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SERUM CONCENTRATIONS OF INSULIN-LIKE GROWTH FACTOR 1 IN COLONIC NEOPLASIA

Several recent studies have focused attention on a possible role of hormones and growth factors in the initiation and growth of colonic neoplasia (adenomas and carcinomas). Specifically, the increased incidence of colonic neoplasia in patients with acromegaly (1-6), a disorder of growth hormone overproduction by a pituitary adenoma, strongly suggests that excess of either growth hormone itself or insulin-like growth factor 1 (IGF-1; synonym: somatomedin C), a polypeptide growth factor whose production is stimulated by growth hormone, can lead to development of colonic adenomas or cancer. These observational studies are supported by biochemical studies, indicating that colon cancer cell lines possess receptors for IGF-1 and that IGF-1 can stimulate mitogenesis and growth of these neoplastic cells (7, 8). As a preliminary step in the exploration of a potential role for IGF-1 in the pathogenesis of colonic neoplasia in the non-acromegalic general-population, we measured the circulating concentrations of this hormone in 334 healthy subjects who underwent complete colonoscopy to assess the presence or absence of colon polyps and colon neoplasia.

Material and Methods. All healthy adult men and postmenopausal women who were undergoing colonoscopy at Walter Reed Army Medical Center from 1984 through 1987 because of occult blood in the stool or because of possible colonic polyps seen on barium enema were solicited to participate in this study. Subjects were excluded if they had a history of colonic adenomas or cancer, familial polyposis, inflammatory bowel disease, malabsorption, alcoholism, recent weight loss, and renal or hepatic disease. In addition, 9 other subjects with cancer in pedunculated colonic adenomas were also included; 8 of these patients were identified during a concurrent study of colonic adenoma recurrence. All subjects underwent complete colonoscopy with biopsy of all polyps; subjects with incomplete colonoscopy or inadequate biopsy specimens were excluded. Histologic evaluation was initially performed by the Department of Pathology, Walter Reed Army Medical Center, with re-evaluation and confirmation by one of the authors (LHS) for 80 subjects, including all those with diagnoses of carcinoma in a pedunculated adenoma, carcinoma-in-situ, and high grade or severe dysplasia. Based on results of colonoscopy, subjects were classified into one of three categories: control, adenoma, or carcinoma. Classification as a control required colonoscopy complete to the cecum, biopsy of all polyps visualized, and no pathologic diagnosis of adenoma or carcinoma. The finding of hyperplastic polyps was not considered in the assignment of subjects to diagnostic categories. Blood samples were obtained from all subjects between 07.00 and 09.30 h after an overnight fast. Blood was allowed to clot at room temperature, centrifuged, aliquotted into air-tight vials, stored at -80°C for 3-7 years, and subsequently shipped on dry ice for measurement of

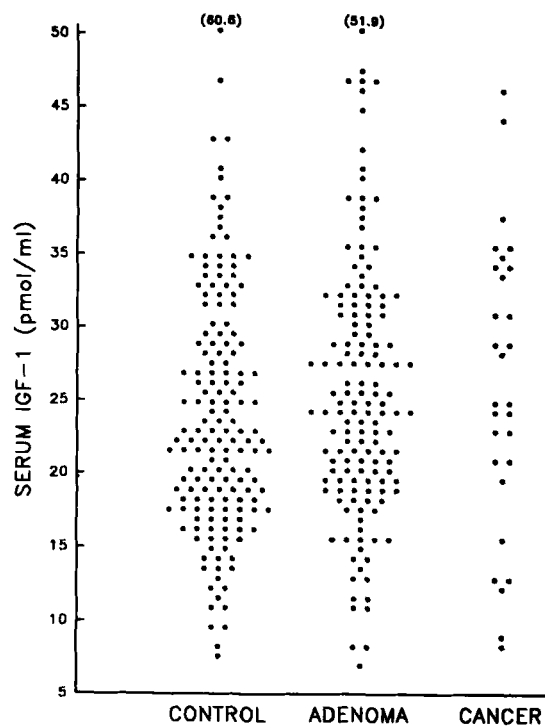


Figure. Serum IGF-1 concentrations in 334 subjects according to diagnostic category. The IGF-1 concentrations of two subjects whose values were off-scale are indicated in parentheses.

IGF-1 (Endocrine Sciences, Tarzana, CA, USA). After acid-ethanol extraction, serum samples were assayed for IGF-1 by double antibody radioimmunoassay using an antibody directed against IGF-1 57-70. Assay sensitivity is 3.3 pmol/ml with interassay variation of 13%. Statistical analysis was performed using Wilks-Shapiro test for normality, analysis of variance, student's t-test, and χ^2 test. This project was approved by the Clinical Investigation and Human Use Committees of Walter Reed Army Medical Center, and all subjects provided written, informed consent.

Results. The mean ages in the 3 diagnostic groups were slightly but significantly different (control = 58.4 years, adenoma = 60.3,

Table

Serum IGF-1 concentrations in colonic neoplasia

	Serum IGF-1 (pmol/ml)	Frequency of high serum IGF-1 (%)
Control (n = 159)	24.0 \pm 0.7	2.5
	NS	NS
Neoplasia (n = 175)	25.7 \pm 0.7	6.3
Adenoma (n = 146)	25.6 \pm 0.7	6.2
Carcinoma (n = 29)	26.2 \pm 1.8	6.9

Serum IGF-1 concentrations are mean \pm SEM. Neoplasia group is a combination of adenoma and carcinoma groups. High serum IGF-1 is defined as greater than 40.3 pmol/ml (mean + 2 SD of controls). NS indicate that values connected by arrows are not significantly different (ANOVA or student's t-test for serum IGF-1 and χ^2 -test for % high serum IGF-1).

carcinoma = 63.9); 20 of the 29 patients with carcinoma had Dukes A disease. Serum IGF-1 concentrations in each of the three subject groups were normally distributed (Figure), and the mean serum IGF-1 concentrations were not significantly different among them (Table). Likewise, the frequency of elevated serum IGF-1 concentrations (more than 2 SD above the control mean) was also not different among the three groups (Table). Since the adenoma and carcinoma groups did not differ significantly from each other, they were combined into a single neoplasia group for additional analysis. The neoplasia group did not differ from control in either the mean serum IGF-1 level nor in the frequency of high serum IGF-1 concentrations (Table).

Discussion. Several clinical studies have reported a high incidence of colon polyps and colon cancer in patients with acromegaly (1–6), and it is now routine to screen such patients for colon neoplasia. Until recently, it has been thought that the peripheral manifestations of acromegaly, including colon neoplasia, presumably reflected the effect on target tissues of high serum levels of IGF-1, most of which appears to derive from the liver in response to the growth hormone overproduction. Consequently, the association between colon neoplasia and acromegaly raised the possibility of a role for high circulating IGF-1 in the pathogenesis of colonic neoplasia in patients without obvious clinical acromegaly. This possibility seems to be excluded by the present study's finding of normal serum IGF-1 concentrations in such patients; in other words, high serum IGF-1 concentrations (i.e. subclinical acromegaly) are not an important cause of colonic neoplasia in the population at large. This conclusion is perhaps not surprising in view of the rarity of acromegaly when compared to the high prevalence of colonic polyps. However, the potential role of IGF-1 in neoplasia has been strengthened by the recent discovery that IGF-1 could be generated in multiple peripheral tissues besides the liver, raising the possibility that some of the tissue effects previously attributed to high circulating IGF-1 concentrations might actually reflect local production and action of IGF-1 within the target tissues themselves. Such local production and action of IGF-1 could occur without spillover of IGF-1 into the systemic circulation or alteration of serum IGF-1 concentrations. In fact, production of a substance similar to IGF-1 by colon cancer cells has been described (9), as has evidence that IGF-1, produced by such neoplastic cells, can have an autocrine action (effect of the growth factor on the cell that produces it) (10). Consequently, although our study suggests that high circulating concentrations of IGF-1 are not important in the pathogenesis of colon neoplasia in the general population, the role of local production and action of IGF-1 and similar growth factors within the gastrointestinal tract itself appears to be a highly promising area for further investigation.

ACKNOWLEDGEMENTS

Funding was provided by the Department of Clinical Investigation, Walter Reed Army Medical Center, and by the National Institutes of Health (NCI grant CA 36978). The opinions and assertions contained herein are the personal views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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August 1993

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BREAST METASTASIS OF THYROID FOLLICULAR CARCINOMA

The breast is an unusual site for secondary malignant tumors (1). The most frequent sites of the primary tumor (excluding the contralateral breast) are the skin (melanoma), the lung, the prostate, the ovary, the stomach and the uterine cervix (1, 2). Only 10 cases of breast metastases of a thyroid carcinoma have been described (2–5). Breast metastasis may be observed in patients with disseminated cancer or, more rarely, be the first sign of an occult extra-mammary cancer (6–8). Fine-needle biopsy for cytology and/or histology of a metastasis is often useful for location of the primary tumor and choice of adequate treatment (7, 9). We now report a case with a history of goiter referred to us for a breast nodule. FNAB of this nodule, together with immunohistochemical techniques, revealed metastasis of thyroid follicular carcinoma.