## **Cancers Complicating Inflammatory Bowel Disease**

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**Introduction:** Bowel diseases as an example, Crohn's Disease and Ulcerative Colitis are considered to be a long-lasting inflammatory bowel disease that starts in the young adult age even though the etiology is unknown. According to the recent statistics, less than one percent of Europeans and North Americans are prone to have inflammatory bowel disease (1).

The proper diagnosis of those patients having Crohn's disease and Ulcerative Colitis is performed by the detection of extensive colitis in the early childhood. (2, 3, 4)

It is considered to be life threatening due to infection, cardiovascular diseases, in addition to inflammatory bowel disease cancerpatients (3). The risk of cancer is highly remarkable for those patients who suffer inflammatory bowel disease and the general population due to the various daily life impacts. As an example, heavy smokers are more likely to be in a high risk among the rest of patients with Crohn's disease, thus it represents a relatively high rate of smoking-related cancers in the overall population having Crohn's disease (2,21,22). On the other hand, nonsmokers show a decreased rate of malignancy in the entire population with ulcerative colitis (4).

The aim of this review is to figure out a reasonable way for prevention of cancer risk in those patients suffering from chronic intestinal inflammation based on epidemiologic criteria and carcinogenesis according to the previous work done.

**Keywords:** Crohn's disease, Ulcerative Colitis, colorectal cancer, immunosuppressant

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## I. Colorectal malignancy

Cancer of the colorectal area is ranked as a highly common cancer all over the world. Colorectal cancers like sporadic colorectal cancers and colitis-associated cancers occur in patients representing inflammatory bowel disease (5,25). Malepatients over 50 years within a previous first-degree family history are highly prone to have a risk of malignancy. However, the impacts of the daily routine show a correlation with alteration in the risk of sporadic colorectal cancer are not revealed in patients with inflammatory bowel disease (6,23,24).

Several studies have been done on the influences of risk in colorectal cancer patients with inflammation of the bowel (7,8,27). Inflammatory bowel disease patients lacking any kind of colonic inflammation in addition to those suffering from ulcerative colitis are not showing a high risk of colorectal cancer (9,10). Conversely, primary sclerosing cholangitis inflammatory bowel disease isconsidered to be at a high risk for colorectal cancer in the early stage of diagnosis (6,7,26). In other inflammatory bowel disease patients, colorectal cancerhas a higher risk in comparison to that among patients of the same age and gender lacking inflammatory bowel disease, has been stated by the extent, duration, and how severe is the colonic inflammation.

#### Adenocarcinoma of Small-Bowel

Generally, small-sized bowel adenocarcinoma is not common. Crohn's disease patients reveal a high ability to be at risk of small bowel carcinoma in comparison to those without Crohn's diseases (28,29). Small-bowel adenocarcinoma could be originated in the ileac era lesions of Crohn's disease patients after several years of proper diagnosis. It is generally correlated with a history of iliac dysplasia that may negatively interfere the chronic ileac inflammation within a dysplasia—adenocarcinoma maneuver (11,30).

#### **Anal malignancy**

Recently, Squamous-cell carcinoma of the anal region shows low evidence in the entire population of patients having inflammatory bowel disease (12,32). Male homosexuals in addition to females having cervical dysplasia are prone to be at a high risk.

Inflammatory bowel disease patients undertaking immune-suppressants risk are still unknown even though, those undergoing immunosuppression after organ transplant are considered to be at a high risk due to the promotion of human papillomavirus (31,33).

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#### Cholangiocarcinoma

Patients with inflammatory bowel disease show a high level of risk of causing cholangiocarcinoma in comparison with those lacking inflammatory bowel disease (13,34,35). However, the absolute risk is still revealed to be low. Patients with primary sclerosing cholangitis are at a high risk of cholangiocarcinoma than those healthy ones. (36)

## **Cancers of the Intestinalarea (Lymphomas)**

According to the previous work done, it was concluded that patients with inflammatory bowel disease are highly prone to present a risk of undergoing primary intestinal lymphomas although the percentage of risk is not that high. An early stage of intestinal lesions treatment has been the main target of inflammatory bowel disease considerable prognosis. In order to achieve this aim, a prolonged utilization of conventional immune-modulators as an example mercaptopurine should be induced (14,37).

Non-Hodgkin's lymphomas are commonly occurring cancers; old males are at a high risk. It has been demonstrated that there is no high risk of lymphoma associated with the inflammatory bowel disease. Males under thirty-five years with EBV sero-negative could be a cause of death in the early development of the post-mononucleosis (38).

Inflammatory bowel disease patients undertaking methotrexate reveals an unknowns risk level with coordination of lymphatic but it was demonstrated that there is no high risk of lymphoma worldwide (13,14,39).

#### Cancers of skin

Basal-cell carcinomas and squamous cell with non-melanomas skin cancer are most commonly existed than the rest of the other cancers causing death. The direct intake of Thiopurines is highly correlated with the excess risk rate increased of nonmelanoma skin malignancy (15)

The carcinogenic Thiopurines mechanism might engage a high level of hazardous ultraviolet rations towards epithelial cells of the skin in addition to the application of a direct mutagenic influence on the PTCH encoding gene. Those patients suffering inflammatory bowel disease reveals a low level of risk towards nonmelanoma skin cancer attributable to the antagonists of tumor necrotic factor alpha has been detected a relatively sufficient cohort drawn from a health plan claims database, after Thiopurines therapy adjustment (15,16).

Inflammatory bowel disease patients could show a little unknown internal excessive risk that leads to melanoma. Thiopurines delivery showed decorrelation mannertowards alteration of this risk. Thus, the risk of having melanoma in inflammatory bowel disease patients who have been exposed TNF- $\alpha$  antagonists was demonstrated to be doubled in comparison to those patients underwent no exposure. Generally, it has been demonstrated that the high risk of skin cancers should a high association with both the inflammatory bowel disease in addition to the drugs used for treatment purpose. Specialists recommended a protocol for inflammatory bowel disease patients include protection from the sunrays in addition to skin surveillance at the proper diagnostic time (40,41).

#### **Human Papillomavirus in correlation with Cervical Cancer**

The level of risk related to HPV-related cervical cancer is still unknown however it increases in females having inflammatory bowel disease and it can be decreased due to the direct to any kind of immunosuppressant (42,43). Although, human papillomavirus vaccination is highly recommended in addition to the frequent tests of Papanicolaou for all females having inflammatory bowel disease (17,44).

## Urinary-Tract area malignancy

Several types of research have been done on urinary tract cancers and it was concluded that those patients who receive immunosuppressive treatment including Thiopurines after an organ transplant are considered to be in a relatively high risk of kidney and bladder. (18,45)

A research was done on a sample taken from Danish population, it was demonstrated that patients undertaking azathioprine show a higher risk of having urinary tract cancers than those under Thiopurines therapy. Even though, patients who were previously treated by azathioprine show a low risk of malignancy. Inflammatory bowel disease patients reveal a low risk of achieving urinary tract cancers after exposure to tumor necrosis factor antagonists.

# The general rate of Risk and the ways of proper Prevention of Cancers in correlationwith the Drugs for Inflammatory Bowel Disease treatment

After a proper application of confounders, the usage of Thiopurines for inflammatory bowel disease patients show an intimate correlation with the high risk of malignancy and that risk decreases gradually within

Thiopurines withdrawal.Generally, it has been reported that patients who take TNF alpha antagonists for the purpose of inflammatory bowel disease treatment show a high risk of undergoing malignancy, however, within the recent utilization of biological materials, a prolonged high risk of malignancy can be relatively diminished. The basic mechanism to face the high risk of cancer for patients undergoing drugs for the treatment of inflammatory bowel disease have been highly elaborated. (19)

Most of the Oncologists have been focusing on administration of irradiation in the pelvic area for inflammatory bowel diseases setting. A proper application of Immunotherapy for cancer treatment is highly suggested especially for those patients suffering a refractory response to the ordinary treatment methodology.

Several types of research have been done in order to figure out the correlation of the chronic inflammatory bowel diseases with the risk of malignancy, and the influence of the profound usage of immunosuppressant for the treatment of inflammatory bowel diseasesand cancer prevention. Despite the sufficient efforts done in this field, many issues have been unknown in association with the inflammatory bowel diseases, the treatment methodology used, the drugs delivered, in addition to the rate of recurrence and any history of malignancy. (20)

In order to understand the chemotherapy impacts, therapies by hormones, radiotherapy in addition to the surgical process for patients have cancer-related to the inflammatory bowel diseases might investigate cases of high-risk metastasis at the time of treatment as well as after treatment, including most of the patients requiring an application of immunosuppressant for treatment. Thus, several types of research have demonstrated some kind of evidence for the safety of immunosuppressant usage for inflammatory bowel diseases patients with a previous history of malignancy (13, 14, 16).

Inflammatory bowel disease (IBD) is a disease involving a bi-conditional case of gut inflammation including Crohn's disease and ulcerative colitis. It can affect humans at any age but some researchers have revealed that it highly occurs between the ages of fifteen to forty years (46).

According to the previous research done, it has been concluded a proper outback of analyzing the rate of being at risk of having cancer with patients having inflammatory bowel diseases than the healthy ones, however those researches lacked the number of individuals indicated and the follow up protocol in order to assist trends in the ageing time in inflammatory bowel disease in childhood (2, 8, 17). According to that, a group of specialists figured out the criteria for analyzing the rate of cancer risk in both the childhood and adulthood.

A research done on a sample taken from a Swedish population, it compared more than nine thousand patients diagnosed with inflammatory bowel diseases located in Sweden within the age range from 18 to 20 with another 92 thousand healthy individuals (47).

They have demonstrated an analysis for cancer risk prior to the eighteenth birthday and the age of twenty-five in addition to the whole study period from 1964 to 2014 and reached the peak at the age of thirty.

That research was insufficient for the aim of recognition whether the drugs have been used for treatment reveal a risk factor. Therefore, the oncologists recommend that the prolongation and time of chronic inflammation could be a basic mechanism derived from the risk cancer increasing.

## **II.** Conclusion

Nowadays, within the chronic inflammatory diseases occurred due to the excessive usage of immunosuppressant, Recently, inflammatory bowel disease is considered to be a model for target for many who are interested in knowing the complication of inflammatory bowel diseases in cancer, immunosuppressant have the ability to diminish the inflammation incidence correlated with cancer due to their ability of having anti-inflammatory influences the for the aim of immunosuppression correlated cancers promotion. Thus, TNF- $\alpha$  antagonists in addition to other new biological materials can help in decreasing the high risk of malignancy, Oncologists highly suggesta prospective method of patients having inflammatory bowel diseases within correlation to the high risk of malignancy keeping into consideration the level of the inflammation activity in order to investigate if the treatment method has the ability of decreasing the risk rate of cancers or not and therefore can decrease the control the level of the drugs having chemo preventive impacts for getting a better prognosis. In conclusion, the high risks inflammatory bowel diseases cancers should be highly considered when dealing with the riskof long-term intake of medications.

Other factors including age and gender and the phenotype of the inflammatory bowel disease should be put into consideration because of their effect on the risk rate of malignancy.

The signs and symptoms differ due to the location and the metastasis of cancer but generally; both bowel cancer and Crohn's cancer share the same signs and symptoms.

#### References

- [1]. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 2012; 142(1): 46.e42-54.e42.
- [2]. Duricova D, Pedersen N, Elkjaer M, Gamborg M, Munkholm P, Jess T. Overall and cause-specific mortality in Crohn's disease: a meta-analysis of populationbased studies. Inflamm Bowel Dis 2010; 16: 347-53.
- [3]. Jess T, Frisch M, Simonsen J. Trends in overall and cause-specific mortality among patients with inflammatory bowel disease from 1982 to 2010. ClinGastroenterolHepatol 2013; 11: 43-8.
- [4]. Jess T, Gamborg M, Munkholm P, Sørensen TI. Overall and cause-specific mortality in ulcerative colitis: meta-analysis of population-based inception cohort studies. Am J Gastroenterol 2007; 102: 609-17.
- [5]. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136(5): E359-E386.
- [6]. Ekbom A, Helmick C, Zack M, Adami HO. Ulcerative colitis and colorectal cancer: a population-based study. N Engl J Med 1990; 323: 1228-33.
- [7]. Jess T, Simonsen J, Jorgensen KT, Pedersen BV, Nielsen NM, Frisch M. Decreasing risk of colorectal cancer in patients with inflammatory bowel disease over 30 years. Gastroenterology 2012; 143(2): 375. e1-81.e1.
- [8]. Beaugerie L, Svrcek M, Seksik P, et al. Risk of colorectal high-grade dysplasia and cancer in a prospective observational cohort of patients with inflammatory bowel disease. Gastroenterology 2013; 145(1): 166.e8-75.e8.
- [9]. Rubin DT, Huo D, Kinnucan JA, et al. Inflammation is an independent risk factor for colonic neoplasia in patients with ulcerative colitis: a case-control study. ClinGastroenterolHepatol 2013; 11(12): 1601.e4-8.e4.
- [10]. Gupta RB, Harpaz N, Itzkowitz S, et al. Histologic inflammation is a risk factor for progression to colorectal neoplasia in ulcerative colitis: a cohort study. Gastroenterology 2007; 133: 1099-105.
- [11]. Lutgens MW, Vleggaar FP, Schipper ME, et al. High frequency of early colorectal cancer in inflammatory bowel disease. Gut 2008; 57: 1246-51.
- [12]. Lutgens MW, van Oijen MG, van der Heijden GJ, Vleggaar FP, Siersema PD, Oldenburg B. Declining risk of colorectal cancer in inflammatory bowel disease: an updated meta-analysis of populationbased cohort studies. Inflamm Bowel Dis 2013; 19: 789-99
- [13]. Rutter M, Saunders B, Wilkinson K, et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. Gastroenterology 2004; 126: 451-9.
- [14]. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut 2001; 48: 526-35.
- [15]. Herrinton LJ, Liu L, Levin TR, Allison JE, Lewis JD, Velayos F. Incidence and mortality of colorectal adenocarcinoma in persons with inflammatory bowel disease from 1998 to 2010. Gastroenterology 2012; 143: 382-9.
- [16]. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA Jr, Kinzler KW. Cancer genome landscapes. Science 2013; 339: 1546-58
- [17]. Ullman TA, Itzkowitz SH. Intestinal inflammation and cancer. Gastroenterology 2011; 140: 1807-16.
- [18]. Itzkowitz SH, Yio X. Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. Am J PhysiolGastrointest Liver Physiol 2004; 287: G7-G17.
- [19]. Galandiuk S, Rodriguez-Justo M, Jeffery R, et al. Field cancerization in the intestinal epithelium of patients with Crohn'sileocolitis. Gastroenterology 2012; 142(4): 855.e8-64.e8.
- [20]. Risques RA, Lai LA, Himmetoglu C, et al. Ulcerative colitis-associated colorectal cancer arises in a field of short telomeres, senescence, and inflammation. Cancer Res 2011; 71: 1669-79.
- [21]. Yaeger, R., Shah, M. A., Miller, V. A., Kelsen, J. R., Wang, K., Heins, Z. J., ... &Kelsen, D. P. (2016). Genomic Alterations Observed in Colitis-Associated Cancers Are Distinct From Those Found in Sporadic Colorectal Cancers and Vary by Type of Inflammatory Bowel Disease. Gastroenterology, 151(2)
- [22]. Beaugerie, L., & Itzkowitz, S. H. (2015). Cancers Complicating Inflammatory Bowel Disease. The New England Journal of Medicine, 372(15), 1441-1452.
- [23]. Ouaissi, M., Maggiori, L., Alves, A., Giger, U., Sielezneff, I., Valleur, P., ... &Panis, Y. (2011). Colorectal cancer complicating inflammatory bowel disease: a comparative study of Crohn's disease vs ulcerative colitis in 34 patients.. Colorectal Disease, 13(6), 684-688.
- [24]. Cannon, J. (2015). Colorectal Neoplasia and Inflammatory Bowel Disease.. Surgical Clinics of North America, 95(6), 1261-1269.
- [25]. Freeman, H. J. (2001). Colorectal cancer complicating Crohn's disease. Canadian Journal of Gastroenterology & Hepatology, 15(4), 231-236
- [26]. Oxenberg, J., Hochwald, S. N., &Nurkin, S. J. (2014). Ablative Therapies for Colorectal Polyps and Malignancy. BioMed Research International., 986352-986352.
- [27]. Markides, G. A., & Newman, C. M. (2014). Medical malpractice claims in relation to colorectal malignancy in the National Health Service. Colorectal Disease, 16(1), 48-56.
- [28]. Vagholkar, K., & Mathew, T. (2009). Adenocarcinoma of the small bowel: a surgical dilemma. Saudi Journal of Gastroenterology, 15(4), 264-267.
- [29]. 29.Fadavi, P., & Zare, M. (2015). Adenocarcinoma of Small Bowel.. Rare Tumors, 7(2), 5517-5517.
- [30]. Dabaja, B., Suki, D., Pro, B., Bonnen, M. D., & Ajani, J. A. (2004). Adenocarcinoma of the small bowel: presentation, prognostic factors, and outcome of 217 patients.. Cancer, 101(3), 518-526.
- [31]. Kochhar, R., Plumb, A., Carrington, B. M., & Saunders, M. P. (2012). Imaging of Anal Carcinoma. American Journal of Roentgenology, 199(3).
- [32]. Weis, S. E. (2013). Current treatment options for management of anal intraepithelial neoplasia.. OncoTargets and Therapy,, 651-665.
- [33]. Shah, B. K., &Budhathoki, N. (2015). Second Primary Malignancy in Anal Carcinoma –A US Population-based Study. Anticancer Research, 35(7), 4131-4134.
- [34]. Ghouri, Y. A., Mian, I., &Blechacz, B. (2015). Cancer review: Cholangiocarcinoma. Journal of Carcinogenesis, 14(1), 1-1.
- [35]. Van Beers, B. E. (2008). Diagnosis of cholangiocarcinoma. Hpb, 10(2), 87-93.
- [36]. Chung, Y. E., Kim, M., Park, Y. N., Choi, J. Y., Pyo, J. Y., Kim, Y. C., ... & Choi, S. Y. (2009). Varying Appearances of Cholangiocarcinoma: Radiologic-Pathologic Correlation. Radiographics, 29(3), 683-700.
- [37]. Catassi, C., Bearzi, I., & Holmes, G. K. (2005). Association of celiac disease and intestinal lymphomas and other cancers.. Gastroenterology, 128(4).
- [38]. Cornes, J. S. (1960). MULTIPLE PRIMARY CANCERS: PRIMARY MALIGNANT LYMPHOMAS AND CARCINOMAS OF THE INTESTINAL TRACT IN THE SAME PATIENT. Journal of Clinical Pathology, 13(6), 483-489.

- [39]. Bairey, O., Ruchlemer, R., &Shpilberg, O. (2006). Non-Hodgkin's Lymphomas of the Colon. Israel Medical Association Journal, 8(12), 832-835.
- [40]. Miller, A. B., &Gaudette, L. A. (1996). Cancers of Skin, Bone, Connective Tissues, Brain, Eye, Thyroid and Other Specified and Unspecified Sites in Inuit. ActaOncologica, 35(5), 607-616.
- [41]. Preston, D. S., & Stern, R. S. (1992). Nonmelanoma Cancers of the Skin. The New England Journal of Medicine, 327(23), 1649-1662.
- [42]. An, H. J., Cho, N. H., Lee, S., Kim, I. H., Lee, C., Kim, S. J., ... & Jeong, J. K. (2003). Correlation of cervical carcinoma and precancerous lesions with human papillomavirus (HPV) genotypes detected with the HPV DNA chip microarray method. Cancer, 97(7), 1672-1680.
- [43]. Munoz, N., Bosch, F. X., De Sanjose, S., Herrero, R., Castellsague, X., Shah, K. V., ... & Meijer, C. J. (2003). Epidemiologic Classification of Human Papillomavirus Types Associated with Cervical Cancer. The New England Journal of Medicine, 348(6), 518-527.
- [44]. Powell, F. C., Bjornsson, J., Doyle, J. A., & Cooper, A. J. (1985). Genital Paget's disease and urinary tract malignancy. Journal of The American Academy of Dermatology, 13(1), 84-90.
- [45]. Shiraishi, K., Eguchi, S., Mohri, J., &Kamiryo, Y. (2003). Role of ureteroscopic biopsy in the management of upper urinary tract malignancy. International Journal of Urology, 10(12), 627-630.
- [46]. Bernstein, C. N., Blanchard, J. F., Kliewer, E., & Wajda, A. (2001). Cancer Risk in Patients with Inflammatory Bowel Disease. American Cancer Society, 854-861.
- [47]. Sun, J., & Kato, I. (2016). Gut microbiota, inflammation and colorectal cancer. Elsevier , 130-143.

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