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Editorial

Diabetes mellitus, medications for type 2 diabetes mellitus, and cancer risk

Diabetes is consistently related to the risk of colorectal, liver, pancreas, and endometrial cancer: the relative risk (RR) is of the order of 1.3 for colorectal cancer and around 2 for liver, pancreas, and endometrial cancer [1-6]. Diabetes is also moderately related to postmenopausal breast cancer (RR = 1.15-1.2) [7,8], but residual confounding by overweight is possible, given the absence of association for premenopausal breast cancer. Diabetes is also possibly directly related to bladder cancer and inversely related to prostate cancer risk [6], whereas no consistent association is observed for any other major cancer site [4-6].

The cross-sectional data of the Diabetes Cardiovascular Risk and Evaluation: Targets and Essential Data for Commitment of Treatment (DETECT) study [9] confirms an excess overall cancer risk among subjects with diabetes. On the basis of 185 cancer cases among nondiabetic subjects and 66 cancer cases among diabetic subjects, the odds ratio for all cancers combined was 1.64 (95% confidence interval [CI], 1.12-2.41).

The point estimate of the DETECT study, however, is somewhat higher than expected on the basis of accumulated evidence on diabetes and cancer [4-6]. Given that, in most populations, liver, pancreas, and endometrial cancers account for about 10% of cancers and colorectal and breast cancers account for an additional 10% each, and taking into account the possible direct association with bladder and the inverse one with prostate, one would expect an overall RR of all cancers in diabetic patients of around 1.15 to 1.20. This is compatible with the lower confidence limit in the DETECT study [9] and hence with the vagaries of chance alone. However, the point estimate of 1.64 may also suggest an increased surveillance for cancer—and hence cancer diagnosis—among diabetic patients, which may lead to an overestimate of the association. Indeed, in a Swedish record linkage study [3], based on 125 126 patients with type 2 diabetes mellitus hospitalized from 1964 to 2007 and a total 10 974 registered cancer cases, the overall cancer RR in diabetic subjects was 1.78 (95% CI, 1.75-1.81); but it decreased to 1.15 (95% CI, 1.11-1.19) 5 or more years after the last hospitalization for diabetes. This points to a relevant role of increased cancer diagnosis in the short time after diagnosis of diabetes, following extensive medical examinations. Likewise, in a cohort of 16 721 diabetic patients from Israel [10], at 8-year follow-up and on the basis of 1639 incident cancers, the RR of all cancers was 1.25 (95% CI, 1.16-1.36) in women and 1.02 (95% CI, 0.94-1.10) in men. Similarly, the cancer-related mortality in the 5-year follow-up period of the DETECT study [9] was 1.25 (95% CI, 0.14-2.13) based on 68 cancer deaths in subjects without diabetes and 32 cancer deaths in subjects with diabetes. This estimate of the excess risk is compatible with most available evidence [3-6,10].

The 32 cancer deaths in diabetic subjects during the 5-year follow-up registered in the DETECT study [9] were further considered in 16 different (but not mutually exclusive) strata according to type of treatment. Of these 16 strata, 5 showed a significant excess risk, that is, monotherapy with insulin, monotherapy or combination therapy with insulin, combination therapy including insulin, any treatment excluding metformin, or any other medication except metformin.

A record linkage study of 36 342 diabetic patients from an Israeli health maintenance organization followed from January 2003 to December 2007 and including a total of 976 female and 1192 male incident cancers also considered purchases of 5 classes of drugs (metformin, sulfonylureas, glargine, detemir, and other insulin [11]). At multivariate analysis, there was no association between glycohemoglobin control and cancer risk. The RR was below unity for metformin and sulfonylureas and above unity for insulin purchases, but the differences were small in the model described. That study, moreover, had inadequate power to consider combination of therapies, as well as various (diabetes-related) cancers sites separately.

Insulin has growth stimulation effects [12]. It is however unclear whether insulin increases cancer risk through its effect on cell growth and proliferation or decreases cancer risk because of its glucose-lowering effects. Thus, in a study from Hong Kong on 973 subjects including new insulin users and 971 matched nonusers [13], hyperglycemia was associated with increased cancer risk; but insulin use was associated with reduced cancer risk. In a meta-analysis [14], colorectal cancer risk was associated with C-peptide/insulin levels (overall RR for the highest level, 1.35; 95% CI, 1.13-1.61) and also with glycemic level (RR, 1.18; 95% CI, 1.08-1.31). Corresponding figures for

pancreatic cancer were 1.70 (95% CI, 1.10-1.63) for high C-peptide/insulin and 1.98 (95% CI, 1.67-1.35) for high glycemia.

Alternatively, as pointed out by Baur et al [9], metformin may reduce cancer risk through reduction of insulin resistance; inhibition of mammalian target of rapamycin, an effector of growth factor signaling often activated in malignant cells; and/or induction of cell cycle arrest and apoptosis [15,16]. Apart from the DETECT study [9], there are other observational prospective studies from Scotland [17], the United Kingdom [18], and the Netherlands [19] indicating that metformin use was associated with reduced cancer risk or cancer mortality compared with other diabetes therapies.

However, the apparent lower risk for metformin users may be due to reduced time of exposure among participants who developed cancer (ie, "time-window bias" [20,21]). Furthermore, the clinical characteristics of diabetic patients treated with metformin are substantially different from those of patients treated with other medications and particularly from those treated with insulin. Consequently, even detailed allowance for available covariates may leave open the issue of residual selection bias or confounding by indication [22] in any comparison of cancer risk according to type of diabetes treatment from observational studies.

Future studies, therefore, should include detailed and valid information not only on diabetes history and timing but also on body mass index, tobacco, alcohol, and other major covariates related to both diabetes and cancer risk. Such studies will benefit from the fact that relevant information could be obtained from existing databases (ie, prescription databases, electronic medical records linked to cancer registration schemes). Also of interest would be patients' data at a variety of time to provide information of their glycemic control.

Although the key public health message remains to avoid overweight and obesity to reduce not only cardiovascular but also cancer risk [23], it is important to monitor various aspects of diabetes management and treatment to better quantify any potential implication not only on cardiovascular but also on cancer risk.

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