TJC Turkish Journal of Cancer
Volume 38, No. 3, 2008

Colorectal carcinomas: Clinicopathologic investigation, correlation with expression of estrogen and progesterone receptors

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ABSTRACT

Correlation in mortality data between breast cancer and colonic cancer, and increased incidence of colonic cancer in women with breast cancer suggest common factors in their etiology. Similarly protective effect of increasing parity from colonic cancer, and relatively better prognosis in women may imply a common role for sex steroid hormones. In this study clinicopathologic parameters as well as estrogen and progesterone receptor expressions of 60 cases of colorectal adenocarcinoma were investigated. Most carcinomas were moderately differentiated; stage B2 tumors were predominately located in the rectosigmoid area. Immunohistochemically, no nuclear staining was demonstrated for estrogen or progesterone receptors; only six displayed cytoplasmic staining with estrogen receptor. Although potential importance of estrogen and progesterone receptors has been emphasized by certain reports, its importance is still controversial in terms of both prognosis and management. Moreover, it is unclear whether to exclude cytoplasmic staining. The significance of these receptors in colorectal carcinoma needs to be further studied. [Turk J Cancer 2008;38(3):118-122]

KEY WORDS:

Colorectal adenocarcinoma, estrogen receptor, progesterone receptor

INTRODUCTION

Colorectal adenocarcinoma is the fourth most frequently diagnosed visceral and the second leading cause of cancer mortality in both genders (1). The correlation in mortality data between breast cancer and colonic cancer, and the increased incidence of colonic cancer in individual women with breast cancer suggest common factors in their etiology (2,3). The protective effect of increasing parity from colonic cancer, similar to breast cancer and relatively better prognosis in women may also imply a common role for sex steroid hormones (4-8). The potential importance of estrogen and progesterone receptors is emphasized by evidence of protection by hormone replacement therapy in women and, by a suggestion that the anti-estrogen tamoxifen may enhance the risk of colorectal cancer (9,10).

MATERIALS AND METHODS

In this study, clinicopathologic parameters of 60 colorectal adenocarcinomas diagnosed in the Department of Pathology in Zonguldak Karaelmas University Faculty of Medicine from November 2001 to March 2006 were retrospectively evaluated in terms of age, gender, patho-

logical diagnosis including tumor location, lymph node status, and perineural and lymphovascular invasion. Using infiltrative ductal carcinoma of breast as control estrogen and progesterone receptor expressions were investigated immunohistochemically; nuclear staining more than 5% of tumor cells were accepted positive.

RESULTS

Thirty-one cases were men and 29 were women with an age distribution ranging from 33 to 90 (average 65.8; SD: ± 13.55). Two cases were younger than 40 years.

Eighteen of the sixty cases were from rectosigmoid, followed by 13 from rectum, 6 from sigmoid, each 5 from ascending colon and descending colon, 4 from transverse colon, and 3 from cecum (Figure 1). 6 cases comprised more than one segment; 4 involving ascending and transverse colon and 2 cecum, ascending and descending colon.

Histologic grading for well, moderately and poorly differentiated tumors were consecutively found 17 (28.3%), 37 (61.7%) and 6 (10.0%). Most cases were classified either in B2 (28 cases; 47%) or C2 (21 cases; 35%) according to the Astler Coller staging; stages B1 (5 cases; 8%) and D (6 cases; 10%) constituted the remainder. The correlation of histologic grade with Astler Coller stages is provided in table 1.

There were vascular and perineural invasion in 23 cases and lymph node metastasis in 24 cases (Figure 2). The correlation of lymph node metastasis with tumor grade is given in table 2.

Immunohistochemically no nuclear staining was demonstrated by estrogen or progesterone receptors with exception of six cases displaying cytoplasmic reaction for estrogen receptor (Figure 3).

DISCUSSION

Colorectal adenocarcinoma primarily affects elderly people; increases by the sixth decade and reaches its peak incidence between 60 and 70 years; mean age for both gender is about 62-63 (4,8,11-13). Its incidence under 50 years reaches up to 20% as much and unless there is an underlying condition with predisposition to colorectal carcinoma, it is exceptionally rare under 40 years (13). Correspondingly, this study revealed similar findings, almost akin to the given data.

Although proximal tumors seem to be increased during the last few decades, approximately 50% of all carcinomas occur in the rectosigmoid area as noted in the current study (4,11,14). However, tumors in cecum and ascending colon were fairly less than expected. Likewise, the proportion of well-differentiated tumors was remarkably higher (28%) than poorly differentiated tumors

Table 1
Correlation between histologic grade and Astler Coller stage

HISTOLOGIC GRADE	ASTLER-COLLER STAGE						
	A	B1	B2	C1	C2	D	TOTAL
Well differentiated	0	1	8	0	7	1*	17
Moderately differentiated	0	3	17	0	14	3**	37
Poorly differentiated	0	1	3	0	0	2*	6
TOTAL	0	5	28	0	21	6	60

* No lymph node metastasis

** Lymph node metastasis in one case

Table 2
Correlation of lymph node metastasis and histologic grade

	Lymph Node Metastasis	
	Positive	Negative
Well differentiated	7	10
Moderately differentiated	16	21
Poorly differentiated	0	6

(10%) on the contrary to general observation in which almost the same incidence for both grades (about 15% to 20%) is shared (12). Indubitably, stage is the most important determinant in predicting the prognosis; and notably localized (i.e. stage A) tumors seem to have a tendency to increase compared to the decline in tumors with advanced stages (13,15). Unfortunately, in our series there was no stage A tumor and stage B1 tumors were relatively low. Consequently, tumors with advanced stages (and probably with poor prognosis) constituted the majority; more than half were stage B2. Another controversial and interesting finding was the absence of lymph node metastasis in six poorly differentiated tumors, which may partially be explained by inadequate lymph node excision due to surgical procedure or specimen handling.

Hormonal basis of colon cancer has also been a matter of consideration besides genetic predisposition and potential role of steroid hormones in both carcinogenesis and tumor progression has been indicated (16,17). When equivalent age groups are regarded colon cancer is relatively less frequent in females (4,5). Nullipara women has

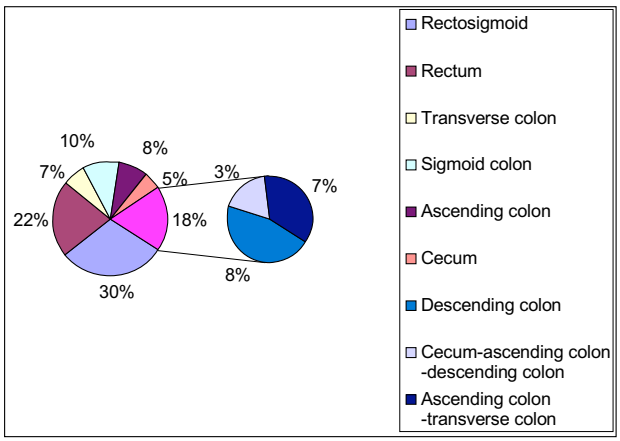

Fig 1. Locations of colonic adenocarcinomas

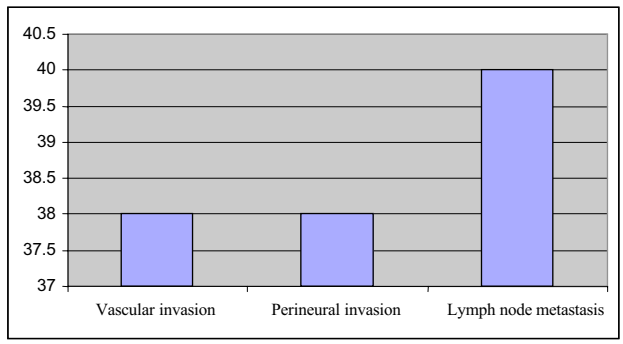

Fig 2. Lymph node metastasis, and vascular and perineural invasion (%)

a greater risk than multipara suggesting the protective effect of increasing parity and hormone replacement therapy is supposed to reduce development of colon cancer (6-11,18). Moreover, coexistence of colon cancer and breast cancer is relatively high (2,3). Expressions of ER and PR have been shown in several extramammary malignant neoplasms including esophagus, stomach, lung, pancreas and gallbladder (3,16,19-26). ER expression in malignant cells of gastric mucosa was proposed to be an independent negative prognostic factor (21); tamoxifen therapy was found to be associated with prolonged survival (19).

Comparable studies, either biochemically or immunohistochemically, revealed that both normal and malignant colonic mucosal cells may express ER and/or PR (9,24,27-37). By biochemical methods, ER exhibited a wide range, varying about 20% to 54% and while PR expression was about 42% (9,24,31,34-39). In addition, ER and PR levels in colonic cancers are usually lower than in mammary cancers and thus it may be difficult to

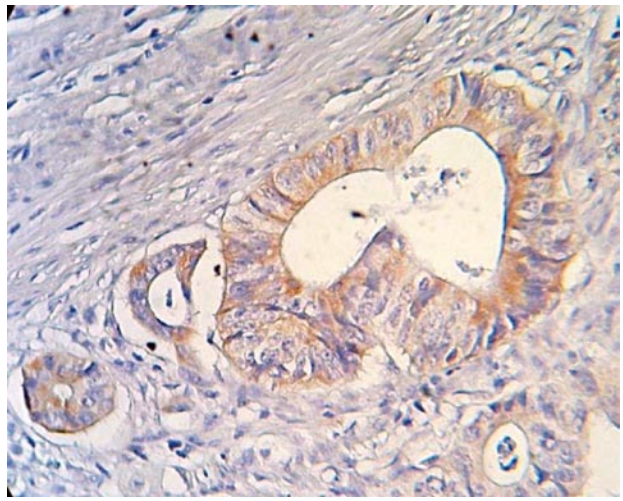

Fig 3. Cytoplasmic estrogen receptor staining in colorectal adenocarcinoma (x200)

detect immunohistochemical expression in gastrointestinal cancers with lower levels (31,36,40). The absence of nuclear staining for both receptors in the current study may also be explained by low levels of receptors probably causing immunohistochemically undetectable expression. In the largest immunohistochemical study composed of 156 colon carcinomas, none was positive for ER, and only one case was reactive for PR while surrounding non-tumoral mucosa was stained with both receptors (9). On the other hand, ER and PR reactions were consecutively found 32% and 23% by Kaklamanos et al. (34). There are also some conflicting reports regarding ER and PR status (32,35,36). In terms of immunohistochemical staining pattern nuclear staining of more than 5% of tumor cells are generally accepted positive while cytoplasmic reaction is considered non-specific. However, some reports proposed that cytoplasmic ER staining should be considered (9). No nuclear reaction for ER or PR was observed in this study; six cases demonstrated cytoplasmic ER. In part, this may be attributed to low receptor levels as previously stated. It may also be associated with other causes such as cell characteristics affected by tissue processing, immunohistochemical method, and perhaps clonality of antibodies (9,35).

The potential importance of estrogen and progesterone receptors is emphasized by evidence of protection by hormone replacement therapy in women and, by a suggestion that the anti-estrogen tamoxifen may enhance the risk of colorectal cancer (9,10). Patients with ER expression are suggested to have a better survival rate (9,39). This observation was supported by animal models and anti-estrogenic therapy was experimentally proved to reduce the incidence of colon cancer (41,42). Nevertheless, patients receiving tamoxifen therapy for breast cancer have a relative risk for colorectal carcinoma (17). Moreover, mechanisms other than receptor status may contribute to positive tamoxifen effect in colorectal cancers (22). Therefore, as well as their detection, significance of ER and PR receptors is still controversial in terms of both management and prognosis.

References

1. Harpaz N, Saxena R. Gastrointestinal Tract, Large Intestine. In: Weidner N, Cote RJ, Suster S, Weiss LM, editors. Modern Surgical Pathology. 1st ed. Philadelphia: Elsevier-Saunders, 2003;749-852.
2. Persson I, Yuen J, Bergkvist L, et al. Cancer incidence and mortality in women receiving estrogen and estrogen-progestin replacement therapy: Long-term follow-up of a Swedish cohort. Int J Cancer 1996;67:327–32.
3. Herrman JB. Breast cancer and associated extramammary malignant neoplasms. Am J Surg 1972;124:620-4.
4. Jemal A, Tiwari RC, Murray T, et al. American Cancer Society. Cancer statistics, 2004. CA Cancer J Clin 200454: 8-29.
5. Potter JD, Slattery ML, Bostick RM, et al. Colon cancer: a review of the epidemiology. Epidemiol Rev 1993;15:499-545.
6. Potter JD. Hormones and colon cancer. J Natl Cancer Inst 1995;87:1039-40.
7. Henderson BE, Feigelson HSH. Hormonal carcinogenesis. Carcinogenesis 2000;21:427-33.
8. Lyall MS, Dundas SR, Curran S, et al. Profiling markers of prognosis in colorectal cancer. Clin Cancer Res 2006;12:1184-91.
9. Slattery ML, Samowitz WS, Holden JA. Estrogen and progesterone receptors in colon tumors. Am J Clin Pathol 2000;113:364-8.
10. Hebert-Croteau N. A meta-analysis of hormone replacement therapy and colon cancer in women. Cancer Epidemiol Biomarkers Prev 1998;7:653-9.
11. Rosai J, Gastrointestinal Tract, Large Bowel. In: Rosai J, editor. Rosai and Ackerman's Surgical Pathology. 9th ed. Philadelphia: Mosby, 2004;776-855.
12. Cooper HS, Intestinal neoplasms. In: Mills SE, Carter D, Greenson JK, et al., editors. Sternberg's Diagnostic Surgical Pathology. 4th ed. Philadelphia: Lippincott Williams&Wilkins, 2004;1543-601.
13. Liu C, Crawford JM, The Gastrointestinal Tract-Small and Large Intestines. In: Kumar V, Abbas AK, Fausto N, editors. Robbins and Cotran Pathologic Basis of Disease. 7th ed. Philadelphia: Elsevier Saunders, 2004;797-875.
14. Greenstein AJ, Slater G, Heimann TM, et al. A comparison of multiple synchronous colorectal cancer in ulcerative colitis, familial polyposis coli, and de novo cancer. Ann Surg 1986;203:123-8.
15. Ponz de Leon M, Marino M, Benatti P, et al. Trend of incidence, subsite distribution and staging of colorectal neoplasms in the 15-year experience of a specialised cancer registry. Ann Oncol 2004;15:940-6.

16. Oshima CT, Wonraht DR, Catarino RM, et al. Estrogen and progesterone receptors in gastric and colorectal cancer. Hepatogastroenterology 1999;46:3155-8.
17. Goldman S, Shalev E. Progesterone receptor profile in the decidua and fetal membrane. Front Biosci 2007;12:634-48.
18. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, et al. Women's Health Initiative Investigators. Estrogen plus progestin and colorectal cancer in postmenopausal women. N Engl J Med 2004;350:991-1004.
19. Alford TC, Do HM, Geelhoed GW, et al. Steroid hormone receptors in human colon cancers. Cancer 1979;43:980-4.
20. Jacobs E, Watson SA, Hardcastle JD, et al. Oestrogen and progesterone receptors in gastrointestinal cancer cell lines. Eur J Cancer 1996;32:2348-53.
21. Kojima O, Takahashi T, Kawakami S, et al. Localization of estrogen receptors in gastric cancer using immunohistochemical staining of monoclonal antibody. Cancer 1991;67:2401-6.
22. Harrison JD, Watson S, Morris DL. The effect of sex hormones and tamoxifen on the growth of human gastric and colorectal cancer cell lines. Cancer 1989;11:2148–51.
23. Radzikowska E, Langfort R, Giedronowicz D. Estrogen and progesterone receptors in non small cell lung cancer patients. Ann Thorac Cardiovasc Surg 2002;8:69-73.
24. Meggouh F, Lointier P, Pezet D, et al. Status of sex steroid hormone receptors in large bowel cancer. Cancer 1991;67:1964-70.
25. Lau SK, Chu PG, Weiss LM. Immunohistochemical expression of estrogen receptor in pulmonary adenocarcinoma. Appl Immunohistochem Mol Morphol 2006;14:83-7.
26. Greenway B, Iqbal MJ, Johnson PJ, et al. Oestrogen receptor protein in malignant fetal pancreas. Br Med J 1989;283:751-3.
27. Deroo BJ, Korach KS. Estrogen receptors and human disease. J Clin Invest 2006;116:561-70.
28. Herynk MH, Fuqua SA. Estrogen receptor mutations in human disease. Endocr Rev 2004;25:869-98.
29. Conneely OM. Perspective: female steroid hormone action. Endocrinology 2001;142:2194-9.
30. Althuis MD, Fergenbaum JH, Garcia-Closas M, et al. Etiology of hormone receptor-defined breast cancer: a systematic review of the literature. Cancer Epidemiol Biomarkers Prev 2004;13:1558-68.
31. Meggouh F, Lointier P, Saez S. Sex steroid and 1,25-dihydroxyvitamin D3 receptors in human colorectal adenocarcinoma and normal mucosa. Cancer Res 1991;51:1227-33.
32. Francavilla A, Di Leo A, Polimeno L. Nuclear and cytosolic estrogen receptors in human colon carcinoma and in surrounding noncancerous colonic tissue. Gastroenterology 1987;93:1301-6.
33. Issa JP, Ottaviano YL, Celano P, et al. Methylation of the oestrogen receptor CpG island links ageing and neoplasia in human colon. Nat Genet 1994;7:536-40.
34. Kaklamanos IG, Bathe OF, Franceschi D, et al. Expression of receptors for estrogen and progesterone in malignant colonic mucosa as a prognostic factor for patient survival. J Surg Oncol 1999;72:225-9.
35. Dawson PM, Shousha S, Blair SD, et al. Oestrogen receptors in colorectal carcinoma. J Clin Pathol 1990;43:149-51.
36. Cameron BL, Butler JA, Rutgers J, et al. Immunohistochemical determination of the estrogen receptor content of gastrointestinal adenocarcinomas. Am Surg 1992;58:758-60.
37. Sciascia C, Olivero G, Comandone A, et al. Estrogen receptors in colorectal adenocarcinomas and in other large bowel diseases. Int J Biol Markers 1990;5:38-42.
38. Hendrickse CW, Jones CE, Donovan IA, et al. Oestrogen and progesterone receptors in colorectal cancer and human colonic cancer cell lines. Br J Surg 1993;80:636-40.
39. Di Leo A, Messa C, Russo F, et al. Prognostic value of cytosolic estrogen receptors in human colorectal carcinoma and surrounding mucosa. Preliminary results. Dig Dis Sci 1994;39:2038-42.
40. Singh S, Sheppard MC, Langman M. Sex differences in the incidence of colorectal cancer: an exploration of oestrogen and progesterone receptors. Gut 1993;34:611-5.
41. Narayan S, Rajakumar G, Prouix H, et al. Estradiol is trophic for colon cancer in mice: Effect on ornithine decarboxylase and cmyc messenger RNA. Gastroenterology 1992;103:1823-32.
42. Ziv Y, Fazio VW, Kitago K, et al. Effect of tamoxifen on 1,2-dimethylhydrazine-HCL-induced colon carcinogenesis in rats. Anticancer Res 1997;17:803-10.