INTRODUCTION

Hormones are believed to play a dominant role as promoters in the growth and development of hormone dependent cancers. In the previous chapters, it was observed that patients with colon/rectal cancer had elevated levels of prolactin and estradiol with concomitant low levels of androgens. Several peptide hormones such as gastrin and cholecystokinin have been shown to exert trophic effects on the growth and differentiation of normal as well as malignant gastrointestinal cells in-vitro and in-vivo (Hudd et al. 1989, McGregor et al. 1989, Watson et al. 1989). However, much less is known about circulating peptide hormones in patients with colon/rectal cancer.

The aim of this study was to explore the significance of follicle stimulating hormone and luteinizing hormone in patients with colon and rectal cancer which might provide a better understanding in the etiology of colon/rectal cancer. The levels of the preoperative hormones were correlated with clinicopathologic prognosticators.
Patients

In this study, a total of 60 male patients with Dukes B or C colon/rectal carcinoma registered at The Gujarat Cancer and Research Institute, Ahmedabad, between January 1989 and December 1990 were enrolled.

The details of clinical history such as age, anatomic site of the lesion (colon/rectum), operative findings, Dukes stage, histologic type, grade of the tumor, were noted from the case files maintained at the Medical Record Department of the Institute and recorded at the Division of Molecular Endocrinology.

The reference group consisted of 30 healthy (nonsmokers and smokers) age-matched controls.

Disease was staged according to modified Dukes classification (Dukes and Bussey 1958). The histologic characteristics were assessed independently by two histopathologists.

Blood collection

Venous blood samples were collected preoperatively in ethylenediamine tetraacetic acid (EDTA), disodium salt
coated tubes (1-2 mg/ml), between 9:00 and 11:00 AM to avoid diurnal variation. Blood was separated within 2 hours, and plasma was aliquoted and preserved at -70 C till analysis.

Peptide hormone assays
Follicle stimulating hormone (FSH) and luteinizing hormone (LH) were assayed in 60 patients using radioimmunoassay (RIA) kits procured from Binax, USA. The assays were performed in duplicate with an intra- and inter-assay coefficient of variation (CV) of 3% to 8%, along with internal quality controls. The sensitivity of the assay kit was 1.6 mIU/ml for FSH and 1.8 mIU/ml for LH.

The normal range of the peptide hormones is listed below:

<table>
<thead>
<tr>
<th>Hormones</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) FSH</td>
<td>4.5 to 20.0 mIU/ml plasma.</td>
</tr>
<tr>
<td>(2) LH</td>
<td>Undetectable to 25.0 mIU/ml plasma.</td>
</tr>
</tbody>
</table>

The levels above or below the normal range were considered elevated or subnormal, respectively.

Statistical analysis
Significance was calculated using an exact contingency table test for order data and Fisher’s two sided exact
test (Mehta and Patel 1983). P values less than 0.05 were considered significant.

RESULTS

Incidence of FSH and LH

The distribution of FSH and LH in patients with colon/rectal cancer is depicted in Table 1.

Circulating levels of FSH (P<0.02) and LH were higher in patients with colon/rectal cancer as compared to controls (Table 1). Elevated levels of FSH and LH were observed in 20% (12/60) and 22% (13/60) patients, respectively. Subnormal levels of FSH were noted in 22% (13/60) patients.

Table 1: Distribution of FSH and LH in controls and in patients with colon/rectal cancer (M ± SE).

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>FSH (mlu/ml)</th>
<th>LH (mlu/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>30</td>
<td>9.37 ± 0.73*</td>
<td>13.78 ± 0.75</td>
</tr>
<tr>
<td>Colon/rectal cancer patients</td>
<td>60</td>
<td>14.56 ± 1.86*</td>
<td>20.96 ± 3.55</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td>1.00 - 65.00</td>
<td>1.00 - 175.33</td>
</tr>
</tbody>
</table>

P value: * P<0.02
Relation of FSH and LH to age

The levels of FSH and LH were lower in younger patients (age <40 years) than in older patients (age >40 years). However, the difference was statistically non-significant (Table 2).

Table 2: Relation of FSH and LH to age of the patients (M ± SE).

<table>
<thead>
<tr>
<th>Hormones</th>
<th>N</th>
<th>Age &lt;40 Years</th>
<th>N</th>
<th>Age &gt;40 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH (mIU/ml)</td>
<td>13</td>
<td>9.42 ± 2.69</td>
<td>47</td>
<td>15.98 ± 2.22</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>13</td>
<td>16.53 ± 4.10</td>
<td>47</td>
<td>22.18 ± 4.37</td>
</tr>
</tbody>
</table>

Relation of FSH and LH to anatomic site of the lesion

Patients when subgrouped according to anatomic site of the lesion, it was observed that the mean level of FSH and LH was higher in patients with colon cancer than in patients with cancer of the rectum. However, the differences were statistically non-significant (Figures 1–2).

Relation of FSH and LH to Dukes stage

A trend towards higher level of LH was observed in
patients with Dukes B disease than in patients with Dukes C disease. Such a trend was not observed for FSH between the two subgroups of patients (Figures 1-2).

Relation of FSH and LH to histologic type of the tumor
The mean level of FSH and LH was higher in patients with adenocarcinoma (N=56) as compared to patients with squamous cell carcinoma and transitional cell carcinoma (N=4). Due to small number of patients in the latter group, the data was not evaluated for statistical significance (Figures 1-2).

Relation of FSH and LH to histologic grade of the tumor
The mean level of LH was higher in patients with grade III tumors than in patients with grade I or II tumors. However, the difference was statistically non-significant. Such a trend was not observed for FSH (Figures 1-2).
Figure 1: Histogram showing distribution of FSH in patients with colon/rectal cancer according to clinicopathologic parameters. C—colon; R—rectum; A—adenocarcinoma; O—others; W—well differentiated; M—moderately differentiated; P—poorly differentiated.
Figure 2: Histogram showing distribution of LH in patients with colon/rectal cancer according to clinicopathologic parameters. C—colon; R—rectum; A—adenocarcinoma; O—others; W—well differentiated; M—moderately differentiated; P—poorly differentiated.
DISCUSSION

Gastrointestinal hormones are chemical messengers which regulate gut functions. Observations from experimental and epidemiologic investigations have suggested that certain hormones important in the development and the maintenance of the mucosa may also be involved in the development of mucosal cancer (Conteas et al. 1988). Moreover, determining their exact role in patients with colon/rectal cancer is difficult. This study demonstrated that the levels of FSH and LH were elevated in patients when compared to controls. Similar results were observed in patients with cancer of the prostate, oesophagus, lung and tongue (Andersson et al. 1993, Bhatavdekar et al. 1994a, b, c).

FSH and LH levels were correlated with age and clinicopathologic parameters. Significant difference in the levels of FSH and LH was not observed between younger (age <40 years) and older (age >40 years) patients. The results were in accordance to those reported by Griffiths et al. (1979). Further, the present study indicated that the concentration of peptide hormones did not influence Dukes stage, site of the lesion, histologic type and grade of the tumor. In
contrast, Andersson et al. (1993) showed a significant correlation of peptide hormones to age, stage and grade of the tumor in patients with prostatic cancer.

These results indicated that peptide hormones may play a role in the etiology of colon/rectal cancer. Moreover, when prolactin, steroid hormones and gonadotrophins were combined it was observed that in 98% (59/60) patients at least one hormone was abnormal which might be responsible for the hormonal imbalance. The mechanism responsible for the hormonal imbalance in patients with colon/rectal cancer is not clear but the most likely explanation is the disturbance in the pituitary-adrenal-testicular axis leading to the development and/or progression of colon/rectal cancer. This is in agreement with the findings of Bhatavdekar et al. (1994a, b, c) in male patients with lung, oesophagus and tongue cancer.

From this study, it can be concluded that both peptide and steroid hormonal abnormalities may presumably favour the onset of colon/rectal cancer and the altered levels might be responsible for the aggressiveness of colon/rectal cancer. These hormonal abnormalities were severe and/or irreparable in colon/rectal cancer.
This study requires the further analysis of hormones in patients with colorectal polyposis, colorectal adenoma and patients with Dukes A disease for the confirmation of hormonal role in the pathogenesis of colon/rectal carcinoma.

**ABSTRACT**

This chapter evaluates the significance of gonadotrophins in patients with colon/rectal cancer (N=60). Follicle stimulating hormone (FSH) was significantly high in patients with colon/rectal cancer compared to controls (P<0.02). The levels of luteinizing hormone (LH) was higher in patients than in controls, however, the difference was statistically non-significant. A trend towards higher mean levels of FSH was observed in older patients (age >40 years) than in younger (age <40 years) patients. Intergroup variation was not observed in the mean levels of FSH and LH when grouped according to anatomic site of the tumor, Dukes stage, histologic type and histologic grade of tumor.
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