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Commentary

Metformin: Are Potential Benefits on Cancer Risk Extended to Cancer Survival?

Carlo La Vecchia,[a,b] Cristina Bosetti[a]

[a]Department of Epidemiology, IRCCS–Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy; [b]Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milano, Italy

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Carlo La Vecchia

Cristina Bosetti

It has long been recognized that patients with type 2 diabetes have an excess risk of cancer of selected sites. These include colorectum, liver, pancreas, and endometrium, while possible associations with postmenopausal breast and bladder cancer have been addressed in several studies, but remain open to discussion [1-5]. When adequate allowance is made for overweight, however, this translates to a relatively modest overall excess cancer risk, i.e., less than 10% for all cancers combined. The excess risk of selected cancers cannot be totally explained by overweight and obesity, which are also associated with diabetes. This risk, therefore, must be linked with metabolic factors related to insulin resistance, hyperinsulinemia, and their influence on the insulin growth factor (IGF) system, which may stimulate cell proliferation and inhibit apoptosis [2, 6].

In addition, there are indications that different types of therapies for diabetes may influence subsequent cancer risk. In particular, metformin, a first-line antidiabetic drug belonging to the biguanide family, has been associated with a decreased risk of subsequent cancers [7, 8]. The relationship between metformin and cancer risk was considered in a comprehensive meta-analysis of 17 epidemiologic studies including 37,632 diabetics [8]. Its main findings are provided in Table 1. Use of metformin versus nonuse of metformin, or versus use of other therapies (sulfonylurea or insulin), was associated with a significantly reduced relative risk (RR) of all cancers (RR = 0.61, 95% confidence interval, [CI], 0.54-0.70), which was consistent across types of studies (cohort or case-control) and antidiabetics used as comparison. The summary RRs were 0.64 (95% CI, 0.54-0.76) for colorectal and 0.38 (95% CI, 0.74-0.91) for pancreatic cancer, two major diabetes-related neoplasms. In contrast, no significant associations were observed for breast (RR = 0.87) or prostate (RR = 0.92) cancer.

With reference to other antidiabetics, there is no evidence that sulfonylurea [8] and thiazolidinediones [9] materially influence subsequent cancer risk, though some excess of bladder cancer has been reported for long-term use of pioglitazone (RR = 1.4), and the issue remains open to further investigation [9]. Insulin, and particularly glargine, have been suggested in the past to increase subsequent breast cancer risk, but the overall data appear now to indicate an absence of any material association [10, 11]. There is, therefore, a clear evidence in favor of metformin as compared with other antidiabetic drugs regarding subsequent cancer risk in type 2 diabetic patients.

There are, however, at least two major difficulties in the interpretation of these data. First, they are based on observational studies, since antidiabetic therapy has to be personalized and cannot consequently be randomized in patients treated for diabetes. There is therefore an inherent indication bias. Second, the baseline clinical characteristics of diabetic patients using metformin are largely different from those of patients using other antidiabetics (particularly insulin), and hence any inference or comparison on their subsequent cancer risk is difficult. Confounding is therefore complex and difficult to allow for, despite the use of multivariate methods of analysis [12, 13]. This is particularly true because most studies were conducted on routinely collected (i.e., administrative) health databases, which have limited or no information on important covariates for diabetes and cancer risk, including body mass index and consumption of alcohol and tobacco [14, 15].

Still, the approximately 40% reduced risk of all cancers in diabetics using metformin and the appreciably reduced risk of colorectal or pancreatic cancer [8] appear to be too large to be totally accounted for by different baseline characteristics of the two groups of diabetic patients. Hence, a real favorable effect of metformin—of potential clinical and public health relevance—is possible. The antineoplastic activity of metformin has been related to reduced

Correspondence: Carlo La Vecchia, M.D., Department of Epidemiology, IRCCS–Istituto di Ricerche Farmacologiche "Mario Negri," Via La Masa 19 20156 Milano, Italy. Telephone: +39 0239014527; Fax: +39 0233200231; E-Mail: carlo.lavecchia@marionegri.it Received October 1, 2013; accepted for publication October 18, 2013. 1083-7159/2013/$20.00/0 http://dx.doi.org/10.1634/theoncologist.2013-0381

Table 1. Meta-analytic relative risk and corresponding 95% confidence intervals for all cancers combined and selected cancer sites in users versus nonusers of metformin[a].

Type of treatment and type of study	Relative Risk	(95% Confidence Interval)
All cancers		
Metformin vs. no metformin		
Cohort	0.52	(0.39–0.69)
Case-control	0.75	(0.60–0.94)
Summary	0.60	(0.50–0.73)
Metformin vs. sulfonylurea		
Cohort	0.68	(0.53–0.89)
Case-control	0.39	(0.22–0.73)
Summary	0.65	(0.50–0.83)
Metformin vs. insulin		
Cohort	0.65	(0.48–0.88)
Case-control	0.21	(0.11–0.42)
Summary	0.56	(0.40–0.78)
Overall	0.61	(0.54–0.70)
Selected types of cancer		
Colorectum	0.64	(0.54–0.76)
Pancreas	0.38	(0.74–0.91)
Breast	0.87	(0.69–1.10)
Prostate	0.92	(0.73–1.17)

[a]Derived from the meta-analyses by Soranna et al., 2012 [8].

hyperinsulinemia and glycemic levels [16-18]. Hyperinsulinemia, in fact, has been associated with increased cancer risk at many sites including colorectal, liver, gallbladder, pancreas, and endometrium [2, 19-22]. Likewise, high levels of C-peptide/insulin and glycemia have been associated with colorectal and pancreatic cancers in a recent meta-analysis [23]. Direct (insulin-independent) mechanisms on the process of carcinogenesis have been also implicated, since metformin has been shown in in vivo and in vitro studies to inhibit global protein synthesis and proliferation in various cancer cell lines, through action on the mammalian target of rapamycin (mTOR) signaling and protein synthesis [16, 17, 24-28]. In addition, metformin selectively blocks the growth of cancer stem cells and inhibits a metabolic stress response that may stimulate the inflammatory pathway associated with a number of cancers [29]. It is therefore not surprising that the use of metformin is associated with a decreased cancer risk, and in particular of colorectal and pancreatic cancer, through both insulin-dependent or insulin-independent mechanisms.

In this issue, Yin et al. [30] add important information on possible benefits of metformin treatment on cancer outcome. On the basis of a meta-analysis of 20 studies, including over 13,000 cancer patients with type 2 diabetes, it gives a hazard ratio (HR) of 0.66 (95% CI, 0.55-0.79) for overall survival and of 0.62 (95% CI, 0.46-0.84) for cancer-specific survival for subjects with cancer (all sites combined) treated with metformin as compared with nonmetformin users. When considering subjects with specific cancers, for both overall and cancer-specific survival, the HRs were significant only for those with major diabetes-related cancers (colorectum and pancreas), whereas the results were nonsignificant for neoplasms not known to be diabetes-related, including lung and prostate, and also for breast cancer.

There are scanty, but suggestive, data that metformin may improve pathologic regression rate particularly in breast cancer patients receiving neoadjuvant chemotherapy [31, 32]. However, the data utilized in the meta-analysis by Yin et al., as well as those on cancer risk discussed above, are derived from nonrandomized studies, and thus suffer from all the limits of observational data, particularly selection by indication of various antidiabetic drugs and lack of adequate allowance for confounding [14, 15]. Still, they are suggestive and, if real, would extend the antitumor activities of metformin from an action on carcinogenesis—particularly on cancer promotion through inhibiting IGFs and cell proliferation [17]—to other tumor-suppressing mechanisms, including interactions with other antineoplastic agents on a cell regulation level, as discussed by Yin et al. [30, 33-36].

Diabetes is a complex disease that requires personalized treatment, and most serious consequences of diabetes are on the vascular and renal systems, with cancer being a comparatively limited additional issue. Still, the accumulating, though suggestive, evidence of a favorable impact of metformin not only on cancer risk but also on cancer prognosis may help optimize treatment in at least a subset of diabetic patients. In addition, metformin may find a scope for utilization in cancer chemoprevention for selected groups of nondiabetic or prediabetic subjects at high risk for specific neoplasms [32, 37]. Moreover, a few clinical trials have been set up to study metformin use in women with breast cancer [38, 39].

As any drug, however, metformin is not devoid of side effects. Of specific concern is a recent report of an association between metformin use and poor cognitive function [40]. This may be related to the downregulation of

metformin on cell proliferation, as well as to metformin-induced alteration of vitamin B levels. Thus, metformin may exert a favorable effect on cancer, but an unfavorable one on cognitive function, this being in line with the inverse relationship observed between Alzheimer's disease and cancer on a population level [41]. This issue is, however, too preliminary for any assessment and risk quantification.

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