Title
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Journal
Cancer prevention research (Philadelphia, Pa.), 9(10)

ISSN
1940-6207

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Publication Date
2016-10-01

DOI
10.1158/1940-6207.capr-16-0173

Published OnlineFirst July 18, 2016; DOI: 10.1158/1940-6207.CAPR-16-0173

Commentary

Cancer Prevention Research

Deciphering the Effect of Metformin on Prostate Cancer Risk by Ethnicity

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See related article by Wang et al., p. 779

Prostate cancer still remains the most common malignancy in American men. In this issue, Wang and colleagues studied the effect of metformin on prostate cancer incidence in the Veterans Administration Health Care System (1). According to their analyses, metformin had a protective effect on prostate cancer risk in the Hispanic Americans but not in non-Hispanic White Americans, African Americans, or Asian Americans. The scope of prostate cancer apparently varies by race, with African American men reported to have a higher incidence, more advanced anatomic stage at the time of diagnosis, and higher cancer-specific mortality. Potential biological explanations for these disparities include racial differences in tumor biology and responsiveness to treatment; potential extrinsic explanations include differences in access to care, patterns of screening, and treatments received. However, when these men of varying race were cared for in an equal-access health care system, differential outcomes most likely reflected variations in underlying biological factors.

Metformin has been widely used as a first-line therapy for type I diabetes, but its exact mechanism is not completely understood. The pharmaceutical effects of metformin are mediated through the AMP-activated protein kinase (AMPK) signaling, as well as AMPK-independent pathways (2). AMPK plays a key role in sensing and regulating ATP–AMP homeostasis. AMPK increases ATP production through fatty acid and glucose metabolism, promotes catabolism, and attenuates oxidative stress and inflammation. Dysfunction of AMPK signaling has been implicated in the development of cancers, but there were conflicting opinions regarding the roles of AMPK signaling in cancer cells (3, 4). The positive action of AMPK signaling on cell growth and its antioxidative stress effect suggested a tumor-promoting effect, whereas the tumor suppressor LKB1 could phosphorylate AMPK-α subunit, and loss of LKB1/APMK signaling might aggravate tumor progression (3, 4). This makes AMPK seem like the two-faced Roman god Janus in cancer biology. There is evidence that metformin has AMPK-independent pharmacologic actions. Metformin may modulate mitochondria oxidative phosphorylation, oxidative stress, and inflammation in the absence of AMPK. However, it is not entirely clear how AMPK-independent actions of metformin regulate cancer biology.

Glycerin-N-methyltransferase (GNMT) is expressed at high levels in prostate and pancreas. GNMT plays a critical role in the development of prostate cancer by catalyzing transfer of methyl group to DNA and histones that eventually transforms neoplastic gene programming (5). Metformin suppressed DNA methylation in pancreatic islet cells (6). Although whether the anticancer effect of metformin in prostate involves this mechanism is not known, GNMT genotyping data raised the possibility that the impact of genetic variations can be divergent in different races. In European Americans, GNMT rs1094859 allele variations were associated with increased risk for nonaggressive prostate cancer but not aggressive cancer (7). However, the same allele was not associated with nonaggressive prostate cancer risk and had a protective association against aggressive prostate cancer in Taiwanese men (8). For diabetes control, there is also evidence that the efficacy of metformin for glycemic control is not uniform across different ethnic groups. For example, African Americans appeared to be more responsive to metformin than Caucasians (9). Further study is needed to analyze the effect of metformin on prostate cancer risk in the context of genetic polymorphism across different ethnicities.

The effect of metformin on cancer risk and prognosis has not been consistent in previous studies (10). The anticancer action of metformin may vary under different genetic backgrounds, antineoplastic drugs, and metabolic status. Metformin can modulate hyperinsulinemia and insulin resistance, which had been linked to higher prostate cancer risk (11), but the status of hyperinsulinemia was rarely investigated in the context of metformin and prostate cancer in epidemiology studies. Mitochondria is a target of metformin actions, and mitochondria-mediated apoptosis plays a key role in prostate cancer response to nonsurgical treatments. Diverse mitochondrial DNA haplogroups have been recognized in different female inheritance lineages through human evolution and dates back to the human ancestors in Africa and subsequent migration around the world (12). Each ethnic group and subgroup retains unique mitochondria genetic signatures. Specific haplogroups had been associated with human cancer and metabolic diseases (12, 13). It will be interesting to analyze whether differential effects of metformin on prostate cancer in different ethnicity can be explained by mitochondria genetics or the genetics of nuclear genes that modulate mitochondria function.

Metformin is one of the most prescribed medications in the United States, and prostate cancer is the most common male malignancy. To clarify the effect of metformin on prostate cancer in future studies, there is a need to better integrate race-specific genetics and metabolic profile in a mechanistic carcinogenesis model with cancer incidence and survival.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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doi: 10.1158/1940-6207.CAPR-16-0173

Published OnlineFirst July 18, 2016; DOI: 10.1158/1940-6207.CAPR-16-0173

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Development of methodology: E. Uchio, P.H. Wang
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): E. Uchio
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): E. Uchio
Writing, review, and/or revision of the manuscript: E. Uchio, F.L. Meyskens, P.H. Wang
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): E. Uchio, P.H. Wang
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Received July 1, 2016; accepted July 6, 2016; published OnlineFirst July 18, 2016.

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