Clinical Digest

Cancer Mortality

Diabetes May Increase Risk of Cancer Death

After analyzing prospective data on 18,280 adults (599 with and 17,681 without diabetes), researchers from CLUE II (Give Us a Clue to Cancer and Heart Disease) suggest diabetes is more likely to have a deleterious impact on survival in people with cancer than to influence whether they get cancer in the first place.

Previous studies have investigated the effect of diabetes on particular aspects of cancer outcomes, the researchers say, but none have tried to quantify the impact of diabetes across the full continuum of cancer control, from development to survival. Their study was designed to test the hypothesis that preexisting, treated diabetes would predict cancer incidence and cancer mortality in people at risk for cancer, as well as cancer fatality and all-cause mortality in adults who later develop cancer.

The researchers found that preexisting diabetes was an independent risk factor for death from cancer. During 17 years of follow-up, 116 participants with diabetes and 2,365 without diabetes developed cancer; 51 patients with diabetes and 856 patients without diabetes died. After age 60, the cumulative cancer incidence for adults with diabetes was elevated constantly. Compared with patients without diabetes, patients with diabetes were slightly more likely to develop cancer overall—especially cancers of the pancreas, digestive system, and cancers related to smoking.

Overall, 69% of patients who had cancer died of cancer compared with 13% who died of circulatory disease. As with incidence, diabetes was also associated with a higher risk of cancer death after age 60, particularly for cancers of the digestive system. Moreover, cancer patients with diabetes experienced a rapid decline in survival within the first 3 years after cancer diagnosis.

Diabetes was associated with greater cancer-specific case fatality for adults with cancer. The researchers say this may be related to tumor proliferation

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due to hyperinsulinemia and hyperglycemia, less aggressive cancer treatment resulting from the presence of diabetes-related comorbidities, poorer response to cancer treatment in adults with diabetes, and suboptimal cancer screening practices related to diabetes status. They also point to diabetes-related cardiovascular disease as playing a possible role and say that cancer's adverse effects on thrombosis and oxygenation could create "adverse biological interactions."

Source: Yeh HC, Platz EA, Wang NY, Visvanathan K, Helzlsouer KJ, Brancati FL. *Diabetes Care.* 2012; 35(1):113-118.
doi: 10.2337/dc11-0255.

Heart Disease

Nonfatal MIs Can Cast a Long Shadow

Lumping together clinical outcomes can make evaluation easier in clinical trials where sample sizes of individual endpoints may be quite small—but some important information may be squeezed out, say researchers from the Duke Clinical Research Institute, Durham, North Carolina. In particular, they cite nonfatal myocardial infarctions (MIs), which may be weighed equally with other components, such as fatal MIs. Nonfatal MIs "clearly affect" short-term clinical outcomes, but what about long-term effects? An information gap exists, the researchers say, that "impedes interpretation of cardiovascular clinical trials where nonfatal MIs contribute heavily to a composite endpoint." So they looked at data from patients in the Duke University Medical Center database to estimate the long-term clinical implications of nonfatal MIs occurring after diagnostic catheterization.

The primary endpoint was all-cause death. Secondary endpoints were composites of death or MI and death or MI or revascularization procedure; event rates for death, nonfatal MI, percutaneous coronary intervention procedure, and coronary artery bypass grafting surgery; and days survived.

Patients with coronary artery disease who experience a nonfatal MI during the first months after a catheterization procedure may have a higher risk for later fatal and nonfatal clinical events, the researchers say. Of 14,890 patients who were alive after the 3-month follow-up, 669 had a nonfatal MI during the landmark interval of 3 to 6 months, compared with 14,221 who were event free. The 6-month landmark analysis excluded 958 patients who died or were lost to follow-up. Of the remaining 14,646, 804 had a nonfatal MI in the first 6 months of follow-up; 13,842 were event free.

The increased risk was nearly the

same for individuals with a nonfatal MI in the initial 3- and 6- month follow-ups. Having an MI during the initial 3-month period was a significant predictor of reduced survival at 4 years (6.4% increase in adjusted mortality). Having a nonfatal MI in the first 6-month follow-up was associated with a 4.9% increase.

Their findings have important clinical implications, the researchers say—such as for the design of future clinical trials. First, studies with a year or less of follow-up will underestimate the overall benefit of reducing MI rates, as the differences between the MI and no-MI groups continue to expand over time. Second, because the benefits associated with reducing nonfatal MIs begin almost immediately for all endpoints, follow-up periods that are insufficient for detecting downstream events may not reflect the full benefit of a therapy with composite endpoints.

Source: Eisenstein EL, Kong DF, Cowper PA, Bae JP, Ramaswamy K, Anstrom KJ. *Am Heart J.* 2012; 163(1):95-103. doi:10.1016/j.ahj.2011.09.024.

KIDNEY DISEASE

Can Inflamed Gums Cause Kidney Problems?

Recent research has been piling up evidence of the adverse effects of periodontal disease, mainly because of its potential role in chronic inflammation. Now, researchers from the Niigata University, Nigata, Japan; the University of Michigan, Ann Arbor, Michigan; and the University of Groningen, Groningen, the Netherlands are linking periodontal inflammation to reduced kidney function.

A cohort of 317 adults of 75 and older was drawn from a Japanese longitudinal study of aging. The researchers calculated periodontal tissue inflammation for each participant, then divided the groups according to periodontal inflamed surface area (PISA).

During the 2-year follow-up, kidney function worsened in 45 participants (14%). Participants in the highest PISA quartile had nearly 3 times the risk of reduced kidney function compared with participants in the lower PISA quartiles.

Inflammation has been highlighted as contributing to, most notably, heart disease and atherosclerosis. Bacterial antigens are associated with increased production of inflammatory mediators, which accelerate atherogenesis, among other things. And the researchers point out, because atherosclerotic renal artery stenosis is the primary cause of ischemic renal disease, chronic inflammation could ultimately lead to reduced kidney function. They add that other studies have suggested potential links between kidney disease and serum antibody to oral pathogens, citing one that showed that elevated levels of immunoglobulin G to periodontal pathogens are significantly associated with reduced kidney function.

However, the researchers emphasize that "[a]lthough accumulating evidence suggests that increased inflammation may mediate most of the effects of risk factors on kidney disease, the association between inflammation and kidney disease is not yet unequivocally established."

Source: Iwasaki M, Taylor GW, Nesse W, Vissink A, Yoshihara A, Miyazaki H. *Am J Kidney Dis.* 2012; 59(2):202-209. doi:10.1053/j.ajkd.2011.08.027.

ORGAN FAILURE

Protein C Deficiency May Predict Organ Failure

Severe protein C (PC) deficiency may be a useful predictor of specific organ failures in severe sepsis, say Duke University researchers. They compared development of organ dysfunction in 775 adult patients with severe sepsis with and without severe PC deficiency.

The patients were enrolled in the placebo arm of the Recombinant Human Activated PROtein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial. Both groups were similar in age and comorbid conditions, but those with severe PC deficiency were significantly more likely to have had recent surgery. Patients with severe PC deficiency (less than half the lower limit of normal or a mean activity level of ≤ 40%) at baseline had lower arterial blood pressure, greater serum creatinine concentration, elevated markers of thrombosis and inflammation, and impairment of fibrinolysis; all markers of organ function were worse at baseline in those patients, except for respiratory function. They had greater organ failure at day 7; cardiovascular and renal function remained significantly worse and respiratory dysfunction was greater.

The data reveal "an important association between severe PC deficiency at baseline and markers of thrombin generation, inflammation, and impaired fibrinolysis, all of which are likely to be involved in the pathogenesis of organ dysfunction and failure," the researchers say. Further, severe PC deficiency was associated not only with worse organ function at baseline, but also with later worsening of organ function. Thus, low levels of PC could be used to predict specific organ failure in severe sepsis patients. They point to other research that has suggested low PC is a clinically relevant biomarker, but advise further studies.

Source: Shaw AD, Vail GM, Haney DJ, Xie J, Williams MD. *J Crit Care.* 2011;26(6):539-545. doi:10.1016/j.jcrc.2011.05.006.

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