

ABSTRACTS

Cancer

Dietary fat intake and risk of prostate cancer: a prospective study of 25,708 Norwegian men.

The relationship between incidence of prostate cancer and intake of dietary fat and foods rich in fat was studied in 25,708 men aged 16-56 years attending a Norwegian health screening in 1977-1983. Linkage to the Cancer Registry of Norway and the Central Bureau of Statistics of Norway ensured a complete follow-up until December 31, 1992. Diet was recorded on a semi-quantitative food-frequency questionnaire at the time of screening, and 72 cases of prostate cancer were identified during follow-up. At the end of follow-up, mean age of the total study sample was 56 years (range 19-68), while mean age at diagnosis of prostate cancer was 60 years (range 47-67). No association was found between energy-adjusted intake of total fat, saturated fat, mono-unsaturated fat or poly-unsaturated fat and the incidence of prostate cancer. Significant positive associations were found for body mass index (BMI) and consumption of hamburgers/meatballs, while no association was found with consumption of frankfurters/sausages and a significant negative association with the weekly number of main meals with meat. A significantly increased risk of prostate cancer was associated with skim milk as compared to whole milk. Milk preference (skim vs. whole) was associated significantly positively with BMI. Our study of a relatively young cohort does not confirm previous case-control and cohort studies suggesting that dietary fat, especially from animal sources, is associated positively with risk of prostate cancer.

Int J Cancer. 1997 Nov 27;73(5):634-8

A prospective study of dietary fat and risk of prostate cancer.

BACKGROUND: The strong correlation between national consumption of fat and national rate of mortality from prostate cancer has raised the hypothesis that dietary fat increases the risk of this malignancy. Case-control and cohort studies have not consistently supported this hypothesis. **PURPOSE:** We examined prospectively the relationship between prostate cancer and dietary fat, including specific fatty acids and dietary sources of fat. We examined the relationship of fat consumption to the incidence of advanced prostate cancer (stages C, D, or fatal cases) and to the total incidence of prostate cancer. **METHODS:** We used data from the Health Professionals Follow-up Study, which is a prospective cohort of 51,529 US men, aged 40 through 75, who completed a validated food-frequency questionnaire in 1986. We sent follow-up questionnaires to the entire cohort in 1988 and 1990 to document new cases of a variety of diseases and to update exposure information. As of January 31, 1990, 300 new cases of prostate cancer, including 126 advanced cases, were documented in 47,855 participants initially free of diagnosed cancer. The Mantel-Haenszel summary estimator was used to adjust for age and other potentially confounding variables. Multiple logistic regression was used to estimate relative risks (RRs) when controlling simultaneously for more than two covariates. **RESULTS:** Total fat consumption was directly related to risk of advanced prostate cancer (age- and energy-adjusted RR = 1.79, with 95% confidence interval [CI] = 1.04-3.07, for high versus low quintile of intake; P [trend] = .06). This association was due primarily to animal fat (RR = 1.63; 95% CI = 0.95-2.78; P [trend] = .08), but not vegetable fat. Red meat represented the food group with the strongest positive association with advanced cancer (RR = 2.64; 95% CI = 1.21-5.77; P = .02). Fat from dairy products (with the exception of butter) or fish was unrelated to risk. Saturated fat, monounsaturated fat, and alpha-linolenic acid, but not linoleic acid, were associated with advanced prostate cancer risk; only the association with alpha-linolenic acid persisted when saturated fat, monounsaturated fat, linoleic acid, and alpha-linolenic acid were modeled simultaneously (multivariate RR = 3.43; 95% CI = 1.67-7.04; P [trend] = .002). **CONCLUSION:** The results support the hypothesis that animal fat, especially fat from red meat, is associated with an elevated risk of advanced prostate cancer. **IMPLICATIONS:** These findings support recommendations to lower intake of meat to reduce the risk of prostate cancer. The potential roles of carcinogens formed in cooking animal fat and of alpha-linolenic acid in the progression of prostate cancer need to be explored.

J Natl Cancer Inst. 1993 Oct 6;85(19):1571-9

Dairy products, calcium, and prostate cancer risk in the Physicians' Health Study.

BACKGROUND: A high calcium intake, mainly from dairy products, may increase prostate cancer risk by lowering concentrations of 1,25-dihydroxyvitamin D(3) [1,25(OH)(2)D(3)], a hormone thought to protect against prostate cancer. The results of epidemiologic studies of this hypothesis are inconclusive. **OBJECTIVE:** We investigated the association between dairy product and calcium intakes and prostate cancer risk in the Physicians' Health Study, a cohort of male US physicians. **DESIGN:** At baseline, the men answered abbreviated dietary questionnaires. During 11 y of follow-up, we documented 1,012 incident cases of prostate cancer among 20885 men. We estimated dairy calcium intake on the basis of consumption of 5 major dairy products and used logistic regression to estimate relative risk. **RESULTS:** At baseline, men who consumed >600 mg Ca/d from skim milk had lower plasma 1,25(OH)(2)D(3) concentrations than did those consuming < or =150 mg Ca/d [71 compared with 85 pmol/L

(30.06 compared with 35.64 pg/mL); $P = 0.005$]. Compared with men consuming $< \text{or} = 0.5$ daily servings of dairy products, those consuming >2.5 servings had a multivariate relative risk of prostate cancer of 1.34 (95% CI: 1.04, 1.71) after adjustment for baseline age, body mass index, smoking, exercise, and randomized treatment assignment in the original placebo-controlled trial. Compared with men consuming ≤ 150 mg Ca/d from dairy products, men consuming >600 mg/d had a 32% higher risk of prostate cancer (95% CI: 1.08, 1.63). **CONCLUSIONS:** These results support the hypothesis that dairy products and calcium are associated with a greater risk of prostate cancer.

Am J Clin Nutr. 2001 Oct;74(4):549-54

Assessment of oestrogenic potency of chemicals used as growth promoter by in-vitro methods.

Three in-vitro bioassays were used to compare the oestrogenic potency of chemicals used as growth promoter in beef cattle in certain non-European Union countries (17 β -oestradiol, alpha-zearalanol, testosterone, trenbolone, trenbolone acetate, melengestrol acetate) or found as food contaminant such as the mycotoxin zearalenone and some of their metabolites (17alpha-oestradiol, oestrone, 17alpha-epitestosterone, 19-nortestosterone, androstendione, zearalanone, alpha-zearalanol, beta-zearalanol, alpha-zearalenol, beta-zearalenol). The strong oestrogens 17alpha-ethinyl oestradiol and diethylstilboestrol were used as standards. The first bioassay was based on the activation of a reporter gene by oestrogens in recombinant yeast expressing human or rainbow trout oestrogen receptor. In the second bioassay, the vitellogenin gene induction of rainbow trout hepatocyte cultures was used as a biomarker for the exposure to oestrogens. The third bioassay was based on the alkaline phosphatase gene induction by oestrogens in the human endometrial Ishikawa cell line. The assessment of oestrogenic potency of these chemicals clearly demonstrates the strong oestrogenicity of the mycotoxin zearalenone and its metabolites and particularly alpha-zearalenol which was as potent as ethinyl oestradiol and diethylstilboestrol in the human endometrial Ishikawa cell line.

Hum Reprod. 2001 May;16(5):1030-6

Role of the insulin-like growth factor family in cancer development and progression.

The insulin-like growth factors (IGFs) are mitogens that play a pivotal role in regulating cell proliferation, differentiation, and apoptosis. The effects of IGFs are mediated through the IGF-I receptor, which is also involved in cell transformation induced by tumor virus proteins and oncogene products. Six IGF-binding proteins (IGFBPs) can inhibit or enhance the actions of IGFs. These opposing effects are determined by the structures of the binding proteins. The effects of IGFBPs on IGFs are regulated in part by IGFBP proteases. Laboratory studies have shown that IGFs exert strong mitogenic and antiapoptotic actions on various cancer cells. IGFs also act synergistically with other mitogenic growth factors and steroids and antagonize the effect of antiproliferative molecules on cancer growth. The role of IGFs in cancer is supported by epidemiologic studies, which have found that high levels of circulating IGF-I and low levels of IGFBP-3 are associated with increased risk of several common cancers, including those of the prostate, breast, colorectum, and lung. Evidence further suggests that certain lifestyles, such as one involving a high-energy diet, may increase IGF-I levels, a finding that is supported by animal experiments indicating that IGFs may abolish the inhibitory effect of energy restriction on cancer growth. Further investigation of the role of IGFs in linking high energy intake, increased cell proliferation, suppression of apoptosis, and increased cancer risk may provide new insights into the etiology of cancer and lead to new strategies for cancer prevention.

J Natl Cancer Inst. 2000 Sep 20;92(18):1472-89

Plasma levels of insulin-like growth factor-1 and binding protein-3, and their association with bladder cancer risk.

PURPOSE: Because insulin-like growth factors (IGFs) and their binding proteins have been implicated in the development of prostate, breast, colon and lung cancer, we examined the role of IGF-1 and IGF binding protein-3 levels in bladder cancer risk. **MATERIALS AND METHODS:** We used an enzyme-linked immunosorbent assay to compare plasma levels of IGF-1 and IGF binding protein-3 in 154 patients with bladder cancer and 154 controls from an ongoing case-control study. **RESULTS:** Mean IGF-1 was significantly higher in cases than in controls (175.8 versus 153.2 ng./ml., $p < 0.01$). Mean IGF binding protein-3 was significantly lower in cases than in controls (2,632.9 versus 3,056.6 ng./ml., $p < 0.01$). The highest quartile plasma levels of IGF-1 were associated with an increased risk of bladder cancer (OR 3.10, 95% CI 1.43 to 6.70) and the highest quartile plasma levels of IGF binding protein-3 were associated with a reduced risk of bladder cancer (OR 0.38, 95% CI 0.19 to 0.78). The effects were more striking when IGF-1 and IGF binding protein-3 levels were analyzed together. In addition, a higher molar ratio of IGF-1-to-IGF binding protein-3 was associated with an increased risk of bladder cancer (OR 4.30, 95% CI 1.99 to 9.28). Dose-response relationships were evident when subjects were categorized into quartiles by the values of IGF-1, IGF binding protein-3 and the molar ratio in controls. **CONCLUSIONS:** To our knowledge this is the first study to suggest that patients with bladder cancer have higher plasma levels of IGF-1 and lower levels of IGF binding protein-3 than controls. Thus, measuring plasma IGF-1 and IGF binding protein-3 may be useful for assessing bladder cancer risk.

J Urol. 2003 Feb;169(2):714-7

Effect of an accelerated finishing program on performance, carcass characteristics, and circulating insulin-like growth factor I concentration of early-weaned bulls and steers.

Sixty-three Angus x Simmental calves were allotted to a bull or a steer group based on sire, birth date, and birth weight to determine effects of castration status on performance, carcass characteristics, and circulating insulin-like growth factor I (IGF-I) concentrations in early-weaned cattle. At 75 d of age, calves in the steer group were castrated. Calves were not creep-fed prior to weaning. All calves were weaned and weighed at an average age of 115 d and transported by truck to the OARDC feedlot in Wooster, OH. Performance and carcass characteristics were measured in three phases. Phase 1 was from 115 to 200 d of age, phase 2 was from 201 to 277 d of age, and phase 3 was from 278 d of age to slaughter. Before implantation, four bulls and four steers were selected for serial slaughter and carcass evaluation. Steers were implanted with Synovex-C at 130 d of age and with Revalor-S at 200 and 277 d of age. Serum samples were collected from all calves on the day of implantation, 28 and 42 d after implantation, and at slaughter and analyzed for circulating IGF-I concentration. Bulls gained 9.7% faster (1.75 vs 1.60 kg/d; $P < 0.01$), consumed 25 kg more DM (521 vs 496 kg; $P = 0.11$), and were 3.3% more efficient (282 vs 273 g/kg, $P < 0.10$) than steers in phase 1. However, steers gained 10.5% faster (1.62 vs 1.46 kg/d; $P < 0.02$), consumed similar amounts of DM, and were 6.5% more efficient than bulls (214 vs 201 g/kg; $P < 0.06$) in phase 2. Overall gains and efficiency were similar between bulls and steers; however, bulls consumed 140 kg more DM ($P < 0.05$), were 27 kg heavier ($P < 0.05$), and had to stay in the feedlot 18 more days ($P < 0.05$) than steers to achieve a similar amount of fat thickness. Implanted steers had greater concentrations of circulating IGF-I than bulls ($P < 0.01$), and the pattern of IGF-I concentration over time was affected by castration status (castration status x time interaction; $P < 0.01$). Synovex-C had a lower impact on circulating IGF-I concentration (implant effect, $P < 0.01$) than either Revalor-S implant. Eighty-five percent of both bulls and steers had marbling scores sufficient to grade low Choice or better. Bulls achieved their target fat thickness later, increased muscle growth, and deposited fat more favorably than steers, possibly due to a gradual increase in IGF-I concentration as the testicles grew rather than the large fluctuations in IGF-I concentration observed in steers following implantation.

ABSTRACTS

Effects of restricted feeding, low-energy diet, and implantation of trenbolone acetate plus estradiol on growth, carcass traits, and circulating concentrations of insulin-like growth factor (IGF)-I and IGF-binding protein-3 in finishing barrows.

Effects of restricted feeding (80% ad libitum), feeding a low-energy diet containing 84% DE (2.95 Mcal/kg) of the control diet, and implantation of Revalor H (140 mg trenbolone acetate plus 14 mg estradiol-17beta) on growth, carcass traits, and serum concentrations of insulin-like growth factor (IGF)-I and IGF-binding protein-3 (IGFBP-3) were studied in crossbred finishing barrows beginning from 59 +/- 0.9 kg of body weight. Blood samples were taken every three week and the animals were slaughtered at approximately 105 kg body weight. Restricted feeding caused a decrease ($P < 0.01$) in ADG; feeding the low-energy diet was effective in reducing backfat thickness but decreased gain:feed; the implantation caused a decrease in ADG, feed intake, and backfat thickness and increased gain:feed. Overall pork quality based on pH, drip loss, and the lightness in color of longissimus muscle was not affected by any of the treatments. Serum IGF-I concentration increased following the implantation but did not change ($P > 0.05$) due to other treatments. Immunoreactive IGFBP-3 concentration was not changed by any of the treatments. Overall ADG was positively correlated with early-stage (d 21) IGF-I and IGFBP-3 concentrations only in unimplanted barrows, whereas backfat thickness was negatively correlated with d-42 IGF-I concentration in all but unimplanted barrows with ad libitum intake. A strong positive correlation ($P < 0.01$) between IGF-I and IGFBP-3 concentrations was apparent with increasing age of the animals. Results suggest that growth rate and backfat thickness are decreased by a moderate restriction of feed or energy intake with no accompanying changes in circulating IGF-I and IGFBP-3 concentrations and that the beneficial effect of Revalor H implantation on feed efficiency may be mediated, in part, by IGF-I. Moreover, both IGF-I and IGFBP-3 concentrations may be useful as growth indices in pigs.

Anim Sci. 2002 Jan;80(1):84-93

Molecular targets for green tea in prostate cancer prevention.

Prostate cancer (PCa) is the most frequently diagnosed malignancy and the second leading cause of cancer-related deaths in American males. For these reasons, it is necessary to intensify our efforts for better understanding and development of novel treatment and chemopreventive approaches for this disease. In recent years, green tea has gained considerable attention as an agent that could reduce the risk of several cancer types. The cancer-chemopreventive effects of green tea appear to be mediated by the polyphenolic constituents present therein. Based on geographical observations that suggest that the incidence of PCa is lower in Japanese and Chinese populations that consume green tea on a regular basis, we hypothesized that green tea and/or its constituents could be effective for chemoprevention of PCa. To investigate this hypothesis, we initiated a program for the chemoprevention of PCa by green tea. In cell-culture systems that employ human PCa cells DU145 (androgen insensitive) and LNCaP (androgen sensitive), we found that the major polyphenolic constituent (-)-epigallocatechin-3-gallate (EGCG) of green tea induces 1) apoptosis, 2) cell-growth inhibition, and 3) cyclin kinase inhibitor WAF-1/p21-mediated cell-cycle dysregulation. More recently, using a cDNA microarray, we found that EGCG treatment of LNCaP cells results in 1) induction of genes that functionally exhibit growth-inhibitory effects, and 2) repression of genes that belong to the G-protein signaling network. In animal studies that employ a transgenic adenocarcinoma of the mouse prostate (TRAMP), which is a model that mimics progressive forms of human prostatic disease, we observed that oral infusion of a polyphenolic fraction isolated from green tea (GTP) at a human achievable dose (equivalent to 6 cups of green tea/d) significantly inhibits PCa development and metastasis. We extended these studies and more recently observed increased expression of genes related to angiogenesis such as vascular endothelial growth factor (VEGF) and those related to metastasis such as matrix metalloproteinases (MMP)-2 and MMP-9 in prostate cancer of TRAMP mice. Oral feeding of GTP as the sole source of drinking fluid to TRAMP mice results in significant inhibition of VEGF, MMP-2 and MMP-9. These data suggest that there are multiple targets for PCa chemoprevention by green tea and highlight the need for further studies to identify novel pathways that may be modulated by green tea or its polyphenolic constituents that could be further exploited for prevention and/or treatment of PCa.

J Nutr. 2003 Jul;133(7 Suppl):2417S-2424S

Melatonin and cancer

Melatonin as a chronobiotic/anticancer agent: cellular, biochemical, and molecular mechanisms of action and their implications for circadian-based cancer therapy.

Melatonin, as a new member of an expanding group of regulatory factors that control cell proliferation and loss, is the only known chronobiotic, hormonal regulator of neoplastic cell growth. At physiological circulating concentrations, this indoleamine is cytostatic and inhibits cancer cell proliferation in vitro via specific cell cycle effects. At pharmacological concentrations, melatonin exhibits cytotoxic activity in cancer cells. At both physiological and pharmacological concentrations, melatonin acts as a differentiating agent in some cancer cells and lowers their invasive and metastatic status through alterations in adhesion molecules and maintenance of gap junctional intercellular communication. In other cancer cell types, melatonin, either alone or in

combination with other agents, induces apoptotic cell death. Biochemical and molecular mechanisms of melatonin's oncostatic action may include regulation of estrogen receptor expression and transactivation, calcium/calmodulin activity, protein kinase C activity, cytoskeletal architecture and function, intracellular redox status, melatonin receptor-mediated signal transduction cascades, and fatty acid transport and metabolism. A major mechanism mediating melatonin's circadian stage-dependent tumor growth inhibitory action is the suppression of epidermal growth factor receptor (EGFR)/mitogen-activated protein kinase (MAPK) activity. This occurs via melatonin receptor-mediated blockade of tumor linoleic acid uptake and its conversion to 13-hydroxyoctadecadienoic acid (13-HODE) which normally activates EGFR/MAPK mitogenic signaling. This represents a potentially unifying model for the chronobiological inhibitory regulation of cancer growth by melatonin in the maintenance of the host/cancer balance. It also provides the first biological explanation of melatonin-induced enhancement of the efficacy and reduced toxicity of chemo- and radiotherapy in cancer patients.

Curr Top Med Chem. 2002 Feb;2(2):113-32

Five years survival in metastatic non-small cell lung cancer patients treated with chemotherapy alone or chemotherapy and melatonin: a randomized trial.

Numerous experimental data have documented the oncostatic properties of melatonin. In addition to its potential direct antitumor activity, melatonin has proved to modulate the effects of cancer chemotherapy, by enhancing its therapeutic efficacy and reducing its toxicity. The increase in chemotherapeutic efficacy by melatonin may depend on two main mechanisms, namely prevention of chemotherapy-induced lymphocyte damage and its antioxidant effect, which has been proved to amplify cytotoxic actions of the chemotherapeutic agents against cancer cells. However, the clinical results available at present with melatonin and chemotherapy in the treatment of human neoplasms are generally limited to the evaluation of 1-year survival in patients with very advanced disease. Thus, the present study was performed to assess the 5-year survival results in metastatic non-small cell lung cancer patients obtained with a chemotherapeutic regimen consisting of cisplatin and etoposide, with or without the concomitant administration of melatonin (20 mg/day orally in the evening). The study included 100 consecutive patients who were randomized to receive chemotherapy alone or chemotherapy and melatonin. Both the overall tumor regression rate and the 5-year survival results were significantly higher in patients concomitantly treated with melatonin. In particular, no patient treated with chemotherapy alone was alive after 2 years, whereas a 5-year survival was achieved in three of 49 (6%) patients treated with chemotherapy and melatonin. Moreover, chemotherapy was better tolerated in patients treated with melatonin. This study confirms, in a considerable number of patients and for a long follow-up period, the possibility to improve the efficacy of chemotherapy in terms of both survival and quality of life by a concomitant administration of melatonin. This suggests a new biochemotherapeutic strategy in the treatment of human neoplasms.

J Pineal Res. 2003 Aug;35(1):12-5

Role of melatonin in the regulation of human circadian rhythms and sleep.

The circadian rhythm of pineal melatonin is the best marker of internal time under low ambient light levels. The endogenous melatonin rhythm exhibits a close association with the endogenous circadian component of the sleep propensity rhythm. This has led to the idea that melatonin is an internal sleep "facilitator" in humans, and therefore useful in the treatment of insomnia and the readjustment of circadian rhythms. There is evidence that administration of melatonin is able: (i) to induce sleep when the homeostatic drive to sleep is insufficient; (ii) to inhibit the drive for wakefulness emanating from the circadian pacemaker; and (iii) induce phase shifts in the circadian clock such that the circadian phase of increased sleep propensity occurs at a new, desired time. Therefore, exogenous melatonin can act as soporific agent, a chronohypnotic, and/or a chronobiotic. We describe the role of melatonin in the regulation of sleep, and the use of exogenous melatonin to treat sleep or circadian rhythm disorders.

J Neuroendocrinol. 2003 Apr;15(4):432-7

Cancer anorexia-cachexia syndrome: current issues in research and management.

Cachexia is among the most debilitating and life-threatening aspects of cancer. Associated with anorexia, fat and muscle tissue wasting, psychological distress, and a lower quality of life, cachexia arises from a complex interaction between the cancer and the host. This process includes cytokine production, release of lipid-mobilizing and proteolysis-inducing factors, and alterations in intermediary metabolism. Cachexia should be suspected in patients with cancer if an involuntary weight loss of greater than five percent of pre-morbid weight occurs within a six-month period. The two major options for pharmacological therapy have been either progestational agents, such as megestrol acetate, or corticosteroids. However, knowledge of the mechanisms of cancer anorexia-cachexia syndrome has led to, and continues to lead to, effective therapeutic interventions for several aspects of the syndrome. These include antiserotonergic drugs, gastroprokinetic agents, branched-chain amino acids, eicosapentanoic acid, cannabinoids, melatonin, and thalidomide--all of which act on the feeding-regulatory circuitry to increase appetite and inhibit tumor-derived catabolic factors to antagonize tissue wasting and/or host cytokine release. Because weight loss shortens the survival time of cancer patients and decreases performance status, effective therapy would extend patient survival and improve quality of life.

CA Cancer J Clin. 2002 Mar-Apr;52(2):72-91

Extrapineal melatonin in pathology: new perspectives for diagnosis, prognosis and treatment of illness.

During the last decade, attention was concentrated on melatonin -- one of the hormones of the diffuse neuroendocrine system, which has been considered only as a hormone of the pineal gland, for many years. Currently, melatonin has been identified not only in the pineal gland, but also in extrapineal tissues -- retina, hardierian gland, gut mucosa, cerebellum, airway epithelium, liver, kidney, adrenals, thymus, thyroid, pancreas, ovary, carotid body, placenta and endometrium as well as in non-neuroendocrine cells like mast cells, natural killer cells, eosinophilic leukocytes, platelets and endothelial cells. The above list of the cells storing melatonin indicates that melatonin has a unique position among the hormones of the diffuse neuroendocrine system, which is present in practically all organ systems. Functionally, melatonin-producing cells are certain to be part and parcel of the diffuse neuroendocrine system as a universal system of response, control and organism protection. Taking into account the large number of melatonin-producing cells in many organs, the wide spectrum of biological activities of melatonin and especially its main property as a universal regulator of biological rhythms, it should be possible to consider extrapineal melatonin as a key paracrine signal molecule for the local coordination of intercellular relationships. Analysis of our long-term clinical investigations shows the direct participation and active role of extrapineal melatonin in the pathogenesis of tumor growth and many other non-tumor pathologies such as gastric ulcer, immune diseases, neurodegenerative processes, radiation disorders, etc. The modification of antitumor and other specific therapy by the activation or inhibition of extrapineal melatonin activity could be useful for the improvement of the treatment of illness.

Neuroendocrinol Lett. 2002 Apr;23 Suppl 1:92-6

Gastrointestinal melatonin: localization, function, and clinical relevance.

The gastrointestinal tract of vertebrate species is a rich source of extrapineal melatonin. The concentration of melatonin in the gastrointestinal tissues surpasses blood levels by 10-100 times and there is at least 400x more melatonin in the gastrointestinal tract than in the pineal gland. The gastrointestinal tract contributes significantly to circulating concentrations of melatonin, especially during the daytime and melatonin may serve as an endocrine, paracrine, or autocrine hormone influencing the regeneration and function of epithelium, enhancing the immune system of the gut, and reducing the tone of gastrointestinal muscles. As binding sites for melatonin exhibit circadian variation in various species, it has been hypothesized that some melatonin found in the gastrointestinal tract might be of pineal origin. Unlike the photoperiodically regulated production of melatonin in the pineal, the release of gastrointestinal melatonin seems to be related to the periodicity of food intake. Phylogenetically, melatonin and its binding sites were detected in the gastrointestinal tract of lower vertebrates, birds, and mammals. Melatonin was found also in large quantities in the embryonic tissue of the mammalian and avian gastrointestinal tract. Food intake and, paradoxically, also longterm food deprivation resulted in an increase of tissue and plasma concentrations of melatonin. Melatonin release may have a direct effect on many gastrointestinal tissues but may also well influence the digestive tract indirectly, via the central nervous system and the sympathetic and parasympathetic nerves. Melatonin prevents ulcerations of gastrointestinal mucosa by an antioxidant action, reduction of secretion of hydrochloric acid, stimulation of the immune system, fostering epithelial regeneration, and increasing microcirculation. Because of its unique properties, melatonin could be considered for prevention or treatment of colorectal cancer, ulcerative colitis, gastric ulcers, irritable bowel syndrome, and childhood colic.

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