Trial Watch

INSULIN AND PANCREATIC CANCER

Type 2 diabetes mellitus and glucose intolerance have been shown to be risk factors for pancreatic cancer, but it is not clear whether diabetes is involved in pancreatic carcinogenesis or is the result of a subclinical malignancy. Data from a prospective study of the cohort of 29,133 male Finnish smokers enrolled in the α-Tocopherol, β-Carotene Cancer Prevention (ATBC) study between 1985 and 1988 now show that high concentrations of insulin or insulin resistance are associated with a high risk of pancreatic cancer in men.

The investigators hypothesized that diabetes mellitus might be involved in pancreatic carcinogenesis through the growth-regulatory effects of insulin, concentrations of which are increased in the early stages of diabetes mellitus. Insulin is known to have growth-promoting and mitogenic effects on pancreatic cancer. This case–cohort prospective study included 400 randomly sampled control participants and 169 incident pancreatic cancers that occurred after the fifth year of follow-up in the ATBC trial (to reduce the possibility of a subclinical cancer being present before the study began). The presence of biochemically defined diabetes mellitus (glucose ≥126 mg dL^{-1}) and an insulin concentration in the highest quartile showed a twofold increased risk of developing pancreatic cancer.

Owing to the prospective study design, the authors conclude that the associations for diabetes mellitus, insulin concentration and insulin resistance are unlikely to be a consequence of pancreatic cancer. If confirmed, these results could have important implications for cancer-preventive strategies that modify the insulin-resistance pathway.

ORIGINAL RESEARCH PAPER Stolzenberg-Solomon, R. Z. *et al.* Insulin, glucose, insulin resistance, and pancreatic cancer in male smokers. *JAMA* **294**, 2872–2878 (2005)

FIBRE AND COLORECTAL CANCER

Findings from studies on the effects of dietary fibre on the risk of colorectal cancer have been inconsistent, although the hypothesis has been that fibre reduces risk. A pooled analysis of 13 prospective cohort studies, involving 725,628 men, concludes that, when other dietary risk factors have been adjusted for, high levels of dietary fibre are not associated with reduced risk of colorectal cancer.

During 6 to 20 years of follow-up of the men, 8,081 colorectal cancer cases were identified. An inverse association was seen in an age-adjusted model (relative risk (RR) = 0.84), but when other risk factors were accounted for the association was no longer significant (RR = 0.94). If a low dietary fibre intake per day (<10 g) or high intake per day (≥30 g) was compared with a medium intake per day (10–<15 g), the people with low intake had slightly higher risk (RR = 1.18), but ≥30 g per day had no effect on risk (RR = 1.0).

The authors stress that although these data do not support an inverse association with colorectal cancer, a diet high in fibre has been related to lower risks of other chronic conditions.

ORIGINAL RESEARCH PAPER Park, Y. *et al.* Dietary fiber intake and risk of colorectal cancer: a pooled analysis of prospective cohort studies. *JAMA* **294**, 2849–2857 (2005)

CHEMOPREVENTION

G-force

Non-steroidal anti-inflammatory drugs (NSAIDs) prevent colorectal cancer, but their anticancer mechanism has not been resolved. In *Science*, Maria Domenica Castellone *et al.* report that by blocking the activity of the pro-inflammatory cyclooxygenase 2 (COX2) enzyme, NSAIDs interfere with a G-protein-coupled-receptor signalling pathway that normally promotes cell proliferation.

NSAIDs inhibit two enzymes that are involved in prostaglandin synthesis (COX1 and COX2), and can reduce the number and size of adenomas in patients with familial adenomatosis polyposis — a cancer predisposition syndrome associated with mutations in the adenomatosis polyposis coli gene (*APC*). NSAIDs also prevent colon cancer in the $Apc^{min/+}$ mouse model of this disease. Many studies have implicated the contribution of COX2 and one of its metabolites, prostaglandin E2 (PGE2) in colon cancer development, so Castellone set out to identify a link between PGE2 and APC-regulated signalling pathways.

PGE2 is a mitogen in colon cancer cells that carry inactivating mutations in *APC*. In a search for downstream mediators of APC signalling that are affected by treatment of colon cancer cells with PGE2, Castellone found that this prostaglandin increased the transcriptional activity of β-catenin. Sorting the pathway out piece by piece, they discovered that PGE2 activates one of its receptors, EP2, which is linked to a heterotrimeric G-protein that consists of α, β and γ subunits. On receptor activation, these G-protein subunits dissociate. Free G_{α} interacts with axin, a scaffold protein that forms a large molecular complex with APC. This interaction causes the complex to release glycogen synthase kinase 3β (GSK3β). Concurrently, the free G_{β} and G_{γ} subunits directly stimulate phosphatidylinositol 3-kinase (PI3K) and the kinase AKT, leading to phosphorylation and inactivation of GSK3β. Dissociated from its axin complex and inactivated, GSK3β can no longer phosphorylate and inactivate the transcription factor β-catenin.

Stabilized β-catenin can therefore translocate to the nucleus, where it interacts with the transcription factors TCF and LEF to activate genes that promote colon cancer cell proliferation. Identification of this novel signalling pathway provides alternative therapeutic strategies for colon cancer chemoprevention.

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ORIGINAL RESEARCH PAPER Castellone, M. D. *et al.* Prostaglandin E2 promotes colon cancer growth through a novel Gs–Axin–β-catenin signaling axis. *Science* **310**, 1504–1510 (2005)