on the clinico-pathological stage assessed by microscopic examination of the resected colon [43]. The higher the stage at histological diagnosis the poorer the prognosis and the expected 5-year survival rate [44]. In this study, only 9.5% of the patients had localized disease (Duke's stage A) with as many as 40.7% having advanced stage of the disease (Duke's stage C) at the time of histological diagnosis. Although there have not been any published data in Ghana comparing stage at diagnosis and survival rates, the advanced stage at diagnosis coupled with the fact that 63.8% of the patients presented after 3 months of noticing the symptoms may translate into poor and a low expected 5-year survival rate and this may be in accordance with findings in England [44,45] and Finland [46,47] where studies has been conducted regarding stage at diagnosis and the 5-years survival rates.

5. CONCLUSION

There was a gradual rise in the mean age at diagnosis of patients with colorectal cancers with the number of cases of colorectal cancers over the period of the study also increasing steadily. Close to 19.2% of the cancers were in patients younger than 40 years. The patients presented late with symptoms of advanced disease, most being in Duke's stage C.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Approval for this research was given by the head of Department of pathology.

ACKNOWLEDGEMENT

We will like to thank all residents and the biomedical staff of the Department of Pathology for their support.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. World Health Organization. The global burden of disease: 2004 update. Geneva: World Health Organization; 2008.
2. Ferlay J, Shin HR, Bray F, Forman D, Mathers CD, Parkin D. GLOBOCAN 2008, Cancer incidence and mortality worldwide: IARC CancerBase No. 10. Lyon, France: International Agency for Research on Cancer; 2010.
Available: <http://globocan.iarc.fr>
Last accessed 8/17/2010.
3. Weitz J, Koch M, Debus J, Hohler T, Galle PR, Buchler MW. Colorectal cancer. *Lancet*. 2005;365:153–165.
4. Biritwum RB, Gulaid J, Amaning AO. Pattern of diseases or conditions leading to hospitalization at Korle Bu Teaching Hospital, Ghana in 1996. *Ghana Med J*. 2000;34:197–205.
5. Wiredu EK, Armah HB. Cancer mortality patterns in Ghana: A 10-year review of autopsies and hospital mortality. *BMC Public Health*. 2006;6:159.
Available: <http://www.biomedcentral.com/147-2458/6/15910>
6. Center MM, Jemal A, Ward E. International trends in colorectal cancer incidence rates. *Cancer Epidemiol Biomarkers Prev*. 2009;18:1688-1694.
7. Center MM, Jemal A, Smith RA, Ward E. Worldwide variations in colorectal cancer. *Cancer J Clin*. 2009;59:366-378.
8. Chu KC, Tarone RE, Chow WH, Hankey BF, Ries LA. Temporal patterns in colorectal cancer incidence, survival, and mortality from 1950 through 1990. *J Natl Cancer Inst*. 1994;86:997-1006.
9. Mitry E, Bouvier AM, Esteve J, Faivre J. Benefit of operative mortality reduction on colorectal cancer survival. *Br J Surg*. 2002;89:1557-1562.
10. Sant M, Capocaccia R, Coleman MP, et al. Cancer survival increases in Europe, but international differences remain wide. *Eur J Cancer*. 2001;37:1659-1667.
11. Badoe EA. Malignant tumours of the large bowel (including rectum) Korle-Bu Hospital, Accra; 1970–75. *Ghana Med J*. 1977;16:157–159.
12. Badoe WA. Malignant diseases of the gastro-intestinal tract in Korle-Bu Hospital, Accra, Ghana; 1956–1965. *West Afr J Med*. 1966;15:181–185.
13. Naaeder SB, Archampong EQ. Cancer of the colon and rectum in Ghana: A 5-year prospective study. *Br J Surg*. 1994;81:456–459.
14. Dakubo JCB, Naaeder SB, Tettey Y, Gyasi RK. Colorectal carcinoma: An pupdate of current trends in Accra. *West Afr J Med* 2010;29:178-183.
15. Stewart BW, Kleihues P. World cancer report. World Health Organization, International Agency for Research on Cancer. 2003;198-202.
16. Yiu HY, Whittemore AS, Shibata A. Increasing colorectal cancer incidence rates in Japan. *Int J Cancer*. 2004;109:777–781.
17. Lu JB, Sun XB, Dai DX, Zhu SK, Chang QL, Liu SZ, Duan WJ. Epidemiology of gastroenterologic cancer in Henan Province, China. *World J Gastroenterol*. 2003;9:2400–2403.
18. Yang L, Parkin DM, Li LD, Chen YD, Bray F. Estimation and projection of the national profile of cancer mortality in China: 1991-2005. *Br J Cancer*. 2004;90:2157–2166.
19. Martin JJ, Hernandez LS, Gonzalez MG, Mendez CP, Rey Galan C, Guerrero SM. Trends in childhood and adolescent obesity prevalence in Oviedo (Asturias, Spain) 1992-2006. *Acta Paediatr*. 2008;97:955-958.
20. De Kok IM, Wong CS, Chia KS, et al. Gender differences in the trend of colorectal cancer incidence in Singapore, 1968-2002. *Int J Colorectal Dis*. 2008;23:461-467.
21. Parkin DM, Nambooze S, Wabwire-Mangen F, Wabinga H. Changing cancer incidence in Kampala, Uganda, 1991-2006. *Int J Cancer*. 2010;126:1187–1195.
22. Amoah AGB. Sociodemographic variations in obesity among Ghanaian adults. *Public Health Nutr*. 2003b;6:751-775.
23. Biritwum RB, Gyapong J, Mensah G. The Epidemiology of Obesity in Ghana. *Ghana Med J*. 2005;39:82–85.
24. Ghana Statistical Service. 1970 Population census of Ghana. Special report 'A'. Statistics oftowns with population 10,000 and over. Accra. Census office of Accra, Ghana. 1978;715–717.
25. Ghana Statistical Service. 1984 population of Ghana. Demography and economic

- characteristics, greater Accra Region. Accra. Statistical service Accra, Ghana; 1987.
26. Ghana Statistical Service. 1984 population census of Ghana. The gazetteer 1 (AA-KU). Alphabetical list of localities with statistics on population, Number of houses and main source of water supply. Accra. Statistical service Accra, Ghana. 1989;10.
 27. Ghana Statistical Service. 2000 population and housing census; Greater Accra Region. Analysis of District Data and Implications for planning. Accra. Statistical Service Accra, Ghana. 2005;10.
 28. Ghana Statistical Service. 2010 population and housing census; Greater Accra Region. Analysis of District Data and Implications for planning. Accra. Statistical Service Accra, Ghana.
 29. SEER*Stat Database: Incidence - SEER 17 Regs Limited-Use + Hurricane Katrina Impacted Louisiana Cases, Nov 2009 Sub (2000-2007) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2007 Counties [computer program]: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2010, based on the November 2009 submission.
 30. Canadian Cancer Statistics 2015–Canadian Cancer Society, Statistics Canada, Provincial / Territorial Cancer Registries, Public Health Agency of Canada.
 31. Rusthoven JJ, Fine S, Thomas G. Adenocarcinoma of rectum metastatic to oral cavity. Two cases and review of the literature. *Cancer*. 1984;54:1110-1112.
 32. Odone V, Chang L, Caces J, George SL, Pratt CB. The natural history of colorectal carcinoma in adolescents. *Cancer*. 1982; 49:1716-1720.
 33. Rao BN, Pratt C, Fleming ID, Dilawari RA, Green AA, Autin BA. Colon cancer in children and adolescents. A review of 30 cases. *Cancer*. 1985;55:1322-1326.
 34. Griffin MP, Bergstralh EJ, Coffey RJ, Beart RW Jr, Multon LJ III. Predictors of survival after curative resection of cancer of the colon and rectum. *Cancer*. 1987;60:2318-1324.
 35. Der EM, Naaeder SB, Clegg-Lampthey JNA, Dakubo JCB, Edusei L, Tettey Y, Gyasi RK. Anatomic categorization of gastrointestinal malignancies using haematoxylin and eosin stains: A10-year retrospective histopathological study at the Korle-Bu Teaching Hospital Accra. *J Cancer Res Ther*. 2015;3:8-14. Available: <http://dx.doi.org/10>
 36. Murphy G, Devesa SS, Cross AJ, Inskip PD, McGlynn KA, Cook MB. Sex disparities in colorectal cancer incidence by anatomic subsite, race and age. *Int J Cancer*. 2011;28:1668–1675.
 37. Mohamad AP, Mohsen V, Bijan MD, Asma P, Fatemeh G, Elham M, et al. Burden of hospitalization for gastrointestinal tract cancer patients - results from a cross-sectional study in Tehran. *Journal: Asian Pacific J Cancer Prev*. 2009;10:107-110.
 38. Ratto C, Sofo L, Ippoliti M, Merico M, Doglietto GB, Crucitti F. Prognostic factors in colorectal cancer. Literature review for clinical application. *Dis Colon Rectum*. 1998;41:1033–1049.
 39. Data were provided by ISD Scotland on request, April 2012. Similar data can be found here: Available:<http://www.isdscotland.org/Health-Topics/Cancer/Publications/index.asp>
 40. Data were provided by the Welsh Cancer Intelligence and Surveillance Unit on request, April 2012. Similar data can be found here: Available:<http://www.wales.nhs.uk/sites3/page.cfm?orgid=242pid=59080>
 41. Netscher DT, Larson GM. Colon cancer. The left to right shift and its implications. *Surg. Gastroenterol*. 1983;13-18.
 42. Stewart SL, Wike JM, Kato I, Lewis DR, Michaud F. A populationbased study of colorectal cancer histology in the United States, 1998-2001. *Cancer*. 2006; 107(5 Suppl):1128-1141.
 43. Steinberg SM, Barwick KW, Stablen DM. Importance of tumour pathology and morphology in patients with surgically resected colon cancer. Findings from the Gastrointestinal Tumour Study Group. *Cancer*. 1986;58:1340-1345.
 44. Downing A, Aravani A, Macleod U, Oliver S, Finan PJ, Thomas JD, et al. Early mortality from colorectal cancer in

- England: A retrospective observational study of the factors associated with death in the first year after diagnosis. *Br J Cancer*. 2013;108(3):681-5.
DOI: 10.1038/bjc.2012.585
45. McPhail S, Johnson S, Greenberg D, Peake M, Rous B. Stage at diagnosis and early mortality from cancer in England. *British Journal of Cancer*. 2015;112: S108–S115.
DOI: 10.1038/bjc.2015.49
46. Finnish Cancer Registry: Cancer Incidence in Finland 2000 and 2001. J Helsinki: Cancer Society of Finland; 2003.
47. Nea M, Afiti A, Matti H. Colorectal cancer screening in Finland; details of the national screening programme implementation in Autumn 2004. *J Med Screening* 2005; 12:28–32.

© 2016 Der and Gyasi; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:
The peer review history for this paper can be accessed here:
<http://sciencedomain.org/review-history/15402>