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Leading article

Oestrogen and colonic epithelial cell growth

Oestrogen may play a physiological part in regulation of colonic epithelium cell growth and the development of large bowel cancer. Circulating oestrogens are present in men in similar concentration to that found in postmenopausal woman, and oestrogen receptors have been shown in various sites including bone, liver, and kidney. This article reviews the evidence for oestrogen action in the large bowel.

Oestrogen exposure and incidence of large bowel cancer

Sex differences

There are differences between men and women in incidence of large bowel cancer. Site specific incidence rates show a female predominance for cancer of the caecum and ascending colon while rectal cancer is male predominant.[1] A male predominance is also seen in experimentally induced bowel cancer, male rats have a twofold increased risk of dimethylhydrazine induced bowel tumours and a shorter survival compared with female rats.[2 3] There is also a sex difference in prognosis in humans with large bowel cancer where women on average survive longer.[4]

Association with breast cancer

Breast cancer is an oestrogen dependent malignancy. International mortality data show a positive correlation between cancer of the colon and breast cancer.[5] Furthermore women with breast cancer experience a near doubling in the occurrence of a second primary cancer or adenomata of the large bowel.[6] Those with cancer in the large bowel are also at increased risk for the development of breast cancer. A similar relation exists between large bowel cancer and cancer of the endometrium. An increased colonic crypt cell proliferation rate has been measured in women with breast cancer compared with controls.[7]

Effect of parity

In pregnancy both oestrogen and progesterone concentrations are greatly increased and parity protects against breast cancer. Several studies also suggest a protective effect of parity on the risk of developing large bowel cancer. Some studies show that the risk of large bowel cancer diminishes as parity increases.[8] Parity also influences prognosis with a longer five year survival rate in parous women (45%) compared with nulliparous women (37%).[4] Whether this difference reflects biological variation in tumour behaviour or social differences affecting the time of presentation is not yet clear.

Effect of exogenous hormone

A recent large prospective study of hormone replacement therapy (HRT) in postmenopausal women has found a diminished mortality from bowel cancer in women treated with hormone.[9] The relative risk of mortality from colonic cancer in those who had ever used HRT was 0·71 and in current users was 0·55. This important finding is consistent with a number of previous smaller studies. It is not clear whether HRT diminishes incidence of colonic cancer or improves survival after diagnosis. Alternatively the effect may be due to some lifestyle factor associated with use of HRT. The recent finding that tamoxifen use may enhance risk of colonic cancer suggests that the effect of HRT is through a direct endocrine mechanism.[10]

Association with obesity

Obesity is a risk factor for breast and endometrial cancer in women. Some evidence suggests that it is also a risk factor for large bowel cancer. An increased mortality from large bowel cancer in men and women 30–40% in excess of their ideal weight has been reported.[11] An increased incidence of colonic adenomata has also been described in the obese.[12]

The mechanism through which obesity influences the risk of large bowel cancer and breast cancer is uncertain but could be endocrine. Free oestradiol concentrations are higher in obese men and women as they have lower concentrations of sex hormone binding globulin.[13] It is interesting that the Japanese have a comparatively low incidence of both breast cancer and large bowel cancer, and Japanese women have lower free oestradiol values than British women.[14]

Is oestrogen receptor present in the large bowel?

To be directly responsive to oestrogen, the receptor needs to be expressed in large bowel mucosa. Studies confirming or refuting the presence of oestrogen receptor usually use a radioligand binding assay, a technique of limited sensitivity. Alford *et al*[15] first demonstrated receptor-like binding of oestrogen in large bowel mucosa and cancer although many samples were negative for the receptor. Using more sensitive techniques of oestrogen receptor enzyme immunoassay we[16] and others[17] have detected small amounts of oestrogen receptor in large bowel mucosa and cancer ranging between 1–7 fmol/mg protein. Our finding of specific receptor mRNA supports the presence of oestrogen receptor in the large bowel. The amount of receptor detected is much less than that found in breast cancers, which commonly express more than 100 fmol/mg, and where receptor expression less than 10 fmol/mg is conventionally accepted as non-significant. Yet the amount expressed in the colon is not dissimilar to that expressed in normal breast tissue – that is, 2–10 fmol/mg – depending on the phase of the menstrual cycle.[18]

Attempts to localise oestrogen receptor by immunohistochemistry have been unsuccessful. However, immunohistochemistry for oestrogen receptor is comparatively insensitive where even normal breast tissue fails to stain in the luteal phase of the menstrual cycle.[19] In situ hybridisation for oestrogen receptor mRNA produced an unexpected result, with localisation of signal to cells in the lamina propria.[20] However, oestrogen receptor is probably also expressed in the epithelial cell layer as mRNA and protein for oestrogen receptor have been detected in cell lines derived from colonic epithelium.[17 21] Thus, small amounts of oestrogen receptor are expressed in large bowel mucosa and cancer but the cellular location has yet to be identified.

Function of oestrogen receptor in the large bowel

It cannot be assumed that the receptor in large bowel mucosa serves some physiological role. We have measured by enzyme immunoassay oestrogen receptor expression elsewhere in the gastrointestinal tract[22–24] (Table), and found that oestrogen receptor is differentially expressed, with receptor level in the large bowel lower than in the stomach, but higher than that expressed in pancreas and large bowel muscularis propria. This suggests that oestrogen receptor expression in the gastrointestinal tract may be purposeful.

There are few in vivo studies on the effects of oestrogen on colonic epithelial growth. Galand *et al*[25] reported a growth stimulatory effect in mice. Hoff *et al*[26] found that ovariectomy led to colonic crypt atrophy, although oestrogen did not have a growth stimulatory effect. We have examined the effect of oestrogen on adenoma derived and carcinoma derived colonic epithelial cell lines. Moderate growth stimulation was seen in a slow growing adenoma cell line, but none was detected in a chemically transformed derivative or a carcinoma derived cell line.[21] If these results are reflected in vivo then oestrogen could promote the growth of adenomatous polyps but exert little effect on cancers. The lack of therapeutic effect of tamoxifen in advanced large bowel cancer is therefore not surprising.[27]

Oestrogen receptor fmol/mg total protein in the gastrointestinal tract and pancreas determined by enzyme immunoassay

	Large bowel mucosa	*Stomach mucosa*	*Pancreas*	*Large bowel smooth muscle*
Normal	3·3	13·7	1·0	1·9
Cancer	2·8	1·8	0·5	

In breast cancer expression of the proteins pS2 and ERD5 correlates with the presence of oestrogen receptor, and response to tamoxifen therapy.[28 29] pS2 is a peptide now recognised to participate in mucosal regeneration. ERD5 is a heat shock protein (HSP27) closely associated with oestrogen receptor. Both pS2 and ERD5 are inducible by oestrogen in breast cancer cells.[30 31] We have with colleagues at the Imperial Cancer Research Fund, sought and found expression of pS2 and ERD5 mRNA and protein in large bowel epithelium.[20] This lends support to the presence of functional oestrogen receptor in large bowel epithelium.

The functional role of oestrogen in the large bowel remains to be specified. Progress towards this goal is unlikely by in vivo animal experiments. Parenteral treatment with oestrogen of an animal is a non-specific stimulus. Colonic cell lines and short-term primary cultures need to be further studied in vitro. Oestrogen responsive genes need to be identified. Some progress has already been made in the small bowel, the proto-oncogene c-fos has been shown to be oestrogen responsive in a mouse small intestinal cell line, which expresses an amount of oestrogen receptor similar to that found in colonic derived cell lines.[32]

Oestrogen and progesterone may have actions on the gastrointestinal muscularis propria, which is equipped with receptors for the two hormones.[23] A sex difference in gastrointestinal transit time has been shown in several studies. A recent study by Lampe *et al*[33] compared bowel transit in women of reproductive age, with men of similar age. Total gut transit time, as measured by radio-opaque markers was some 30% faster in men when identical amounts of fibre were taken. Segmental transit studied by a single film *x* ray technique showed that the sex difference in transit was most apparent in the right colon.[34] In addition, many women experience a cyclical variation in their bowel habit with the menstrual cycle, usually with loose stools at the time of menstruation.[35]

Unexpected sources of oestrogen

Diet itself can influence the endocrine milieu through modulation of the enterohepatic circulation of corticosteroids. Women eating a vegetarian diet have lower circulating oestrogen concentrations and increased faecal excretion of steroid metabolites than women eating an omnivorous diet.[36] Similar findings have been reported in men.[37] High fibre diets also increase the concentration of circulating sex hormone binding globulin and thus decrease the availability of free hormone.[38]

Any protective effect of high fibre or vegetarian diets on risk from large bowel cancer might be through modulation of the enterohepatic circulation of sex steroids, or through direct hormone-like effects. Dietary lignans and phyto-oestrogens seem to be partial oestrogen agonists and dietary phyto-oestrogens have been identified as the cause of outbreaks of infertility in sheep in Australia.[39] Lignans and phyto-oestrogens are found mainly in soy, grain, and other fibre rich food. Other oestrogenic compounds have been identified in foods. Yams contain diosgenin, which can stimulate mammary gland epithelium in ovariectomised mice.[40] Indeed in the past yams were used to manufacture oestrogens for human and animal use. The congener component of the alcoholic beverage bourbon whisky has oestrogenic activity in an in vivo assay, causing an increase in the size of the uterus in ovariectomised rats.[41] Differences in the incidence of cancer of the prostate between Japanese men (low incidence) and Western men (high incidence) may be related to these dietary oestrogens as Japanese men have plasma

concentrations of some phyto-oestrogens up to 100 times those of Western men.[42]

Some modern industrial and agricultural chemicals have oestrogenic action and may be responsible for changes such as the change in sex ratio in salmon swimming in polluted rivers, and the fall in sperm count seen in men. Whether such environmental agents have effects on the gastrointestinal tract is unknown.

The future

Current work supports the presence of oestrogen receptor in large bowel mucosa. The comparatively low expression of receptor in bowel tumours makes it unlikely that anti-oestrogen therapy will be effective. Yet oestrogen may play a part in the control of epithelial growth in adenomata and possibly normal mucosa. Future progress will rely on identification of oestrogen responsive genes in colonic cell lines in vitro.

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